

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Meeting of:

SECRETARY'S ADVISORY COMMITTEE

ON

XENOTRANSPLANTATION

February 20, 2001

DoubleTree Hotel
Rockville, Maryland

Reported By:

CASET Associates
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
(703) 352-0091

TABLE OF CONTENTS

	<u>Page</u>
Welcome - William Raub	1
Swearing in of Committee Members - David Satcher	3
Opening Remarks - David Satcher	4
Introduction of the Committee	6
Remarks by the Chair - Harold Vanderpool	13
Overview of the Federal Advisory Committee Act - LaVerne Stringfield	14
Ethics Rules for Federal Advisory Committee Members: Conflict of Interest, Outside Activities and Affiliations, and Confidentiality - Karen Dalheim, Fran Plyler	16
The Experimental and Clinical History of Xenotransplantation - David K.C. Cooper	22
The Science of Xenotransplantation:	
Immunological Aspects - Hugh Auchincloss	28
Pre-Clinical Animal Models - David White	41
Infectious Disease Risk - Jon Coffin	47
Public Comment	57
PHS Guideline on Infectious Disease Issues in Xenotransplantation - Louisa Chapman	63
FDA Regulation of Xenotransplantation and Current Policy - Eda Bloom	71
Overview of Xenotransplantation Clinical Trials - Louis Marzella	79
Presentations on Xenotransplantation Clinical Trials (Part I)	
The Excorp Medical Bioartificial Liver System - Daniel Miller	82
Schedule for Future SACX Meetings - Mary Groesch	88

COMMITTEE MEMBERS PRESENT:

Harold V. Vanderpool, Ph.D., Th.M., University of Texas Medical Branch, Galveston, Texas

Jonathan Allan, D.V.M., Southwestern Foundation for Biomedical Research, San Antonio, Texas

Bradley H. Collins, Ph.D., Duke University, Durham, North Carolina

Catherine Crone, M.D., INOVA Fairfax Hospital, Falls Church, Virginia

James Finn, Newport, Rhode Island

Richard A. Kaslow, M.D., M.P.H., University of Alabama, Birmingham, Alabama

Sharon C. Kiely, M.D., M.P.M., Allegheny General Hospital, Pittsburgh, Pennsylvania

Karren King, M.S.W., A.C.S.W., L.C.S.W., Consultant, Kansas City, Missouri

Robert Mendez, M.D., F.A.C.S., St. Vincent Medical Center, Los Angeles, California

Marian G. Michaels, M.D., M.P.H., Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Lilly-Marlene Russow, Ph.D., Purdue University, West Lafayette, Indiana

Daniel Salomon, M.D., Scripps Research Institute, La Jolla, California

William Scheckler, M.D., University of Wisconsin, Madison, Wisconsin

Robyn S. Shapiro, J.D., Medical College of Wisconsin, Milwaukee, Wisconsin

M. Michael Swindle, D.V.M., Medical University of South Carolina, Charleston, South Carolina

Megan Sykes, M.D., Harvard Medical School, Boston, Massachusetts

EXECUTIVE DIRECTOR:

Mary E. Groesch, PhD., Office of Science Policy, Office of the Director, National Institutes of Health

EX OFFICIO COMMITTEE MEMBERS PRESENT:

Lily O. Engstrom, M.S., Office of the Secretary, Department of Health and Human Services

Jon L. Nelson, Health Resources and Services Administration

Daniel Rotrosen, M.D., National Institutes of Health

Thomas J. Spira, M.D., Centers For Disease Control And Prevention

Kathryn C. Zoon, Ph.D., Food and Drug Administration

PROCEEDINGS

(8:35 a.m.)

Agenda Item: Welcome

DR. RAUB: Good morning, everyone. I am Bill Raub. I am the deputy assistant secretary for science policy at the Department of Health and Human Services. I have the privilege today of welcoming you to the first meeting of the Secretary's Advisory Committee on Xenotransplantation.

By way of background, I will take just a few minutes to describe some of the key events that led up to today. As many of the members of this committee know much better than I, interest in xenotransplantation goes back a long time, at least to the 19th Century and arguably before.

The U.S. public health policy in xenotransplantation began in earnest in the mid-1990s. At that time, due to the shortage of human organs for transplantation, many medical centers around the United States were considering turning to animals as a source of organs. Serious concerns about the risk of transferring infectious agents from animals to humans kept the enthusiasm in check, for the most part.

To begin to assess these public health concerns, the then-assistant secretary for health, Dr. Philip Lee, requested in late 1994 that the Public Health Service agencies launch a process to develop a consensus regarding the infectious disease risks and safety issues raised by xenotransplantation.

Around the same time, the Food and Drug Administration heard from a number of institutional review boards, otherwise known as IRBs, that had concerns about proposed xenotransplantation clinical trials at their institutions. These IRBs indicated that a wide spectrum of facilities were being proposed as sources of animal tissues, ranging from sterile laboratories to local slaughterhouses, and the IRBs requested guidance on evaluating these proposals.

Although there were many well-documented cases of humans infected with organisms transmitted by animals, there were no extant guidelines governing the adequate screening of source animals, or of animal cells, tissues or organs intended for human transplantation. Nor were there any recommendations for the post-transplantation monitoring of patients.

Consequently, the Public Health Service working groups were formed in 1995 to develop public health guidelines on xenotransplantation. The working groups were composed of staff from the Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Health, and the Health Resources and Services Administration, and also included representatives from the Department of Defense, the Institute of Medicine and other groups. The goal was to identify baseline safety requirements for the procurement, screening and use of the xenotransplantation product, and for clinical follow up of the patient.

In growing recognition of the importance of public discussion of the issues raised by xenotransplantation, Institute of Medicine workshops and open sessions of Food and Drug Administration advisory committee meetings, in 1995 and 1996, focused on the scientific, medical, and ethical aspects of xenotransplantation.

Another noteworthy milestone was a 1996 meeting between Public Health Service agencies and the American Society of Transplant Surgeons and the American Society of Transplant Physicians. The transplant community provided expert input on public health considerations in xenotransplantation and endorsed the basic elements of the PHS guideline that had been discussed in public meetings.

The draft PHS guidelines on infectious disease issues in xenotransplantation, published in the fall of 1996 for public comment, was the culmination of the department's consensus process to that point. The recommendations within the draft guideline were intended to minimize the risk of transmission of infectious agents from xenotransplantation products to human recipients, and from recipients to their close contacts and beyond. The draft document addressed a variety of critical topics including source animal care, screening and selection, the expertise needed to conduct clinical trials safely, informed consent and patient education processes relevant to infectious disease transmission, health monitoring of xenotransplant recipients and close contacts, hospital infection control procedures, and the need for long-term maintenance of patient records and biological samples. It also foreshadowed additional tools that we have been developing or considering to address public health issues raised by xenotransplantation.

Since 1997, I have had the privilege to chair the HHS interagency working group on xenotransplantation. The working group includes members from the FDA, CDC, NIH, HRSA and the Office of the Secretary, including the Office of the General Counsel. The working group has been striving tirelessly to advance an integrated and coordinated HHS-wide strategy for addressing xenotransplantation issues. The strategy features five elements, and I will touch upon each very briefly.

The first is an evolving regulatory framework. All xenotransplantation clinical trials conducted within the United States are subject to regulation by the Food and Drug Administration. We will hear more about this later today, including FDA's efforts to extend and refine the regulatory framework for xenotransplantation. In addition, xenotransplantation clinical trials are subject to review by local oversight bodies at the institutions where the research will be performed.

The second element is the PHS guideline. Since publication of the draft guideline in 1996, PHS agencies have been working to revise it in response to public input and recent scientific meetings. As most of you are probably aware, the revised guideline was issued earlier this year, and I congratulate the members of the interagency working group and their colleagues, who persevered in this important effort, more than most of us will ever know. You will hear more about the revised guideline today.

The third element in our xenotransplantation strategy is a national data base of xenotransplantation clinical trials. Accurate, timely information from xenotransplantation clinical trials is essential for the regulatory oversight and disease surveillance efforts warranted by this technology. Thus, we are developing a data base to systematically gather information from all clinical centers conducting xenotransplantation clinical trials, and all biomedical animal facilities supplying animals and tissues for these trials. A limited, but functional, pilot program has been developed to determine the requirements for data collection and reporting, system design, start up, and operation. We will hear more about this project at a future meeting of the committee.

The fourth element in the department's array of tools for addressing xenotransplantation is an archive of biological specimens for public health investigations. The need to maintain biological specimens from both xenotransplantation patients and source animals is evident. Long-term archival storage of biological samples from source animals and patients is critical to ensuring our ability to conduct appropriate investigations in the event of a xenogeneic infection that could potentially adverse public health. Currently, individual sponsors of xenotransplantation clinical trials are responsible for achieving such samples and archiving them. A centralized storage facility could ensure immediate access to, and availability of, adequately preserved biological specimens for public health investigations.

This brings us to the final component and to today, the Secretary's advisory committee for xenotransplantation, a national advisory body and a forum for public discussion of xenotransplantation.

The charter for the committee was developed by the HHS interagency working group. There has been widespread, strong support for the establishment of such a national advisory group, as evidenced by comments received in response to the publication of the draft guidelines in a variety of published opinion pieces, and in discussions at numerous public meetings on xenotransplantation.

In the spirit of interagency collaboration, FDA, CDC and NIH have assumed lead agency roles for many of the elements that I have described briefly. NIH is providing the administrative support for this committee. FDA is leading the development of the national xenotransplantation data base, and CDC will assume responsibility for the biological specimen archive.

Xenotransplantation raises issues that transcend the mission of any single Public Health Service agency. For this reason, we are committed to continued coordinated Public Health Service oversight of xenotransplantation, and to development of better understanding of this potentially promising technology. This committee will do much to help ensure that we succeed in that goal.

I now have the distinct honor of introducing our speaker for this morning. I have known Dr. David Satcher beginning with his time as the president of Meharry School of Medicine, his service as the director of the Centers for Disease Control and Prevention, his dual service as the Assistant Secretary for Health and the Surgeon General of the United States Public Health Service, and his continuing role as Surgeon General, just a few milestones in a very distinguished career.

Ladies and gentlemen, please welcome the nation's doctor, Dr. David Satcher.

[Applause.]

Agenda Item: Swearing in of Committee Members.

DR. SATCHER: Good morning. I am very pleased to be here today and to join Dr. Raub in welcoming you to this inaugural meeting of the Secretary's advisory committee on xenotransplantation.

I have had a long-standing interest in xenotransplantation and have supported and guided the development of this advisory committee during my tenure as assistant secretary for health and surgeon general. I also have an interest going back especially to the time when I served as director of the Centers for Disease Control and Prevention.

I bring you greetings this morning from Secretary Tommy Thompson, now Secretary of the Department of Health and Human Services.

I have a few prepared remarks, but before making these, I have been asked to administer the oath of office to committee members. I note that each of you has already signed this oath as part of a considerable paperwork that came along with membership on a federal advisory committee. Nevertheless, I think that it is appropriate and fitting to say the words aloud. I think they will remind us of the responsibilities that you accept as special government employees.

Will the members of the Secretary's Advisory Committee on Xenotransplantation please rise. I would like for you to raise your right hands and repeat the oath after me.

I -- state your full name -- do solemnly swear or affirm that: I will support and defend the Constitution of the United States against all enemies, foreign and domestic; That I will bear true faith and allegiance to

the same; That I take this obligation freely, without any mental reservation or purpose of evasion; That I will well and faithfully execute the duties of the office on which I am about to enter, so help me, God.

[Oath is spoken by committee members.]

Thank you. So, welcome. You are now one of us, at least during the time that you are serving as advisors and we are delighted to have you.

Agenda Item: Opening Remarks.

DR. SATCHER: I would like to take a few minutes to just talk about why the department has established this committee. Dr. Raub has just described a series of events and the processes that sort of brought us to this day. I would like to comment on why, from a public health perspective, xenotransplantation warrants the focused attention of the group of experts that we have assembled here today.

In our lifetime, we have been privileged to witness remarkable successes in human organ and tissue transplantation. With this success, however, the demand for human cells and tissues and organs, in the treatment of human disease, has increased far beyond the supply. Despite focused efforts to increase the number of organ donors, there is, today, a critical shortage of human organs available for transplant. In fact, today, almost 75,000 Americans are on waiting lists for organ transplantation. Yet, only about 22,000 organ transplants take place each year. In 1999 alone, 6,100 Americans died while on waiting lists for human organ transplant.

I must say that Secretary Thompson, as he has entered the position of Secretary of DHHS, has made this issue one of his priorities, and is speaking out throughout the country on the importance of organ donation. I have seen how the often dramatic life-saving outcomes achieved through transplantation have frequently seemed to heighten the frustration of physicians and the desperation of patients, who continue to wait for human organs to become available.

This unmet, and yet growing, demand for human cells, tissues and organs has renewed interest in the experimental use of live animal cells, tissues and organs to treat a wide variety of diseases. The potential clinical application of xenotransplantation include severe, life-threatening illness such as liver failure, chronic diseases that affect large segments of Americans, including diabetes and certainly neurodegenerative disorders, such as Parkinson's disease.

There is another impetus for the recent emphasis on xenotransplantation. As you will hear in more detail later, recent advances in immunology, in molecular biology and bioengineering have made important strides in overcoming the formidable immunological barriers to the survival of animal transplants in humans. These advances include potent immunosuppressant drugs, genetic engineering techniques, and new biomaterials for encapsulating xenotransplantation products.

Now, although immune rejection and failure to engraft are still the primary medical and scientific challenges in xenotransplantation, the recent successes seen in this area have dictated that we consider carefully the long-term implications of xenotransplantation. Along with the potential promise that xenotransplantation brings, concerns have been raised about the potential infectious disease and public health risk associated with xenotransplantation, and about the social, legal and ethical implications.

Experience has demonstrated that infections can be transmitted from donor to recipients through

transplant. In fact, none of us would like to relive that experience of the early 1980s of HIV infections through the blood supply, before we had the ability to screen it out, but also hepatitis B and hepatitis C. We are familiar with this experience.

Thus, the use of live animal cells, tissues and organs for transplantation or high profusion in humans raises critical public health concerns about potential infections of the patient with both recognized and, indeed, unknown, novel infectious agents. We know that animal diseases can be transmitted to humans through exposure to household pets and wild animals, animal husbandry activities and consumption of animals. We know about rabies and we know about mad cow disease.

Xenotransplantation differs significantly from the natural circumstances in which people are exposed to infectious animal agents. First, as you know, surgery disrupts the normal anatomical barriers to infection, such as skin and membranes. Second, transplant recipients are usually immunosuppressed, to facilitate graft survival. Third, patients have these underlying diseases, such as AIDS or diabetes, which may compromise their immune response to infectious agents. Finally, the xenotransplantation product may provide a potential ongoing source of continuous exposure to an infection.

The infectious disease risk inherent in xenotransplantation also extends beyond the xenotransplant recipient, since the infectious agent may be transmitted to the patient's contacts and, subsequently, disseminated throughout the general population.

Thus, xenotransplantation presents a major public health challenge. How do you balance the potential promise of such a developing technology for treating a wide variety of human diseases and for alleviating the shortage of human organs now available for transplantation. How do you balance that with the risk of infecting patients and their contacts with both known and novel infectious agents transmitted by xenotransplantation products.

That is where you come in. That is where this committee comes in. You are charged with the challenging task of advising the Secretary on all aspects of the scientific development and clinical application of xenotransplantation.

Your purview includes not only this complex, scientific, medical and series of public health issues which I have touched on briefly this morning, but also the very thorny social, ethical and legal issues raised by xenotransplantation, which I have only mentioned. Your recommendations on policies and procedures regarding xenotransplantation will certainly facilitate the department's efforts to develop an integrated approach to addressing emerging public health issues in xenotransplantation.

I commend you for your willingness to serve the American public in this important arena. Your task is not a simple one. Your task is certainly not an easy one. It is at times like this that I like to remind people of the words of John Gardner, who served as the Secretary of Health, Education and Welfare back in the 1960s, when those departments are combined. John Gardner used to say -- and I guess he still says -- life is full of golden opportunities, carefully disguised as irresolvable problems. Thank you.

[Applause.]

DR. VANDERPOOL: Thank you, Dr. Satcher. We take very seriously the charges you have given us and we take, with utmost seriousness, the issues that lie before us.

Now comes a time in which all of us sitting around this U-shaped set of tables are to introduce ourselves

in an approximate two-minute period of time. So, no long biographies are permissible. Let's do it this way. Give our full names. I will say something about myself. Then we will begin over here with Megan Sykes and then we will go around the table until we end to my far right.

Agenda Item: Introduction of the Committee.

DR. VANDERPOOL: My name is Harold Clive Vanderpool. The interest and expertise that I bring to this committee extend back to my decision to leave undergraduate college teaching for a career in bioethics. Having secured two graduate degrees from Harvard, I began to direct American studies at Wellesley College and teach courses in the religious and Biblical studies department. Having been premed as a major in my undergraduate years, I was truly seized by the ethical and cultural significance of the Karen Quinlan case in 1975, such that I returned to Harvard as a Kennedy Fellow in bioethics. Upon completing a post-doctorate master's degree as a Kennedy Fellow, I, with my family, returned to Texas, where I took a position in the Institute for the Medical Humanities in Texas' oldest medical school, the University of Texas Medical Branch in Galveston, which at the time was the largest city in the state.

In the early 1990s, I began to focus my bioethics and history of medicine teaching and publishing on the broad topic of research involving human subjects. I was nevertheless, once again, seized with the ethical and cultural challenges of xenotransplantation in 1995, when I was chosen to serve on the Institute of Medicine xenotransplantation committee. Since 1995, I have remained intrigued over the promise and the perils of this multifaceted and complex set of innovative and hopefully beneficial medical developments. I am profoundly indebted to scientific and clinical colleagues, both outside and within government agencies, a number of whom are present here today, for my continued education in these important matters. Thank you.

DR. SYKES: My name is Megan Sykes. I was born and educated in Toronto, Canada, obtained my medical degree in 1982 and did an internal medicine residency afterwards. In 1985, I moved to the NIH to do a research fellowship in transplantation and began to develop my interests there in tolerance induction, immune tolerance, for allografts and xenografts, and in the separation of graft-versus-host disease from graft-versus-leukemia effects.

I continue to work in all of these areas of transplantation biology with a major goal of inducing xenotransplantation tolerance, and moved to the Massachusetts General Hospital in 1990. I am currently an immunologist at the Massachusetts General and a professor of surgery and medicine at Harvard Medical School. I continue to have an active laboratory program in these areas. I have served on the founding council of the International Xenotransplantation Association, and am a counselor of the Transplantation Society, and serve on a number of editorial boards of a variety of transplantation journals.

DR. VANDERPOOL: I will go ahead and introduce a word about Dr. Lubiniecki, who is not yet with us, and then Karren King will follow. Dr. Lubiniecki is vice president and director of worldwide biopharmaceutical research and development with GlaxoSmithKline in King of Prussia, Pennsylvania, and adjunct professor of chemical and biological engineering at the University of Maryland, on the Baltimore County campus. He has extensive experience in the development of therapeutic, prophylactic, and diagnostic biopharmaceutical products for human and animal use. He is a recognized leader in the development of manufacturing processes and control methods for biopharmaceutical products, which effectively protect product recipients from exposure to viral contaminants inherent in the manufacturing processes.

MS. KING: My name is Karren King and I am from Kansas City, Missouri. My background professionally is that of nephrology social worker. I have worked for over two decades in the field of nephrology social work. Ten years of that was working specifically in the clinical arena with those who are on dialysis and awaiting transplant, as well as those who have received a kidney transplant, and basically dealing with the psychological and social aspects of that. Then, for the last decade, I have been involved basically in education of those individuals.

What I think I specifically can bring to this committee is that I have also been very extensively involved in the National Kidney Foundation in a variety of areas, for the board of directors and executive committee. I also chaired their patient services committee. At that time, we undertook a survey, both of their own transplant constituents, but also worked with a firm that actually did a survey of attitudes about xenotransplantation, both within the transplant population as well as those awaiting transplantation, the public arena and then physicians. I am also extensively involved, in Kansas City, in the Midwest Bioethics Center in a variety of capacities.

DR. SALOMON: Daniel Salomon. I had my first mid-career crisis about 10 years ago. At the time I was reasonably successful in clinical transplantation, running two large kidney and heart transplantation programs, and NIH funded to do some basic research. It was just such a strain to try to do what I thought was cutting edge research, particularly with the exciting developments that I saw on the horizon. So, at the time I sort of left all that and went back and retooled at the National Institutes of Health. I am not a professor at the Scripps Research Institute in La Jolla, California.

My laboratory has essentially two major interests. One is in cellular transplantation and tissue engineering, and in that we are looking at the transplantation of islet cells, particularly the use of pig or xenotransplants, and looking at angiogenesis and other different mechanisms to engineer such successful cellular transplants. The other area in the lab is in gene therapy, for allogeneic stem cell transplantation, in the treatment of cancer. In that, we also got interested in the whole idea of how cellular transplants carried with them the potential risk of porcine endogenous retroviral infection and have built models to begin to study the possibility of transference of this virus in settings that we felt were modeled on a clinical trial.

Currently, I think the dynamic that I see that is most important to the way I approach the committee is that this is a tremendous nexus of an incredible set of new technologies that really do raise a whole series of questions about science and ethics and public responsibility. I very much look forward to participating.

DR. RUSSOW: My name is Lilly-Marlene Russow. I am a professor in the department of philosophy at Purdue University, specializing in bioethics. I started out working on animal ethics and the treatment of animals. In fact, I have sat on our IACUC for 16 years, since there first was one. I quickly got into issues that involved more traditional biomedical ethics. Certainly things having to do with genetic engineering and xenotransplantation quickly became things that I sort of developed an interest in and have done quite a bit of work in those areas.

DR. MENDEZ: I am Robert Mendez. I am a transplant surgeon and my interests basically are in renal transplantation and pancreatic transplantation. I got interested in organ allocation and the dearth of organ availabilities as a clinician, and thus embarked upon trying to increase our organ donation activities in the nation, and developed and chair, I am the president of our organ procurement organization for Southern California, and later became president of UNOS, our national organ procurement and allocation organization for our nation. Although we were able to, and are continuing to increase the organ donation

through various means, it became evident to me that we would have to perhaps move on to something else.

I became interested in xenograft transplantation, starting with tiny steps at first, trying to cross the abial blood barrier in humans and, thereafter, trying to see about moving into xenograft transplantation, using the vehicle of islet cell transplants. I did accomplish some islet cell -- encapsulated islet cell -- transplants in the early 1990s. We have not moved on to xenograft transplants because of the moratorium.

I feel that it is a distinct honor and pleasure to be on this committee. It is an awesome responsibility for all of us. I hope that, in some small way, I will be able to contribute. Lastly, I am on the board of the USC School of Law Center for Medical Ethics and the Law.

MR. FINN: My name is James C. Finn. I am from Newport, Rhode Island. I am a xenotransplant recipient. I hope to bring some of my knowledge to help this group out and I know this group will help me out a great deal also. That is it.

DR. VANDERPOOL: I have to comment a little bit further on James. We are truly pleased and honored to have him with us. Ever since the Institute of Medicine began its deliberations, I think we realized that we don't know how to do ethics or policy without the voice of patients. So, James is that voice for us on a regular basis, and we are profoundly happy that you are with us. We may have to tease you out a time or two to get you to speak, as much as you have to the public medica in their interviews of you. We value your role with us. Thanks.

DR. MICHAELS: I am Marian Michaels. My medical training was at the University of Pennsylvania, as was my training in pediatrics. I did pediatric infectious diseases at Great Armand Street in London and at Children's Hospital of Pittsburgh, where I remain on the faculty as an associate professor of pediatric infectious diseases.

My clinical research has been in transplant infections, since I have been in Pittsburgh. My involvement with xenotransplantation started in 1990, when I first began to question the potential risk of infections coming from xenotransplantation to humans, and became involved in trying to investigate this and decrease the risk or find out how to study it, with Dr. Thomas Starzl's baboon liver transplants into humans with hepatitis B. I have had the pleasure of serving on the Institute of Medicine and the WHO boards with xenotransplantation, and continue to do research on looking at primate CMV and transmission to humans.

DR. SCHECKLER: I am Bill Scheckler, a native of Kenosha, Wisconsin. I went to the University of Notre Dame and also to the University of Pennsylvania to medical school, but then went back to Wisconsin to get my training as a general internist at the University of Wisconsin. The next fateful decision was to become an academic intelligence service officer at the then-Communicable Diseases Center, from 1968 to 1970, where I was one of the first people involved in hospital infection control. So, for the last 33 years, I have been trying to understand how we can better protect patients and their safety through our efforts and processes in hospital infection control.

I am here because I am currently an active member of the CDC's now called Health Care Infection Control Practices Advisory Committee, and have been involved in that. I am also a professor of family medicine at the UW Medical School, and have the privilege of being named last year as the mentor for the incoming medical school class. Our school is one of three in the country that has a senior faculty member follow a class through their four years of medical school. I am spending half my time with the

students in their lecture, gross anatomy labs and so forth.

Yesterday morning at 8:00 o'clock, I was listening to a lecture on immunology taught by a Hungarian that I somewhat understood. I bring no preconceived notion whatsoever about xenotransplantation. I have zero experience with xenotransplantation. I have a great deal of experience with hospital infection control and hope that that will be helpful to this group.

DR. CRONE: I am Catherine Crone. I am a psychiatrist who works at INOVA Fairfax Hospital, right across the river. My particular focus has been on psychiatry in the medically ill, and that has been my particular interest. My particular focus, though, for over a decade has been in working with transplant patients and family members. I think that is a perspective that I bring. My interests are in regard to psychological issues related to transplantation and also neuropsychiatric complications of transplantation and immunosuppressant medication.

DR. KASLOW: I am Richard Kaslow. I began my education in Omaha, Nebraska, where I grew up. Then I continued in New Haven and Boston and New York and Atlanta and San Francisco, and then back to Atlanta, and then finally to Bethesda. I got tired of learning, I guess, or I got tired of moving, and stayed at the NIH for about 16 years, where I was involved with a whole variety of studies of the epidemiology of infectious diseases and immune diseases, particularly in AIDS as it emerged.

I am currently the professor of epidemiology, medicine and microbiology at the University of Alabama at Birmingham, where I have been for six years, continuing studies of HIV and other infectious diseases, both acute and chronic. My interest in xenotransplantation began two or three years ago, when I was appointed to the FDA subcommittee for the Committee of Biologics. I look forward very much to continuing that interest and contributing in whatever way I can.

MS. SHAPIRO: I am Robyn Shapiro. I am the Ursula Van de Rogh professor of bioethics at the Medical College of Wisconsin in Milwaukee, and I also direct the bioethics center at the Medical College of Wisconsin. My interest in bioethics began in law school at Harvard, where I took all the courses I could involving the intersection of law and medicine.

My interest in transplantation has been over a period of years. I have had the pleasure of testifying before the United States Senate on some of these issues and I serve on the ethics committee of the American Society of Transplant Surgeons.

DR. GROESCH: I am Mary Groesch with the NIH Office of Science Policy. I came to NIH eight or nine years ago after completing some post-doctoral studies in cell biology. Within the Office of Science Policy, I have been working on a variety of issues, including xenotransplantation.

For the past four or five years, I have been a member of the departmental interagency working group that Bill Raub mentioned this morning. We have been working on revising the PHS guideline on infectious disease issues in xenotransplantation, and working to establish this committee. During that time, I found the range and complexity of issues associated with xenotransplantation to be quite compelling and fascinating. When the committee was established and it was determined that NIH, in particular the Office of Science Policy, would administer the committee, I thought it would be very interesting and challenging to focus on xenotransplantation, rather than having it be one of many issues that I addressed. I applied for the position of executive director. The rest is history.

I am looking forward to working very closely with the members of the committee and the agency

representatives in what I think is a very important task.

DR. ALLAN: I am Jon Allan from the Southwest Foundation for Biomedical Research. I am a virologist and I started studying chicken viruses back in the 1970s in graduate school and went on to get a degree in veterinary medicine at Michigan State. I then went to Harvard School of Public Health to do a post-doc and I just happened to show up in 1984 when HIV was discovered. There was nothing known about it. I worked on the envelope structure function of HIV. With my veterinary degree, I decided to go into simian models for AIDS. For the past 14 years, I have studied simian models for AIDS, particularly in understanding the nature of the natural host resistance to infections in African monkeys, non-human primates, and why it is, in one species a virus doesn't cause any disease but, when transmitted to another species, does cause disease.

That is relevant, obviously, to the xenotransplant setting. Particularly, I study viruses in baboons, African green monkeys, and have published several papers on viruses that are sort of ubiquitous in one species, such as foamy viruses and STLV, which causes lymphomas and leukemias in baboons. I have served on the FDA's subcommittee on xenotransplantation for the last several years. I think what I probably bring to the table is the perspective of infectious disease risks in the animal transplant setting.

DR. KIELY: Good morning. My name is Sharon Kiely. I am a general internist from Pittsburgh, Pennsylvania, where I direct the Center for the Care and Study of the Medically Underserved at Allegheny General Hospital in Pittsburgh. I am a general internist. I got my medical degree from Georgetown University and, in the mid to late 1980s, did my primary residency program training in internal medicine at St. Vincent's Hospital and Medical Center in New York City, at one of the peaks, if you will, of the AIDS epidemic there.

I moved to Pittsburgh, Pennsylvania, where I started to focus my academic interests on equity issues and access to health care and social determinants of health. I did a White House Fellowship here in Washington, D.C. with Secretary Donna Shalala, worked on a number of issues related to equity and access. Subsequently, I returned to Pittsburgh and received a master in public management degree at Carnegie Mellon University.

Since 1995, I have been an advocate for the Juvenile Diabetes Research Foundation International, and now serve on its government relations board. I am their key volunteer for transplant issues for the Diabetes Research Foundation, which is the number one private funder of diabetes research in the world. Thank you.

DR. COLLINS: Good morning. My name is Bradley Collins. I am a native of Tuskegee, Alabama. I grew up in Greensboro, North Carolina. I first became interested in xenotransplantation in the early 1990s when, as a surgical resident at Duke University, we were presented with an 18 year old, who had fulminant hepatitis B. At that time, under the guidance of Dr. Bill Meyers and Jeffrey Platte, we had the opportunity to procure several livers from pigs, and we were able to bridge that young man to allograft, or liver transplantation, from a human donor. Some eight or nine years later, he is still alive. He finished college. He has a family, a couple of kids, and he is actually working on his commercial pilot's license. So, that is when I first became interested in it.

I joined Duke's faculty in 1999. I am a clinical transplant surgeon. My organ specialties include liver, kidney and pancreas. I am concerned about the shortage of organs. We have a lot of patients on our list, and a lot of them don't get transplanted because of the severe shortage.

I welcome the opportunity to serve on this committee. I think it is important to discuss the issues. Certainly there are risks. I hope to bring some of the experience of my patients to this committee. Thank you.

