

Transcript

**Fifth Meeting of the
Secretary's Advisory Committee on Xenotransplantation,
U.S. Department of Health and Human Services**

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Agenda Item: Opening Remarks

DR. VANDERPOOL: Everyone, thank you. Take your respective places, and let's begin our meeting. I welcome everyone to this very important and full agenda of items for our committee meetings. I especially welcome the non-voting agency representatives with us, who always provide essential perspective to us. Also are several presenters from industry, and from agencies. We are very pleased to have Dr. Carolyn Wilson to present and also Dr. Howard Zucker.

My thanks always to Mary Groesch, Dr. Groesch, for her invaluable and sustained contributions to our organization, and the content of our meetings. Dr. Groesch has decided not to make opening remarks herself, so I will simply compliment her and recompliment her for her contributions.

We have a full agenda of items, so we'll seek to stay on schedule as we can, and as I believe we will, for the most part, we have a number of industry updates. We have important questions that are being asked for us to think about and deliberate with respect to questions the FDA has. We have members of the public who will be able to offer comments and suggestions at appropriate times, and then we are going to spend a particular amount of time on the two reports of the subcommittees of SACX: The report on informed consent, and that on the state of the science.

Since these reports have been formulated by subcommittees, it is extremely important for all of us who are not on the respective subcommittees to give our candid and open and thoughtful input so that these reports will indeed be representative of the entire committee.

With respect to these reports and our work on them, both in terms of public presentations and public analysis and the plenary sessions and work in respective working groups tomorrow, it is particularly important for us to be contemplating when we want to have these reports completed. My own concern is that we move with all due diligence to have them completed, however much work and revision that may take. And so at the end of the meetings tomorrow, I will raise the question about what date of completion we can establish for each of these important reports.

The other question, which we need not discuss this time, is what is the destination of these reports, and Dr. Groesch and I had a brief conversation about this, and she will be thinking and talking with her agency colleagues about where these reports will go with respect to federal agencies. And also I think I can speak for members of the committee, that we would also like to in some way get these reports into print, but that is not something for us to discuss now, but I think that various members of the committee can think about the place where these could be published, and hopefully should be published. But that is down the line, but nevertheless, on my mind.

So let us begin with our 8:40 to 9 a.m. topic that has to do with meeting updates, new items, and activity updates. We have two items on this agenda today and then again tomorrow we'll begin the day with additional meeting updates and news items -- we have two very important reports from Drs. Zucker and Wilson in that section.

I do suggest that we add a brief time tomorrow for an open-ended set of brief announcements from anyone on the committee who has been involved in talking about xenotransplantation and going to conferences pertaining to xenotransplantation. In other words, what activities have committee members been doing that they are on our work? I know a lot of that is going on, and sometimes I'm afraid that a lot of us are doing all kinds of things that the others don't know about. So we want the right hand to know what the left hand is doing, and we'll provide that opportunity tomorrow. So without further introductory remarks, I'll open the subject up, do any of you have any important pieces of information or comments to make as we now begin?

***Agenda Item: Xenotransplantation Meeting Updates, News Items, Activity Updates (Part I)
Follow-up on PRIM&R Workshop on Xenotransplantation Issues***

So let's move on to the -- the first topic, which is a follow-up on the PRIM&R workshop on xenotransplantation issues that Robyn Shapiro and I participated in, in San Diego, and so I suppose the thing for me to do is to begin, and state a little bit about the background, and then Robyn Shapiro will make further comments about this workshop.

Now for those of you who do not know about PRIM&R, I was informed some years ago that the correct pronunciation is not prim and R, but it is "Primer," for those who are insiders, so to make us all insiders, we'll refer to it as PRIM&R. PRIM&R is the largest organization in the United States that deals with public meetings on the ethics and regulations of research. My guesstimate is that some 2000 or more persons throughout the United States, a lot of whom are members of IRBs, or are responsible for administration of IRB activities, attend this meeting, and so it was very important for this committee's concerns to be represented there, and we can thank Dr. Groesch and others in her office for opening the door to myself and Robyn's being able to make a presentation.

We gave a break-out session in the first day, so that we would be more visible, and not be consigned, as they wished, to the second or third day. We sponsored a break-out session in which, if you will look at your two hand-outs, one from myself entitled "PRIM&R Workshop," and the other by Robyn involving informed consent, we presented these two topics. It is not exactly correct to say we presented them, because what we wanted to do was to encourage those who attended the workshop to give their comments and input about the things we were about, and the issues that they felt were important regarding xenotransplantation. And so although we made, quote, presentations, we walked through these documents rather quickly, summarizing things and urged discussion as we went along.