MR. BERGER: My name is Allen Berger. My academic background is really in the business fields. I have a master's in business administration. I have finished course work in a PhD program in non-profit management. My early years have really been in private industry, working in financial management and personnel and general management. As a matter of fact, my first job out of graduate school was on the audit staff of Arthur Anderson and I was a health care specialist, which was my real beginning interest.

About 12 years ago, I went through a midlife crisis as well, and decided that I really wanted to devote my life to nonprofit and social issues and really got involved strictly in the non-profit area, particularly in human and social services. I have been involved with AIDS, domestic violence, rape crisis, child abuse, homelessness and a number of other fields. About 10 to 12 years ago, I got involved in the animal rights areas because of my two daughters. When they were around 12 years old, they came to their father and said, I decided I can't eat animals any more. As a matter of fact, I don't want to wear animal products either. It made me really research my own thinking in terms of the way in which we approach animals.

About six and a half years ago, I became the executive director of the Animal Protection Institute, which is a national animal advocacy organization. We also operate a primate sanctuary in Dilly, Texas called the Texas Snow Monkey Sanctuary. For many years, probably for the last six years, I have researched the area of xenotransplantation, made numerous presentations, attended conferences, starting out with the view of how animals are being used, but really ending up developing my interest in some of the social and economic issues facing xenotransplantation. For many years, I pushed the Federal Government to kind of broaden the people who were getting involved in this kind of discussion. So, they got even with me and appointed me to this committee. Thank you.

DR. SWINDLE: I am Michael Swindle. I am professor and chairman of the department of comparative medicine at the Medical University of South Carolina in Charleston. I have a veterinary degree from Texas A&M and did a residency in lab animal medicine and pathobiology at Johns Hopkins. I am a diplomate of the American College of Lab Animal Medicine.

I am on the committee for my expertise in using swine as an experimental surgical model, which I have done for the past two decades, and have a background in a number of studies involving the swine model, mostly cardiovascular but also some transplantation. I am kind of here as the committee's pig expert. Thank you.

MS. ENGSTROM: I am Lily Engstrom. I am from the Office of Science Policy within the Office of the Assistant Secretary for Planning and Evaluation, which is a component of the Office of the Secretary. Our office is responsible for coordinating the development of science-related policies that affect several agencies within the department. That is to say, if there is a science-related issue that cuts across multiple agencies at the same time, our office is responsible for developing an integrated position that we can recommend to the Secretary.

One of the areas of responsibility of mine is xenotransplantation. With that job has come the privilege of working and convening the HHS interagency working group in xenotransplantation that Bill Raub and a number of others have mentioned. This working group consists of my colleagues from NIH, FDA, CDC, HRSA and Office of General Counsel. My other areas of responsibility include genetic testing, bioterrorism, and the protection of human subjects in research.

Over recent years, the department has been trying to develop, and has finally developed a plan to provide regulatory oversight on genetic tests and genetic testing. Like xenotransplantation, genetic testing is a highly promising technology. It is also a technology that carries with it some non-trivial risks that must be addressed. With respect to bioterrorism, since 1999, our department has been undertaking an initiative that basically is trying to help the department and the nation as a whole prepare for, and respond, to the medical and public health consequences of bioterrorism. This means that we are talking about trying to enhance the security and operation of labs. We are talking about strengthening the public health infrastructure to detect outbreaks of diseases. We are talking about developing and maintaining a national pharmaceutical stockpile, and also the kinds of resources needed to address mass casualty events and, of course, I mustn't forget the research and development of vaccines, therapeutics and rapid diagnostics.

Prior to coming to the Office of the Secretary, I occupied several positions at the National Institutes of Health. The most recent one was as assistant director of extramural research.

I would like to simply say to those who are here on the committee that my colleagues and I have waited very, very long and really looked forward to the formation of this committee. I join Dr. Satcher and Dr. Raub, for whom I am an alternate, in welcoming all of you today.

DR. ROTROSEN: I am Dan Rotrosen. I am director of the Division of Allergy, Immunology and Transplantation at the National Institute of Allergy and Infectious Diseases. My clinical background is in infectious diseases and immunology. I am here as the representative of the National Institutes of Health, where a little more than a dozen institutes fund the majority of research on transplantation and a little over half a dozen institutes currently support research related to xenotransplantation.

DR. ZOON: My name is Catherine Zoon. I am currently the director of the Center for Biologics Evaluation and Research at the FDA. My background is, I am a PhD in biochemistry from Johns Hopkins University. From there, I went to the National Institutes of Health, where I post-doc-ed and did staff fellowships in protein chemistry, and where I started my research, which I have been doing now for 25 years, on interferon structure and function.

In 1980, I became a member of the Center for Biologics and held a number of positions until 1992, when I became the center director. Our center has the direct regulatory responsibility on xenotransplantation products. We also regulate tissues, blood safety, vaccines and many other biotech products, including recombinant DNA-derived proteins, monoclonal antibodies, gene therapies, cellular therapies. Clearly, many of the issues that we deal with have centered impact on the discussion of this agency. Adventitious agents, by their nature, are inherent in biological products, and the protection from those agents is clear with biological products.

I am really very honored to be on this committee, and I look forward to participating in the discussions and the advice from this committee. Thank you.

DR. SPIRA: I am Tom Spira. I am from the Centers for Disease Control in Atlanta. My training has been in infectious diseases and immunology. I came to CDC originally with an interest in immunodeficiency diseases and worked both in adult and pediatric immunodeficiency diseases originally. When the HIV/AIDS epidemic hit about 20 years ago, I was part of the original working group at CDC on that issue and have continued to work more recently in HIV and AIDS infection.

My involvement with xenotransplantation began with the PHS working group that ultimately wrote the guidelines for infectious disease issues in xenotransplantation. We have all been awaiting the final

publication of that with great anticipation. I am involved with other members at CDC in some investigations involving exposure to simian foamy virus, for example, in animal workers. I am also an IRB chair at CDC, and some years ago chaired a workshop on IRB issues in xenotransplantation.

I am especially interested in the issues of balancing public health interests to monitor and ensure that there is no infectious disease, or minimize the infectious disease risk in xenotransplantation, and issues of autonomy for subjects that are receiving xenotransplantation.

MR. NELSON: Finally, I am Jon Nelson. I am the director of special programs at HRSA. Following family tradition, I became an engineer, attending the University of California in Berkeley. War in Southeast Asia intervened. After two years in the army, I returned to California, attended Stanford University where I received advanced degrees. After a short while, my wife thought that I should become suitably employed. I came to Washington, D.C. She still would prefer that I become suitably employed.

The Office of Special Programs in HRSA is responsible for the administration and the management of the organ procurement and transplantation network, whose contract, the United Network for Organ Sharing, commonly known as UNOS, is our current contractor. We also have responsibility for oversight and management of the contracts with the National Marrow Donor Program in Minneapolis. Thank you.

DR. SCHECKLER: Mr. Chairman, I have one footnote to add.

DR. VANDERPOOL: Proceed.

DR. SCHECKLER: This probably shouldn't be recorded, but coming from Madison, Wisconsin, as I do, I can't resist. [Portion off microphone.]

DR. VANDERPOOL: Thanks, Bill. We will look forward to your stories over time. I have a folder on Tommy Thompson. Most of it is from the Houston Chronicle and the Wall Street Journal, so it is probably biased in one or two respects. We now have remarks from the chair, after which Dr. Mary Groesch will take charge of our program for the rest of the day.

Agenda Item: Remarks by the Chair.

DR. VANDERPOOL: I thank all of those who have given their expertise, time and thought to the formation and work of this committee, without whose efforts we would not be here and, if we were here, we would be much more of a rag tag organization than we already appear to be. I deeply appreciate all support staff who really are the left hand behind the right hand of everything we do. Now, as I mentioned your names, I hope it is not embarrassing and that you will stand. I don't have a complete list, but I want us all to recognize these persons. If I don't mention you, and you are part of the support staff, please stand, as we applaud your efforts.

First of all, our executive director, Dr. Mary Groesch. [Applause.] Mary Nuss, who piloted our special government employee statuses through mountains of paperwork. Thanks, Mary. [Applause.] Terry Fischer, who was busy today, as she has been, apparently, for weeks upon weeks. Thank you. [Applause.] Then Margaret May and others, who take care of countless details that make our lives more pleasurable and directed. Is Margaret here? She is probably outside at the desk. So, all support staff, please stand for applause. [Applause.]

I am so very pleased that all of us are here, including all of you who are visiting this committee's first set

of deliberations. One of the truly fascinating things about xenotransplantation is that it pertains to a great range of scientific, clinical, social, ethical and other issues. This committee, including its ex officio members, reflects a broad range of issues which, because all of them are so interdependent, means that we will need to rely on each other.

I know that I speak for each of us and all of us when I say that this group bears a very great responsibility regarding both the promise and the perils of xenotransplantation. We are the ones who have been chosen to further learn, talk and deliberate over this committee's charter and its mandates.

So, when presenters come before us, we should be bold, to probe, to ask for clarification and so on, with the realization that when our expert speakers leave our midst, we are the ones responsible for having grasped essential elements of what they have presented.

As the chair of this committee, I will register four very brief points about my modus operandi. First, I will make every effort, within our time constraints, to involve each and all of us in our deliberations and discussion. If I ask some of you who may seem to be squeezed out by the articulate comments of others, you can always say, thank you or, I would rather wait a little longer. Second, I will make every effort to keep our discussion and thinking open to all ideas and suggestions. None should be considered off limits, even though our staying on task may mean that weighty, controversial suggestions may need to be tabled before they are fully aired. Third, I surely share with all of you an abiding commitment to our being receptive and open to the public, to our being responsible public servants to both the U.S. citizens and our private and governmental institutions. Fourth, even though I relish the give and take of intelligent discussion, I will, when necessary, enforce our time limits and constraints.

Finally, as we now begin to hear background information and reports, I hope that all of us will be taking notes about the important issues that these presentations raise, with the realization that our central task during this two-day meeting, a task that we will undertake tomorrow, will be to identify and hopefully to prioritize the issues that need to be addressed in the meetings that follow. With these comments, shall we begin with our presentations? Dr. Groesch will take charge of that portion of today's meeting. Thank you.

DR. GROESCH: Our next couple of presentations are part of the education process for the committee members. A number of members are old hands at this, but we also have people who are new to this. We wanted to talk a little bit about what it means to be part of a federal advisory committee and also what the roles and responsibilities are for special government employees, and each member of this committee is considered a special government employee.

I would urge the members to take advantage of the experts we have here today, and to ask them questions and engage them. You can always contact them, but we have a unique opportunity today.

Our first presentation is by LaVerne Stringfield. LaVerne is from the National Institutes of Health, the Office of Federal Advisory Committee Policy. She is going to give us an overview of the Federal Advisory Committee Act.

Overview of the Federal Advisory Committee Act.

MS. STRINGFIELD: There are a number of laws that govern how we manage our advisory committees. The primary law is the Federal Advisory Committee Act. So, I am going to just briefly cover some of the highlights of this law, and how it relates to your role as an advisory committee

member.

First of all, one of the major advisory committees in history was during 1794 during the Whiskey Rebellion, when President George Washington convened a group to give advice and recommendation. Since that time, advisory committees have become very, very popular within the executive branch of the Federal Government. In fact, right now we have about 1,000 advisory committee members across the government doing a number of impressive things, like your committee will be doing.

Congress enacted the FACA in 1972, in order to put some guidelines and uniformity and accountability to these groups. In doing that, they decided to establish a definition, and the definition is before you. Basically what it speaks to is that any group that is convened to give advice and recommendations to the President or a federal official or federal agency is considered a federal advisory committee. Congress realized the uniqueness of these groups and also wanted to make sure that they were used uniformly, that they were accountable, and that there was public disclosure.

There is a lot of text here, but basically what it boils down to is that advisory committees have to be accountable. There are reporting requirements. There is public disclosure. The public has to be informed of the activities, the number of committees, the cost of the committees, and this is an ongoing activity. It is handled in a number of reports that are required throughout the year.

Congress also wanted to make clear that the advisory committees are advisory in nature. They are not decision-making bodies, but they are to give advice and recommendations to the President or federal officials or the agency.

There are some primary requirements of the FACA. You have a charter in place. That is the very first requirement, and that is, that you have a clear purpose. You must be established within public interests and the membership has to be balanced. As we go around the room and we hear the expertise and we hear people from different areas of the country, we can see that this committee is certainly diverse and balanced in terms of points of view, expertise, gender, ethnicity and so forth.

Financial records have to be kept and one report is submitted by the President to the Congress each year, which discusses the committee's activities, membership, costs and a number of other things. This is an administrative function and it will be handled by your executive director, Mary Groesch, in addition to other individuals at the NIH and the department that would be involved in the administrative functions.

Notice of all meetings has to be published within the Federal Register. There is a requirement that, whenever you have a meeting, the notice has to be prepared at least 15 days before the meeting. It has to be announced in the Federal Register.

The committees have to adhere to the provisions of open and closed meetings. What that means for us is that most of our meetings will be open to the public. There are some exceptions that we use on rare occasions for closing meetings. However, as much as possible, we do want to have our meetings open to the public. When there are exemptions for closing a meeting, that activity would be discussed with your executive director and the chair, and then it would be discussed with my office and we would do the appropriate language in the Federal Register to close the meeting. Generally, we only close meetings if there are some personal, confidential privacy issues that are going to be discussed, there is some trade secret information, or if there is some action that is going to be handled by the committee that we can absolutely say with certainty that it will frustrate the agency's action or plan. Then we can close the meeting. We do look at these very, very closely, because we do want to make sure that our meetings are

open to the public as much as we possibly can.

There is a requirement that transcripts and reports be made available to the public as well. Mary Groesch is your executive director. In the FACA, that term is called, designated federal official. You will see here on the slide, designated federal official, but just keep in mind that that is your executive director. The responsibilities of your executive director are to approve or call the meeting of the advisory committee, approve the agenda, attend the meeting and adjourn the meeting when it is in the best interests of the government. Upon request, she may be required to chair the meeting, and she ensures that detailed minutes are taken and that they are certified by the chair. There are very important functions of the executive director and also the chairs.

The members also have a very, very important role. The service by special government employees is a very, very special one and it gives you the full right to participate in the advisory committee, including voting on matters and deliberating on issues that normally would not be handled by anyone else outside of your committee. You are compensated and I need not go into details on that. If there are any questions that arise from the public, the advisory committee members are encouraged to direct those questions to the executive director. Again, in this case, it would be Mary Groesch.

You are responsible for conflict of interest certifications, and that has been accomplished and done, because everyone is sitting at the table here. Otherwise you would not be here. That is a requirement before you can be appointed as a special government employee. The standards of ethical conduct will be discussed later, but I think you have been given information on that. That is a standard, as a special government employee, that we all have to abide by. Federal employees, regular employees and special government employees must adhere to the standards of ethical conduct.

The emoluments clause is in the Constitution. Basically what it says is that, if you are a federal employee, including a special government employee, you cannot hold a position with a foreign clause, nor can you accept salary, any other type of emolument from a foreign government.

That concludes my brief presentation. There are a number of laws and regulations and policies that govern how we manage and how we run the advisory committees. If you would like more information, here is a web address. You can feel free to contact my office, or you can contact your executive director if you would like more information.

There is an issue, I understand, concerning what responsibilities members have for discussing issues outside of the official advisory committee meeting. I will provide a policy memo to Mary that describes in detail what those guidelines are for your committee. Thank you very much.

DR. GROESCH: Thank you, LaVerne. Any questions from the committee members? That was very comprehensive. We appreciate it.

Our next presentations relate to the ethics rules for federal advisory committee members, in particular talking about conflict of interest, outside activities and affiliations and confidentiality. Our presenters are Karen Dalheim from the Office of the General Counsel in the Department of Health and Human Services, and Fran Plyler, who is the NIH ethics coordinator. Karen and Fran, welcome and thank you.

Agenda Item: Ethics Rules for Federal Advisory Committee Members: Conflict of Interest, Outside Activities and Affiliations, and Confidentiality.

MS. DALHEIM: As Mary said, I am with the Office of the General Counsel at Health and Human Services. I am specifically in the ethics division. Fran Plyler, who is back here, is with the NIH ethics office. Customarily, we both deal with the same sort of issues. People might call us if they have a question, they are looking for advice, or they are not sure if they are having some sort of ethical dilemma. So, my office or her office are both places that you should utilize and can utilize if you have any issues that you are not sure of.

Generally, ethics in the Federal Government, there are criminal statutes, there are regulations and the Constitution that all deal with ethical issues. The Office of Government Ethics actually puts out a book. I think you got a copy of this, Standards of Conduct. I am sure you all read it, every page. I am going to try to give you a quick little overview of some of the concerns, ethical concerns, now that you are employees in the executive branch.

The main concern are the criminal statutes that have to do with conflict of interest. Let me just read you quickly, just a quick little definition of conflict of interest. It arises when an employee is involved in a particular matter as part of his or her official duties, with an outside organization with which he or she also has a financial interest. Here, for instance, many of you come from universities. If there was an issue that came before the committee that had to do with your own university, then you would have a conflict of interest acting in your official capacity, because you also have a relationship with the university in your personal capacity. Those are the kinds of issues that you need to be aware of, that you need to keep in mind when you are dealing with issues before the committee.

Mary, I am assuming that most of the issues are going to be general here, as opposed to particular? Is that correct?

DR. GROESCH: Yes, certainly for this meeting. It is pretty much background.

MS. DALHEIM: What people should be aware of, for each meeting, if there is an agenda, you can look at the agenda and you can see if there are any particular matters on the agenda that you think are going to raise a conflict of interest for you. If you feel that there is a problem, then you can talk to Mary or, as I said, you can call up my office or Fran's office. That is really what you need to worry about most, is the criminal code, and that is at USC 208.

A particular matter, again, is a matter that focuses on a specific institute as opposed to general, for instance, Harvard as opposed to universities. If you are talking about all universities, then you are not going to have a problem. If you are talking about your specific university, if you are at Harvard, then you would have to recuse, if there is some kind of decision before the committee at that time.

As LaVerne mentioned, you all have to file, we call them 450s. They are confidential financial disclosure forms. It is very important that you fill these out clearly and correctly, because this is how we determine whether there is some kind of conflict between your duties and what the committee is going to be doing.

Just because you came or are now an SG employee doesn't mean that you can't continue many of the activities that you do in your private capacity. For instance, teaching, speaking and writing in your personal capacity are all fine, as long as they are not directly related to what you are doing with this committee. You shouldn't have a problem with those.

In terms of, there are restrictions on employees accepting gifts. If someone wants to give you a gift and

you think it is because you serve on this committee, then you probably should not accept the gifts, or at least talk to Mary, and find out if that is going to be problematic for you.

Besides conflict of interest, there is something called impartiality. If you are asked to review maybe a grant for someone who is a friend, it would look as though you are making a decision based on your relationship. It might be a conflict of interest under the criminal statute, but it appears that you are not being impartial, and that is another thing you want to be aware of in your role here.

Misuse of position. While you are here, you should not use your title, your government title, in your private capacity or any of the government equipment or resources in performing your private work.

LaVerne touched on the emoluments clause. That is if you have any affiliations with foreign universities or foreign governments, that could be problematic. Again, all these things, you just need to touch base with an ethics person to make sure there are no violations of the law.

In terms of post-employment, when you finish your SGE position here, if you work on any particular matters, you have to be careful not to, when you are back in your private capacity, representing back before the government on that specific matter. You would be restricted from doing that. For the lifetime of that matter, you would be restricted from it.

Does anybody have any specific questions about any of their own concerns? Confidentiality, you know that anything you learn here you cannot use --

DR. SWINDLE: Yes, I would like for you to make a distinction. Foreign governments I understand, but when you said foreign universities, for instance, if you speak at a European institution and take an honorarium, is that a violation?

MS. PLYLER: An awful lot of foreign universities are actually funded by the foreign government and are considered entities of the foreign government and yes, that would be a violation. That is why it is important to find out, does the foreign university actually -- is it part of the government. It may be operating on its own, but is still funded by and considered a government entity. Some foreign universities are private and private doesn't matter. But if it is an entity of the foreign government, then yes, you cannot take the honorarium.

DR. VANDERPOOL: That is an important question for those on the committee who consult abroad. I guess, is it fair to say one of the things to do is, when you are in doubt, ask. It may well be that the honorarium would be acceptable if you are lecturing in a university in France or Germany, but it may well be that that would be off limits to this committee. Given the expertise and the travel of this group, I mean, all you need to do is sit around and listen to this group talk over dinner and see how many people travel all over the place. We may have some questions on those issues, too.

MS. DALHEIM: The best advice I can give you for any of these type of issues is to ask first. When you are invited to speak somewhere or you are asked to serve as a director, maybe, on some sort of non-profit anything, if you are not sure if it is going to conflict with your position here, that you can call us, you can get some sort of advisory opinion, and it is always best.

There usually are ways to work within the system, so that it is not going to be a problem for you down the road. Certainly that is good advice. Any time anything comes up that you are not sure of, just call and get some kind of an opinion.

Also, Fran's office has a web site that has a lot of information, just general information, on outside activities, gifts, use of title, anything. What web site is that?

MS. PLYLER: <http://Ethics.od.nih.gov>. That is the NIH ethics web site. One of the things we have there is a list of foreign universities and organizations which are not part of the foreign federal government, and there, outside activities are permissible. I add to that list every time we identify whether a particular foreign entity is or is not part of their government. So, that is an ongoing source to find out. If you can't get a hold of us you can go say, oh, this one is listed in the okay part.

MS. ENGSTROM: Karen, one of the last words you mentioned, as you were finishing your prepared remarks, was the word, confidentiality. I wonder if you or Fran could take a few moments to embellish on that a little bit. For those of us in the committee who are not in the Federal Government, it may mean something very different.

There are provisions, particularly at this committee, with reviewing issues and documents, particularly those that come to the Federal Government under certain regulatory processes that really bear a certain degree of confidentiality in the way they are treated. I wonder if you could spend just a few minutes talking about that.

MS. PLYLER: We look at confidentiality from two angles. First, anything that comes before you that is brought to you and you are told that this is a confidential document, you have an obligation to not release, not to go back to your organization, talk about it, tell people what is in it and say, well, let me just tell you this but don't tell anybody else. You truly must keep it confidential, if it is presented to you as confidential information.

For you personally, it also means that if you find out something here, whether or not you perceive it as being told to you that it is confidential, but if you find out something here as part of your official duties, you cannot use that information to turn around and help yourself financially. For instance, somebody talks about a particular drug that is going to be very useful for reducing rejection. You cannot tonight, on your way home, call up your stock broker and say, buy me a bunch of that stock because I know it is going to go up, nor can you call spouses, friends or anybody else. You are using confidential information.

It is your responsibility, while you are here as a federal employee, to not release or use that confidential information until you have been given permission or it becomes public. Things that go out in the minutes eventually become public. That doesn't mean that maybe during a closed session you may see something that does need to be kept confidential.

MS. ENGSTROM: Particularly documents that come through the regulatory process, the FDA for example. There are confidentiality restrictions on them.

MS. PLYLER: Right.

DR. KIELY: I was just going to ask you to please repeat that web site again. I didn't catch it.

MS. PLYLER: [Http://Ethics.od.nih.gov](http://Ethics.od.nih.gov).

DR. VANDERPOOL: I have a question regarding our communication with the news media and other people who may call us. I assume that these committee deliberations are public but, at the same time, we

need to exercise care in speaking on behalf of the committee. We can speak, I suppose, to news media and journal editors and researchers, in terms of, I suppose, our personal views. Can you comment on the member's communication with journalists who call for interviews or news media, personnel who call for interviews.

MS. PLYLER: First of all, depending on how the committee has been setting up, I am assuming, Mary, that all of that should go through you, if they are asking for an official report, response, they want you to talk about what went on here officially. Please don't do that on your own. Please call Mary first.

If they are asking about a personal opinion about something, you are certainly entitled to give your personal opinion. Do not give your personal opinion in conjunction with your title as an SGE here. Don't say, I am a member of this committee, this is my personal opinion. Keep that separate. This is my personal opinion. I think this, this and this. If people try to pressure you -- and that will happen -- newsmen may try at times to pressure you -- just say, this is my personal opinion.

For official opinions, unless the group has said everybody is going to talk about it and say this is our official opinion, or unless Mary has given permission, please go through Mary for official stands of the committee. When you express an opinion in your official capacity, you are in effect saying, this is what the department says is their policy. You may not have the permission, the authority, to state government, departmental policy, without going through the appropriate channels, which, of course, we have. That is why, if you get asked for an official opinion, please either refer the people to Mary or tell them you will get back to them and call Mary. Does that work with you, Mary?

DR. MENDEZ: Just a clarification. For instance, the incorporation of some information that we may get during these committee meetings with regard to new advances or molecular studies or whatever, if they are done in a public setting such as this, I assume that it is public information. It might be incorporated into lectures that we may be given or not. Is that a wrong assumption or correct?

MS. PLYLER: That is a correct assumption. This is a public meeting and anybody here can hear what is presented, can read it in the minutes and use it. When you have closed sessions, assuming you may some time have a closed session, it is what is presented in that closed session that is not public. That you could not turn around and, unless it is your own work, publicize it without permission.

MS. SHAPIRO: I think I understand and know the answer to this question, but just to be sure. If, for example, the media would call and say, what did you talk about, since they could be here, that would be all right to answer. If they then went on to say, what do you, in your personal capacity, think about that, and not what is the official position of this group, but what do you think about that, would that be all right, to answer that question?

MS. PLYLER: Yes, emphasizing, of course, my personal opinion is. That doesn't mean that you are going to get quoted, but at least you tried. I mean, you get quoted, but they may still use your title, but I think most journalists understand that issue. I mean, a lot of people understand the government ethics issue. You have done what you could by saying, my personal opinion is.

DR. VANDERPOOL: Could I give an example and you supply the answer. A couple of weeks ago, before the members of this committee or my being chair was public information, I was called by a journal editor who very enthusiastically said, well, I understand, Dr. Vanderpool, that you are going to be the chair of this new committee, and I would like to talk to you about X, Y, and Z.

My first question was, I used a little Latin that I will not quote, how in the world did you get to know that I was chair and who some of the members of this committee are. So, there was some leakage there. Then the person proceeded to ask me about my views of this, that and the other thing. Was it appropriate to say, I am speaking now as a professor at the University of Texas Medical Branch, and not as a member of a committee, and I will not speak as chair of a committee without appropriate release of the right to do that. Is that okay?

MS. PLYLER: Perfect answer.

DR. VANDERPOOL: Okay. If I have questions, I will be calling.

DR. KIELY: Could you just make a comment about issues related to lobbying? I see this section here in the printed materials about lobbying activities, meeting with members of Congress and such. Could you expand a little bit on that?

MS. PLYLER: While you are a federal employee, the days you are actually here in a meeting, until the time that the meeting closes, you are considered an on-duty federal employee, and you cannot engage in lobbying activities. If a meeting ends officially at 1:00 o'clock, at 1:30, you can be downtown talking to anybody. But during the time that you are here in a meeting, so from 8:00 o'clock this morning until tomorrow at 3:00 or whatever, you are on duty. During that time frame, so you are not doing it while you are an official employee, you cannot lobby.

DR. KIELY: Thank you, and that also would apply to testifying and things of that nature? Thank you.

DR. GROESCH: I noticed in some of the material we had that there was a statement about, if you are a lawyer, there are some restrictions. That would apply to some members of the committee. Could you just talk about that a little bit?

MS. PLYLER: Restrictions on what they can do as a lawyer?

DR. GROESCH: A statement that you may be prohibited from receiving compensation as a result of your firm's representing a specific client.

MS. PLYLER: As part of the statutes that prohibit representational activities, and I think if you read farther along, you see most of that is really reduced for SGEs, because you are not a full-time employee, so that you are not running up against doing it at the same time you are an employee.

The issue of representation, while you are a federal employee, you can't represent somebody else back to the government in another agency. The comment that she brought up is, you cannot even receive compensation. If you are a partner and your firm represents somebody back to the government on a matter that you dealt with here, you can't get your partner share that came from that particular case. So, you in no way are receiving compensation in your one job for what you did here. As SGEs, you will probably never run across that. Farther down, it will tell you how most of that is really backed off for SGEs.

DR. GROESCH: Any other questions from the committee? Thank you very much. Thank you, Karen, thank you, Fran. I am sure you will be hearing from us as we proceed, with lots of questions.

I think we have a bit of an unprecedented situation here, a committee meeting that is actually running a

bit ahead of schedule. I think we will expand our break a little bit. I think we could take a break maybe 25 minutes, if we go to about 10:35, and reconvene her.

For committee members, Fran and Karen will be around here, if you have some specific questions that you would like to ask them. Also, just a housekeeping item. The committee members have been given a menu selection sheet. If you could fill it out, we will collect that. That will expedite your lunch. Let's meet back here at 10:35 or so.

[Brief recess.]

DR. VANDERPOOL: Let's call the session into order. We are ready for a period of presentations. Dr. Groesch will take charge at this point.

DR. GROESCH: Over the course of the break, some interesting questions came up and discussion about confidentiality issues. We have asked Karen Dalheim, who just spoke to us, to just come back for a couple of remarks in that area. Again, feel free to ask any questions that you may have.

MS. DALHEIM: I was just asked to really emphasize and re-emphasize the importance of filling out your confidential financial disclosure, the 450 form. It is very, very important that you put all the interests down.

If you get a chance to look at the agenda, I don't know how much in advance you will get a copy of the agenda, but if you see something on the agenda that maybe has to do with a competitor, that is also something that you should bring to Mary's attention. That might be an issue that you also need to be recused from being involved in.

As you know, that form, you update it before every meeting. So, as things change, as your interests change, then that should all go on the form. If you see anything that you think is a conflict, please, bring that to Mary's attention so that she can address it. That form is very, very important for us to determine whether there are going to be any conflicts with your service on the committee and any of your outside activities.

DR. GROESCH: Are there any questions for Karen about this?

DR. SCHECKLER: Just one. My wife manages her own stock portfolio. I have no idea what she is doing or why. She prints out a list for the 450 forms, which we dutifully now have to send to both the CDC and to you. She probably has less knowledge about xenotransplantation than I do. You are going to inspect that and then tell me that I shouldn't have done something?

MS. DALHEIM: Yes, your spouse's information is also relevant.

DR. VANDERPOOL: At least that is your wife. I have several stocks in my portfolio that I don't know what I am doing. At least you have good counsel.

DR. GROESCH: Any other questions? Thank you very much, Karen. Okay, this begins -- we kind of end the administrative education and now we start with a little bit more of the meat and potatoes of the meeting, some background presentations on the history and science of xenotransplantation.

Our first speaker is Dr. David Cooper. He is an associate professor of surgery and immunology at

Harvard Medical School and also is affiliated with the Transplantation Biology Research Center at Massachusetts General Hospital. Some of you may be aware that David has recently published a book on xenotransplantation and he is here today to tell us a little bit about the experimental and clinical history of xenotransplantation.

Agenda Item: The Experimental and Clinical History of Xenotransplantation.

DR. COOPER: Thank you very much. I am going to talk Very briefly about the development of xenotransplantation over a number of years. I am going to keep it very simple because I know there are some people here who have virtually no background in xenotransplantation. For those who do, I apologize that it is going to be relatively simple.

I am glad you mentioned my book because I was going to put that as a commercial to start with. This book was written with a colleague of mine, specifically for the intelligent, interested lay person. I really would recommend it to you. It does cover every aspect, not only of the science, but also the legal aspects, the ethical aspects, the financial aspects and so on. I did ask Mary if one copy could be given to each member of the committee, but evidently the FDA budget doesn't go that far and they can't quite afford to do that. I would think, for those of you who do not have a background in it, I think it would give you a good general start.

Now, xenotransplantation, the idea goes back a long time. There are all these mythological animals like the chimera, which is a term now that is used in transplantation science to define an animal made up of cells from more than one other animal, more than one of the same species or of different species. Here, the original was of different species, but if we have somebody with a bone marrow transplant, say mixed chimerism, we call that chimerism because they have cells from one person, themselves, and cells from a donor. So, the idea is very old. In fact, back in the 18th Century, they started doing blood transfusions from animals into humans, not very satisfactorily and not very successfully, but they did this.

Even as late as the first world war, I am told that they took sheep into battle with them to act as donors of blood for some of the soldiers. There was a phase, particularly in the 19th Century when they did a lot of skin grafts from animals to humans. The frog was the most popular animals because the skin was nice and clean and didn't have feathers and so on, but they did do skin transplants from all sorts of animals, including chickens and so on, which must have been a bit bizarre. One really bizarre thing is that they actually often skinned the frog when it was alive, which sounded pretty gruesome, but that is what they did.

Now, back in 1912, Alexis Carrel here, a Frenchman who was working in New York and actually won the Nobel Prize for medicine for his contributions to vascular surgery, he was the first person who could really join up blood vessels satisfactorily. This enabled him to do all sorts of transplants. So, he was the first person who really did a lot of organ transplants in experimental animals. Quite remarkably, he said here, back in 1907, that the ideal method would be to transplant on man organs of animals easy to secure and operate on, such as hogs, for instance, but it would in all probability be necessary to immunize organs of the hog against the human serum, which is just what people have been trying to do recently; that is, to protect the pig, by genetic engineering, from the human antibody response. He says, the future of transplantation of organs for therapeutic purposes depends on the feasibility of heterotransplantation, which was the old word for xenotransplantation. So, here is somebody almost 100 years ago getting it spot on right for what we are trying to do now, which is quite remarkable. It is no wonder he won a Nobel Prize.

Now, one other interesting character in the 1920s was this Russian, Serge Voronoff, who worked in Paris at the College de France. He was renowned for transplanting chimpanzee and baboon testicles into aging men, who needed a bit of a kick up. It was the viagra of the day. Looking at this photograph, it looks to me as if he needed a bit of a chimpanzee testicle himself, because he looks a little bit waylaid. He actually had three beautiful wives, one of whom was a Texas millionairess, who left him a lot of money. His last wife, when he was 75, she was 21. So, he obviously didn't need this sort of treatment himself.

Although I make fun of him a little bit, in fact, he really was a visionary. These days, we have listed a whole host of different cells that could be replaced by, say, pig cells that might replace endocrine function or some function that we are lacking including, for example, insulin for diabetics, neural cells for Parkinson's disease, and so on. So, he really was a man ahead of his time.

Now, if you look over the last hundred years, starting in the very early part of the 20th Century, there were a number of kidney, heart and liver transplants, a total of 33 kidney, nine hearts and 12 liver transplants, performed between animals and humans. Most of these, you can see, are obviously non-human primate to human. That includes, for example, the kidney transplants performed by Keith Reemtsma where he used the chimpanzee as the donor, one of whom, remarkably, survived for nine months. The woman went back to work as a schoolteacher and died of what they thought was an electrolyte disturbance. The kidneys were completely normal, no signs of rejection, at the time that she died at nine months. So, it is quite remarkable, particularly in those days, in the 1960s, where they only had very primitive immunosuppressive therapy.

The longest heart survival was Leonard Bailey's Baby Fae case in 1984. I see Leonard sitting here today. He can tell us about it later on if he wants to. Again, the first time that a baby received a baboon heart transplant with cyclosporin. It was not greatly successful, of course, as one would anticipate, but certainly opened up the era of transplantation in infants and children. It became well known after this, the tremendous shortage for infants and children, and this did a lot to actually get that going.

The liver transplants include those two that Marian Michaels was involved with in the early 1990s at Pittsburgh, when Professor Starzl carried out two liver transplants from baboon into human subjects. The non-human primates are mainly pigs and sheep as the donors. You can see very, very poor survival, really. Virtually none of them survived function for more than a few hours at most.

I put this up to show you. This is the first heart transplant ever performed, not Professor Barnard's one in Capetown in 1967, but the one by James Hardy in Mississippi in 1964, which is often forgotten. He used the chimpanzee as a donor, because he didn't have a human donor at the time that he needed one. He also did the first lung transplant the year before, using a human donor.

I put this up to show you. This was the consent form that the patient's relatives signed. The patient was semi-conscious and couldn't sign a form. The patient's relatives signed this form. It is one paragraph. It says that no heart transplant has ever been performed before, but it makes no mention that they might use a chimpanzee heart. Although I think the family was told about this, it is not on the form. I put this up, not to criticize people in 1964, because this was the norm at the time, but just to show you how things have changed today, when you would consider what sort of consent form you would need today if you were going to do this procedure.

Here is Baby Fae from 1984, from Leonard's study. Since then, we haven't seen much of transplantation. This is Jeff Getty, who you may remember had some baboon bone marrow cells, I believe it was, infused into him. There was a lot of discussion at that time as to whether it was safe to be putting baboon cells

into patients. Evidently the baboon cells were not documented to survive very long. He had AIDS and it was thought that baboon cells would actually overcome his AIDS. He has actually remained, I believe, very well since then, although there was no evidence that the cells survived for very long.

The other areas that we have been looking at are the brain cell transplants using pig cells. This is an example of something that we forget about. This is a clinic in Switzerland, Clinique La Prairie, which has been giving on for a long time, which gives people rejuvenating shots of sheep cells, sheep fetal cells. It is evidently quite a big business and very profitable and a lot of people go there from all over the world for these rejuvenating shots. So, there is xenotransplantation actually going on in this way, and has been going on for a long time.

Now, I mentioned that most of these transplants were from non-human primates to man, because of their similarity. In the last, say, 15 years, we have moved over to looking at pigs, partly because, as Time Magazine pointed out, that men are pigs anyway, to some extent, but because of a number of reasons. Not only is infection risk believed to be much higher if you use non-human primates as donors, and Jonathan Allen was one of the first to really raise that to our awareness, but a lot of other logistic reasons why the pig is going to be particularly suitable. So, most of the work in the last 15 years has been directed toward the pig as the donor.

If you put a pig heart into the baboon -- this is just into the neck so it beats -- within a few minutes or certainly within a few hours, in the vast majority of cases, it will be black and it will stop beating and it will be swollen and hemorrhagic. If you look at the histology of the normal heart -- here are the pink myocardial cells -- within minutes, that is totally disrupted in a xenograft, with huge areas where there is fluid lost from the circulation, edema fluid, and hemorrhage. These are red blood cells that spread all through the myocardium and the whole thing stops functioning. The same thing happens with the liver and the same thing happens with a kidney and so on. So, it is a very dramatic rejection, quite different from a human organ. When you put a human organ in, it will take perhaps about a week to reject if you didn't give any treatment. Here, you have something that happens maybe within five minutes.

The first people to really investigate this in a scientific manner was John Najarian and his colleagues up in Minneapolis, or a few other centers around at the same time, back in the 1960s, looking at this. They clarified that this so-called hyperacute rejection was the result of antibody-mediated complement activation. This is basically what has happened here on the left side. These are antibodies against the pig. They are in the circulation and they latch onto the pig's cell surface of the blood vessels and they activate complement, and it is the complement that actually does the destruction.

So, we have two keen points here. One is anti-pig antibodies, and secondly, complement activation. You might say, well, why do we have anti-pig antibody if we have never exposed to the pigs. Well, unfortunately, pigs have, on the surface of their blood vessels, a sugar which is also present on the surface of a lot of bacteria and viruses. As infants, when our bowel is colonized with these bacteria and viruses, we develop these antibodies as sort of a defense mechanism. At least, that is the theory.

My own group, when I was in Oklahoma with Heather Good from Canada, we identified that these anti-pig antibodies were particularly against this sugar, this galactose sugar, and groups in Australia, Mauro Sandrin, had also identified this a little later. Uri Galili, who is now in Chicago, had first identified these anti-galactose antibodies, but we were the first to actually demonstrate that these were the important ones in xenotransplantation.

In fact, to our surprise, to some extent, and pleasure, we found that every blood vessel of the pig -- and

these are the fluorescent sort of stains in here in the heart -- every blood vessel throughout the whole body of the pig has this sugar on the surface, and we don't have this sugar. You can see the differences here, between the pig, who has three sugars on the surface with this galactose as a terminal epitope on one of them, and the human has three sugars, where we have our A, B, or O blood group antigen on the surface. We have A, B, O blood group antigens not only on the red cells, but all over the surface of the blood vessels of our body.

This, surprisingly, is the one key difference between the pig and the human, which is good news, because it makes it a little easier to deal with. We are really only dealing with one set of antibodies against one epitope, rather than a whole host of them. If you put a pig organ into a baboon, for example, you develop a host of new antibodies, which actually can be prevented.

Initially, as far as natural antibodies, what we actually have circulating in our blood at all times, it is only this one antibody against this galactose epitope. You can remove that specific antibody by using a plasmapheresis machine. You put the patient's blood through this plasmapheresis machine. Then you put the plasma through a little column here which consists of a synthetic sugar, identical to the galactose on the surface of the blood vessel. So, as the plasma goes through this little column, it absorbs out all the anti-gal antibodies and leaves all the other antibodies that may be beneficial to us in our protection against infection and so on. It leaves those in. Having removed all the antibody, and then you put a pig organ in, that will survive about a week. Then, antibody returns and eventually causes rejection.

Every single pharmacologic agent that we and many other groups have tested does not suppress the production of this natural anti-gal antibody. So, at the moment, we are in a bit of a quandary as to how to overcome this problem.

Now, the next big step forward was by Gus Dalmaso here in the United States, and by David White, who is going to speak to you in a minute, from Britain. They, in the late 1980s, early 1990s, they introduced the concept of changing the pig, genetically engineering the pig, to have some protection, not against the antibody, but against the complement that the antibody initiates. So, we are protected from our own complement activity. We have a complement in our blood at all times which would theoretically destroy all of our tissues. We have, on the surface of our tissues, what are known as complement regulatory proteins. They protect us largely from our own complement. So, David and Gus Dalmaso, independently, suggested that if you transgenically modify the pig to put in one of the human complementary regulatory proteins, this will give the pig some protection against human complement.

In fact, they were quite right. By this genetic technique, you can put genes into a pig relatively easily, although you can't take genes out. We would like to take out the gene that makes this sugar, but it has not been possible as yet, although hopefully cloning may make it possible.

Here, David White's group and several other groups, particularly the Nextran group over here in the States, have shown clearly that you can extend survival just by genetically engineering the pig tissues. You can get out a week or longer. If you add immunosuppressive therapy or, as the Nextran group has done, you also add removal of the antibody, you can get out even further. Even so, eventually the whole system is overwhelmed, and we believe it is the antibody that is the main problem. The antibody comes back again if you remove it. It overwhelms the complement regulatory proteins, and causes rejection by various mechanisms, although we are not quite sure what they are.

The longest survival of life-supporting kidneys, of pig kidneys, in primates has been about two to three months and of life-supporting hearts has been only a couple of weeks. Actually, it has been longer, it has

been about 39 days, but the mean has been about a couple of weeks. So, we have still go a way to go.

I mentioned earlier that recent work has shown particularly the brain cells, these are dopamine producing cells, and this is an autopsy of a patient who had had this procedure done of Parkinson's disease. He died of other problems about seven months later, and still had pig dopamine producing cells in his brain, which hopefully were doing something to alleviate his Parkinson's disease. So, these trials of pig cells in the brain are still progressing, as are trials using pig cells as an artificial liver.

You heard from Brad Collins of their work using a pig liver to try to keep a patient alive until they got a human transplant, and there is similar work using pig cells in this apparatus to keep patients alive until they get a human liver transplant. Now, once all this got going and people realized that we were making some progress with the science, people began to worry about the infection risk even from pigs. You will hear later from Jon Coffin some of the risks involved here. So, this work stimulated a lot of thought about the other problems of xenotransplantation.

The other area that requires a lot of further work is, will the pig organ function well. We are hopeful that, as a pig heart has functioned in a primate for 39 days, keeping the primate alive, that the pig heart will function fairly satisfactorily in a human. As pig kidneys have been seen to keep non-human primates alive for a couple of months or longer, again, we think that they will function well. The experience of Keith Reemtsma, even at nine months, there appeared to be a physiological problem with that chimpanzee kidney, suggesting that there may be other things, that the physiology will not be absolutely 100 percent, particularly with the liver, which makes 2,000 different proteins. It is unlikely the pig liver is going to make the same proteins as the human liver. So, this is a whole new area that we are looking at.

The other areas which you are going to be discussing, the regulation of xenotransplantation, legal aspects, and the financial impact of it all, have all been stimulated by the work that has been produced by these laboratories in the last few years.

Finally, I want to leave you with a quote, really, from Sir Peter Medawar, who was really the father of transplantation medicine, who won a Nobel Prize back in the 1960s, I think it was. He said at the time, in 1966, that the transplantation of human organs will be simulated into ordinary clinical practice, for the single and sufficient reason that people are so constituted that they would rather be alive than dead. I think this puts it on the bottom line, is that people will jump at the opportunity, I think, of having a pig organ if it makes the difference between their being alive or being dead. I think that is something we have to bear in mind all the time.

Now, you as a committee obviously have a lot of backlog work to do. If you look at the right medical journals, you will realize that actually these transplants are going on all the time. [Laughter.] Here is a woman who has a pig heart. Now they can't keep her out of the mud. [Laughter.] Here is a man who lives for 90 years with a dolphin's heart, which seemed to get through the MEDLINE search, somehow or other. [Laughter.] Here is one the other way around, where actually some rich men are getting dogs human hearts. You should really put that into your program as well. [Laughter.]

Finally, I leave you with this thought. As George Bernard Shaw said, the reasonable man adapts himself to the world. The unreasonable man insists on trying to adapt the world to himself. Well, with xenotransplantation, we are all trying to adapt the world to suit ourselves. Therefore, all progress depends on the unreasonable man. So, in your dealings with the scientists who are trying to do this work, you will meet a lot of unreasonable men. Thank you very much.

[Applause.]

DR. GROESCH: Thank you, David. That was great. Any comments or questions for David? We have a couple of minutes.

Okay, our next three presentations deal with different aspects of the science of xenotransplantation. Our first speaker is Hugh Auchincloss. He is professor of surgery at Harvard Medical School. He is going to talk to us about some of the immunological aspects of xenotransplantation.

Agenda Item: The Science of Xenotransplantation: Immunological Aspects.

DR. AUCHINCLOSS: Thank you very much. I knew it would happen, that David Cooper would get up and that would be the end of my talk. I think he has told you most of what I was going to say, and I will try to run through this quickly. I would also suggest to the committee that at least half a dozen members of this committee -- perhaps more than that -- can give the following talk better than I can. I apologize to those people. I am not going to speak to you and I am not going to try to teach you something that you don't already know. I am going to turn, instead, to the members of the committee who are not familiar with the science of xenotransplantation and talk to them about that. So, this is a talk about xenotransplantation, primarily concentrating on the scientific obstacles. I will mention the ethical issues that connect to various of the scientific issues as well, as we go through.

As you know, xenotransplantation is the transplantation of tissue or organs from members of one species to another species, in contrast to allogeneic transplantation between different members of the same species, or isografts, between genetically identical members of the same species, and autografts, tissue from an individual to that same individual. I want to concentrate primarily really four, but they are not quite listed here correctly. Physiologic function, scientific obstacles, hyperacute rejection, delayed xenograft rejection. Then I am going to talk briefly about cell-mediated rejection.

I want to tie those to several ethical issues. When is an animal really a human. What about the risks associated with xenotransplantation or preparing for xenotransplantation to the animals. What about the risks that might be acceptable or not acceptable to the individual patients. Then, the larger question of how much risk is acceptable to the society at large.

Why xenotransplantation? I think you have heard from a number of different people already. Simply, the number of people who are looking for organ transplants is growing much faster than the number of people who are receiving them, with that number down here being actually relatively constant over the course of the last decade or two. Not so the scientific interest in xenotransplantation. This is a rough listing of the number of published articles about xenotransplantation per year over the course of the past roughly 50 years.

There is a blip in the curve when Keith Reemtsma described in 1963 his cases of chimpanzee kidney transplantation into human beings that David Cooper just described to you, with a period of interest at that time in xenotransplantation primarily during the 1960s and early 1970s, at a time when we did not have widespread availability of cadaver donor organs, nor very satisfactory long-term life support devices.

Actually, allotransplantation then became so successful, and the availability of allogeneic organs from cadaver donors became more widespread, that the interest in xenotransplantation, particularly because it wasn't working, diminished in the early 1970s and started again with the Baby Fae case that David

Cooper described just a moment ago, with a surge in interest that really continues, at this point, unabated, as far as I can tell.

David Cooper has again mentioned to you some of the recent transplants that have taken place in xenotransplantation. I want to stress the fact that a number of these transplants involved cell transplants rather than organ transplants, with islet transplantation over the course of the past decade, bone marrow transplantation in the case of the patient with AIDS, and ongoing trials of neural cell transplantation. Xenotransplantation is, in fact, happening right now. People frequently say, when will this field get started. It already has started. Clinical trials are in progress at this time, not only with neural cell transplants, but with the use of xenogeneic hepatocytes. Indeed, we are not very far away from learning the results of the first randomized, double blind, controlled trial of xenotransplantation, which I think you will hear described over the course of the next two days by members of Genzyme and Diacrin.

So, the field is in progress. Again, David, I think, has mentioned to you that in some of the patients who received tissue from pigs for the treatment of Parkinson's disease, there has been evidence for ongoing survival of that xenogeneic tissues. One patient in particular, died after approximately eight to nine months, and within his brain, as described in this article, it was clear that there was surviving pig tissue. Not only is xenotransplantation in progress clinically at this time, there is evidence that xenogeneic tissue can survive in human beings.

Before going into the scientific aspects of xenotransplantation, the only other comment I wanted to make is that, of course, there are potential alternatives, not just in the field of allotransplantation. What about the question of artificial organs instead of xenotransplantation, or animal organs, for human beings. The fact of the matter is that this is a constant tension in the field, not only for xenotransplantation but for allotransplantation, and it always will be, the back and forth between various forms of life support that do not involve transplantation and might involve artificial organs or tissues.

Perhaps the closest to a major competitive event for xenotransplantation would be the use of the LVAD or even a totally implantable heart, where the progress in that field over recent years has been, at least in my view, so dramatic that I think that you might be looking at less of a need for heart transplantation from xenotransplantation, but you will be hearing about people for whom these devices are not acceptable. There will be a constant ongoing tension between the use of totally implantable hearts and the real biologic tissue coming from animals if, in fact, the biologic problems could be overcome.

We have artificial lungs, as you know, but they are not satisfactory for a quality of life existence. There are extracorporeal liver support devices that have been used in clinical practices, but many of them, in fact, use xenogeneic tissue, so that is not a distinction from xenotransplantation. There are efforts to make implantable dialysis devices to replace the trips to the dialysis center for patients with kidney failure, but I don't see these as close, near-term clinically applicable treatments. There is also a tremendous amount of interest in the world of islet transplantation in the alternative of non-invasive glucose monitoring, coupled with an insulin pump to create a so-called closed loop system, that might achieve really tight glucose regulation in patients with diabetes. Again, that will be a form of treatment as, indeed, insulin therapy is today for patients with diabetes, that would potentially compete with xenotransplantation of islet cells for patients with type I diabetes. So, the alternatives to xenotransplantation are not simply allotransplantation, and they will always be there in shifting degrees of priority.

Now, let me turn to four scientific problems in xenografting. First, I want to talk about the function of organs in a species from which the organ was originally derived. Secondly, I want to talk about natural

antibodies, which David has alluded to, and the problem of hyperacute rejection. Then I want to talk to a problem that we believe is primarily due to induced antibody or delayed xenograft rejection, also called acute vascular rejection, although antibody may not be the only cause of this form of rejection. Then I want to mention at the end the problem of cell-mediated xenograft rejection.

Function, physiologic function of xenogeneic organs in another species. We actually know very little about this problem because so few experimental or clinical examples exist, in which we know we have had long-term survival of xenogeneic tissue, in order to enable us to evaluate the physiologic function of the animal tissue in a different environment. We do know that there are some cases in which xenogeneic tissue can function adequately to support human life.

We know, for example, that David Cooper mentioned to you that there is at least one patient who survived with a chimpanzee kidney with apparently normal function from that chimpanzee kidney over the course of nine months. So, there is nothing inherently incompatible between animal organs and human beings. We know, of course, also, that humans have existed taking porcine insulin for many, many decades. Also, again, it is possible for xenogeneic tissues to support human life. Again, we know from the baboon to human liver transplantation experience that this physiologic function is not always intact.

We know, for example, that the patients who received baboon livers to replace their own liver function, had their serum uric acid, the molecule associated with gout, go essentially to zero, because the baboon liver does not metabolize uric acid the way it is metabolized in the human liver. We know that their cholesterol fell to a very low level compared to normal human levels. Again, we know from these examples, that there are going to be cases in which animal organs cannot, in fact, support human physiologic function.

We know of apparent examples in the experimental literature where it appears that pig kidneys, in non-human primates, trying to support life of these animals, has apparently led to a failure of erythropoietin, the hormone produced by the kidney, that encourages red blood cell formation. This erythropoietin does not work across species. Therefore, these recipient animals become severely anemic. The point, then, is that there is no question that in some cases physiologic function of animal organs is not going to be sufficient to maintain human life.

There is the vague sense that the more complex the organ, the greater those problems are going to be, that xenotransplantation of livers is perhaps going to be more complicated over widely disparate species than, for example, islet cells or perhaps the heart. Those of us who are heart transplant surgeons think that the heart is sort of dumb and can be used to function in any species, but they tell me that that is not necessarily true. So, physiologic function will be a problem and is something that you need to think about.

There is also a more general principle that I think emerges from consideration of the physiologic issues, and that is, that one of the fundamental features in general of xenotransplantation is that some of the molecules produced by one species will not work with their receptors or their counterparts and ligands in another species. That will introduce a number of problems in the immunologic aspects of xenotransplantation that make for a generalization about the difference between xeno and allotransplantation.

I said I was going to jump back to the issue of ethical issues. In this case, when is an animal a human. If you have a pig kidney that does not produce human erythropoietin, then one of the solutions to that is to, in fact, put the human gene for erythropoietin into the pig, and that will solve that physiologic problem.

In doing so, the question then comes up from some people, at what point does putting the gene into the animal make that animal into a human. In fact, some people would start with the assumption that there is no fundamental distinction between animals and humans. If you start with that assumption, then xenotransplantation is not going to look attractive from an ethical point of view.

However, if you worry about the introduction of single genes from the human species into an animal, and when that will turn the animal into a human, I would urge you to consider the fact that there appears to be only one percent of our genome that distinguishes humans from mice, in terms of the genes that we produce, and less than 0.1 percent of our genome in terms of new genes that we have, that monkeys don't have. So, one more gene from a human into a pig hardly makes a difference in whether that animal is a pig or a human.

Now, let's talk about the three immune responses associated with xenograft rejection. David Cooper mentioned to you the problem of natural or preformed antibodies. Many of you, even if you are not experts in xenotransplantation, will be familiar with the most common clinical example of preformed antibodies, natural antibodies, that prevent transplantation, and these are the blood group antibodies.

Well, I am blood group O and, as a result of that, am able to form anti-A and anti-B antibodies, that will cause destruction of blood cells that express either the A or the B antigen, even though I have never been exposed to blood group A or blood group B. As David mentioned, these natural antibodies appear to have developed, not because I have ever been exposed to blood products from another individual, but because there is a cross reaction with environmental pathogens that occurs very early in life.

So, we have natural antibodies that lead to the destruction of red blood cells. Indeed, these same natural antibodies are capable of causing the destruction of an organ, a kidney transplant, from a person with a different blood group, because these same antigens are not only expressed on red blood cells. They are expressed on the endothelium of the vascularized organs. So, I can't receive a kidney transplant from somebody who is blood group A, and I can't receive a kidney transplant from somebody who is blood group B.

If I do, the kidney transplant that I would receive would end up looking like this. This is an organ that has undergone hyperacute rejection as a result of these preformed antibodies. Within 10 to 15 minutes, in many cases, the organ becomes swollen, blackened and blue, as a result of extravasation of blood and thrombosis of the blood vessels. There is nothing that we know of that can stop this process, once it comes into operation. So, preformed antibodies are the first immunologic barriers to xenotransplantation by causing hyperacute rejection, which is fundamentally a complement-dependent process.

The reason this is a major immunologic barrier in xenotransplantation is, again, exactly as David has pointed out to you. In effect, all pigs have another blood group determinant that no human has. Now, it happens to have the fancy name of the alpha 1-3-gal epitope, or the gal determinant, or the gal epitope that you will hear discussed numerous times in the field of xenotransplantation. It comes about as a result of the function of the gene called -- this is actually the alpha galactosyl transferase gene, which pigs and many other mammal species have, but which is not functional in the higher non-human primates, or in human beings. For all the terminology and all the complexity of the names and terms involved in this, it is simply nothing more than that the pigs have a blood group determinant that humans don't have and we call it the gal determinant, but you might just as well call it blood group G. Therefore, all humans have natural antibodies against this blood group determinant.

This is a slide that I borrowed from perhaps Jeff Platte. It might even have been David Cooper, I can

never remember. It is showing the structure, the carbohydrate structure of blood group A, blood group B, and of the gal determinant. It simply, again, is designed to emphasize the point that this is just another blood group determinant that exists in this animal species that humans don't have.

Now, the pathophysiology of hyperacute rejection is diagramed in this slide. The gal determinant exists on the vascular endothelium of an organ, a kidney or a heart transplant. The anti-gal antibodies that exist in all of our circulations binds to this determinant. The crucial step in hyperacute rejection is that the binding of the antibody to the antigen leads to complement activation. That complement activation leads to an activation of the endothelium. We call it type I endothelial activation, and type I occurs very rapidly, without a requirement for protein synthesis over the course simply of moments. The major effects of this endothelial activation are that the cells, the endothelial cells shrink up and separate from one another, creating spaces between endothelial cells such that there is extravasation of blood and fluid into the interstitial spaces.

Secondly, there is the release of a variety of pro-coagulant molecules into the circulation, such that the two main features of hyperacute rejection occur as a result of this endothelial activation, namely, interstitial hemorrhage and intravascular thrombosis, all occurring over the space of minutes to hours.

Now, one of the crucial findings or elements to understand about hyperacute rejection is that it is not an all or none phenomenon. It is not an absolute guarantee that tickle to the complement system will, in fact, set of a degree of activation that is sufficient to stimulate the endothelium. That is because, again as David Cooper has mentioned to you, humans have a number of complement regulatory proteins which are constantly presented and designed to downplay the activation sequence in the complement cascade. In fact, it is a generalization of human activation and physiologic activation sequences, that they are almost invariably balanced by down-regulatory sequences designed to keep the system in more or less balance. Decay accelerating factor (DAF), membrane co-factor protein (MCP), membrane inhibitor of reactive lysis (CD59), this is CD46, and solumin(?) receptor 1 are four that have been mentioned.

Now, the crucial feature in xenotransplantation hyperacute rejection, again mentioned by David Cooper, is that it was recognized some years ago that one of the problems that leads to the explosive nature of hyperacute rejection in xenogeneic combinations is that, at least in some species combinations, these complement regulatory proteins don't work across species differences. So, the pig DAF is incapable of downregulating the activation of complement when the complement comes from the human recipient.

So, you put the pig organ into the human. The regulatory proteins which come from the endothelium of the organ can't function in the environment of the species that you have gone to as the recipient. Again, I am coming back to this notion that one of the crucial features of xenotransplantation is the failure, the physiologic failure, of molecules of one species to work with their ligands in another species. So, hyperacute rejection, which can occur in human beings from human allogeneic tissue transplants can occur, or does tend to occur, much more vigorously in xenogeneic transplantation, because of the loss of the regulatory mechanisms.

Let me suggest to you that, as we look at this process of hyperacute rejection and try to understand how it comes about, that in fact it provides you with a way of understanding, in a much more general sense, the difference between xenogeneic and allogeneic transplantation. That difference stems from two crucial features. In the xenogeneic situation, there are more antigens. In the case of hyperacute rejection, that is a new blood group determinant, the gal determinant.

Secondly, and at least as important, is the loss of the physiologic regulation that comes about as a result

of the molecular incompatibilities between species. Again and again, when you ask yourself, what is different about xeno and allo, these are the two things that you should think about, more antigens, and a loss of physiologic regulation.

Now, that understanding then brings the understanding of the pathway to solve the problem, in this case, of hyperacute rejection and potentially in the future of other forms of immunologic reaction to xenografts. If the problem that leads to hyperacute xenograft rejection is a gal epitope that the humans don't have and a loss of complement regulatory function, then the solution to hyperacute rejection is to get rid of the gal epitope and to augment the function of the complement regulatory proteins. That has been the extraordinary achievement over the course of the past decade in the field of xenotransplantation, first, the understanding of the pathophysiology of hyperacute rejection in xenogeneic combinations and, second, the development of molecular approaches to overcome these problems.

So, what kind of molecular approaches can you use. You have to be aware that in genetically engineering animals, there are two basic approaches that you can use. One is the so-called transgenic technology which effectively means putting new genes into an animal in some random location. This technology is available for many species, including for pigs, and has been used for a considerable period of time, not just for purposes of organ transplantation but, indeed, to produce healthier livestock and more productive live stock from the point of view of food purposes. The ability to put a new gene in, in an random location, is something that already exists as a possibility for genetic engineering of xenogeneic donors.

Now, a second approach is called homologous recombination, or is based on homologous recombination. Effectively, what it does is not only to put a new gene in, but to put it precisely in the location where the old gene was located. The net effect of that has been to enable the so-called knockout of a particular gene's function. Now, homologous recombination is something that is available at this point only in mice. It is not something that you can do for pigs. Many companies are interested in the possibility of developing the homologous recombinant technology for pigs or other species of animals. Sooner or later, I suspect that that will come.