As you can see by the first page on the hand-out in terms of background information, ah, this introduces the group to the definition of "xeno," it talks about oversight, it talks about regulatory activities, and gives a brief research update that drew almost entirely from the presentation made by Dr. Eda Bloom to us at one of our meetings.

And then I proceeded to give an oversight of the ethical issues inherent to xenotransplantation; and within that flag, the particular topic that Robyn Shapiro would discuss, and so if you look on page two, we talked about the overarching question of the justifiability of the research, and the initiatives to move xenotransplantation products to clinical trials, and hopefully into therapeutic modalities. We talked about the risk of infections, a mention of informed consent with the obvious point that Professor Shapiro would deal with that topic in the second part of the workshop, and then an important set of points regarding trial-related harm/benefit considerations with a set of questions attached. That is almost an agenda for us. But I point to you especially the importance of number four, that we haven't ever really talked about, but is an important issue, should concerns over attempts to avoid discrediting xenotransplantation research and attempts to secure the public's approval of this research influence judgments regarding what preclinical data are needed, which patients are chosen, and what balance of risk and probable harms is acceptable. I know I've heard several comments regarding this topic, but I think it is a question, certainly, to consider in terms of the ethics of xenotransplantation.

I think the laws of nature should research on and the clinical use of clinical xenotransplants be regarded as unethical because they violate what is natural, violate natural laws. Interestingly, this created quite a bit of discussion, particularly involving the question by social workers and psychologists at our group. We had a good representation of people from various disciplines, about the degrees which patients would have negative psychological reactions to having animal organs. That is an interesting topic. We gave some war stories and examples of how this may well be an overemphasized worry. That was interesting.

Questions of justice, in terms of the allocation of healthcare funding were raised. A brief mention of international xenotourism, which the State of the Science Committee has dealt with in some significant length in their report. This topic also “took” because it was quite obvious to the group that there were such concerns, as long as certain rogue or non-regulated researchers and/or clinicians were offering xenotransplantation without the requisite protections.

And then finally public accountability, what should be done to educate and involve the public nationally and internationally with respect to the nature and development of xenotransplantation. This also was an object of discussion. You can already see that in such a brief break-out session, we had an agenda that was chock full of important items, and I think this committee could spend the next day and-a-half airing all of these. But we felt responsible for bringing these and other issues to the group. So now some things about informed consent that Robyn Shapiro presented.

MS. SHAPIRO: Just to highlight for you some of the topics that we talked about in the informed consent portion of this conversation, and I again want to thank Mary Groesch and others for sending us to this conference. I think it was important, in light of our commitment in this committee, to get public reaction about some of the very challenging ethical issues that surround this kind of research.

We briefly went over the elements of informed consent which we'll talk about later this afternoon when we go through the working group on informed consent's white paper. We talked about some of the consent challenges surrounding any complex research, which include that important information may be difficult to explain, or not available at all, that we need to think about the prospective participant's emotional, social and spiritual concerns, which makes it complex. That the forms themselves may be long, jargon-filled, and we'll talk about this later this afternoon. And that the prospective participant's pain and desperation in the face of an overwhelming illness may well have an impact on voluntariness, which is a critical element of informed consent. So what do you do about that? Well, we talked about it, and we'll talk about this afternoon some of the responses to those challenges that get at who should be a part of the informed consent process, the setting, the format, the pacing, the content, and the style of the process. And most particularly, the form.

Then we turned to, and this is where we really wanted to try to have a conversation with people in our small group, the special informed consent challenges in xenotransplantation. And we looked first at the public safety measures with the need for, and we'll talk about this later, recipients to understand and agree to lifetime monitoring. And also the possibility of isolation and autopsy at death. The challenge in meeting this need, and we'll talk about this later, is that currently federal regulations governing research require that research participants be able to withdraw their consent. So what does that say about this “requirement” for the lifetime monitoring. So we threw out some possible responses to that. We'll talk about this later, the commitment of any prospective research subject to adhere to public safety measures as an inclusion criterion, and as a big part of the informed consent process. And then the application of public health laws in certain circumstances where there is non-compliance, and the presence of infection that poses an imminent and serious public health risk.