There may be a short cut to the same outcome through the use of cloning of animals. That is one of the reasons that the cloning technology becomes important in xenotransplantation. At this particular moment, transgenic technology, random insertion of new genes, is the way of developing genetic engineering approaches for clinical application. Again, this is not science fiction. These are the kinds of genes that have been inserted -- human genes that have been inserted -- into pigs over the course of the past decade - - the decay accelerating factor, CD46, CD59 -- enzymes that might remove the gal determinant or produce a different determinant, one that humans do have, by placing the fucosyl transferase into pigs.

There are a variety of genes that a number of different companies have sought to introduce into pigs, with the idea that they might overcome the problem of hyperacute rejection. Not only might, but the extraordinary feature has been, to a surprising degree from my point of view, that for all intents and purposes, I think it is probably fair to say that the problem of hyperacute rejection, which we once 10 years ago thought was the insurmountable problem in xenotransplantation, has actually probably been solved over the course of the past decade. That has been an incredible step forward in the field and fueled much of the optimism from, say, five years ago, that clinical xenotransplantation was just around the corner. The H-DAF pig, the NCP pig and a variety of other pigs really do seem to regulate hyperacute rejection and avoid its onset, and I think you will see some of the data supporting that from David White following my talk.

Just briefly to mention, there are two other ways around the problem of hyperacute rejection. One is the use of cellular transplants, islet cells, bone marrow cells, hepatocytes, other kinds of cells, neural cells, as I mentioned, which are in clinical trials at this time. There, the reason that the cellular transplants avoid the problem of hyperacute rejection is because, as I just mentioned to you, the fundamental pathophysiology of hyperacute rejection is an endothelial issue. The tissues, the cell transplants that come without their own vasculature, don't bring a vascular endothelium. So, the whole process that I was describing is not one that affects these kinds of tissues.

The other way of avoiding hyperacute rejection is to turn to the so-called concordant species. The concordant species are the ones that don't have this new blood group determinant, gal. There are some. Chimpanzees, baboons, are two that are examples. You will hear a great deal of discussion about whether it is suitable, at this point, to use non-human primates for human xenotransplantation. At this point, the FDA has decided, on the basis of expert input, that we should not be considering the further use of non-human primates for clinical xenotransplantation trials, and that is the kind of issue that you will be looking at again, I am sure, in the future.

I want to come back and touch very briefly on an ethical issue associated, this manipulation of animals by genetic technology. What about the risk to the animals? Well, it is apparent to all of you that, in general terms, xenotransplantation presents an ultimate risk to the individual animal that is the donor, in that, in most cases, they will be sacrificed. That, of course, is something that we do for our human food and clothing products at this point, and does not distinguish xenotransplantation. In addition to the individual animal, the colony that you use as your source of xenotransplants will live, throughout their lives under special conditions. Again, that is an issue that affects equally our food sources as well.

There are some special features associated with the genetic engineering of animals for the purposes of xenotransplantation. One example of that is that MCP, the membrane cofactor protein that regulates human complement, happens to be the receptor for the measles virus. Measles gets into human cells by binding to this protein. Now, we are going to introduce this human protein into the pig. The question then comes up, does that place the entire pig species at a risk for measles infection by the human virus, that it would not be otherwise. So, there is a question that has arisen in the ethical world of what happens to the animal species as a result of these genetic manipulations.

That is, in effect, the good news about the immune obstacles to xenotransplantation. The hyperacute rejection, which looked like an insurmountable problem, has been fixed, for all intents and purposes, by genetic manipulation.

I want to turn now to the second immunologic barrier to xenotransplantation, which we believe is largely due to an induced, as opposed to a preformed, antibody response. The process goes by a variety of different terms, delayed xenograft rejection, DXR, acute vascular rejection, AVR, and it has other titles as well. Now, I have described it here, listed it here, as an antibody as opposed to a complement-dependent process. Complement may be involved. Antibody clearly can stimulate this form of rejection. There may be other stimulants to delayed xenograft rejection as well.

I can tell you just very briefly that this is the scientific obstacle to xenotransplantation that is the block to progress in the field at this time. Now, in schematic terms, the simple picture is that an antibody that is formed, it may, in fact, be higher levels of the anti-gal antibody and a different isotype from the IgM that causes hyperacute rejection. Again, binding to a determinant on the endothelium -- again, gal appears to be one of the major determinants -- leads to a different form of endothelial activation which we call type II activation.

I tried to distinguish type I and type II endothelial activation by saying that if you were sleeping at night and there was a huge clap of thunder, the result is endothelial activation type I. You jump up and something dramatic happens.

Endothelial activation type II is what happens if the room is too cold and you don't have enough blankets, and you sleep all night sort of vaguely aware that you are having a lousy night's sleep and you kind of wake up in the morning and say, that was a lousy night, but you never quite got around to getting up and closing the window or putting more blankets on. It is a slower process that doesn't lead to an explosive outcome. Indeed, the events of endothelial activation type II depend on protein synthesis and occur not only the minutes to hours, but over the days to a week or two.

There are two hallmarks, perhaps, in the nature of endothelial activation type II. I guess the most important one to concentrate on is that the changes in the endothelium that result in this activation process lead to a procoagulant state that leads to progressive vascular thrombosis. Again, to stress the fact that -- I have indicated that this is something that happens by antibody, independent of whether complement are present, there are probably other mechanisms which can stimulate the endothelial activation type II besides just constant antibody stimulation. Once again, there are clearly regulatory molecules that change the tendency toward the procoagulant environment.

The problem in the field at this time is that we understand these regulatory processes and the molecular failures of these regulatory processes much less well than we do in the case of hyperacute rejection. If you try to think about delayed xenograft rejection or acute vascular rejection in terms of the two fundamental features that I talked about -- more antigens and a physiologic dysregulation -- it appears that gal is again one of the determinants, but that there are probably others in the way of new antigens.

It appears that there clearly is physiologic dysregulation of the events associated with type II endothelial activation, including the failure of something called tissue factor protein inhibitor, with factor 10-A in humans, and a dysfunction of thrombomodulin, both molecules that influence the clotting cascade. So, the principle is the same, but the fundamental point for you to be aware of is that we understand these factors and have been much less -- we understand these factors much less well, and have therefore been much less successful in controlling them by genetic manipulations.

In the absence of the scientific understanding, the field has turned, instead, to a variety of immunosuppressant agents that are largely directed at B cell suppression, some of which are listed here, coupled with the transgenic animals that avoid hyperacute rejection, in an effort to avoid the delayed xenograft rejection by a pharmacologic means.

You will, again, hear much more about the results of primate studies of this kind of approach to avoid delayed xenograft rejection from David White. Let me show you one data slide from one of the articles describing pig to primate xenotransplantation, using a combination of transgenic animals to avoid hyperacute rejection and an agent to avoid an antibody response. The results shown here show about two months of survival of the xenogeneic organ in non-human primates. That is about where the field is, scientifically, at this point. We can get vascularized xenografts to survive in non-human primates -- and I use the word we very loosely there -- for about two months, in some cases longer, in some cases less. But that is the barrier that we have come to at this point in the field.

This will bring up one of the really critical ethical issues that I think bothers the scientists and surgeons who are considering vascularized organ xenotransplantation. What risk is acceptable for the patients. Is the survival for two months of the xenogeneic vascularized organ sufficient to initiate clinical trials

where we might be able to do better with the kinds of intensive care treatment and different drugs that we can use better in humans than we can in the primates.

Let me just mention risk in general for the individual patient, xeno versus allotransplantation. In many, many ways, xenotransplantation is going to be safer for the individual recipient than allotransplantation is. That includes, especially, infectious disease risk, because of the ability to screen your animal donors for prolonged periods whereas, in fact, a human cadaver donor cannot be screened for that period of time and we know that we transmit infections from one human to another not infrequently, in allotransplantation. So, risks are a problem in all kinds of transplantation and it is not clear that the higher risks are always associated with xenotransplantation, from the point of view of the individual patient.

We do, at this point, face preclinical data that shows this two-month road block, and the question is, when is the survival long enough to justify the clinical trial. On the other hand, if you always say, you have to have perfect results in your experimental animals before you turn to clinical trials, I can tell you that medical progress would be way behind where we are at this point.

Briefly, let me touch on the last of the immunologic responses to xenogeneic donors, and I will talk about it briefly. For the most part, cell-mediated xenograft rejection is something that we don't think about very much because we haven't gotten there yet. The antibody problem and the delayed xenograft rejection, independent of cell-mediated responses, still blocks survival for long enough that the cell-mediated response that probably comes later has not been carefully examined in many cases.

You can artificially create situations where you can look at this form of xenograft rejection. Skin grafts are highly resistant to antibody-mediated rejection. So, in an animal, a nude mouse that does not have any T-cell-mediated immunity but still has B cells, it can accept a skin graft not only from another mouse, which is what this is, but in this case, I believe this is pig skin on the same animal without any further immunosuppression. This is simply a demonstration that there are forms of cell-mediated rejection that are responsible for xenograft rejection.

Let me just highlight what we think are three key points related to cell-mediated xenograft rejection. Study after study suggests that the CD4 T cell subset is very particularly important for xenograft rejection. Second, those CD4 T cells tend to respond in xenogeneic combinations, not exclusively, but very frequently, through what is called the indirect pathway, using the antigen-presenting cells of the recipient, the physiologic antigen-presenting cells from the point of view of the T cell as opposed to the antigen-presenting cells of the donor, which again, are subject to physiologic incompatibilities. So, the indirect pathway appears to be very important in cell-mediated xenograft rejection.

Even though functioning through an indirect pathway, all the evidence that I am aware of at this point indicates that the CD4-mediated xenograft rejection is at least as strong or stronger than the cell-mediated rejection of allografts. It is not at all clear at this point why that should be, whether it is simply more antigens, more proteins with disparities that generate a higher number of peptides, whether the qualitative nature of the response, either in the cytokines produced or some other feature of the response is different or, again, whether or not there is a loss of physiologic regulation that leads to the explosive cell-mediated rejection in xenogeneic combinations. It is a wide open question at this point.

There is one form of cell-mediated response to xenografts in which we can pinpoint a physiologic defect, and that is involving the NK cell response to xenogeneic tissues. In particular, it has been studied in the human NK response to pig tissues, where there clearly are antigens, perhaps even including the gal

determinant, that stimulate NK antigens so there are more antigens, and where there is a physiologic dysregulation. Namely, the inhibitory receptors that exist on NK cells, namely, those that recognize MHC class I molecules may not be triggered by class I molecules from a different species.

We know that that is the case in the human anti-pig situation, giving rise to a higher degree of NK cell activation by human NK cells when they respond to pig endothelium and pig target cells, than in the case of allogeneic combinations. Now, people have looked at a lot of the other human/pig molecular interactions that may be involved in cell-mediated immunity. For the most part, those that have been studied appear to be intact, although not necessarily with the same degree of affinity that exists in allogeneic combinations. The one clear cut exception, as I just mentioned, is the human NK killer inhibitory receptor interaction with the swine leukocyte antigen class I molecule.

The big picture, again, if there is one thing I would want you to take away from my talk, is that when you think about the scientific roadblocks to xenotransplantation, they come about as a result of two distinguishing features that distinguish allo from xenotransplantation. In the case of xenotransplantation, there are more foreign antigens and, of course, the big one that we have been talking about is the gal determinant, and there is a dysregulated regulation, physiological regulation, that stems from the molecular incompatibilities between different species. Therein, again, lies the heart of the solution, scientifically, to the xenotransplantation problem, diminish the number of foreign antigens and restore the physiologic regulation or even create a superphysiologic regulation.

Now, it is not my job to talk about the retroviral issue. We are just about to hear that story from other individuals. That is where the ethical issue arises that applies to society as a whole as opposed to for the individual. Again, I would stress to you that, in considering particularly the infectious risks of xenotransplantation, the risk for the individual recipient of xenotransplantation are going to be dramatically less than the risks of allotransplantation. That is not why the FDA and the national government are concerned about infectious risks of xenotransplantation.

The issue is whether proceeding with clinical trials in xenotransplantation places, not an exceptional risk on that individual recipient, but whether it creates a very small risk of very large size or consequence to society as a whole. The issue, the hardest issue, that I believe that I think you are going to have to face over the course of the next several years, is how it is that you make policy, public policy, when your concern is for individuals who receive high benefit and high risk, and a society that receives low benefit and a potential low risk, but of enormous consequence if it comes to pass. I will conclude my lecture there with some notes about how much progress has been made in the scientific understanding of xenotransplantation, but the prospects continue to elude us, at least for the vascularized organs, until further scientific progress occurs. Thank you very much.

[Applause.]

DR. GROESCH: Thank you, Hugh, for an excellent presentation. Any comments or questions from members?

DR. VANDERPOOL: I have one. Thanks, again, for a very lucid presentation, Dr. Auchincloss.

Is there evidence that humans will or will not tolerate xenografts better than these animal models? I know I am asking for some statements on your part that compare these data arising almost exclusively or greatly from discordant animal trials. How would that relate to how humans are likely to respond in similar trials? Of course, you surgeons and immunologists know much more about the human system.

With that knowledge in mind, do you think some of these risks are more controllable or still mysterious enough to be very wary about.

DR. AUCHINCLOSS: First, I think it is an excellent question and a very important one. Secondly, I hope you will ask David White the same question, because I think it will apply very directly to the kinds of data that he is presented to you, in how to interpret that data. Thirdly, I would say that I am not aware of specific evidence that says the outcome will be different, easier or harder when you turn to humans as opposed to the non-human primates. Fourthly, I would suggest to you that there is no question in any of our minds that certain aspects of the prospect will be easier from a practical, clinical point of view.

You can simply take much better care of a patient in an ICU than you can take of non-human primates in our animal facilities, no matter how much investment you put into it. We have so much more control of the physiologic functions through life support devices. We know how to use the drugs much better. We know how to attain levels that are more meaningful. We have more experience. I don't think that any of us in the field doubt that you could do better in a human in terms of survival, over the course of months to perhaps many months, than you can do in the non-human primates.

Finally, I would suggest to you that I am not aware of any evidence that there is a fundamental biologic difference between the way humans and non-human primates would respond immunologically to these pig organs. To my way of thinking about how to look at the data from the preclinical studies, it doesn't bother me so much whether or not we can get from 60 days to 90 or from 60 to 120. What bothers me is that every group that has approached this problem comes up against a wall at some point in the form of an immunologic response that we don't fundamentally understand. I believe that until we do, and have specific strategies to overcome that biologic, immunologic response, we are not going to have long-term survival of xenogeneic organs.

DR. SYKES: Hugh, I think it is very important that you brought up some of the alternatives to xenotransplantation, the development of artificial organs. One specific question I have about that is the closed loop blood sugar control device, which is an idea that has been around for quite a long time. It seems like it ought to be technologically feasible at this point. I wonder if you could just tell us a bit more about where that technology stands.

DR. AUCHINCLOSS: You and I are biologists. So, we can't understand why the technologists can't solve what seems like a straightforward problem. Can't figure out how to measure blood sugar without six-times-a-day needle sticks. The answer to your question is that I am not an expert in any way. In my involvement with the Juvenile Diabetes Research Foundation, I have sat in, over the course of the past two or three years, on numerous review groups by the experts, watching the progress of non-invasive glucose monitoring. You know that we fundamentally have the capacity to deliver insulin continuously through an insulin pump. The problem of closing the loop is on the other half.

The answer is that they don't find it a trivial problem, not at all. It has been quite frustrating. There are a number of different approaches, the near-infrared spectroscopy, et cetera. The problem, as I listen to is, is that glucose looks a heck of a lot like other molecules when it comes to its shape and structure. Many of the light and spectrographic approaches to measuring glucose non-invasively are having a hard time being specific about glucose levels.

Fundamentally, the other approach is to sample some fluid from the body, interstitial fluid, by a variety of ways, either by permanent indwelling interstitial catheters, or by ultrasonography, to permeabilize the skin so that you can sample it on a periodic basis, the interstitial fluid. Then, do your glucose reading

from the standard enzyme-based assays. Those kinds of techniques have actually moved forward into clinical trials, FDA-approved devices or near approved -- I am not sure I have that right, so don't hold me to it. The level that they have gotten to is the capacity to measure trends and to measure glucose pretty well if you calibrate your device periodically to make sure that it is doing the right thing.

The problem is that the range of error, although not huge, is such that, at this point, it would still be possible to read on your machine that your blood sugar was 80 and have a blood sugar of 40 and, in the clinical world, that is a significant difference. So, they are not there. As I watch the field, if I had type I diabetes, I would be more interested in the progress happening in non-invasive glucose monitoring than I would in pig islet transplantation, because I think that is a closer approach to really giving me the opportunity to control my blood sugar.

DR. SCHECKLER: Question. Let me see if I have this right. In hyperacute rejection, the endothelium goes to pot in a hurry and there is nothing the human can do about it. In a type I allergic reaction, an IgE reaction, let's say to peanut protein or shellfish or something, the entire endothelium reacts and you get the potential of anaphylaxis, hives, asthma and so forth, and it doesn't seem like the human organism can do anything about it. Is there a biological similarity here, other than the fact that the reaction is concentrated on the xenograft organ?

DR. AUCHINCLOSS: I was going to start by mentioning that fact, that this is a concentrated effect that occurs within the organ and there is not, for the most part, a systemic reaction associated with hyperacute rejection. That is not 100 percent true, but from the point of view of the endothelium of the rest of the human body, it is not altered as a result of hyperacute rejection.

Secondly, the antibody that is involved in hyperacute rejection is IgM as opposed to IgE. So, some of the mediators that are involved -- histamines and release of products of mast cells that are associated with a hypersensitivity reaction of that sort are different. The immediacy of the event, the fact that it is antibody mediated, are similar. That it is an endothelial reaction, in part, is similar. The effector mechanisms are different and the actual tissue pathology is somewhat different. The other similarities remain. I would open that to any other immunologist on the panel here, who might be able to answer that better than I can. Close enough?

DR. VANDERPOOL: While you are here, I want to draw on your invaluable work on the FDA subcommittee, and your chairing that committee. In the report that the committee made, and that certainly you had a lot to do with writing and structuring, in June of 1999, you put forth the idea that the FDA subcommittee would think about going toward human trials if we could get 90 percent response, organ survival, for two months with animal models and 50 percent survival for three months. I notice in the international societies for heart and lung transplants, that they have changed that equation a little bit -- we will get to ask David Cooper this question also -- to 60 percent survival for three months rather than 50 percent survival for three months. I realize that those were just guesstimates that the committee was making. Do you have any further thoughts on that sort of threshold of survival that we would need to be able to reach in order to move toward human trials?

DR. AUCHINCLOSS: I have very strong personal feelings, but let me separate personal feelings from the xenotransplantation subcommittee. When I was writing the report, I was trying to reflect the opinions expressed in the group about what they might think was a reasonable experimental outcome in non-human primates that would justify proceeding with clinical trials. I personally wouldn't have necessarily gone along with those numbers because, in fact, they were based on the fact that the first, or at least an early, use of xenotransplantations would be in so-called bridge trials, which I won't develop now, but I

am sure you will be discussing bridge trials. The point is that it would be for temporary survival of the xenotransplant organ.

I was not involved in writing the International Heart Transplantation Association guidelines on this issue, but I was involved with the American Society of Transplantation, the American Society of Transplant Surgeons draft or guidelines for what they thought was reasonable. We put forth somewhat similar numbers like that, and the community couldn't agree whatsoever. So, we ended up with a sort of vague document that said you ought to be able to do pretty well before you move into clinical trials. I think that is important to understand, that nobody does know exactly, or nobody can agree, really, on what the precise number is.

To me, again speaking personally, I am not as worried about the number of days that you can keep a monkey or a baboon alive. I am interested in knowing whether you have made progress in knowing the immunologic barrier and have a solution to that barrier that can be applied in the human recipient. It is a scientific issue, not a statistical issue, from my point of view. I have seen no evidence at this point that we sufficiently understand delayed xenograft rejection to think that we have a therapy that specifically counteracts that. I can imagine a therapy that you could develop on the basis of a better understanding that wouldn't necessarily provide you with much better survival than you have now. The pathology of the rejection would change and you would say, I have solved this problem, and the reason that I can't get the animals to survive longer is because of X, Y and Z, that wouldn't apply in the human being. So, I want a scientific breakthrough, not an experimental breakthrough.

DR. SALOMON: I also serve on the xenotransplant advisory committee with Hugh, and he and I have gone back and forth on this more than once. I think that actually what we have done is set an unreasonably high barrier for moving forward with clinical trials in xenotransplantation, I think a lot higher barrier than we have set in a lot of other emerging technologies, and that does concern me, and I have said that before in committee meetings.

I am speaking now from my personal opinion. I think we are in much better positions when it comes to transplantations than we are veterinarians. I also think that the number of primate species are not to be considered homogeneously. So, baboons are not rhesus, are not cynos, are not African greens and are not chimpanzees. I think in general we have underestimated how different some of those changes are. Therefore, I am also concerned that if we set unreasonably high barriers for these tests to -- for example, six months to one year survival in a non-human primate, those are the kinds of numbers that have been put out, have been supported, again, by the International Society for Heart and Lung Transplantation -- that we are basically forcing companies or forcing the whole field to aim at a barrier that, as yet, has not been well documented as existing in human patients.

If a small number of human patients were done, if the immunobiology in the human patients exactly matched the immunobiology that we are seeing in the non-human primates, let's say in a specific non-human primate model, then actually you could direct the whole field back with confidence to the kinds of investments and time, resources and money to do those kinds of studies. However, is everyone sure that when you did a human study that the immunobiology would be so clear? What if there was another mechanism, slightly different, that you would then spend the next five years in the non-human primates aiming at this goal we have set, and miss that extra mechanism that has never been tested. I have some real concerns about this, and perhaps it will be something that we will have a chance to discuss.

One last comment, it is very nice to have the idea that we will have mechanical blood glucose sensing and we will have mechanical pumps delivering insulin, and I think those are very worthy goals. I think

Hugh may have gone a little too far saying that xenotransplantation of islets is therefore taking a second burner to developing these things. Insulin pumps are still carrying around these little plastic boxes with a needle going into the subcutaneous tissue. I just don't see that as being an ideal target for the future, when cell transplantation, if it could be protected, would be more physiologic.

DR. AUCHINCLOSS: I don't mean to suggest for a second that a closed system insulin pump sensing system is the ideal outcome. As I said in the beginning, I would imagine a long period of tension between the technology and the biology of organ replacement and tissue replacement. Thank you very much.

DR. GROESCH: Thank you very much.

[Applause.]

DR. GROESCH: Our next speaker is Dr. David White. He is the Novartis/Stiller Professor of Xenotransplantation at the Robarts Research Institute at the University of Western Ontario. David is going to talk to us about preclinical animal models and what we have learned from those.

Agenda Item: The Science of Xenotransplantation: Pre-Clinical Animal Models.

DR. WHITE: Thank you very much. I am clearly, as you can see from the slides, one of those unreasonable men, in that I have been committing myself to trying to solve the problems of xenotransplantation by changing the donor. I really believe that our ability to change the donor species is a major opportunity for not only the future of transplantation but actually, if you think about it, the future of therapeutic medicine in general.

What I am going to talk about for the next 15 minutes or so is the question that has really already been raised. What sort of preclinical studies should we be doing in order for us to have some reassurance that xenotransplantation would be of benefit to our patients in our first clinical trials. In order for me to do that, I need to take you through a few of the steps that are actually involved in the genetic engineering of the donor species and, in my case specifically, the pig, which like Alexis Carrel, I would recommend to you.

As an illustration, I will use the data that we generated in producing those pigs, whose organs are resistant to hyperacute rejection. As you have already heard, basically what we did was we took complement regulatory proteins from humans, illustrated here by the little flag with the H, and those flags tell human complement not to attack the human heart. Pigs, of course, will have these complement regulators, but they are pig, and they tell the pig complement not to attack the pig heart.

The trick that we used was simply to put the human flag into the pig, so that now it has both the pig and the human complement regulators. The technology that we used to do that was what I now call the standard old-fashioned transgenic technology with a very small needle and a very steady hand. You micro-inject the genes for those flags -- in this case the decay-accelerating factor or DAF. When you do that, and that cell divides, the pig chromosomes break. There are repair mechanisms in place that will zip up the pig chromosome and, if you are lucky occasionally, you will get the gene that you have put in, integrated into the pig genome and there you have a transgenic pig.

The question has been raised, is this now a pig or is it actually a human being. I always like to show a picture of a transgenic pig, just so that you can see for yourself, still, all pig, and I should say performs in every way and function exactly as a pig. I just show you one transgenic pig. Actually, in order to

produce the line of transgenic pigs that we use, we had to undertake this process 79 times. We produced 79 different transgenics because, of course, it is entirely random.

Hugh Auchincloss has mentioned to you briefly homologous recombination. In fact, the world moves on. With the advent of Dolly and nuclear transfer, we now have an enormous opportunity to make the field move that much faster. Very briefly, if I can just explain the process to you, what happens is that you do all your genetic engineering in the test tube in the laboratory. You start out with a line of fibroblasts. You then undertake this knockout process in cells. You select your target. Now what you do is, having got, as it were, the cell that you like that is flavor of the month, you can then take an alloctye from a pig, remove its nucleus, replace it with the nucleus that you have genetically engineered, and produce a clone of new transgenic pigs, now on a very tight controlled basis. You can select here for extremely rare events, one in a billion, one in ten billion, that sort of thing.

Now, that technology sounds a bit science fiction. Of course, we know about Dolly the sheep. Actually, in the last six months, two different groups have succeeded in producing pigs, albeit not with homologous recombination yet, but producing pigs using this technology. It certainly is only a matter of time -- and I would suspect months rather than years -- before we see the first offspring of pigs actually produced using homologous recombination. We are going to have a lot of animals that need to be tested before they can be put into clinical trials.

Here is the conundrum. Chairman Mao once said, the Chinese are not allowed in the water until they can swim. Of course, how do you prove that you can swim? You jump in the water. On the other hand, Confucius say, a wise man does not test the depth of the water with both feet. So, we clearly are going to have to have some, if you like, toe-dipping process. The toe-dipping process that I think most people accept is to actually get survivorship in non-human primates.

Why use non-human primates? Well, the major reason, of course, is that only the old world monkeys and the great apes are negative for this gal sugar that you have heard about. So, they are the only species, with the possible exception of birds, but they are quite immunologically different. They are the only species that are going to be immunologically appropriate for man. The other thing is, of course, that primates are quite widely accepted as a relevant preclinical model for a whole range of different clinical trials. So, if we are going to select a primate, the first question we have to ask is, does the transgene actually work in the primate. Remember, it is a human gene that is going into the pig, not a monkey gene.

We did this experiment some time ago to actually ask this question about one of the transgenes, the DAF. You can see, with the human immune system, the transgene works extremely well. You get 84 percent down regulation of the immune system. With the cynomolgus monkey, not quite so good, 72 percent. Baboon, it is actually not statistically different, but marginally worse, and the rhesus is useless.

We actually interpret this data as the fact that the human transgene is cross reacting more and more poorly with the different species. That may not be the correct interpretation of that data, and actually I think we need to revisit that study with a fresh eye, as you will see in a moment. Given that data, however you interpret it, the model that we use and that many of our collaborators use, is either to put kidneys into the cynomolgus monkey -- they are really quite small crabbington monkeys from the Philippines.

We started out putting heterotopic -- that is a non-life-supporting heart -- into those monkeys, but then realized that they were too small to have the autotopic, the heart in the correct position. So, we switched to baboons and more recently have actually used the life support for what you might call the proper heart

transplant.

The question has been raised, what my colleague, John Warwick(?), calls the comfort factor. This is the question that this committee is going to have to answer. What is your comfort factor. What results from preclinical research justifies the initiation of a clinical trial. Are the criteria going to be the same for organs themselves? Actually, how valid is the pig to primate model as a surrogate for man.

The question that has been raised is, what length of time should these organs survive in man, three months, six months, a year, three years? Pick a number. Actually, you don't have to pick a number. It has already been done for you because we have historical precedents. People have been testing a wide variety of immunosuppressive strategies for allotransplantation, primate to primate, monkey to monkey. I have done this exercise for you, but you can do it for yourself. You just go to the literature and you ask yourself the question, what survivorship did the allografts have in monkey studies.

This happens to be heterotopic heart allografts. It is probably the easiest of the models, non-life supporting. These are the median survivals plotted here, and the ones in sort of purple never made it into the clinic, and the ones that are in yellow are currently in clinical use, a range of different treatments. The date of publication is along the bottom there. You can see that, surprisingly, many of these median survivals for these treatments are surprisingly low, 40 days, 50 days. There is one up here, 160 days, but that is not used clinically. So, you actually have some guidance. I guess the guidance is what Hugh said and that is, it is more about fundamental biology than actual length of survivorship in the monkey.

So, what can we learn about the fundamental biology. Well, our current results have shown, just to compare it with the allograft, 78 days for kidneys, 99 days for the heart, and up to 39 days for the orthotopic heart, and I will show you that data in a bit more detail in a minute. It is quite nice to be able to show a picture of a pig kidney that supported the life of a monkey for 78 days and you can see it is still actually a kidney in very good shape. The down side is the monkey from which it came is dead, because it got an infection from the immunosuppression that we were giving it. So, the problems clearly aren't solved.

Using immunosuppressive drugs in primate models is difficult. The question is, can you really extrapolate these to man. You have actually seen the data from the primate allografts and you know you can't, because these drugs give many years survival in the clinic. We have to use different doses in primates. They actually have different toxicities. Primates have a different infectivity spectrum, and actually, many of the monoclonals can't be tested on primates at all because of different specificities.

The immunosuppression that we have used is essentially the immunosuppression that is used for allografting, which is cyclosporin A, some steroids and another agent, and I will show you the other agents in a minute. We do one thing quite differently. That is, we have introduced a cyclophosphamide induction regime. At the time of grafting of these pig organs into the monkeys, we give four days of cyclophosphamide, what my old boss used to say was the window of opportunity for immunological engagement. That clearly has a major effect on the outcome of the results.

Here are the results and I think they very adequately illustrate the wall that Hugh was talking about. It really doesn't matter what the third agent is. They are listed there. You can see the results. They are all pretty much identical. Median survival, I suppose about just over 40 days, if you lump them all together.

So, now, the biological question. Why do we hit this wall at 40 days. What is not happening here that is happening out there. The standard answer is, of course, the graft is inducing this anti-pig antibody,

probably anti-gal, and slowly and inexorably the grafts are lost as a result of that antibody. When we measure the antibody in these animals, it is pretty unimpressive. It is there, a little bit, but it is present here just as much as it is present out there. Of course, we are measuring the antibodies in the serum, and you can make the case that the antibody that is actually sticking to the graft, is it a different quality, a different affinity, a different avidity, or it could just be a slow progressive option(?).

I want to suggest to you an entirely different notion. Now, when you think about the results that we have had from these transplants, there is a whole range of reasons why they could be failing, and I don't have the time to go into them in any detail. Of course, the drugs that we used were developed for human beings and not for the monkeys. Even simple things like antibiotics are not developed to treat monkeys. The microbiological background of these animals is very different from that of man. We are very limited in the analytical reagents we can use. We can't even isotype immunoglobulins in these animals.

Diagnostic procedures in these monkeys are quite difficult. For some reason or other, the hospital is loathe to just going and let us do a DTPA or a CAT scan or something on one of our monkeys. Even different primate species, the baboons and the cynomolgus monkeys, behave entirely different, particularly with regard to the drugs that we give them. Using monkeys is ethically sensitive, particularly from the culture that I have just left.

I want to concentrate just on one aspect. I have already mentioned it. Remember the transgenes that we use are human and not monkey transgenes. We asked ourselves the question, could it possibly be that these monkeys actually make antibody against the transgene. So, we started a program -- and this is by no means complete yet -- where we measured the antibody against that little flag, against the DAF transgene. We then asked the question, how did the organ which carries this transgene function relative to the production of that transgenic antibody.

You can see what happens. This is a measure of renal function. When the antibody against the transgene appears, the graft rejects. Now, this in all probability is not going to be the only reason why we have rejection, but it clearly is a major fault of the model, because humans won't make antibody against DAF, because it is a human protein, but the monkeys will.

Now, you have been told that this particular manipulation eliminates hyperacute rejection, and by and large, it does, but it is not absolute. In our own experience, we have seen perhaps eight or nine percent hyperacute rejection in baboons, less in cynos. A colleague, using the same pig, Rafael Manes(?) in Spain, when he did transplants into 50 baboons, found six of them had hyperacute rejection. He was kind enough to send the serum samples from those six hyperacute rejections to our lab, and we measured the antibody against the transgene before the transplant had ever taken place. We found that, in all six hyperacute rejectors, that indeed there was antibody present against the transgene already. He sent us some of the ones that didn't hyperacutely reject, not all 50, only four. You can see one of them actually has antibody. So, it clearly isn't an all or none phenomenon.

I think that may give us a hint as to one of the traps to look out for when we are looking at these preclinical models. It is inappropriate antibody response to these human transgenes is going to limit the value of non-human primates. Clearly we recommend that you at least measure them.

Now, from what I have said, you may think that I don't think much of the value of using these preclinical models for testing xenotransplantation. That is not true. They certainly have an important place. They have an important place really in asking fundamental biological questions, questions about physiology.

I will give you an example. One of the questions that we wanted to know is, when you have one of these transgenic pigs, they grow. That is one of the advantages of them. Whatever size patient you have, you can get a pig that is going to be the right size. Actually, some of them grow up to 500, 600, 700 pounds. So, the question we said is, if you take an organ from a transgenic pig -- in our case they are about two or three weeks old -- and you put that organ into a primate, does the kidney or the heart, does it know that it is now in a monkey or does it still think that it is in the pig and sort of grow accordingly, and would you get to a situation where you would have the kidney from a 600-pound pig in a four-and-a-half kilo monkey. That is the sort of thing you can address.

I will just show you what happens. If you look at the yellow line, that is the rate of growth of a pig kidney in a pig. When you actually measure the growth right after it has been transplanted, which are the dots, you can see for the first two or perhaps three weeks, indeed, the pig kidney does think it is in the pig. Then after that, it clues that it is in the monkey, and the growth rate stops. Those kinds of fundamental questions, I think, these non-human primate studies are absolutely vital for.

I couldn't finish without saying something about cell transplantation, because I think cell transplantation is probably going to be the way we see xenotransplantation entering the clinic. It has already been mentioned. Clinical trials are in progress and I think we can anticipate many more.

Again, you can use primate studies to test your cell therapy. This happens to be a study done by my colleague, Carl Groth where, when he transplants the islets into a monkey -- these are pig islets -- without any protection, you can see they get significantly damaged. If they have protection -- this happens to be SCL-1 -- you can see they are nice and clean at one week, which was when the monkey was sacrificed, and indeed, producing porcine insulin, which is known to work in humans. So, to conclude, I think that the pig primate model is essential for proof-of-concept studies. I think it is of value in survival studies, given the limitations of the model, some of which I have illustrated. Actually, I think it is of absolutely minimal values in defining the details of any immunosuppression regimes, and they can only be done really in the clinic.

In conclusion, if I can leave you with this thought, I think the pig, as a suitable source of organs and cells genetically engineered for man, is something to be recommended. I think the non-human primate is a difficult model for testing these organs but, as yet, we have nothing better. Thank you.

[Applause.]

DR. GROESCH: Thank you, David. That was excellent.

We are now a real committee. We are actually running behind instead of ahead. I think in the interests of time, if you could hold your questions to maybe afterwards and I think David will be around -- no?

DR. WHITE: I have to catch a plane, so if you want to ask me a question, now is the time.

DR. GROESCH: A question or two of clarification?

DR. SYKES: David, could you just clarify the epo, erythropoietin, issue that Hugh touched on in his talk? I would have thought that epo would cross react between pig and primate, mainly because it does between human and mouse, for example. Is this really the problem, or is it actually an immune response to porcine epo that is causing the lack of function?

DR. WHITE: Megan, I don't know. What I can tell you is, if we do a kidney transplant with bilateral nephrectomy into one of these monkeys, its hemoglobin collapses over a period of three or four weeks. Of course, it has had an operation, so it starts off dipped down anyway. If you give human erythropoietin, it does not. That is in essence the data.

Whether it is a question of the epo not working -- in other words, the receptors not binding it appropriately -- whether it is a question of the gal on the epo allowing it to be cleared for the system so that it doesn't work, or whether it is a question of the homeostatic signals that stimulate the induction of erythropoietin from the kidney in the first place, not working in the pig kidney, we don't know, but we are studying. You know, you can give human erythropoietin and you solve the problem.

DR. MENDEZ: Did I misunderstand that in the transgenic pig that you created, you used the human genome rather than the non-primate genome?

DR. WHITE: Yes, we used the human library.

DR. MENDEZ: Why not use the genome of the non-primate?

DR. WHITE: Most of the demand for transplantation is in humans, not in monkeys.

DR. MENDEZ: I know, but it would eliminate the --

DR. WHITE: We could sit down. We could identify the appropriate complement regulators in monkeys, probably different ones for different monkey species. We could produce the libraries. We could get the clones. We could make the pigs. We could then have a lovely pig that would work, perhaps, in a monkey because you have the appropriate transgene. How would that help you? It would be a different clone. It would be a different protein.

You might have moved forward a little bit but, at the end of the day, what you want to put into the human being is the one with the human protein and not the monkey protein. It may come to that. I mean, it will be five years and \$5 million worth of work, but it may come down to that.

DR. ALLAN: I have a question and comment to make. When you talk about the primate model -- and I agree that the physiology, some of the toxicities of the drugs can be far different than humans. The question I have is, when you do the pig to primate, you may be using much higher immunosuppressive therapies than what humans would tolerate. I don't know if you could address that. In the other realm that also suggests that if you do get some success in primates and, say, it is three months or six months, you still have to worry about even going to humans because you may be using such high levels of immunosuppressive therapy.

DR. WHITE: Two very brief points. The first is that we tailor our immunosuppressant specifically based on the clinical model. The blood levels that we give -- in the monkeys, I should say, the blood levels that we give for the cyclosporin A are pretty much the same as we give in clinical. They are a little bit higher. We run them at about 300 nanograms per ml. Humans run at about 200, 150. We do give those big heavy preconditioning regimes. There, again, cyclophosphamide is used in the clinic.

I think that the fundamental evidence is not this is too heavy for human beings. The fundamental evidence is, are all the animals coming down with infections. If the answer to that is yes, then clearly you don't want to go forward. I think that is the acid test as to whether you are over-immunosuppressing, is if

you are getting lots of infections. In some of our studies, indeed, we have.

DR. SALOMON: I am remembering, as chair of one of these committees, the nightmare of trying to make everybody press and unpress their buttons so you don't get the feedback on the microphones.

I think one of the things where Dr. Auchincloss was absolutely brilliant was in his insistence that we use these models to understand the immunobiology of xenotransplantation. I think that there is sort of a point counterpoint here that I didn't want to miss. What I was saying to Dr. Auchincloss is, are the models adequately validated. So, if we do spend years and millions of dollars working on them, then we could then move with some confidence and safety to humans. What Dr. Auchincloss is saying I totally agree with, that we need to study the immunobiology of it.

Part of the problem that has happened in transplantation is, because of our success with increasingly more potent immunosuppressive drugs in human transplantation, we went at xenotransplantation, at least part of our focus in xenotransplantation is, well, just keep throwing it different immunosuppressive drugs. Even if we don't understand what is going on, we will eventually find the right combination and, in the end, we got pretty close to over-immunosuppressing a large number of animals, and that has created a dynamic, David, that I know you have dealt with before.

I think all I want to say here again is, at some point, the dynamic between what Dr. Auchincloss said and what you said, whether the primate model is good or the primate model is bad, we are going to have to come back and deal with that directly and do that in highly reasonable scientific ways. We need to validate whether this model is valid for humans and we have to then say, okay, we are not going to do any more human trials because we have got a perfectly validated non-human primate model. If the answer isn't that, then we need to consider the alternatives.

DR. WHITE: The concept of validation of the model is absolutely critical, as many people here will know. There are lots of studies in rodents where you can get tolerance, you can get xenografts to survive indefinitely in the rodent model. Yet, as you move up to the higher species to the primate, clearly, that rodent model is not valid.

The issue that you raise is absolutely fundamental. Is it valid for the human. I actually am not sure that it is. I think it has a role in looking at the biological paradigms. I don't know that it is a valid model for the clinical trials. The reason I say that is the slide I put up showing you the historical data. Go and look at the historical data. See what happened in the primates and then see what happens in the clinic. I think you will find that the results are surprisingly different.

DR. VANDERPOOL: I think we sufficiently joined the issue and the issue is profound. This committee has the power to call back people. You may be here, hopefully, with Dr. Auchincloss, and we can hash this out over a significant period of time. In the meantime, we are facing lunch time without having heard from Jon Coffin. I am going to go ahead and call this discussion, to suspend this discussion for a later date. It certainly is at the key of what we should be about as a committee. We simply don't have time to really wrestle with it as we should and will at some future time. Dr. Coffin, we need you to speak.

DR. GROESCH: Thank you very much, David.

Our next speaker is Dr. Jon Coffin. He is a professor of molecular biology and microbiology at Tufts University. He will be talking to us about the infectious disease risks.

Agenda Item: The Science of Xenotransplantation: Infectious Disease Risk.

DR. COFFIN: Thank you very much. As was expressed by another speaker, I come with some trepidation because there are a number of members of this committee who know much more about some of the things that I am going to say than I, in fact, do. When the time comes to go back on a lot of these issues, you can do that internally, and you won't necessarily need to call me back, as with the other speakers.

I think one of the main reasons that, in fact, this committee exists and the xenotransplant subcommittee of the FDA exists, on which a number of us are members, is because of the concerns expressed a few years ago by several of us here, about the possibility of unique infectious disease risks that might be associated with xenotransplantation. I want to discuss, in the next short, actually non-existent, time available to me -- which means I guess I have infinite time available to me -- to go over some of the issues that are involved.

I am not going to give you many answers, but I will raise a lot of questions. A lot of these have come up during discussions that the xenotransplant subcommittee and other meetings that preceded that have had, and there has been some progress toward at least developing the tools to address some of these issues, and I will summarize briefly some of these aspects. I will talk about two different areas. I will talk first about exogenous infectious viruses, that is, viruses that are passed from individual to individual or from mother to offspring, in part one here, and in part B, I will talk about endogenous viruses, which are the aspect that gives rise to the most concern.

We think we know about exogenous viruses but I will show you, in fact, we have a little ways to go on that, but in principle these are infectious agents which are controllable by proper monitoring and culling of infectious individuals and breeding measures and so on and so forth. I do not talk about other kinds of infectious agents -- bacteria, fungi and so on -- not because they are insignificant, but because, in my opinion, which is highly uninformed, actually, in this respect, the issues are not much different than they are in other kinds of transplantations and also, as I mentioned, because I really don't know very much about these issues.

So, what is the infectious disease risk that we are concerned about? This was raised in a previous talk. There are actually two levels of risk. There is a risk to the recipient which, given reasonable control measures, we all believe, I think, that the infectious disease risk for the recipient of a transplantation should be less than allotransplantation. The point was raised that, in this respect, then, xenotransplantation would be a step forward in terms of risk.

The concern, and the real reason that we are here, is the potential risk to the public. That derives from the 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. I, and I think everybody who thinks about this, would agree that this possibility is quite remote. However, the potential seriousness of the consequences, and a number of examples from recent history, require us to give it a full and serious consideration.

Here are some examples from recent history that are well documented, and the mechanisms are fairly well understood. At least the first three of these probably all of you have heard of. The canine parvovirus, for example, is a virus that was originally endemic in cats in various places. That virus, by virtue of just a couple of mutations in its genome, allows efficient infection of dogs and quite serious infection of dogs, requiring the development of vaccines and so on.

An important aspect that I want to point out for all of these, and for all cases of emerging viruses, there are always two types of events that one has to consider. The first is, what is the event that actually allowed the infection of a new species. The second is, what are the events that allow that virus, once it infects an individual, to be transmitted from individual to individual and to eventually, if it can, cause a worldwide epidemic or epizootic, in this case. In many cases, both of these things are essential and, often, changes in conditions in both of these aspects are essential for a new public health menace, on a scale of epidemic or pandemic or epizootic or panzootic infection like this to occur.

In this case, there are two things that are involved. One is the mutations and the second is a rapid means of worldwide transmission. So, if you happen to soil your shoe in Sydney, Australia where this mutation might have occurred in some dog there, you get on a plane and end up in Vancouver and some dog comes along and sniffs your shoe, and he then -- you can get a similar transmission chain. This mutation, clearly, once it arose, in fact spread very rapidly worldwide, probably by almost exactly this means.

In the absence of airplanes and rapid ways of getting around, this mutation might well have died out locally and would never have been seen as endemic. An example of that kind of thing is ebola virus, where clearly, cross-species transmission is the important event. We don't for sure know the actual host. There has not been, so far, a means of getting this virus into a worldwide transmission chain. These very scary local outbreaks of ebola occur in Africa, but so far they have stayed there. You can imagine changes in this virus, however, that might make it more accessible to a worldwide transmission, for example, if it became slightly less virulent, so there is a much longer time between infection and disease.

HIV is another case, to make the same point. The two events, again, cross-species transmission from some African monkey, probably a chimpanzee, to humans, and access to a transmission chain. In this case, it is probably the second event that is the most important in terms of generating the worldwide pandemic of HIV. The cross-species transmission, many of us believe, was occurring sort of throughout history in Africa, and its changed conditions, improved transportation and other things, allowed this virus to spread worldwide.

An example many of you may not know about is a new avian mycosis virus, which actually is wreaking havoc among broiler flocks worldwide. This actually is a particularly scary one in this respect because, A, it involves retroviruses and, B, it involves an event that we worry about in terms of the curve, and that is the acquisition of a new envelope gene by recombination with an endogenous virus. Again, there is a requirement for a transmission chain to get this around, probably largely needle-borne transmission, using the same instrumentation to inoculate thousands and thousands of chickens at one time.

So, I will go on to talk briefly about exogenous viruses. The real point I want to make here -- this is thanks to David Onions and I believe published in a recent issue of *Xenotransplantation* -- he and colleagues have generated a very impressive list of the viruses that infect pigs and might be of possible concern in pig to human xenotransplantation. These are classified into five classes. The first of these are agents that are known to infect both pigs and humans, therefore, potentially, for zoonotic infection. I am not going to go through these lists except to note that there are some very familiar viruses -- influenza, rabies, West Nile is currently frequently in the news, eastern encephalitis and so on, some well known viruses, as well as a number of viruses that very, very few, except for veterinary virologists, actually know about.

Another class are viruses which are potentially capable of infecting human cells, although they haven't been known to infect humans. There are another 10 viruses or so in this class. There are also viruses that will not necessarily replicate in human cells, but might potentially be oncogenic in human cells, at least

under the right conditions, because relatives of these are known to be oncogenic in experimental animals, for example, polyoma viruses and certain kinds of herpes viruses. There are viruses that belong to families which are known to change their host range of pathogenicity, and there are a number of those. I don't expect you to be writing this down as we go along. I think you probably have copies if you are really interested. Finally, there is a class of viruses which are not themselves of danger to humans. They are considered a danger to humans but would indicate that there was a break in biosecurity, or that would be of severe risk to the flock of animals that you are trying to maintain. All together, these come to about 60 viruses in pigs that are well known.

I think I would suggest -- maybe John Allen could back this up -- that the number of viruses that we know for baboons is probably much less than that. It is not because there are fewer viruses in baboons, but because we don't know as much about them. This is an important reason for not considering these animals as sources for xenotransplantation, not to mention the fact that we can maintain pigs and we can have a much better opportunity to control these agents. This can be done by deriving breeding stock by hysterotomy, maintaining under gnotobiotic conditions, positive pressure, pest free, sterilized food, maintaining a rigorous health screening of staff that are handling them, so you don't bring influenza virus, for example, which infects the pig and then goes on to infect the recipient, and very close monitoring for infections of concern, using serology, perhaps PCR-based tests.

It is worth pointing out, however, that I listed 60 viruses. Many of these have not yet really had adequate tests developed. This is a big area of concern for the potential development of flocks of animals that are to be used for these purposes, and something that has to be ongoing along with the development of actual xenotransplant procedures. So, more than 60 infectious agents of pigs are concerned, for one reason or another. Considerable challenges in detection and control remain. All in all, however, risk of infection with viruses of this sort are considered to be less than with currently used allotransplant technology, given appropriate control measures.

Now we venture into more unknown territory in certain respects, and that is the issue of endogenous viruses. Retroviruses are unique among infectious agents. They are unique, in that during the regular course of infection, the genetic information for these viruses is turned into DNA and that DNA is regularly and necessarily conjoined with the cellular DNA to form a new gene called a provirus. All retroviruses do this. Most retrovirus infections are ones that are acquired and all cells in which retroviruses are infecting have derived these new genes which are basically the provirus of the retrovirus. Because of this unique property, they also have the property to occasionally infect the germ line of the host. They can get into a precursor to an egg or to a sperm, enter the DNA of that, and simply become a gene that will now be inherited by that individual's progeny and their progeny and so on forever afterward.

In all vertebrate species, and probably all invertebrates as well, probably all animal species, proviruses of this sort, remnants of old retrovirus infections that go back millions and millions of years in some cases, form a significant fraction of the genome DNA. We may, in fact, have more proviruses than genes. The counts on these are just coming out. The recounts are just being done. Once the chads are all sorted out that there is more provirus in our genetic information than genes. There is more of them than us, in other words. Fortunately, most of them -- in fact, all of them in humans, as far as we know -- are dead. They don't do anything and a few of them may even have some useful functions, but I am not going to get into that. So, they are derived by infection of germ line with exogenous retroviruses, and as I said, we carry remnants of such things that are at least 30 to 50 million years old, and probably much older.

Many, but not all, known groups of exogenous retroviruses -- as I say, retroviruses that we recognize as

infectious agents -- passed from individual to individual, have endogenous relatives. HIV is a notable exception. There is no endogenous relative for HIV known. Some of these actually do some good. One of the notable ways in which they do good in some well-known animal models, is that they confer protection against infection with related viruses, and that may be a selective influence that led to their being fixed at a fairly high rate in the genomes of our ancestors and the ancestors of all other mammals, at least. Many are old and defective. They have acquired numerous mutations, just because they have been sitting in the germ line not doing anything for so long.

Some of them, found in some species, including pigs, cats, mice and baboons, can yield infectious virus. A particularly large group of this is the type of virus called a gamma retrovirus. It used to be called a mammalian C-type virus. These are simple retroviruses. They have only a small number of genes as compared to HIV, for example, that include murine leukemia virus, until recently, everybody's favorite vector for gene therapy; feline leukemia virus, obviously an important disease of cats; gibbon aleukemia virus; and reticular endotheliosis virus, which is an important infectious agent in birds of some economic importance. They cause a wide variety of diseases. All of these have endogenous relatives in the genomes of mammals and many other vertebrates. Most of them are transmitted vertically from mother to offspring and can affect only newborns. FeLV is something of an exception to this, but many of these viruses do not transmit well from one individual to another, except from mother to offspring.

Viruses derived from endogenous proviruses are generally non-pathogenic and replicate slowly but some, at least, for example, murine leukemia virus, can become pathogenic by recombination with related viruses or by mutation. There are various kinds of mutations which can increase their replication capacity. When pigs were originally proposed as donors for xenotransplantation, it was already well known that pigs carried endogenous retroviruses of this group, and that, from many pigs or at least from many cell cultures from pigs, one could isolate, with some ease, actually, replicating virus closely related to murine leukemia virus and feline leukemia virus.

It is very distinct, but there is a very high level of sequence similarity to these viruses and virtual identity in terms of the overall genetic make-up. This is a fairly tightly related group. They are present as multiple proviruses, in all breeds of pigs that have been examined so far, including also wild pig species. They are highly polymorphic in location among different breeds and individuals. What this high degree of polymorphism means is, that when you look at at least two different breeds, the introduction of these into the pig genome probably post-dated the separation of these breeds, or at least post-dated the original species. Therefore, the probability that among these are likely to be ones that are biologically active is much higher, because they have had a much shorter residence time in the genome.

There expresses infectious viruses from many cell lines in primary cultures from a number of different tissues. They can be divided into three groups based on the host range and sequence, particularly of the envelope gene, the gene that encodes the ability of these viruses to bind to their receptor for infection. Subgroups A and B infect human cells relatively well. They do not replicate to high titers compared to the viruses that virologists like to use and study over the years, murine leukemia virus and feline leukemia virus in culture. Whether that means -- to some extent, that is likely to be associated with pathogenicity, but we cannot be sure that that always holds up perfectly well. Some of the most pathogenic viruses, important pathogens, replicate even much more poorly than these do, for example, human T cell leukemia virus. They have not been found as infectious viruses, nor have they ever been associated with any disease in pigs, unlike murine leukemia virus and feline leukemia virus.

There are actually a couple of studies, which I will mention briefly in a few minutes, that have shown that at least some laboratory animals can be infected with these, as well as cell lines. Even though you

don't see virus from pigs, low level viremia has been detected in some animals. There is considerable polymorphism, as I said, but at least six proviruses are common to all pigs, but we don't know what their infectivity is. This is important because if there is a lot of polymorphism in genetic location from one animal to another, and one can identify proviruses which give rise to infectious virus, then at least in principle one could design breeding programs to remove those proviruses, and greatly reduce the risk of cells from that pig giving rise to this virus.

Efficient isolation requires co-cultivation with a particular cell line with, as far as I know, the only negative pig cell line. So, these viruses replicate well on pig cells as well as, in some cases, on human cells. There may be some adaptation as virus is passed from pig into human cell, and actually that is a point well worth studying further, because that is very relevant for what might happen in the co-cultivation situation following xenotransplantation.

This just shows some data from a paper a few years ago from Jonathan Stoye and Robin Weiss' lab. This is a standard way of looking at endogenous viruses. It is a southern blot where you digest the DNA with a restriction enzyme and run it out on a gel. You then probe it with a probe that specifically recognizes viruses of one of these two groups and, where you get a different band on this gel represents a provirus that is very closely related to all of the other proviruses on the gel, but at a different location. This tests, not for the relatedness of these, but for their location in the genome. So, to a rough estimate, you can guesstimate the number of proviruses in a genome by counting the number of bands, and you can also learn about their distribution.

So, this is four different strains of pig in each case, four different breeds, including mini-pigs, which are being developed in some places for this purpose, and others are sort of standard meat pigs. You can see the numbers and locations, as given by the exact positions of these bands on these gels, varies considerably from one breed of pigs to another, but none is completely clean of either of these two. If you look, these arrows indicate bands that look like they are the same size in all of these gels, implying that there are at least some proviruses that are identical in all of these and could not be removed -- these could not be easily removed by a breeding program. In other cases, where you see these differences, you could imagine making crosses and so on.

So, there is, I believe, some effort in a number of laboratories to try to identify which of these proviruses actually makes infectious virus. It is completely doable, but a very laborious process, and then eventually, perhaps, to try to come up with breeding programs to remove them. The other thing one could conceive of doing, if you can get knockout technology going, is to directly remove them. In the course of removing galactose transferases, one could also remove proviruses using the same type of technology, once one had the exact sequence of the ones that you wanted to remove and the DNA that flanks them.

So, what is the risk of this to recipient and what is the risk of this to the public at large, who may come in contact with this person or may come in contact with contacts of this person and so on and so forth. The first point is we really don't know. So, the risk is unknown. That is to say, it is unquantified. We can say there is a risk, we can say what we think the risk might be based on the precedent we have from other viruses.

The risk to the recipient requires spreading infection, some sort of pathogenic mechanisms, of which we know a number of the retroviruses can avail themselves of. It almost certainly is acceptable, as in the case of the other viruses, and certainly in life-threatening situations, it would be as acceptable as allotransplantation, if not more so, in many circumstances.

Of much greater concern is the remote possibility also of generating a virus that could be transmitted from one individual to another. This risk may well vary with the nature of the transplant, where you would introduce relatively small numbers of cells. It is a rather different thing than when you introduce whole organ transplants. It is a rather different thing in terms of the exposure and the chances for the right kind of circumstances to occur, due to differences in the size of the transplant, the numbers of cells you are introducing, the extent of chimerism that is being created, the amount of time that these are in contact, the extent of immunosuppression and so on. All of these factors are likely to play in, but we don't really know how, because we don't know where we are starting from, still, in terms of numbers.

The risk is likely to be reduced actually -- here is the good side of natural immunity. It is likely that this risk is somewhat removed by natural immunity because the natural antibodies against the galactose antigens that we have been talking about are likely to be highly strongly neutralizing for these viruses, because these viruses have the same antigens on their surface that the cells do, for at least one round of infection. However, once the virus passes once through a human cell, all of that is removed, and they now have the human surface, and they are seen as cells in that respect by the recipient. However, measures to circumvent this response will actually somewhat increase this risk.

I want to point out, this risk never goes away, because it is unquantified to start with. No matter how many factors you divide it by, you still have unquantified risk at the end. At what point does it go to zero, or at what point does it become acceptable. Is it acceptable when we start or is it acceptable at the end. That is for you to struggle with.

One of the early attempts at this is what is known in the field as the Stoye scale, for Jonathan Stoye, a colleague of mine, and a close friend. He came up with this at one of the early meetings, to put a level of likelihood on the -- well, in the first place, to make it clear the chain of events that has to happen in order for there to be finally a spreading epidemic transmission, and then to put some sort of likelihood on these.

So, we have expression of infectious virus from the transplant. We are, in fact, quite certain that that will occur. Localized infection of host cells is probably likely to occur. Spreading infection in the host cell is unlikely. Persistent viremia, which is necessary to give rise, probably, to a real pathogenic consequence, to disease in the host, is very unlikely. A real disease, for example, lymphoma or immunodeficiency of some kind, the scale is very, very unlikely. Then transmission, you add another very, and then finally, a spreading epidemic transmission is very, very, very, very unlikely.

What one has to do is decide what the number is here and what the scale that goes with these "verys" is, and we have solved the problem of estimating the risk. This is probably some kind of a log scale, I would guess, but what the base for the logarithm is, I would not hazard a guess.

So, a number of tests have been developed. You may hear some more about these in subsequent talks, including serology, for example, a western blot for the major antigen of the virus, RT PCR-based tests for RNA in plasma or for DNA in lymphocytes, very, very sensitive assays for reverse transcriptase, a characteristic enzyme of the virus. If one is looking in transplant recipients, there is the problem of trying to distinguish the DNA that comes from infection of cells of the recipient from the DNA that is due to persistent pig cells in the tissue that you see -- that is to say, microchimerism. So, it is essential in such things to also use mitochondrial or some sort of specific pig DNA. For example, mitochondrial DNA is commonly used or centermeric DNA or something else, to detect this.

To date, as far as I know -- and maybe there is more now -- but I know of two animal models that have

shown some signs of infection by virus, or by following a myelotransplant, and I will mention those in more detail in just a second. A number of patient samples -- which I will mention in more detail later on, and perhaps a further speaker will talk about later on -- has been negative. The first of these, at least, that came to my attention was presented by David Onions in an FDA meeting about a year ago. I haven't seen this published yet. I don't know if it has been or not, but I couldn't find it in the literature.

This is eight guinea pigs that were injected with virus. So, there was no transplant here, a simple virus injection, of a million virions, some unknown number of infectious units of human cell grown PERV-B, although these were guinea pigs, so the natural immunity wouldn't be an issue anyway. There actually is some natural immunity problem in the other direction, in fact. All these became PERV antibody and DNA positive, but no RNA can be detected. This is interpreted to mean that there was a transient spread of virus. There was far more RNA and DNA than what was actually put into the animal. So, there clearly had been a transient spread and replication of virus for at least one cycle, but the infection was probably then suppressed by an induction of immune response. I don't know much more about this. Perhaps at a future meeting you could invite Dr. Onions to talk about this and some of the other issues he is expert at.

Another experiment, in which the senior author is actually on the committee, from Dr. Salomon's lab, was a model transplantation of pig islets into mice, immunodeficient mice. Then at various times, PCR was used to look for PERV DNA and pig DNA in various organs at various times after transplant. This group was able to find evidence for infection and persistent microchimerism in a number of organs in the pig -- and Dr. Salomon can expand on this at great length if you choose to ask him -- as late as eight weeks post-transplant. Again, I don't think there was any evidence for an ongoing fulminant infection in these animals at the time they were looked at, but there clearly is evidence that the virus can be activated, and can infect some of the cells in the host.

There is as yet no evidence, as far as I know, of any kind of pathogenic consequence either. In a study that was published about a year and a half ago, 160 patients that had been exposed to pig tissue or cells -- this is now in humans, what happens in humans -- were examined. Just the PBMCs were examined for PERV proviral DNA by PCR antibody. Again, in this case, no evidence for infection could be found, either by antibody or proviral DNA, given the limitations of the tissues and so on that were looked at, although they could find viral DNA that, because of, again, testing for mitochondrial DNA, could be attributed to the survival of pig cells for up to eight years after treatment.

So, what can be done to minimize the risks of this? This is actually a lot of discussion time at the xenotransplant committee. They have gone around this. Certainly, and I think what absolutely has to be done, is to monitor recipients for suitable evidence of infection or associated disease. Within the last year or two, tests have been developed which should be reliable for doing this, although using the animal models, I think, will be important to tell us where to look. We don't know for sure that this virus could get into PBMCs, although that was the tissue that was examined in the previous study.

Also, it is advisable to minimize the ability of these people to transmit infection, for example, by deferring them from blood donation, counsel them regarding transmission. These are clearly things that can, should, and I hope are being done in the context of these studies. The other things are more questionable, and I have the level of questionability indicated by the number of question marks. One can, at least in theory, identify active proviruses and remove by selective breeding or knockout. This would take a very long time. It is a complex process, but it is at least scientifically doable.