There are remaining concerns, though, most particularly situations where a non-compliant recipient is asymptomatic. That situation may not be properly or adequately addressed by public health laws. We talked about this some; we didn't get any, I don't think, magic answers, but we threw it out. Another special concern in informed consent with xenotransplantation research has to do with third parties, and public safety measures that implicate them. The need, of course, is for the education and/or involvement of third parties who may be at risk, which includes intimate contacts and healthcare professionals. The challenge here is that there is no legal requirement for getting consent from third parties in any situation.

Another challenge is that when we talk about intimate contacts, they of course may change over time so that the recipient's intimate contacts at the time of the procedure may be very different than those later. And also obtaining consent from them is going to involve disclosing otherwise confidential information about the recipient. So those are some of the challenges, with the possible responses being: Well, we can stress this in the informed consent process, include a component that informs the recipient of his or her responsibility to educate not only current, but future intimate contacts about the possibility of infections and behaviors that may transmit infectious agents, methods to minimize that, and the need to report any unexplained significant illnesses.

Healthcare workers, too, as a possible response to this, need to be informed about potential risk behaviors that transmit infectious agents, methods to minimize, and the need to report illnesses. There should be additional monitoring for healthcare workers involved in these procedures, we suggested, and the centers that do these procedures should have post exposure evaluation and management protocols, and should monitor adherence to infection control measures.

Concentric circles going outward, we now have the community involved in this possible public health risk. So what do we do about that? We need to educate and involve the community also, in light of these risks. And there are significant challenges. How do we define the community, given that we live in a highly mobile society. And then, even if we could do that appropriately, and I don't think we can, short of the global community, how should the community be educated and/or involved? We talked about possible responses, which we've talked about here in past meetings, all of which have their drawbacks, at least the first four, focus groups or town hall meetings, polls or referenda, surveys, Internet, all of them having drawbacks, which we'll talk about more later, and our suggested best possible response being this committee itself.

Then we talked about two additional challenges, which we will want to talk about with you much more, I think, in the course of this meeting. One is incapacitated adults. Much of what we have talked about to date in this committee talks about the inclusion of decisional adults in xenotransplantation research. We have many more problems when we get to incapacitated adults who might benefit from participation, but who pose special informed consent challenges, not only because of the complexity of the procedure, but because of the lifetime monitoring, and so forth.

In addition, as a challenge, federal law is extremely quiet about criteria that legally authorized representatives should utilize in deciding whether to enroll a prospective participant who is decisionally incapacitated. It just doesn't help. The federal regulations just do not help. And when we look at case law, or statutes that address when incapacitated patients' surrogates should decide about healthcare in general, not inclusion in research, but healthcare in general, we don't get much more help.

Then of course there is the additional problem of a decisional recipient who becomes incapacitated later during the time in which life-long monitoring requirements continue. Later we'll talk about some suggestions that the informed consent working group has come up to address this challenge, but we threw it out at PRIM&R.

And finally, we talked a bit about children, which also presents challenges. The need, of course, is that children might well benefit from participation in xenotransplantation research, but there are special informed consent challenges for them, too, some of which parallel those that relate to incapacitated adults. But we have the additional burden, I suppose we could say, of the lifetime monitoring requirement being agreed to by somebody who is not going to have to live up to that. What criterion should guide enrollment of children, and should we allow parents to commit a child to life-long monitoring? Again, we, in our working group, have come up with a possible response that we'll talk about later today.

DR. VANDERPOOL: Thank you so much, Robyn. As you know, we will be talking about all of these informed consent issues in some detail, because it is a central topic of one of our subcommittee reports. You can see that, as a phrase from literature, we took the message to Garcia, namely the message from this committee, and the concerns of this committee to a wider audience at that meeting. We felt that was very important. Now for the second update issue, we have Franziska Grieder from the National Center for Research Resources of NIH to talk about a swine research and resource center.

***Agenda Item: Xenotransplantation Meeting Updates, News Items, Activity Updates (Part I)
RFA for a National Swine Research and Resource Center***

DR. GRIEDER: Thanks very much for inviting me and having this chance to share with you what we have developed at NCCR, or the National Center for Research Resources in terms of developing a new swine resource. Obviously xenotransplantation would be one application for that. This is all based on an NCCR council action last fall. And based on that council action, we at NCCR together with NIAD, went forward and actually put this RFA, or request for application, on the street. It was published just before the holidays, and has been out there for approximately a month. I have received quite a number of inquiries, and I think this will be interesting to see what develops.

So what is the purpose of this new RFA to develop the National Swine Research and Resource Centers, or the NSRRC. It is clearly to deposit, maintain and preserve pig strains which are important for biomedical research, and to make sure they are distributed to investigators in the field to study issues related to human health and disease.

It also should ensure that research technologies are pushed forward, are improved, both for maintenance husbandry of swine, and swine models in general. So this resource hopefully will help to advance both those issues. And one important issue is preservation of these strains. It is very expensive to have these swine -- I almost said on the shelf, because we have many more animal models which are very much smaller mice, so this swine in the pens, it is very expensive, and so if we can preserve them and make these strains stable by cryopreservation and storage that way, that is obviously very helpful. So the objectives of this new RFA are to breed and distribute what we call purpose bred swine strains, and these will include inbred strains, hybrid strains, and genetically altered, or modified strains. And I know you will hear much more about these genetically altered strains later on today.

However, we also envision that this resource will have organs, tissues and cells from those donor species available, again, with the goal to aid and help xenotransplantation.

You all have heard and discussed the issues of infections, so surveillance and improvement of health of these pig strains is obviously important. As I already mentioned, an active research program will be going on at this newly established center, and it should be integrated and an integral part of the resource, to use those swine strains, and that would lead into the last point on this slide, to also allow for training and education. Invite other investigators, researchers in, and help them better understand the models, and potentially aid in setting up either certain experiments, or developing of new models.

So the mechanism of support which we chose for this center is what we call the animal models and biological materials resource, and we are going to use what is called a cooperative agreement. In a cooperative agreement, the NIH does not take a dominant role. The NIH's purpose is to help and stimulate, to support the resource.

The funded investigator still has the leading role in it. We expect applications in at the end of these months, and hope that reviews will be completed by the end of the fiscal year so we can award the one resource which we plan to fund by September of this year.

Let me tell you a little bit about some special requirements. I have already mentioned, that is obviously very important, that the resource will maintain and distribute pig strains of importance to the biomedical research community. And I am saying this very lightly. This usually entails a whole bunch of licensing agreements and legal issues, which are attached to certain of these strains.

The resource will also focus on both phenotyping and genotyping, with the genetically engineered strains making sure that on a genetic background, they are really what we think they are, and that from a phenotypic background, that they are what is expected, and that obviously also entails infectious disease control.

An important component of this resource will also be the electronic database. The center will develop a catalog of pigs, a web site, which describes all the pig strains which are in the center.

They'll also then allow investigators who have pig strains, and would like to send them to the center, and have the center distribute them to researchers access via the web, and submit potential new strains to be distributed, and at the same time it also should allow investigators who are interested in receiving pig strains from the resource to access the site through the electronic database.

Usually developed with these resources is a so-called cost recovery system. This is a partial defrayment of costs for the distribution of these strains. And as I mentioned before, cryopreservation clearly plays a significant role.

A couple other specific requirements for the resource will be the structural backbone behind the resource. It is important that there will be a steering committee where the primary investigators and his support personnel, obviously, take a major role. They will develop standard operating procedures, and have the clear oversight. However, they will also be in charge of appointing a so-called advisory panel. The advisory panel will be a group of scientists, researchers, or ethicists who will actually select the swine strains which will go into this resource, and will be accepted and then distributed.

And, finally, I've already talked about this a bit, is the coordinated database with a catalog which have all live and cryopreserved swine strains available. We envision that this center might not just have pig -- live pigs and frozen materials, but possibly be also a resource for antibodies, DNA sequences, and other biological materials. And as I said, one should be able to both submit pig strains and request them through this database.

So the peer review will obviously be done, standard as for all NIH application. All complete and responsive applications will be reviewed. There will be a two-part review, as I said, for all NIH application. The scientific review panel will meet and use the written criteria in the RFA, and you actually received in your hand-outs a little write-up about this with the RFA attached to it. The criteria are very clearly spelled out in there, and those will be the major points the review panel will use, and there will be, as in all of these applications, a secondary review by NCRR council.

So what do we expect as an outcome from this? Well, we hope that we will be able to establish a swine research and resource center, to make sure that these important strains will be made freely available to investigators in the fields of biomedical sciences. And a number of potential applications are listed there, so it is xenotransplantation, but there might be a whole bunch of other applications as well.