Monitoring of contacts is at least probably possible to some extent, but there are, as have come up numerous times in discussion, considerable ethical and practical problems, and this is maybe something

that you will have to chew on again. The issue of treating for the infection that you don't know has happened has come up. I have a great deal of trouble with this. For one thing, there is only one -- there are a couple of papers on this. There are only one or two of the antivirals that are active against HIV that are also active against PERV. One of those is AZT, which has a fair amount of toxicity over the long term. I don't quite understand how you can develop a treatment for an infection that you don't know exists, that you don't know whether or not it causes a disease. How do you approve it, how do you test it, how do you balance the risks. Such a treatment would probably have to be for life, given the microchimerism issue. So, I don't see this as a modality, but you may want to raise the issue again. If one could develop a transgene in pigs that would actually suppress PERV expression, that might be helpful as well, but I don't know how to do this.

This is my last slide, and this is sort of the hand slide. Depending on how many hands you have, you can consider the following kinds of factors in estimating risk. On the good side, viruses like PERV do not infect adult animals very well, and are generally transmitted vertically to immuno-incompetent, or immuno-immature offspring. However, there are a number of exceptions like FeLV and a few others, among this group of viruses. Endogenous viruses replicate poorly and have low pathogenicity in general. However, in some models -- for example, the GALV model I mentioned or in some murine leukemia models -- certain kinds of mutations or recombination with endogenous closely or distantly related proviruses, can restore pathogenicity and replication competency. There has been no evidence for human infection with these viruses, and certainly no evidence for disease, despite millennia of close pig-to-human contact in butchering and so on. This is a very good way to transmit zoonotic infection.

However, this is a novel kind of close contact, and the extent to which that can promote the different ways of introducing infectious agents remains to be considered and discussed. So far, there is no evidence for infection following xenotransplantation with several hundred patients that have been examined, but are we looking in the right place. Infection of at least some experimental animals has been seen. I will close with this and thank you for your attention.

[Applause.]

DR. VANDERPOOL: Dr. Coffin, traditionally, is very humble in the beginning but very articulate and stimulating as he moves along, with slides full of issues. One of the advantages we have, since our time is short, is that when we get down to identifying the issues involving safety and public health tomorrow with Marian Michaels and Bill Scheckler, we will revisit some of the critical points that you have raised.

Mary Groesch and I have matched thoughts here, and we think that our questions should continue for, at most, 10 minutes at this point. Then we will take a lunch break that will last until 2:20, since the public comments will be briefer, we believe, than that time slot gives us. Put down the need to be back pronto at 2:20, to begin this afternoon's deliberations.

But now, let's open it for questions for Dr. Coffin.

DR. SYKES: John, could you just clarify something for me? With all the endogenous retroviruses in the human genome, is there a fundamental difference between those of the human and the pig, such that they are all non-productive in the human? If not, do we not subject ourselves to the same risk of recombinant retroviruses unleashing infection only from allotransplants in immunosuppressed hosts.

DR. COFFIN: Or we have babies, for that matter. The fundamental difference is one of age. In many species -- pigs, mice, cats, chickens -- we can detect evidence -- there clearly has been, and in fact is

ongoing, a process of reinfection of the germ line by viruses that are in there. There are good viruses, replication-competent viruses, in the germ line that can go on, or there are exogenous viruses infecting that are still capable of getting into the germ line in these species. In other species -- humans, probably dogs and even some birds closely related to chickens -- that process does not seem to be occurring.

I think it is a matter of chance. Our evolutionary history, the evolutionary history of all mammals, is to have waves of infection of these viruses that leave behind this endogenous virus as a fossil record of this wave of infection, but eventually gets shaken off. Then, a new wave of infection can sweep through a species again. Humans probably just happen to be between these waves. One of our goals actually is to keep it that way. Mice are being subjected now to a current epizootic of these related viruses. Cats are, chickens are, just, I think, by chance. As far as we know, in humans, the most recent proviruses were probably introduced on the order of five million years ago. Most of the proviruses we carry are common to us and chimpanzees. There is a small number that seem to be uniquely human but seem to have been infected just after the human/chimpanzee split, which is on the order of five million years.

One of the things, actually, we are interested in finding out is whether or not there are, in fact, new infections. This is something my lab is working on. We clearly have evidence for some change in these proviruses. We don't yet know if we can see any kind of new infection, because some of these proviruses aren't so old that they have accumulated large numbers of mutations. Most of them have accumulated at least a few mutations that render them non-infectious, but the combinations are such that you might imagine that they could get together. We don't know if they have yet in humans.

DR. SYKES: If there are any that are productive at all, then theoretically the allotransplant situation should be particularly risky, because you are dealing with an immunocompromised host.

DR. COFFIN: If, in fact, the infection occurs and the infection has some pathogenic consequence. It could well be that these infections are occurring and do not have significant pathogenic consequence. It could also be these infections are occurring and are giving rise to consequences like lymphoma, that one is attributing to something else and actually hasn't looked very carefully to see if these proviruses are involved. That is absolutely true, that we haven't looked very carefully.

DR. SYKES: The potential for recombination should be quite enormous.

DR. COFFIN: The potential is there. That is something, as I said, my lab is intensely interested in learning about.

DR. KASLOW: John, in HIV, of course, there is a lot of evidence, whether you believe it or not, that although you may not see antibody after exposure to infection, you may see CTL and other evidence of cell-mediated immunity. Is there any evidence that PERV have epitopes that have produced or could produce CTL? Any analogies there?

DR. COFFIN: I know of -- maybe somebody else can enlighten me on this. I know of no CTL studies relevant to PERVs. I don't know if anybody -- I mean, we are still a long way from that, I think, in terms of studying these viruses. So, the answer is I just don't know.

MR. BERGER: You gave one example earlier, but are we creating a potential of creating a new disease by using a genetically altered animal?

DR. COFFIN: Well, the genetic alterations extend to very specific things, and particularly the

elimination of this gal antigen. I wouldn't say you would necessarily create a new disease, but you create more of an opportunity for the virus to infect, because the natural antibodies, we believe -- I don't know if this has actually been tested, this could be tested, I don't know if it actually has been -- that the natural antibodies would very strongly react against these viruses. This is known for murine leukemia virus, actually.

DR. SALOMON: Yes, the natural antibodies will eliminate PERV.

DR. COFFIN: And by eliminating that, one adds a slightly greater -- we don't know how much greater because we don't know how to scale any of these risks -- but must add a somewhat greater risk of at least one round of infection occurring from virus made from pig cells into human cells.

DR. VANDERPOOL: I think it is fair to say that the science of xenotransplantation, which was slotted into a one hour and 20 minute time frame, is just a jigger on the way to something that is much more important to imbibe in the future. We are planting seeds now, John, and we may need to bring you and others back, in order to really air these issues out with the latest data, if we are wrestling with certainly an advice of some kind toward the federal agencies. Of course, many of these experts know much more about these things than some of us on this committee.

Thank you so very much for this extremely stimulating discussion, and for all of you who have given talks to the science of xenotransplantation section.

[Applause.]

We will meet back in an hour at 2:20. Let's be sure to try to make that on time.

[Whereupon, at 1:17 p.m., the meeting was recessed, to reconvene at 2:20 p.m., that same day.]

AFTERNOON SESSION

(2:28 p.m.)

DR. GROESCH: Our first session this afternoon is public comment. I just wanted to say that I think this is a very important part of the meeting. We welcome hearing from members of the public. We have heard from speakers today and we will hear some discussion from members, but it is also very important to hear from members of the public. At each meeting, there will be time scheduled for public comment. We encourage people signing up in advance, just so that we can know and allot enough time for it.

Today we have two people who have signed up and they will be giving brief remarks, a few minutes each. Then we will open it up to the floor. If anyone does want to make comments, please introduce yourself and say what group or organization you are with, if that is appropriate.

Our first public commentor is one of our speakers, wearing a different hat. David Cooper is going to be making some remarks on behalf of the International Society for Heart and Lung Transplantation.

Agenda Item: Public Comment.

DR. COOPER: Thank you. I am sorry to speak again, but as I was going to be here, the society asked me to make a couple of comments. The president of the International Society of Heart and Lung Transplantation, Bob Kormos, about a year or so ago, wanted to have a white paper from the society on their attitude to xenotransplantation. I was co-chair of this committee and we did a fairly comprehensive

review of the literature and discussed at length how we felt xenotransplantation might contribute to heart and lung transplantation. We came up with this report, which I believe you all have a copy of.

The first point that I would like to make is that the committee, we particularly selected the committee with more than half the people on the committee who were cardiologists or pulmonary physicians or cardiac transplant surgeons, but who did not have any special interest in xenotransplantation, had had actually no background at all. Part of the initial effort was to bring them up to date with what is going on in this field, by reviewing the literature on all aspects of xenotransplantation. I was particularly keen to have people who had nothing to do with xenotransplantation, so that the report reflected a general opinion of members of the society, rather than just the enthusiasts of xenotransplantation.

Having reviewed all the literature and the discussion of the points, we came up with a number of conclusions and recommendations, which I won't go through, relating to what we believed the role that xenotransplantation may play. This was after reviewing possible alternatives, such as mechanical organs and gene therapy and so on and so on.

We also came up with some guidelines for those in research as to what we would expect them to -- what results we would expect them to achieve in the animal model, the pigs and non-human primate model, before we felt that one should consider a clinical trial. Harold Vanderpool briefly mentioned that this morning, that we thought there should be a fairly consistent run of at least 10 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 those animals going on to at least six months, and without any disability caused by the over-intensive therapy. Now, those of us who are used to looking after non-human primates felt that this was a fairly tough goal. Those who were not involved with non-human primates actually started out asking for one or two-years survival. They said they wouldn't want to put their patients through it unless you could show that it was achievable in animals. I think this shows quite a discrepancy between those who actually know the difficulties of looking after animals under these conditions and those who do not.

Finally, we hit upon this sort of compromise, which was felt by all of us to be a reasonable prospect. If you can get animals to three and six months without being too debilitated, then I think there is a very good chance that you will get patients out longer than that, because of the ease of looking after patients.

There were a number of interesting points. I at first felt that we should not include infants and children in any clinical trial. The pediatric cardiologists and the pediatric pulmonologists came back quite vehemently and said, you mustn't exclude them because they are going to die and their families are willing to accept sort of any risk. So, there were some things that opened my eyes about this, putting this together. So, I just draw it to your attention.

Our final conclusion was that we felt, with the present state of the science, that we were not ready for a clinical trial at the moment. We felt that we should only go ahead with the clinical trial when the science was ready, and also when questions of the potential of risks of infection to the public had also been looked into very carefully and experts had decided that the risk was minimal. I just draw it to your attention. It is a report by a group interested in this field and I think a very balanced report. Thank you.

DR. VANDERPOOL: Does anyone have questions to ask of Dr. Cooper?

DR. AUCHINCLOSS: I have been asked the question a number of times. What happens to the FDA subcommittee? Does it continue to exist, and what is its relationship to you and such issues?

DR. VANDERPOOL: I see what you mean by a separate question. Let's deal with that in just a minute. Any particular questions to Dr. Cooper? I had a couple.

David, one has to do with the international society saying that all clinical trials should be monitored by an international body that would coordinate the trial and disburse information widely, and the society would play a leading role in that respect. That seems as if that is a fairly extensive commitment, to be such a monitoring agency. What relationship would that have, for example, to national monitoring groups such as the FDA?

DR. COOPER: I think we felt that monitoring -- regulation in particular -- and monitoring has to be a national body. We felt it would be impossible to do it internationally. We felt that a group such as the International Society of Heart and Lung Transplantation should actually perhaps make results available internationally. It would be easier for them to coordinate exchange of information, or there should be somebody doing it. We are not trying to find a role just for our own organization. We felt that any results in one country should be available to people in another country so that the learning curve is shortened. We felt that regulation and official monitoring should be at a national level.

DR. VANDERPOOL: The second question is, as you know, which you have already articulated, the question of including infants and children in early trials, partly due to the Baby Fae worries and criticisms, is really quite controversial. On one hand, I suppose one could argue that their immune systems would allow for greater success than adults. On the other hand, you have the question of who goes first. We often assume that adults should go first. Do you have any further comments on the inclusion of children or infants early on?

DR. COOPER: I personally was a little bit against including children and infants, but was swayed by the pediatricians. Certainly there is some evidence that it may be easier in infants and young children than in adults. There is some recent work on ABO incompatibility that Hugh referred to, with the same sort of problem here. If you have an ABO incompatible transplant, you are more likely to reject it and undergo the hyperacute rejection.

There is some work recently from Toronto Children's Hospital showing that you can get across the ABO barrier in infants with heart transplants without really an excessive treatment, because their immune system has not yet developed these antibodies against the other A or B blood group antigens. Therefore, it is reasonable to think that you may be able to overcome the gal problem more readily in infants.

I think we should probably not rely on that and we should have evidence that we can overcome the problem anyway, even in adults. I do take the pediatrician's point that one shouldn't necessarily rule out infants in an early clinical trial.

DR. VANDERPOOL: Thank you. That is certainly a consideration to put on the list of ethical issues.

DR. MENDEZ: With regard to that ABO incompatibility problem in infants in heart transplants, perhaps if Dr. Leonard Bailey is in the audience, he might comment on that, or any thoughts on neonatal transference.

DR. BAILEY: I guess this is open. I am Len Bailey from Loma Linda. I was responsible for Baby Fae. We certainly made some errors with Baby Fae and perhaps crossing the ABO barrier was one of them. Her donor was a B, she was an O, and it was a fairly strong mismatch. There were other errors in her care that may have contributed to her death and to her early demise. I would be happy to come back sometime

and tell you more about that story, if you would like.

Having said that, it seems unreasonable to me to eliminate particularly the newborn infant from consideration as an experimental model in cross species transplantation. We have every evidence to suggest that there is a window of opportunity there that doesn't exist in people like myself, for the success of cross-species transplantation. We have, since Baby Fae -- she has left quite a legacy. We have done nearly 100 newborns with allotransplantations. They have the best survival in the history of solid organ transplantation with more than three quarters of them surviving out to 12 years. You can say that about hardly any other organ in existence. That is done with a minimum of immunosuppression.

We have, since Baby Fae, in the laboratory studied a number of cross-species transplantation in primate models. We have now survival out beyond two years with rhesus monkey into infant baboon using clinically applicable immunosuppression.

What we don't have presently are the infectious disease pieces that are going to be required by this panel and by others and the FDA. I am hoping for some support, some help by the federal agencies perhaps, and by private organizations, to help us probe the archived specimens from Baby Fae, a perfect example of the potential for transfer of infectious disease. Yet, those specimens have never been looked at. We have a number of specimens archived from donors and recipients of survivors of cross species transplantation, well on beyond the year, 18 months and now beyond two years.

We believe that concordant transplantation, at least, holds great promise for the newborn humans. I know there are others here who differ in their opinions about that. We have continued to stay focused on that issue and I will bring it before this committee in a formal way any time you like.

DR. VANDERPOOL: Thank you. That certainly raises an important issue for future discussion and certainly would warn any of us from making precipitous decisions about how certain problems in the past should determine what we should do in the future. Other comments?

DR. GROESCH: Dr. Auchincloss had raised a question. I think we might get some comments from Lily Engstrom from the Office of the Secretary. Jay, would you be able to address that?

DR. SIEGEL: Probably. It is our committee. The xenotransplantation subcommittee, for those who don't know, is an advisory committee to the Food and Drug Administration. It is a subcommittee whose members are not all a member of the parent committee, but it is a subcommittee of the biologic response modifiers advisory committee. It was formulated about somewhere in the four or five year ago range to provide us advice regarding xenotransplantation applications and policy development, including the guidelines that you will be hearing about more shortly.

There are actually a couple of developments, one being the formation of this committee, which I think call into significant question, as Dr. Auchincloss pointed out, what the role is of that subcommittee. The other is that the parent committee, which Dan Salomon chairs, the Biologic Response Modifiers Advisory Committee, we have shifted its focus and expertise over the last year or two to concentrate more on issues involving immunology and transplantation and microbiology, by no means a specific focus on xenotransplantation, but a lot of relevant expertise there as well.

I think those of us at the agency involved in this area are thinking that it is not unlikely that we may no longer need to maintain that as a separate committee. That said, everybody who has been involved in the formation of this committee, I am sure, is quite aware that it is very difficult to get an advisory committee

started and very easy to stop one. So, we have not made a definitive decision yet to end the role of that committee, and I think we want to wait. There are timing issues, if we are facing critical regulatory decisions, expertise issues and so forth, to see whether these committees will fully meet the needs we have. It is our hope that, in fact, they will and we should, over the next several months to a year or so, make a final decision in that regard.

MS. ENGSTROM: I just wanted to add to what Jay has just said. I think that it is very true that it takes a while to get a committee established and running, as witness the formation of this committee. Also, FDA has certain regulatory responsibilities. Therefore, in the process of carrying out those responsibilities and functions, there may be a need for them specifically with regard to special deadlines that apply to FDA products, for a group of experts to be assembled for that specific function.

Until I think we put it to the test in terms of how this particular committee will function and also the kinds of specific needs that FDA will have, I think that at this point in time the agreement generally, in terms of the internal staff discussions, has been that the xeno subcommittee that Jay just mentioned is probably going to be sort of dormant for a while, unless it is called upon to deal with a specific product that would be going through the FDA regulatory products, and the kinds of policies that pertain to the regulation of those products.

DR. SIEGEL: I guess I would add that, even if that committee disbands for the reasons you pointed out, the parent committee will sometimes deal with issues related to xenotransplantation. I would also like to assure this committee that we have a not-dissimilar relationship in gene therapy in general, with the NIH-operated recombinant advisory committee, as well as FDA advisory committees. I think that the charters of the committee are different, the roles of the committee are different. There is overlap of membership. I think that it should be quite possible to coordinate efforts rather than have any sense of inefficiency or conflict.

DR. GROESCH: The other scheduled commenter is Mrunal Chapekar. She is representing the advanced technology program at NIST, which is the National Institute of Standards and Technology.

MS. CHAPEKAR: Good afternoon. My name is Mrunal Chapekar and I am a technical program manager in the advanced technology program, or ATP, at the National Institute of Standards and Technology, which is part of the U.S. Department of Commerce. ATP funds for-profit companies to develop high risk innovative enabling technologies with high technical risk but have potential for broad national benefits. A list of all the ATP-funded projects is available on the ATP web site and the address is www.atp.nist.gov.

Some of the ATP-funded technologies pertain to the development of xenogeneic tissues and also cells for transplantation in humans. However, these projects involve only preclinical stage research. None of these projects involve clinical trials. Only in rare cases, ATP funds clinical trials at the phase I stage as a part of the ATP funded projects, and these trials require approval from local IRBs, NIST administrative review as a co-funding agency, and the FDA. The ATP awardees may conduct clinical research in the post-project phase, but these trials must go through the FDA approval process.

ATP is interested in commercialization of the ATP-funded technologies and realizes the potential of xenotransplantation. At the same time, it is aware of the public safety and other issues associated with xenotransplantation, and therefore fully supports the HHS efforts in seeking scientific review and public discussions and input on xenotransplantation. NIST follows current FDA guidelines regarding xenotransplantation and will follow any future statutory requirements, regulatory policies and statements

of Presidential policy imposed on, or adopted by NIH or any other federal agencies. Thank you.

DR. GROESCH: Thank you. Any comments or questions? Would anyone else like to make a comment?

DR. AUCHINCLOSS: Sorry, one other question for the committee. What is the current thinking about how you are going to deal with the fact that the viruses don't know national borders and your regulatory authority or the regulatory authority of the NIH, FDA, et cetera, does. In particular, we know that some other countries have come up with guidelines and regulations, et cetera, for xenotransplantation that, in some ways, are at variance with what currently exists for this country. Specifically, what kinds of interactions with other countries and how do we work out an international regulatory policy when nobody has the authority to do so?

DR. GROESCH: Well, we certainly have participated in discussions in the past and have been at meetings where we had international presenters, and talked about the different policies. A couple of years ago -- I think it was in 1998 -- the department sponsored a workshop on policy issues in xenotransplantation. We heard from a number of different countries about where they were in their policy making.

I think that our draft guideline has served as a model, even though it was still in a draft state, for a number of other countries. We will be hearing, I think, in future meetings, and have presentations from representatives of other countries. I think it is, as you said, very important that we all talk about this, because if it affects one person, it affects all.

DR. SALOMON: Can I make a comment to that?

DR. GROESCH: Yes.

DR. SALOMON: I very much agree with Dr. Auchincloss, and he and I have discussed this before. I think the bottom line is, right now, today, anyone can set up a pig, baboon, chimpanzee transplant program anywhere in the world, except perhaps in a very small number of countries where it might be considered illegal right now.

We know that this isn't a fantasy. We know that there are so-called rogue xenotransplantation programs going on. Dr. Cooper mentioned one in Switzerland. I know of one in Germany and two in Tijuana, Mexico. The bottom line is that I can do that. The bottom line is that one of my patients can get on a plane, go there, and get a chimpanzee, or a baboon, or a pig organ, tissue of any sort, get back on an airplane, come here, get sick, check into a hospital. I can't do any retroviral testing on them. I can't insist that they even tell me that they had a xenotransplant. If I know about it, I can't do anything. I have to provide care for them.

To me, I think one of the challenges of this group, if we are going to give advice to the Secretary, I strongly believe that one of the things we are going to have to grapple with is how we are going to deal with this internationally. I believe that the United States and some of our colleagues in Europe have an absolute duty to create a set of new laws, and to create a set of bodies that are going to deal with these issues straight on in the developing world, to protect this. Otherwise, all of this is for nothing. We can regulate ourselves beautifully and leave here at the end of the day feeling very comfortable, and the reality isn't going to add up.

MS. SHAPIRO: I agree with you, that is important to think about. In my comments tomorrow, I will talk about the international implications. I don't know that you are as helpless as you think you are, though. If you really do know that one of your patients got some xenotransplant and is infected and is a public health risk, then the public health laws of this country could be utilized at that point. Short of that, I think you are right. We are pretty helpless.

DR. VANDERPOOL: I agree with both of these comments. This is our first meeting and we have the real task ahead of us tomorrow in identifying these issues. We have, by no means, identified the issues by asking a few questions of some of the speakers.

Dr. Auchincloss' questions about the purview of the FDA committee vis-a-vis this one, to me, is very important. This committee has a learning curve that is fairly steep. What will this expertise be vis-a-vis the FDA subcommittees, and over how long a period of time.

Certainly these international issues would appropriately belong to a DHHS group. We may well end up tomorrow identifying this as one of the critical issues we need to pursue soon. I think those issues that we will identify tomorrow will depend, in part, on our learning curve, on what the issues are intrinsically, and what the agencies want to hear from us. So, we have some open doors that we hope we will close a little bit before tomorrow is over with.

MS. ENGSTROM: I want to make a couple of comments. Number one, I think the issue in front of us is a very real one. Those of us on the interagency working group on xenotransplantation has, in fact, discussed it. You are right, viruses do not carry passports. Therefore, when you are talking about a consenting regional boundary, that can happen very easily, in certainly the very mobile world we live in now. When you made your statement, Dan, the first thing I thought when you said rogue nations, it is very analogous to bioterrorism where you have rogue nations. Even if we have a nice body of laws, as Robyn pointed out, you can only apply them to those who are law abiding. Those who are not law abiding, I am not sure how to handle it. None of us pretends to know how to deal with it.

I do want to mention one thing. When we were talking about forming this committee, one of the questions that came up was, should not various international bodies, entities and foreign governments have a role or at least an opportunity to participate. Mary, you can probably respond to this much better than I, in terms of either invitations or extending opportunity to other nations that are thinking about xenotransplantation, giving them the opportunity to come and participate and make their voices and the sentiments of their governments known to our group here.

DR. GROESCH: We certainly extended an invitation to many of our contacts in other countries to attend the meeting. I think that we will be inviting some organizations to serve as like official observers here, some of the over-arching organizations like the World Health Organization and OECD. We are in regular contact with our contacts in, for example, Health Canada. They have a very active program here, and we can certainly have presentations from people, too.

Tomorrow morning we have another session of public comment scheduled. Someone did point out that it might be useful to be able to make some comments after we have had the issue identification session. Our session tomorrow is scheduled in the morning and we will certainly try to accommodate that, because some of the discussion that goes on may spur some comments. So, we will be opening up the floor for a little while tomorrow as well.

I think we should move on to our next speaker, who is Dr. Louisa Chapman, from the Centers for Disease

Control and Prevention. Louisa will be giving us an overview of the revised PHS guideline on infectious disease issues in xenotransplantation.

Agenda Item: PHS Guideline on Infectious Disease Issues in Xenotransplantation.

DR. CHAPMAN: The U.S. Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation provides guidance to xenotransplantation researchers, and to sponsors of clinical trials, on how to prevent or minimize the risk of infection associated with xenotransplantation, and how to control infections if they occur. The guideline was developed jointly by four PHS agencies, the Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, and National Institutes of Health. This work was coordinated by the Office of Science Policy, Office of the Secretary, DHHS.

The guideline was first made available for public review in a draft form in 1996. Written public comments and public discussions, both in the United States and internationally, as well as advances in science were considered in drafting the 1996 draft into its current form. The revised PhS Guideline on Infectious Disease Issues in Xenotransplantation was finalized and published on January 19, 2001, and it is now available at this web site, www.fda.gov/cber/gdlns/xenophs0101.htm. I also have a copy of it at my chair, if anyone wants to review it later.

The PHS Guideline emphasizes the importance of protocol development and review, of the informed consent and education processes, and of the development of adequate protocols and diagnostic tools for screening and for surveillance for infectious diseases.

The PHS defines xenotransplantation as any procedure that involves the transplantation, implantation or infusion into a human recipient of either, a, live cells, tissue or organs from a non-human animal source or, b, human body fluids, tissues or organs that have had ex vivo contact with live non-human animal cells, tissues or organs.

The guideline addresses only issues that are specific to xenotransplantation. It doesn't generally comment on other things that are standard in the fields. So, with regard to xenotransplantation research and clinical teams, they should include, in addition to other members who are obviously there, infectious disease physicians with expertise in zoonoses, transplantation and epidemiology, veterinarians with expertise in infectious diseases of the specific source animal, specialists in hospital epidemiology and infection control, and experts in research and diagnostic, microbiology, laboratory methodologies, all as active participants in the development team.

Clinical xenotransplantation centers should have expertise with comparable allotransplantation procedure, utilize accredited microbiology laboratories, and have the capability to identify human and animal infectious agents using both in vitro and in vivo methodologies. This could either be on-sight or through established collaborations.

Clearly defined methodologies for pre-transplantation screening for known infectious agents and post-transplantation surveillance for xenogeneic infections are essential parts of any clinical xenotransplantation protocol.

Investigators must submit an investigational application -- for example, an IND or another type of application -- to the FDA for review and for permission to proceed with a clinical trial. Responsibilities for the design and conduct of xenotransplantation clinical trials rests with the IND sponsor.

Issues in xenotransplantation clinical proposals are also subject to review by this committee, the Secretary's advisory committee. The protocol must also be approved at the local level by appropriate review bodies, which would include the institutional review boards, institutional animal care and use committees, and the institutional biosafety committees.

The informed consent and education process has some aspects that are special to xenotransplantation. The guideline also addresses those. In particular, it emphasizes the need for xenotransplantation product recipients to comply with long-term or perhaps life-long surveillance, the importance of an autopsy upon death, and the long-term need for access by appropriate public health officials to the recipient's medical records, regardless of the outcome of the clinical trial or the status of the graft.

The patient should be informed of the uncertainty regarding the risk of infection to both the recipient and potentially recipient's close contacts. The sponsor should ensure that counseling regarding behavior modification and other issues associated with risk of infection is provided to the patient and made available to the patient's close contacts, both prior to, and at the time of consent, and that such counseling remain available on an ongoing basis thereafter.

The recipients of certain xenotransplantation products and possibly certain of their close contacts should be actively deferred from donation of body fluids and other parts for use in humans. The issue of exactly who should be deferred and whether, and in what, context they should be included is a source of ongoing active discussions by one of the FDA blood advisory committees.

The Guideline describes a system of safeguards that conceptually is built around two key concepts, pre-transplantation screening to minimize the risk of xenogeneic infections with recognized pathogens, and post-transplantation surveillance for previously unrecognized xenogeneic infections. The concept of pretransplantation screening is nested in animal husbandry techniques that limit and define the lifelong exposure history of source animals. The risks that human recipients will be infected with identifiable infectious agents can be reduced to negligible levels by limiting the geographic origin and the lifelong contacts of potential source animals, combined with adequate pre-transplant screening of both the source animal, the colony from which it is chosen, and the xenotransplantation product itself.

Source animal facilities should meet the requirements for accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International. Operating practices should be consistent with the National Research Council's Guide for the Care and Use of Laboratory Animals from 1996, the animal welfare regulations as amended in 1985, and the Public Health Service policy on the humane care and use of laboratory animals.

Source animals for xenotransplantation should be procured from facilities that have a closed herd or colony of stock raised in barrier facilities that are optimally cesarian derived, and adequate surveillance programs for infectious agents. The feed components, including antibiotics or other additives, should be documented for a minimum of two generations prior to the source animal. The absence of mammalian materials, other than pasteurized milk products for early weaning, including recycled or rendered material, should be specifically documented.

Imported animals, or the first generation of offspring of imported animals, should not be used unless the animals belong to a species or strain that is not available in the United States. Imported animals must be documented to meet all standards for breeding and maintenance that are required for domestic animals. All animals introduced into the source colony, other than by birth, should meet the standards for animals raised within the facility and also go through a well-defined quarantine and testing period.

The source animal facility, the production process and the records are all subject to inspection by both the FDA and the USDA. Programs for screening and detection of known infectious agents in the herd or colony, in the individual source animal and in the xenotransplantation product should be developed by the sponsor, in consultation with appropriate experts, including oversight and regulatory bodies. As part of the surveillance program, routine serum samples obtained from randomly selected, representative animals should be tested for indicators of infectious agents relevant to the species, and the epidemiologic or potential epidemiologic exposures of that animal and that herd. All incidents that may affect herd or colony health should be recorded, for example, breaks in the environmental barrier of a secured facility, disease outbreaks or sudden animal deaths. An infection in one animal justifies a larger clinical and epidemiologic evaluation of the herd or colony.

Assays used for screening and detection of infectious agents should have well defined and documented sensitivity, specificity and reproducibility in the setting in which they are employed. The health of xenotransplantation product source animals should be monitored for life. When the source animal dies, a complete necropsy should follow, regardless of the amount of time that has lapsed between graft procurement and the death of the animal. In general, individual source animals should be quarantined for about three weeks prior to -- for at least three weeks prior to xenotransplantation product procurement. During this quarantine, individual source animals should be screened for infectious agents that are relevant to the particular intended clinical use of the planned xenotransplantation product.

The screening program should be guided by the surveillance and health history of the herd or colony. Microbiological isolation of a source animal or a xenotransplantation product during transit is critically important. Transported source animals should be quarantined for a minimum of three weeks after transportation and, again, appropriate screening should be performed during the quarantine.

All xenotransplantation products intended for clinical use should be as free of infectious agents as possible, and the procurement and processing of cells, tissues or organs should be performed using aseptic conditions in facilities which, themselves, are also subject to FDA inspection. Regardless of the rigor of pre-transplantation screening, post-transplantation surveillance will remain necessary to identify infectious agents that were transplanted with the xenotransplantation product, either because they were not known to exist -- an example of this is porcine hepatitis E prior to 1997, or Nipah virus prior to 1999. They were known to exist, but diagnostic tools were inadequate to detect them. The obvious example here are prions, or they could not be removed from the xenograft. At the time that would include primarily endogenous retroviruses.

Recipients should be routinely evaluated for adverse clinical events potentially associated with xenogeneic infections throughout their lifetime. Diagnostic assays and methodologies for surveillance of known infectious agents from the source animal must be available prior to the initial of clinical trials. The sensitivity, specificity and reproducibility of these testing methods should be documented under conditions similar to those that will be employed in the xenotransplantation procedure. Laboratory surveillance should be conducted for evidence of recipient infection with xenotropic endogenous retroviruses. Xenotropic, I am not sure if that term was used earlier, but it just means endogenous retroviruses that are capable of infecting cell lines from other species.

Laboratory surveillance should be conducted for evidence of recipient infection with xenotropic endogenous retroviruses, as well as any other infectious agent known or suspected to have been present in the xenotransplantation product. When the infectious agents of concern have similar human counterparts -- an example here is human CMV and baboon CMV -- assays that are able to distinguish between the two should be used in the post-transplantation laboratory surveillance.

The appropriateness of infection control measures should be considered at the time of the transplant and re-evaluated after each readmission and each health care contact. Archiving of acute and convalescent sera obtained in association with acute, unexplained illnesses should be performed when appropriate, as judged by the infectious disease physician and/or the epidemiologist.

Biosafety level 2, or BSL-2, standard and special practices, containment equipment and facilities should be used for activities involving clinical specimens from xenotransplantation product recipients. Particular attention should be given to sharps management and to bioaerosol containment. BSL-3 standard and special practices, and containment equipment, can be employed in a BSL-2 facility when propagating an unidentified infectious agent isolated from a xenotransplantation product recipient. These are very similar to the current guidelines for dealing with HIV or potentially HIV-infected specimens.

The sponsor should work with the occupational health service and with the infection control program in each clinical center to ensure that a comprehensive occupational health service program is developed to educate workers regarding the risks associated with xenotransplantation and to monitor for nosocomial exposures and possible xenogeneic infections in workers. The sponsor should develop protocols for the collection and archiving of sera collected from potentially exposed health care workers prior to the exposure to xenotransplantation products or to xenotransplantation product recipients. These will serve as the baseline specimen for comparison with a serum collected following any potential nosocomial exposures.

The serum and specimens should be maintained for at least 50 years from the time of the xenotransplantation, despite any changes in employment of the health care workers or discontinuation of the xenotransplantation procedure at the center. Systematically archived biological specimens and record keeping that allows rapid and accurate linking of xenotransplantation product recipients to the individual source animals are essential for public health investigation and containment of any emergent xenogeneic infections. The sponsor should maintain a cross reference system that links the relevant records for the xenotransplantation product recipient, the xenotransplantation product or source animal or animals, the animal herd and the animal procurement center, and any significant nosocomial exposures, including documentation of the relevant infectious disease screening and surveillance programs. Again, the sponsor should maintain these record systems for at least 50 years beyond the date of the transplant.

Aliquots of serum samples collected at animal facilities during routine surveillance and specific disease investigations should be archived and made available for public health investigations, if necessary -- if the investigations are necessary, I mean, not if the archiving is necessary. Source animal biologic specimens designated for Public Health Service use should be archived at the time of procurement of the xenotransplantation product. Biological specimens obtained from the xenotransplantation product recipient, and designated for public health investigation, should be archived prior to, and at periodic intervals, after the xenotransplantation procedure.

In the event of the death of the recipient, snap frozen samples, frozen at -70 degrees centigrade, paraffin-embedded tissue and tissue suitable for electron microscopy should be collected at autopsy from the xenotransplantation product, and from all major organ systems that are relevant to either the xenotransplantation procedure or the clinical syndrome that resulted in death, and these should be archived as well.

Again, all archived specimens should be maintained for 50 years, and the written material submitted for review by this body, by the FDA and by the local review body should justify both the types and the quantities of biologic specimens that are taken from storage in association with each proposed

xenotransplantation procedure.

Now, I put this slide in just as a reminder that the guideline that I have been talking about, although the focus of a great deal of work, is part of an ongoing and evolving matrix of safeguards that are intended to maximize the safety of the public, as xenotransplantation moves from laboratory research into clinical trials. I have focused on -- I have tried to summarize the highlights of the document, but there is much that hasn't been discussed. I thank you for your attention and open the floor for questions.

DR. GROESCH: Thank you very much. Are there any questions for Dr. Chapman?

DR. SCHECKLER: I have a question. Relating to this archival surveillance, if you will, of materials and the lifelong surveillance of patients, is there any parallel in human allograft, in terms of worrying about retroviruses in this very long list of concerns that were raised this morning about different types of unknowns? Is there any parallel in what is currently being done in human allograft transplantation?

DR. CHAPMAN: The transplant physicians and surgeons in the audience can probably answer better. I am not aware of any parallels with allotransplantation. In allotransplantation, most of the time we know what the risks are. Although we add to the list periodically, like we thought we knew what the risks were of blood transfusion before 1982, there is still some precedent there.

In determining this 50 years, the things that were taken into consideration by the interagency working group were precedents for record keeping by OSHA, precedence for maintaining tissues in storage, like the American type culture collection, and the incubation period of known pathogenic persistent viruses that have clinical latency periods and are endemic in human infections. This includes HIV, which has a latency period of about 10 years, HTLV, which can have a latency period of actually 40 to 60 years, hepatitis B, hepatitis C, which can have latency periods, again, measured in decades.

The 50 year is, first of all, an initial benchmark. This guideline document itself, even though I referred to it as the final form, like all aspects of policy here, are living and evolving policies. This is an evolving document. The initial draft published in 1996 talked about storing these indefinitely. The public comment was very loud on the fact that that was not realistic. In this version, we talked about 50 years based on the considerations I have just described. The expectation is, of course, that that will be under continual scrutiny and review and may be foreshortened before the 50-year period, or may be prolonged at the 50-year period.

DR. SCHECKLER: My main point here was, we are exquisitely concerned about the potential infectious disease risk or other unknown consequences of xenotransplantation. Shouldn't we be equally concerned about allotransplantation? Do we have something to learn from what has been done there? Are we over-reacting? Is there a model that we should be thinking about? Are we under-reacting for allo and over-reacting for xeno? That is more of a philosophical question. Perhaps you don't choose to answer it.

DR. CHAPMAN: I don't know what the answer is. Now that I understand the thrust of your question, I can say that there are some precedents for this sort of record keeping, not to my knowledge in allotransplantations, but in occupations where people are routinely exposed to non-human primates. It is a routine part of many research facilities that employ people in contact with non-human primates, to store baseline sera and do periodic storage all along.

It is actually, in theory, a routine part of my agency. When I first came, I had to donate a baseline sera

that will be available for testing, if there is ever a question of infection I acquired on an epi-aid on an outbreak in Africa or due to laboratory exposure. There are precedents. More of the precedents are in occupational health than in allotransplantation.

DR. ROTROSEN: There is one loosely analogous effort that is funded by NIH, which is the registry for post-transplant lymphoproliferative disease, which involves long-term follow up, but nowhere near the extensive efforts we are talking about here in terms of specimen archiving.

DR. ALLAN: Just to get back to your question or a comment that you made, is the difference between xeno and allo -- and Jon Coffin pointed this out and I think you are familiar with this, too -- is that you are dealing with a previously unknown risk, which means a new introduction of the virus into the transplantation. Allotransplantation, you are probably not introducing a new virus. You are just transferring a virus from patient to patient. With xenotransplantation, you may be introducing a whole new virus, which could disseminate into the population. That, I think, is the major reason for the 50-year archiving. Is that correct?

DR. CHAPMAN: Yes, the concern is that it took us several generations of transmission of HIV for us to recognize that something new had come into the human population from simians. It is reasonable -- we thought it was reasonable to ask for storage for a long enough period of time for there to perhaps become a recognition that there was something that needed to be investigated.

DR. VANDERPOOL: I will make an historical comment. I think in certain ways this document is the result of the history of our concerns. If one simply read the report of the IOM committee and the Nuffield report, both published in the summer of 1996, and that is all you had, you would say, hey, this is very, very worrisome. We have got to take many steps, every conceivable safety measure possible, in order to move forward with this treatment modality that holds promise.

I think this is reflective of that concern and we haven't laid it to rest yet. We even went through a period when we had to call for a moratorium, when we found out that PERV seemed to be replicating itself in vitro. Historically, this is a reflection of very great concern, and desire to be just as safe as humanly possible.

It may appear to be overkill, for those who have not sat in the trenches a little longer, to feel some of those worrisome things come at us. Maybe I am wrong, Louisa. If I am, let me know. It seems to me that this is, in part, a product of history where we had data, we have had concerns, they haven't been laid to rest. Some of the data has not ended up as worrisome as we thought. Yet, data keeps coming. So, until we have greater assurance of greater safety, we are assuming that these types of mechanisms are necessary.

DR. CHAPMAN: Yes, conceptually I think those of us who have worked on the document think of these calls for record keeping and archiving for prolonged periods of time as sort of a very expensive public health insurance policy. Our hope is that, in fact, they will never be needed and 50 years from now people can criticize us for spending a great deal of money for no good cause.

DR. MENDEZ: Although not anywhere as close to this stringent, OSHA and HCFA do have regulation for archivings for all histocompatibility sera, for cadaveric allogeneic transplants. I don't know if it is five or 10 years. I know we keep ours for 20 years.

DR. SALOMON: The problem I have is, who is going to pay for this. This is one of these wonderful

things, and you just mentioned yourself, I think your quote was something like expensive insurance. The fact is that an NIH grant is typically three to five years. Biotech companies go every five to 10 years. The .com breakout kind of shows us what can happen there. An investigator can leave, decide to go on to some other area, et cetera.

I mean, on one hand, big multinational pharma companies is where you think that you are going to get away with this, because they are going to come back around with the next drug, even if they got out of xeno five years ago. So, you realize that you will be able to hold them to this sort of enforcement. I think we ought to be realistic here. A large number of xeno trials could go forward in circumstances where there is much, much less certainty who is going to fund these sorts of things.

You have to be really careful with this. If that were the case -- for example, if I wanted to do a xeno trial at the Scripps research institute, under this sort of thing, I would either have to sell myself off to a big pharma company -- forget a biotech company -- and why would you be forcing me to do that, or I would have to get insurance before I started the trial, so that I had enough money to archive the specimens for 50 years, even though I left the research institute 10 years later. I think there are some really serious, serious issues here that are not very clear.

DR. CHAPMAN: The original draft guideline in 1996 talked in terms of this archiving and record keeping all being the responsibility of the individual principal investigator. Again, this is a place where public response was very loud and very clear, with just the comments that you have and the argument strongly that, for this to be a realistic possibility for 50 years of archive, there would have to be some public responsibility for it.

We do, I believe Bill Raub described in his opening comments that this committee, this guideline, are all part of an evolving matrix of public health policy safeguards being put into place. One of the plans is to develop a central national xenotransplantation data base that will record a lot of the essential record information. That is currently in pilot form. It is not fully active yet.

We also have plans to try to develop some feasible plan for a central archive which will be, at least in part, publicly funded. That is still at the drawing board stage. We recognize the concerns that you have. It is in the plan. We just haven't gotten there yet.

MS. ENGSTROM: I want to add to the point Louisa made. This document really is an evolving document. There is nothing final about it. In fact, if you have read your charter closely, you will see that one of the tasks and responsibilities before you is that, over time, as we learn more scientifically and clinically about xenotransplantation, the guideline is going to be subject to change, and one of your responsibilities is, in fact, to revise the guideline as appropriate, over the course of time.

It may well be that the 50-year number may change. It actually may be extended or it actually may be decreased. I think we are erroring in the direction of being more conservative at this point in time.

DR. SYKES: Just a point of clarification. One of your slides, that xenograft donors should optimally be cesarean derived. Given that you can exclude so many exogenous viruses that way, are there circumstances under which you would envision not cesarean deriving? Why is it worded that way?

DR. CHAPMAN: It is worded that way to give latitude to the production facility and the sponsors, to justify the way that the herds are produced. There are lots of arguments for cesarean-derived pig herds. There are certain liabilities associated with them, particularly to the pigs. There are other species -- cows,

for example -- and cows are not, that I am aware of, currently a source of xenotransplantation products in clinical trials, but they have been in the past, where it is much less feasible to cesarean derive herds, and there may be other ways to develop appropriate levels of safeguard.

It is put in with that wording specifically to allow latitude for the individual circumstance, that we may not be able to envision clearly developing the guideline. It will have to be justified by the sponsor in terms of adequate provision of safety to the FDA before they will be allowed to proceed, and to the SACX before it will be allowed as an adequately screened and protected herd or colony.

DR. VANDERPOOL: Let's have one more question.

DR. KIELY: I have a very simple question, maybe not simply answered. I am curious to know, regarding the individual recipients, what enforcement did you envision in the discussions leading to this guideline, enforcement of compliance with the guideline?

DR. CHAPMAN: In terms of the lifelong surveillance and the responsibility to educate their contacts?

DR. KIELY: The responsibility of the individual to maintain records, to submit to autopsy at death, all those things.

DR. CHAPMAN: This is one of the issues my colleague, Dr. Spira, referred to, when he introduced himself as the CDC ex officio and commented on his particular concern with the potential for conflicts between the recommendations for public safety and the autonomy of the individual research subject. There has been a lot of discussion in many forums about enforcement potential, what we have, what we should have, whether we should have it.

The bottom line at present is that, in the United States and in the Public Health Service and in the U.S. government, we hold the autonomy of the research subject as central, as a central human rights issue in human experimentation. No one at my agency, and I think in the PHS, is proposing that that should be abrogated.

So, what do we have in terms of enforcement? We have an ability to screen and educate people beforehand and try to select, for the procedure, people who are likely to accept seriously this responsibility. We have counseling methods, and we have public health laws that allow us to invoke quarantine if an individual shows a clear and present danger to others. This is usually applicable in situations like smallpox, measles, chicken pox, infectious tuberculosis where you would have a pulmonic plague if you were able to walk around, where you have an easy way to casually infect the other people around you. These laws have not generally been considered applicable in the kinds of things we are envisioning here, where you may be talking about a long-term latent period of infection. We have not found incarceration, in this country, as an acceptable way to try to prevent, for example, the spread of HIV/AIDS.

The answer is that you have very little in terms of enforcement and want to think carefully about whether you want to put in any ability to enforce, something that can hold someone to a contract in the future, but they made it in good faith in the present, other than your ability to screen recipients for the degree of responsibility they feel with regard to living up to these requirements.

DR. VANDERPOOL: Again, this is an extensive set of issues that deserves more airing. The best we are doing, during these meetings, are identifying issues. Hopefully we will prioritize those. I think we

have identified several issues regarding enforcing long-term surveillance, involving the expense and the detailed regulations here, that we may deem very important to discuss as we go along, in part because this is a request by the federal agency itself.

Let's move on to the next important topic on the agenda.

DR. GROESCH: Thank you, Louisa. Our next speaker is Dr. Eda Bloom of the Food and Drug Administration. Eda will be talking about FDA regulation of xenotransplantation and current policy.

Agenda Item: FDA Regulation of Xenotransplantation and Current Policy.

DR. BLOOM: Good afternoon. The subjects that I am going to summarize -- and I am sorry that it will only be a summary -- include, once again, you are going to hear the definitions of xenotransplantation, some background. I am going to talk with you about how CBER in particular deals with xenotransplantation INDs and how we regulate it. I would like to briefly discuss our FDA advisory committees -- and there has been some question about those. I am going to also briefly summarize a few FDA guidance documents, a proposed rule that we have recently published on public disclosure, in collaboration with other HHS agencies, in particular, in regard to the national xenotransplantation data base, which Dr. Chapman has mentioned. Then I am going to summarize and tell you how you can get additional information from FDA. By the end of this afternoon, you will all have these committed to heart.

Xenotransplantation is any procedure that involves the transplantation, implantation or infusion into a human recipient of either, a, the life cells, tissues or organs from a non-human animal source, or b, human body fluids, cells, tissues or organs that have had ex vivo contact with live non-human animal cells, tissues or organs. The xenotransplantation products are the live cells that are used in xenotransplantation, or tissues or organs. The reason I mention this again is because this definition has a number of implications for FDA. The first implication is that, by definition, xenotransplantation encompasses a very broad range of products.

FDA is charged with considering the specifics of any application we get, and proposals from each sponsor, to determine whether the specifics of the application and the proposals adequately address the applicable laws and regulations, including those intended especially to address safety in phase I. You will hear more about clinical trials very shortly from Dr. Marzella. There is also, inherent in this definition, a need for continued public discussion of the risks posed by different types of xenotransplantation products.

What I mean by types of xenotransplantation products is shown on this slide. For example, you have heard extensive discussion this morning of whole non-human organ transplantation, because that is generally what is thought of when people think of xenotransplantation. However, as was also made clear, it also includes the implantation of non-human cells or tissues, and we do have ongoing clinical trials in those. It also includes the extracorporeal perfusion of human blood through non-human cells or organs.

As we heard from Dr. Collins earlier, in 1990, he was involved in at least one instance of ex vivo perfusion that helped his patient. At that time, FDA was not regulating xenotransplantation. Now we are. So, I hope you are under IND if you are still doing it. If not, you will hear from us.

It also includes the administration to human recipients of human cells that have been previously cultured ex vivo with non-human cells. I believe you will hear an example of that later by an industry

representative. The reason for including that is the concern that we know that non-human viruses can certainly infect human cells in cell culture, and those cells can then be transferred back to a human recipient.

Just as a brief background, in 1993, FDA published a document entitled, *The Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products*. In that document, we first mentioned xenogeneic cells as being covered by this policy, and therefore, regulatable by FDA. The first xenotransplantation product IND was received at FDA in 1994, and it was quickly realized, as you heard, of the unique safety concerns involved in xenotransplantation, including the transmission of xenogeneic infectious diseases to patients, but more important, the potential subsequent transmission to close contacts and to the public. At that point, there began a number of cooperative efforts among PHS agencies and outside agencies, and the draft PHS guideline that you have heard about was published in 1996.

There ensued a number of public meetings held by FDA, held by the Institute of Medicine and the Public Health Service. There has also been international concern and cooperation that you have heard about, to the extent that we have been able to carry that out. The FDA xenotransplantation action plan was created in 1998, making xenotransplantation the focus of the agency, and the development of a cohesive policy an important goal. The xenotransplantation action plan of XAP, as it is fondly known, has its own web site, shown here on the slide. Since that time, there have been several new FDA documents and, as you just heard about, the revision of the PHS guideline.

Within FDA we currently apply the existing regulations, which are found under Title 21 of the Code of Federal Regulations for all xenotransplantation products. Regulations have the force of law and this is where the requirements are applicable and where they come in. In reviewing xenotransplantation INDs, we involve large review teams, because of the complex issues that xenotransplantation encompasses. We need individuals with multiple areas of expertise and always have veterinary reviewers and consults on the review of such INDs. The review teams have to be responsive to new data.

As an example of that, you may remember, in 1997, when it was shown that pig endogenous retrovirus could infect human cells, all xenotransplantation INDs involving porcine sources were put on hold until the sponsors could provide information to show that they could screen their animals and test patients for infectious PERV. We also have an ongoing IND reviewer focus group in which we discuss new ideas, new data, and other issues that may arise through scientific developments or policy developments.

Now, almost everybody thinks, I hope, of FDA as a science-based agency. What you may not realize, but I would like you to, is that the Center for Biologics has a very important research component, that regulators are also involved in research. The research into the area of xenotransplantation has significantly aided in our policy development. Dr. Carolyn Wilson's findings that PERV could be activated from fresh porcine cells and then infect human cells had regulatory impact on that clinical hold that I just mentioned. Dr. Aretha Kahn's research on simian foamy virus had impact on a guidance document which we issued in 1999 that involved the use of non-human primates as sources of xenotransplantation products.

Now, as far as the FDA advisory committees, we have a significant history of relying very heavily on the advice of our advisory committees, in the area of xenotransplantation, of course, as well as other areas. The committees that have been involved specifically in xenotransplantation include Our Biologic Response Modifiers Advisory Committee, or BRMAC, and the xenotransplantation subcommittee that we have discussed a little bit this afternoon. We have also used our Blood Products Advisory Committee,

known fondly as BPAC.

Highlights of the recent meetings include discussions in June of 1999 and January of last year, in which the BRMAC subcommittee supported and accepted the definitions of xenotransplantation and xenotransplantation products that we are currently using, along with the PHS. In January of last year, the BRMAC subcommittee discussed a particular xenotransplantation product which is known as Epicell, in which human cells are expanded ex vivo on a monolayer of murine feeder layer cells. The feeder layer cells are irradiated, but they are still alive and still providing whatever it is that the human cells need to expand. They are derived from a very well-characterized cell line. The committee agreed that certain risk-based use of precautions would be appropriate for such a product, where a well-characterized non-human cell line may be used.

In January and March of last year, the subcommittee and the BPAC both recommended changes to a blood donor -- I call it a blood donor referral document. It is a guidance document that we will discuss again in a short while, but it recommended deferral and appropriate handling of certain blood derived products from xenotransplantation recipients and their contacts. This is just a list of the three documents. I am going to go by this particular slide quickly, because we are going to go into each of the guidance documents in more detail.

The first was published in April of 1999, entitled, Public Health Issues posed by the use of non-human primate xenografts in humans. This was issued by FDA to address concerns regarding the use of non-human primates for the source of xenotransplantation products. It was particularly issued because of the infectious disease risks based, in part, on historical data and concerns regarding non-human primates and the viruses they may carry, not to mention the timely findings that, timely at that point, that HIV type I probably originated from a chimpanzee. Moreover, non-human primates have close proximity to the feral state. You don't have long-standing inbred colonies of primates. Even when you do, the husbandry issues still are of concern. That is, the manner in which it is possible to maintain primate colonies makes it very difficult to meet the kinds of criteria that Dr. Chapman discussed, for example, that would qualify them as xenotransplantation sources.

This approach was accepted by other PHS agencies, the DHHS working group, and our BRMAC subcommittee. In that document you will see that the title contains the word xenograft. That predates the adoption of the word, xenotransplantation products. They are equivalent in that sense. In that document, FDA published certain conclusions. The use of non-human xenotransplantation raises health concerns within the scientific community and general public. Current data indicate that recipients, their close contacts and the public would be exposed to significant risk by the use of such xenotransplantation products, and that additional research and evaluation would be needed to assess and reduce the risks posed by the use of non-human primate xenotransplantation products.

We made basically three recommendations based on these conclusion. First, that a federal advisory committee, such as the current one, should address protocols and issues raised by the use of non-human primate xenotransplantation products. Clinical protocols proposing such products should not be submitted to FDA until sufficient scientific information exists addressing the risks posed by such products. At the current time, we don't believe that there is sufficient information to assess such risks. This latter statement would therefore make such protocols, since we would not be able to assess the risk, subject to clinical hold regulations.

The next document, the next guidance document, that I wish to discuss was issued in draft form in December of 1999. That meant that it was open for comment and is currently under revision. The

document recommended that -- and I am sorry, I don't have the title on this slide. I guess I passed through it before. It has to do with the precautions to prevent zoonoses and the transmission of xenogeneic infections through blood donations. Now, the PHS had earlier recommended that xenotransplantation product recipients not donate whole blood components including source plasma and source leukocyte, tissues, breast milk, ova, sperm or any other body parts for use in humans. This recommendation had been discussed at a previous advisory committee, a couple of them, regarding contacts with recipients. In 1997, the BRMAC subcommittee and, in 1998, the BPAC, both addressed this issue.

Oh, here is the guidance for industry. This culminated in our issue of *The Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and their contacts*. This was published late in 1999 and discussed subsequently at two advisory committees, both our subcommittee and the BPAC. The recommendations concerning xenotransplantation product recipients in this document, and certain of their contacts, are with regard to donor deferral -- that is, the deferral from blood donation -- and also in regard to the withdrawal and quarantine of blood products from such recipients and their contacts. It also suggests certain questionnaires that would have been added to the blood donor questionnaire. The document is currently under revision in response to public comment, in response to the discussions of the advisory committees, and will be re-issued again as a draft for comment.

The third guidance document is entitled *Draft Guidance for Industry, Source Animal Product, Pre-clinical and Clinical Issues Concerning the Use of Xenotransplantation Product in Humans*. This was published for comment a couple of weeks ago. It is basically consistent with the PHS guideline that Dr. Chapman has just described, but it provides additional detail in areas that are addressed by the guideline, for example, additional guidance on source animal characterization. One example is that the FDA guidance document recommends that donors of semen be qualified in the same manner as donors of xenotransplantation products, to maintain the integrity of the herd. It also provides additional guidance on patient monitoring and informed consent. An example of that is that FDA recommends that the informed consent be updated when knowledge is updated.

In addition, it provides guidance on new subjects beyond the PHS guideline, because the emphasis of the PHS guideline is on infectious disease issues. In addition, the FDA guidance provides recommendations on preclinical studies, on manufacturing issues such as product characterization that is not covered by the PHS guideline, and quality control in areas outside of viral contamination, for example. It also provides guidance on the development of a xenotransplantation manufacturing facility, and current good manufacturing processing issues, as they would impact on xenotransplantation. So, it is not a quick read, but it is full of information and advice.

The last document that I want to discuss with you is a document that is entitled, *Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation*. This is a proposed rule. It is not a guidance document, as the others have been. That means that, when it is adopted, it would be added to the Title 21 CFR and have the force of law.

It was published for comment on January 18 of this year in the Federal Register, and I have listed the docket number there, in case anybody wants to write us their opinions about this. By the way, if anyone would like copies of my slides, I would be happy to provide them. Just let me know. The proposed rule on public disclosure, as we refer to it, applies, as I have said, to xenotransplantation and gene therapy.

The reason these two areas are combined in this one proposed regulation is that they are unique areas of

clinical research with potential for unique public health risks, such as xenotransplantation or modification of the human genome, such as human gene therapy. Both areas of product development have histories of public discussion through the recombinant advisory committee of NIH for gene therapy, through the xenotransplantation subcommittee of FDA, through various other public meetings, publications, SEC documents, and so forth.

We believe that public availability of information regarding the development of these types of products would facilitate further public education, discussion of public health issues and, importantly to us, be able to involve FDA participation. As of now, our regulations are such that we cannot even acknowledge the existence of an IND if it has not been publicly acknowledged by the sponsor. Public availability would enable consistent public information throughout the life of an IND, so that every patient, family or public citizen who is concerned about xenotransplantation or gene therapy would have access to the same information.

This proposed rule does not pertain to patient identifiable information or trade secret information. These would not be publicly disclosed. Trade secrets would pertain specifically to production process. It requires the sponsor to submit to FDA the complete IND that they normally submit, as well as a redacted version. That redacted version would then be available in public docket for anyone to access, and it wouldn't involve FOIA requests. It would just be there.

The kinds of disclosable items that the rule proposes include product and patient safety data. The examples that I put up on this slide apply specifically to xenotransplantation. There are other examples in the rule itself that apply more to gene therapy. Biological activity and evidence for the immune response, or energy to the product, the results of product safety testing, including tests for infectious agents, qualifications of the source herd, source animal and source organs, tissues or cells. Information on how monitoring would proceed, or prevention of health risk to the recipient, close contacts and health care workers should all be included in the redacted version.

In addition, what would be publicly disclosable would be the name and address of the sponsor of the protocol, of the IND, the clinical indications for which the product would be used, a protocol for each planned study, sample patient informed consents, IND safety reports. These are adverse experience reports that are submitted to FDA so that the public would then see what kinds of adverse events are received or not. Certain information in the IND annual report would also be disclosable, including significant pre-clinical and clinical toxicities that are reported to the agency, evidence of infection, adverse experiences, and numbers of patient deaths.

In addition, the redacted version should include identification of the biological products and general description of the product features that may impact safety again. These include the source of the xenotransplantation product, the method used to procure and prepare it, impurity and testing for adventitious agents, what other products are used in its preparation, the herd, colony and individual source animal maintenance and surveillance records, and the biological specimens that are going to be archived. In addition, we would require that the regulatory status of the IND be disclosable; that is, whether the IND is active, inactive, withdrawn or on hold.

Now I would like to move to how FDA has been collaborating with the other DHHS components. You have heard a lot about this already today, including several areas, the guideline that you heard discussed, this committee itself, and the national xenotransplantation data base which, as you have heard, is in pilot phase. I am just going to have a couple of comments on the national xenotransplantation data base or, as we call it, the NXD. Again, I want to emphasize that it is in pilot, it is not ready for prime time, but we

are working on developing it, together with the other HHS agencies.

The purpose is to provide a means for rapid recognition, the accurate assessment and appropriate response, in the identification of an infectious disease agent or other clinical event associated with a xenotransplantation product that may have public health consequences. This is basically, I think I am describing a surveillance tool. The functions would be to identify epidemiologically significant common features among different events, to identify the rates of occurrence and be able to identify clustering of events. Such would allow for outcomes from xenogeneic infections, allow for the accurate linkage of these two events to exposure, so that we could actually connect any event that might be seen to exposure to a xenotransplantation product.

Another purpose is to provide a framework for the assessment of patient outcomes, to identify areas for laboratory and clinical research, and provide a data base for assessment of long-term safety. Now, we are constructing a data base in order to be able to maintain the records, as Dr. Salomon asked earlier, that we are currently asking that sponsors maintain. This kind of data base should allow us, if there were to happen the kind of event that we have heard discussed, which we have acknowledged is probably going to be -- well, it has got an indefinable occurrence, that that could be recognized.

In summary, the approach to regulation of xenotransplantation involves a comprehensive FDA agenda involving the existing regulations, regulatory and policy initiatives, multidisciplinary expertise and research activities. It also involves interagency collaboration as well as international collaboration and cooperation. We have had interactions with a number of regulatory agencies from other countries, although the issue still is a problem about those who don't regulate it. Then, of course, public input is a major part of our agenda, and it enables us to be able to update, appropriately, our policies.

Finally, if you wish to get information from CBER, there are a number of different ways to do so, either by fax, by telephone, or on the web. You can also e-mail and get bounce back e mail. So, we try to communicate by all means possible. Thank you.

[Applause.]

DR. VANDERPOOL: As chair, I suggest that we have about 10 minutes of discussion and identification of the issues in this excellent and thorough overview that Eda has provided us with. Then we will take a 15-minute break and convene when we decide where we are in terms of that break, and we will give the time in just a moment.

This overview presents all kinds of issues. We could spend, I suppose, the rest of the afternoon and tomorrow morning on just the new public disclosure requirements. Let's identify the issues we see here as important and spend some time identifying those and having comments from the committee for Eda Bloom.

Well, I have one question, I guess, regarding the disclosure. I know that some of that will be controversial for sponsors of trials. I see that you are walking a line between not disclosing trade secrets, and yet, disclosing things that are in the public interest in terms of protecting the public in a responsible way. I guess my concern, my one question would be, in spite of the similarities between gene therapy and xenotransplantation, it strikes me that to include those together sort of puts this committee a little bit under the gun, as if maybe a few things have happened in xenotransplantation also recently. Now, they could, and that is the possible forecast. At the same time, I was a little bit concerned that gene therapy and xenotransplantation are linked so closely together that xenotransplantation becomes a bit guilty by

association. Could you just comment on that?

DR. BLOOM: The reason we included specifically those two areas has nothing to do with guilt by association. I think in this country people in clinical protocols are innocent until proven guilty. We have no such proof at this point. They share the previous public disclosure. So, they really have been very open to the public. You will hear a couple of sponsors today discuss their protocols -- today and tomorrow, I think, discuss their protocols.

The fact that they have been open, and the fact that the public is concerned about xenotransplantation, as they are about gene therapy, are the two main features that these two types of therapies have in common, and why they have been grouped. They are also both very cutting edge biotechnology. They share that.

DR. SALOMON: Harold, I would amplify that to say that from my viewpoint, as chair of the BRMAC, that has seen both gene therapy and xenotransplantation issues now over the last several years, in many ways our approach, as far as the public is concerned, is very similar, since we are talking about either genetically engineering animals that are then introduced into the world of living things, or genetically engineering vectors and giving them to cells that are then, in some way, shape, or form, given to human beings which, again, is basically shuffling genetic material in different ways around within living organisms. I think from that point of view, these things are very appropriately considered together at the level of disclosure and risk.

DR. BLOOM: I might also add that we have some therapies that fall under both umbrellas, that are xenotransplantation gene therapies.

DR. VANDERPOOL: A comment from the public?

AUDIENCE: [Comment off microphone.]

DR. BLOOM: We have a 90-day comment period and we are always very responsive to comments that come in. We are responsive to anyone who wanted to comment a document to the docket. We read them all. You will notice that the PHS guideline, for example, was modified between 1996 and 2001. In fact, that is partly why it took so long, was trying to respond appropriately to all the comments. So, all comments are considered. They may not all be incorporated, but the document is not written in stone. That is the purpose of the comment period in rule making. In fact, I mentioned that as far as the guidance document on blood donor deferral, it is going to come out for a second round of comments, because we are not sure whether or not we captured everyone's concerns in the first revision.

No, the guidance document was not in response to any particular incident at all. It has actually been under development at the agency for quite some time. It would be nice to say that we could turn around like that and write a proposed rule, but it takes us a long time to do anything. So, it was not in response to any particular incident.

MR. BERGER: I have had the opportunity to read this proposed rule. It seems to me that there are two points. Number one -- and it is stated over and over again -- that this proposed rule is nothing more than meeting the same requirements of other governmental agencies. So, it doesn't appear to me that there is anything new in terms of public disclosure. It is what is already being done by all other government agencies. If there are any attorneys here to comment, I would assume that it also meets with the Freedom of Information Act requirements as well.

DR. BLOOM: In fact, I believe that what we have proposed to disclose under this rule could be obtained. In fact, we have certain, right now, on the books, regulations that talk about commercial confidential information. That puts us in a big bind about what we could disclose, and this would make that much easier for us.

DR. ALLAN: In both the PHS guidelines and the guidance to industry on xeno products, when you are dealing with the issue of the animal, again, can you give me the sort of rationale why to sort of -- you are saying C section, it should be a closed herd and it should be no introduction, all in, all out, there are several different wordings. At the same time, there is also the sense that, well, you know, under some circumstances you could introduce animals, you could use imported animals. Does that create confusion? Does that make your job much more difficult in terms of dealing with INDs in this area?

DR. BLOOM: Well, we need to leave open the opportunity for the manufacture of certain xenotransplantation products that may necessarily require a species that may not be available in the United States, for example, regarding import. There may be countries that may provide animals that may be equivalent to what we provide here. However, once they would be here, we would still require a certain quarantine and qualification of those animals. We don't want to, a priori, throw those out the window. Yes, it does make our job more difficult. On the other hand, they may be reasonable. If the sponsor can show us, by providing data, that what they are doing provides the same level of security and freedom from infectious agents than what we recommend, we would consider that.

MS. SHAPIRO: I haven't read the proposed rule. How does it define patient identifiable information?

DR. BLOOM: It would be any information that one could directly use to identify a patient. This is something that I think is of concern. If you identify the clinical center and that clinical center has treated only one patient, that could be problematic.

MS. SHAPIRO: Then if that were true, then that center would not have to comply with any of these reporting requirements.

DR. BLOOM: Everyone would have to comply with it.

MS. SHAPIRO: But they wouldn't have to turn in anything because it would disclose otherwise confidential patient information.

DR. BLOOM: I think that is one of the issues that would be open to public comment at this point. We see everyone complying with it.

DR. VANDERPOOL: While I made what could be taken to be a bit of a critical comment about the association between xenotransplantation and gene therapy, I do think that these new disclosure rules are admirably fulfilling the desire for public education and public education and public input. That is part of what this committee is about. In that sense, it is very friendly to what this committee may well see one of its chief aims as being.

Okay, let's take a break. It is about five after. Let's be back here by 20 minutes after 4:00 to assume the order of the meeting.

[Brief recess.]

We have been told that we must be out of this room by 5:30, so we can't go that far overtime. We are supposed to be adjourned by 4:40. By the way, be sure not to leave anything here. Who knows, this may become a dance studio between now and the time we meet in the morning. So, be sure to take everything with you, and we will have to be through by 5:30, wherever we are.

DR. GROESCH: Our next speaker is Dr. Louis Marzella of the Food and Drug Administration. Louis will be giving us an overview of xenotransplantation clinical trials.

Agenda Item: Overview of Xenotransplantation Clinical Trials.

DR. MARZELLA: Mr. Chairman, ladies and gentlemen, good afternoon. My task this afternoon is to give a brief overview of the clinical development of xenogeneic products.

The Code of Federal Regulations divides the stages of clinical development into three stages called phases. Phase I is basically the first introduction of a product into man. The focus of the study is an assessment, initial assessment, of the safety of a product. In phase II, the preliminary evidence of safety is built upon, and now one begins to collect information on the activity of a product. This then leads to phase III, where the clinical benefit of a product becomes established. Now, this division of clinical development into stages is, of course, somewhat arbitrary. With particular regard to this product, the development of safety profiles sometimes takes much longer than the actual clinical development phase. One has to go into post-marketing. For these particular types of products, safety monitoring and safety data collection will be essentially a goal that would be ongoing.

Now, as you have heard, then, the agency has the authority to regulate xenogeneic products, and the initiation of a clinical study requires the submission of an investigational new drug application. These applications contain product manufacturing data, preclinical and, where applicable, also clinical study information. Finally, they contain the detailed clinical protocol that describes how the product will be studied in patients.

Within 30 days of the submission of the application, a study goes in effect, an IND goes in effect, unless it is placed on clinical hold by the FDA. The decision to place a study on clinical hold is basically based on risk benefit assessment. At the beginning, one focuses on safety and it becomes paramount to try to assess the potential risks, the potential harm, the harm to which subjects will be exposed who are participating in the clinical trial. As you have heard, in the case of xenogeneic product, it has also been established that there are also public health concerns. For that reason, then, assessment of potential risks to the public health, in terms of understanding what they are and trying to minimize them, is also critical.

At the initial start of the IND, of course, there are not clinical benefits. It is only potential benefits. The issue then becomes to make sure that the patient population that is being studied is an appropriate one, where a significant enough benefit is reasonably -- there is at least a reasonable likelihood that it may be realized, so that risk benefit would then be favorable for the study proceeding.

Now, in evaluating the clinical trial, as has been discussed previously, monitoring is particularly important. The objective of monitoring is to assess and minimize the health risks of the product to the recipient, to close contacts, as well as to health care workers. As has been discussed by previous speakers, what we look for, is for a monitoring plan which essentially involves periodic lifetime testing, archiving of specimens and critically, also, reporting of adverse events, both in the pre and post-marketing periods.

Now, the agency also has the authority, then, to prevent a study from beginning, or has the authority to place a study on hold, if it determines that there is an unreasonable and significant risk to subjects for a clinical study. Another reason, as other speakers have indicated, is also the lack of sufficient information to assess risk to subjects.

Another important thing that we look for in the review process is to make sure that the investigators that are going to participate in the trial have the appropriate training and qualifications. There are specific recommendations that were issued to ensure that only the principal investigator but also his colleagues, that there would be in place an appropriate team with the expertise to deal with the various aspects of these types of products. Finally, particularly for phase II and phase III trials, inadequacy of study design could also be a ground for placing a trial on clinical hold.

Then moving briefly through the various stages, again, phase I, the safety is the primary objective. The aim is to develop and understand a treatment protocol which would be safe and well tolerated by the subject, which then can be further evaluated in phase II studies. The initial studies are typically small, on the small side, 20 to 50 patients. They are typically uncontrolled. One of the goals is also to collect information about activity.

Phase II trials, the aim again shifts to trying to collect data for activity, continue to collect data on safety, particularly toxicities which are perhaps less common than would be obvious from the study of only a handful of patients. The studies are larger. Again, they may be either controlled or uncontrolled. The importance of study design for phase II trials is that they are used as a prototype for the efficacy study. One thing that is particularly important is an estimate of the magnitude of the treatment effect and of the variability around that estimate.

Finally, we go on to phase III trials, then, where the aim is to establish the clinical benefit of a product, and determine the risk benefit. It is hoped, of course, that these types of trials will then lead to a license application. One of the issues in designing phase III trials is also to ensure that sufficient information is collected to form the basis for informative product labeling addressed to patients and to consumers. These studies, then, are a little bit larger, in the range of maybe 100 to 1,000 subjects. They are randomized, controlled, blinded, and they are usually multicenter.

A number of issues that are critical in the design of phase III trials are the issue of using placebo controls and also of using randomized treatment allocation. For xenogeneic product trials, the control group is typically a placebo group. So, the typical design is that patients in all treatment arms get optimal standard of care. On top of that, then, there is the add-on of the experimental treatment.

Another critical feature of experimental design for phase III is also the need to identify prospectively outcome measures by which clinical benefit will be defined. Of course, it is important for these outcome measures to be clinically meaningful. In addition to primary outcome measures, secondary outcome measures are also used to provide additional information that supports the evidence of clinical benefit.

Now, this definition you have seen already a couple of times. Again, xenotransplantation products are products that consist of live cells, tissues and organs from a non-human animal source, that are either transplanted or implanted into human recipients. Included in this definition, for primarily safety reasons, there are also human body fluids, cells or tissues that have had either in vivo or ex vivo contacts with live, non-human animal cells, tissue or organs.

I would like next, then, to provide a very brief overview of the types of products that are currently under

IND. Let me also add that all of this information is in the public domain. One major class of products, it is hoped to be, will be solid organ xenotransplants. There are currently no INDs filed for these products, but there have been extensive pre-IND discussions between agencies and manufacturers, to try to reach agreements on proof of concept, which will be necessary to allow these types of studies to proceed.

The next major class of products involves implants, xenogeneic cell implants. Some examples are porcine fetal neuronal cells, which are implanted intracerebrally for the treatment of various serious and life-threatening neurologic conditions. Some examples are Parkinson's disease and Huntington's Disease. Another example of xenogeneic cell implants would be porcine hepatocytes implanted intrasplenically in patients with acute or chronic liver failure. Another example that I might mention is the one of bovine adrenal chromaffin cells implanted intrathecally, for management of intractable pain in patients with malignancies.

Another major class of xenogeneic products is the class of artificial biologic organs. A lot of these are used extracorporeally to profuse either blood or plasma through these tissues to provide temporary support for patients in life-threatening conditions. One specific example of this particular product class would be the hemoperfusion of whole porcine liver in patients with acute liver failure. Another one would be plasma profusion of hollow fiber devices containing porcine hepatocytes in patients with acute liver failure. I think you will hear soon a speaker from industry elaborate on one example of such products.

Then finally, there is the class of products which are either autologous or allogeneic, but which have had, during the manufacturing process, either in vivo or ex vivo contacts with non-human cells. One example might be, for instance, leukemic cells expanded in SCID mice as immunotherapy in patients with metastatic cancer.

So, in conclusion, the xenogeneic products that are currently under IND consist of bioartificial organs and cell implants, primarily. There have been some discussions of xenogeneic solid organs, but these discussions are still in the pre-IND stage.

Human tissues exposed to xenogeneic cells are also another concern. There are no specific clinical trial considerations, really, into these products, but they also fall under this regulatory umbrella, because of the safety risks. The sources of these products are primarily porcine, but others have also been proposed or actually studied. Examples are bovine or murine or even invertebrate types of cells.

In terms of the proposed uses to justify the risk to patients, potential risks to patients and to the public health, the initial indications, at least, are all for serious and life-threatening conditions. The products are designed to provide either temporary assistance, primarily through ex vivo profusion, or they are intended for permanent replacement of function. Finally, these products are in a range of clinical stages of development, from pre-clinical to pivotal trial stage.

Thank you. I think I will stop here and take some questions if there are any.

DR. GROESCH: Thank you very much. Are there any questions for Dr. Marzella? Okay, thank you again. That was very helpful.

[Applause.]

DR. GROESCH: Our next and final presentation for the day is the first of three presentations that we

will be having on current xenotransplantation clinical trials. Our speaker this afternoon is Dr. Daniel Miller. He is the president of Excorp Medical, Incorporated, from Oakdale, Minnesota. He will be talking to us about the Excorp Medical bioartificial liver system.

Agenda Item: Presentations on Xenotransplantation Clinical Trials. Part I. The Excorp Medical Bioartificial Liver System.

DR. MILLER: Thank you very much. It has been a long day and I imagine that many of the panelists are awash in new information. I am not going to help any between now and dinner time. I am going to contribute to your information overload.

As I get started here, there are a couple of things that I wanted to preface my presentation with, and they are the following comments. First of all, we have been, in one form or another, engaged with FDA through much of the formative process in xenotransplantation with our particular technology. I think, to some degree, we have grown up with the agency, as the regulatory philosophy and the regulatory body has matured during the course of the last four or five years. So, that is the first thing I would want to say. The second is that, fortunately, it has been a collaborative relationship. That has, I think, been helpful for us, as well as the evolution of the regulatory strategy in this area.

I also wanted to add a couple of other things. One is that, while this is a U.S. forum here today, I think it is important to remember that this is actually an international problem, particularly in our area related to liver failure, which is of enormous proportions elsewhere in the world, places where, frankly, the debate that we are having today may be considered something of a luxury, just one other thing to keep in mind.

What I am going to do is run through this presentation relatively quickly. I am not going to attempt to make it highly technical, out of deference for the audience, both the time of day and the composition. Please feel free to interrupt with questions, at the end, or buttonhole me later, and I would be happy to answer anything that I possibly can. My first disclosure here is that we do, in fact, have an active IND in front of the agency. So, we are already complying with the new reg.

Let me talk a little bit about liver failure. This is the problem that we are trying to address. Liver failure, in its major form, really relates to about 40,000 deaths per year in the United States and perhaps three quarters of a million hospitalizations. The common number that is given is about \$10 billion a year in hospital charges. That only includes the direct charges, not the quality of life, lost productivity kinds of issues, which have a huge multiplier effect in the health care economic considerations. Currently, there are over 17,000 patients listed for liver transplantation in the United States. We manage to perform roughly 4,500 transplants a year in the United States. The comparable number in Europe, serving roughly the same population, is about 2,700 transplants.

From the point of view of a bioengineer, we have a very difficult problem. The liver is a complex biochemical factory. We know very little about what it actually does, except for the fact that it regulates most of the body's chemistry. Everything we eat is processed through the liver, most of the drugs we take are processed. The composition of our blood is largely regulated by the liver, and there are many other things that could be put into this list. It is absolutely essential for life. A patient without a liver, an anhepatic patient, will survive for perhaps 24 hours, without a transplant. Fortunately for us, the liver is very resilient, and it has an ability to regenerate which is unique among the solid organs of the body.

This is a slide to show, as others have done today, a little bit about the status. Liver transplant patients represent the second largest number on the organ transplantation list. This is taken from UNOS' web site.

The list is growing. It is growing exponentially, as the clinician's skill in performing transplants allows a broadening of the indication for inclusion on the list. Sadly, the number of deaths for liver transplant candidates is also growing at roughly the same rate.

There are an enormous number of ways in which patients find themselves in liver failure. This is a slide which is not going to be easy to read, and it is really not intended to be. You can imagine going to the ICD-9 data base that is maintained by the National Institute for Health Statistics and identifying the patients who find themselves in liver failure conditions. The red numbers across the bottom represent figures for a particular year. This happens to be 1996.

So, the summary here is that what we need is a system, a bioartificial liver system, which offers temporary support for the metabolic processes of patients who experience acute liver failure. In the clinic, this will be used as a bridge to transplant for some patients, but we also feel that there is a high likelihood that it will also serve as a means for permitting liver regeneration for many others.

What we are attempting to do from the engineer's point of view, in contrast, by the way, to the scientific point of view, is to devise a means for providing this temporary support. We are going to require that the complex metabolic functions are provided by viable liver cells, and in our case, they happen to be porcine hepatocytes. We have designed a system which is intended to be self contained, such that the hospital personnel have little or no contact with the inner workings, something that is easy to use and, in fact, in practice is really very little different from renal dialysis in its application.

The nature of the bioreactor that we use is disclosed in a U.S. patent. Our technical solution, schematically, looks like this. It is a simple extracorporeal blood loop. We remove blood from a patient using venous access, and usually a vein in the neck which appears to be preferable for our purposes. We have the means of adding heparin, although liver failure patients are often auto-anticoagulated, and actually don't need any additional assistance in that direction.

We include an oxygenator that makes it possible for us to oxygenate the patient's blood which provides high level, essentially arterial levels, of O₂ saturation, by the time the blood stream reaches the bioreactor, where the pig liver cells live. We also use this oxygenator as a means of adjusting the pH of the patient's blood. Liver failure patients have an enormous range of metabolic and physiologic abnormalities that make it difficult for them to autoregulate their body's acid base balance. If that blood were to impinge on our bioreactor in the state that it emerges from the patient, we would have a much shorter lived reactor and one which is likely not to be as effective.

So, we use the oxygenator to add or adjust the CO₂ concentration to provide the pH control that is necessary. Then it returns to the patient through a standard dialysis bubble trap. You will notice that we use whole blood. This has the advantage of simplicity and it also has the advantage of providing a means of getting a lot of oxygen to the hepatocytes in the reactor. Many of you will know that hepatocytes are enormous consumers of oxygen for many of the metabolic processes.

We also provide a means of separating the porcine cells from the patient's blood. In our bioreactor, which is essentially, in real life, a hollow fiber renal dialysis cartridge, the molecular weight cut off is around 100,000 daltons. This has a number of features for us. One is that it prevents the naturally occurring antibodies, the alpha gal antibodies that you heard about this morning, from attacking the pig liver cells and destroying them through a complement-mediated process.

The second feature is that it provides a means of separating many of the products or the molecules that

might be present on the porcine side, from gaining access to the patient. Among the particles that we are concerned about are the possibility of either known or novel adventitious viruses. Across the face of this slide, you can see the apparent molecular weight of many viruses. This is, in many ways, a specious slide, and I apologize to the scientists in the room. It does give a sense of where we are operating in terms of the ability of this membrane to provide a molecular barrier between the patient and the pig cells.

The other sort of subtle point here is that most of the therapeutic benefit, if there is to be any, will occur by the availability of molecular species under 100,000 daltons to gain access to the compartment where the pig cells are

This is the device in its current form. This is a clinical prototype system. It is a computer controlled system. If you follow the blood path from the right of the screen to the left, it is this blue line. All of the components that -- here is the blue line, a blood pump, a heparin pump, a blood warmer to keep the blood warm, the oxygenator that I mentioned. There is a pH probe to monitor, in line, the pH of the patient's blood, the bioreactor itself, the bubble trap, and it returns. This is all driven off a computer. So, it is a menu-driven process and bioengineers have a secret story when we talk about this. This is called doctor-proofing the system, because knobs and dials are meant to be twiddled, and we wanted to minimize that.

Now, turning to our development program, all of our development has been done in association with the University of Pittsburgh, and specifically, the Thomas C. Starzl Liver Transplantation Institute at Pitt. We conducted our laboratory and preclinical studies there, and our limited clinical experience has also occurred at the University of Pittsburgh. The preclinical studies were based on an animal model of liver failure that replicates, in most major respects, actual human liver failure.

The list of characteristics that the model demonstrates are shown in this slide, going from top to bottom in terms of increasing severity and, remarkably, copy that which a clinician will see in the liver failure ICU. Those animals treated with the system show a survival advantage. The red line is treated animals, the blue line the untreated animals in this animal model.

We are also able to show a benefit to the study subjects in terms of controlling ammonia, which is one of the molecules which is classically, although not invariably, elevated in patients in acute liver failure. A third example of the kinds of things we saw in our preclinical study related to their ability to control metabolic acidosis. Again, it is a characteristic of liver failure that this phenomenon is observed, and without going through the whole slide, the red line here at the bottom are the treated animals, the blue line are the untreated animals in this particular study group.

Finally, one of the hallmarks of liver failure is an inexorable rise in intracranial pressure. This contributes partly to the coma that these patients experience, although there are other pathophysiological contributors as well. There is a second component to this, which is the rapid rise shown at the end of this trace, where the rise in intracranial pressure in the animal's brain becomes sufficiently great that the animal begins to experience neurological events, seizures, and ultimately death. Again, this is very similar to what is seen with human liver failure patients.

Armed with these results, we devised a phase I/II clinical protocol in consultation with FDA. As Dr. Marzella just mentioned, the principal objective of a phase I/II study is to demonstrate safety for the device and the technology. We have an objective to verify the major bioengineering assumptions and, in our case, we are interested in a whole variety of characteristics. Are we removing blood from the patient fast enough to stay ahead of the disease process. Are we interfering with the patient's other forms of therapy that might be advisable for the patient. You get the idea of the kinds of logistical issues we are

concerned with. Finally, and least, we are hoping to see some sign of clinical benefit. Without that, you don't know if it is going to be possible to design a phase II, III protocol.

In our case, we have chosen a clinical trial design that involves a 12-hour baseline observation period for a patient, once they are accrued and consented into the study. During this period, we try to assimilate as much information about their metabolic and physiologic condition as possible. This is followed by 12 hours of hemoperfusion through the hepatocyte bioreactor and ends up with a third 12-hour window, but a second baseline period. Under the terms of the protocol, we are allowed to repeat this procedure one time.

With a specific patient we see some of the same sorts of things that we saw with our animal studies. Across the bottom you will see our treatment monitoring protocol paradigm here with the second treatment window. Bilirubin, ammonia, lactate are three molecules which are classically deranged in liver failure patients. The implications here are fairly obvious. We also looked at one or more physiological conditions with a patient. This happens to be a measure of the pulmonary efficiency, the ability of the patient's lungs to extract oxygen from respired air. In the case of this particular patient, during the preliminary baseline period, this efficiency was dropping precipitously. At the time that hemoperfusion began, during this window, we saw an improvement. There was, again, a deterioration during the intertreatment period, and then during the second window, a steady improvement. In this case, the monitoring went on and the patient never deteriorated below the threshold for clinical concern from that point forward.

So, that is the nature of the clinical program. I have just three or four additional slides to talk about, which I think relate largely to the manufacturing process that goes into this program, and may perhaps get at the heart of some of the xeno issues in this area.

We approached this from the beginning with the idea that, as with any regulated product, it was necessary to think in terms of complete traceability. We need to be able to connect a pig with a bioreactor, with a patient, in our system, and know that that pathway, that production process maintains its integrity. Some of the basic features, most of which have appeared in the FDA's regulatory guidelines at this point, involve controlled personnel access to the facility, quarantine of new breeding stocks, defined herd genetics.

This perhaps doesn't get a real high amount of profile but we have discovered that all strains of pigs are not created equal, to paraphrase a George Orwell term, and that certain animal genetics are preferable to others. We systematically test the source herd which, in this case, are sows. There are no boars on the farm. They show up in little tubes from somewhere else. We also test the donor animals for specific infectious diseases, or signs of specific infectious diseases.

We segregate the donors shortly after birth, generally at 10 days, which provides them an opportunity to absorb as much colostrum as possible. This is the maternal immune response transfer mechanism to baby pigs. We then get the pigs away from the sow as quickly as possible for two reasons. The major reason for animal husbandry, by the way, is because every now and then the sow will actually lay on the pig with negative results, but also for the potential transference of disease. We create a cohort at that point and this pool, this cohort of animals, are the pool from which our individual donor animals are drawn.

A few other major features, the diet is free of reprocessed animal material. That includes the sow as well as the weaned pig. It is an all in, all out flow with retention of a sentinel animal from each cohort, which stays on the farm for a period of time, and then finds its way to an animal path lab for a thorough

evaluation. Then the ability to archive specimens from specific donors.

This is the slide that covers much of the zoonotic considerations that apply to pigs. Every sponsor in this field has this list of organisms, and there are minor variations. Many of these organisms do not actually infect humans. However, they are great for monitoring the quality of the herd and as an evidence for the maintenance of the biosecurity program. So, we found it helpful to include a fairly broad list of particular organisms.

Finally, and I will close at this point, the guidance documents that have appeared so far and been referred to in the past few minutes, have been actually very helpful to this process. As I said earlier, it has been a collaborative arrangement, I think, at least, with this sponsor and FDA in terms of the evolution of these documents. From the point of view of the sponsor, having that clarity is important for moving forward with the industrial commercial development of this technology. So, that is an important point to make. Going forward, I think it is important that we try to preserve a regulatory environment which leaves some room for the commercialization of this technology. At the end of the day, I guess, if we are not able to commercialize it, we probably haven't accomplished what we set out to do here.

With that, I will close and I am interested in any questions. Thank you.

[Applause.]

DR. SYKES: As I understood you, your sows are kept in a closed herd, but the boars are brought in from outside.

DR. MILLER: No, ma'am.

DR. SYKES: Could you clarify that?

DR. MILLER: The boars are on a different farm altogether. That is characteristic in a commercial pig production operation, where virtually all the insemination is done artificially. It allows for timing the pregnancy and is conducive of the all in, all out process. I am saying things that probably could better come from a more expert source, but that is basically the approach. By the way, everything that I mentioned here is actually standard in a well-run commercial herd. These are not special processes for xenotransplantation, at least as far as the pig is concerned.

DR. SYKES: The second question is, are you monitoring your recipients for the production of antibodies, not only to gal, but also to a variety of hepatic products that are obviously necessary for normal life? This could provide a baseline for later studies in patients on immunosuppression with solid organ transplant.

DR. MILLER: Right, the answer is yes. We are archiving specimens per the guidelines for those kinds of evaluations. We haven't actually conducted any of that at this point. I agree with you. I think that it is going to be very instructive as to what the patients are exposed to.

It is important to understand that our patients, classically, are not pharmaceutically immunosuppressed. They may be to some degree immunosuppressed by their liver failure process. In our view of the world, these patients would actually leave the hospital with their native organ rather than someone else's.

MS. SHAPIRO: What kind of insurance do you have and/or, in the event that this goes to market, how

are you dealing with the rather significant liability concerns?

DR. MILLER: That is a great question. We actually have not had trouble finding medical product liability insurance. It has not been enormously expensive beyond what you might expect for any new technology and the coverages are, we feel, adequate. So, the insurance community is comfortable with this.

DR. ALLAN: In terms of infectious diseases, because that is where my background is, the membrane that you are using, there was a publication a couple of years ago by David Pershing, when he looked at a membrane. I am not sure that it is exactly like the one that you use, but he was able to demonstrate that viruses do pass through those membranes and PERV actually can pass through that membrane. I just want to clarify that for the committee.

The question I have is, you listed the number of viruses that you screen for. There are newer viruses that are coming out and there are circoviruses that I didn't see on the list, and gamma herpes viruses. How do you work with the FDA on this? Does the FDA have a position on some of these newer viruses that seem to be becoming more of an issue?

DR. MILLER: The specific answer is that we have some assays available to us for circo and for porcine hepatitis E and for porcine CMV that we are evaluating at this point. So, they are gradually being worked into the process. I think again, with each of those agents, because each has slightly different viral biology, it is important to make sure that they are part of the overall screen.

Regarding the transmission of viruses across the membrane, again, our membrane is actually quite tight. We have conducted some pilot studies which would not qualify as virus validation removal studies, so I don't want to misrepresent what I am about to say. In that, we find that you can see viral subunit particles. You can see nucleic acid, for example. You can see some subunit proteins which can only have appeared by transmembrane migration. But we don't see intact particles. This is specifically in the case of PERV.

DR. VANDERPOOL: Other questions? We truly appreciate your coming. I have been told that it has been a challenge to get industry representatives to bring their research to this committee, and we certainly appreciate your doing that, and serving us and giving us a chance to hear what you are doing.

DR. MILLER: Thank you. I am actually not sure why there would be reticence. In order for this technology to go forward, there is a need for public awareness and acceptance and public education. To be real blunt about it, I don't know how I am going to sell something if that public awareness isn't there. If this is a mechanism by which we can evaluate the issues, get them out into the open and understand them, I think we are all far better off.

DR. GROESCH: Thank you very much. I have just one announcement to make and then Dr. Vanderpool has a couple of remarks. The next item on the agenda is about scheduling the next committee meetings.

Agenda Item: Schedule for Future SACX Meetings.

DR. GROESCH: I think I can take care of this in 30 seconds. We need to wait for a little bit. I think it makes a little more sense to schedule the meetings after we have had the issue identification and after we have had some input from the federal agency representatives about what they would like to hear about and how soon. We can do this by e-mail once we have a little more input. Having said that, we do

anticipate having the committee meet three to four times a year. So, it is quite possible that our next meeting would be in like May or June, but we will get back to you and kind of canvass the group for availability.

DR. VANDERPOOL: It has been a good and very full day and we are beginning to get to know the members of the team. For those of you who have not had the experience of hearing discussions of xenotransplantation at this level, take heart. It gets better. Familiarity breeds greater control and confidence.

To end with a metaphor, still building out on the question of team members, I feel like we are in the baseball spring training. The first day, you get out in the midfield and you have the coaches batting long fly balls to you, and you act as loners. You catch the fly balls and hopefully throw one or two back to the coaches. That has been more like today, with people hitting fly balls. Most of us have caught two or three and thrown them back to the coaches and the committee. Tomorrow is going to be much better. We are going to take the field and we are going to start paying baseball. So, thanks very much.

[Whereupon, at 5:10 p.m, the meeting was recessed, to reconvene the following day, February 21, 2001.]