Further, we hope that this resource also will foster new research endeavors allowing new opportunities to produce more transgenic potential developing of new pig strains, advance our knowledge, diagnosis of infectious diseases, and obviously make sure that these pigs are exactly what they are. And with that, if

there are any questions, I would be happy to answer them, otherwise thank you very much.

DR. VANDERPOOL: At this point, we have so much to talk about and so little time, so I think the thing to do would be for all of you to realize that Dr. Grieder, Professor Shapiro and myself are available to discuss with any and all these reports at our breaks, or at other times.

We need, then, to move forward toward industry updates on xenotransplantation studies. A very important number of presentations will be made to us, and to facilitate this part of our discussion up to the time that we discuss the questions that the FDA has posed to our committee, Dr. Dan Salomon will take over. Thanks, Dan.

Agenda Item: Updates on Xenotransplantation Studies

DR. SALOMON: Thank you, Mr. Chair. I'd like to take one prerogative to change the title to updates on xenotransplantation studies, because two of the speakers are from two academic institutions, and I think that even if they are in collaboration with industry, which I think is an extremely important and valuable thing and we should acknowledge them.

It has been a difficult couple years for xenotransplantation, both for academic research and for industry. And what I think we will hear in the next two hours or so, demonstrates the truth of two things. Number one, the compelling clinical and scientific forces that were driving xenotransplantation several years ago, when it was in its golden period, are still there. There is still a terrible donor organ shortage, the scientific imperatives of xenotransplantation, and some of the newer strategies that were being hatched several years ago are moving forward. So science is good.

The second thing that I think this should show us, is, if you'll forgive an impossibly old saw, when the going gets tough, the tough get going. So with that introduction, I'd like to introduce the first of a series of tough guys who have done some beautiful work to advance this field to where it is today, and that is Chris McGregor, who is professor of surgery and director of the transplant programs at Mayo Clinic. He is going to talk about cardiac xenotransplantation, continuing progress in the laboratory. Chris.

Agenda Item: Cardiac Xenotransplantation: Continuing Progress in the Laboratory

DR. MCGREGOR: Dr. Salomon, Dr. Vanderpool, members of the committee, ladies and gentlemen, good morning. I'd like to thank Dr. Groesch and her colleagues for the invitation to speak at what I think is going to be a very important meeting this morning.

I would like to reiterate Dr. Salomon's point that in fact I am reporting data from a collaboration between an academic medical center, private foundation, as well as industry. I direct a preclinical program at the Mayo Clinic, am the clinical cardiothoracic surgeon, and I would like to say that, although this work has been funded in part by Nextran, that I have no personal financial interest in Nextran or its parent company, Baxter International.

As Dr. Salomon indicated, there remains a pressing need for organ replacement, and this projection indicates that there are 80 thousand people waiting for solid organ transplants in the United States at the present time, with perhaps only 20 to 25,000 donors. This number of 80,000 could be double if in fact a fairly rigorous patient selection criteria were not applied. Obviously I'm particularly interested in the thoracic organs. It has been estimated that the total unmet need in the United States per annum is around 47,000 cases. Again, that is a conservative estimate. That is likely to be about half of the need.

As many of you know, the only cardiological diagnosis that is increasing in the United States at the

present time is heart failure, with 500,000 new cases per year, and with half of these patients dead in a period of three to five years. So there continues to be an ever-pressing need for treatment of patients with end stage heart failure.

There are a number of potential solutions to the donor shortfall, and I won't talk about these one by one, but I would mention the use of artificial heart systems and left ventricular assist devices. These are important developments. I have been involved with these devices from the early days, and they show great promise. But I would remind you that Congress first voted funding for artificial heart systems in 1964. That is 39 years ago. About half a billion dollars of government funds, and probably twice that from private industry, and even after 39 years, only for the first time do we have a device approved for off-the-shelf use, and that was in November of last year.

That device that compared with medical therapy did show improvement in two-year survival. The two-year survival was 25 percent of patients receiving the device. The 27-month survival in those patients was eight percent. The average improvement in life span in these patients with the device was four months, six weeks of which was spent in the hospital. This is not in any way to take away from artificial systems. It is simply to indicate that these roads are long, that they are difficult, and that we need an alternative to mechanical systems. I would also remind you that the Barney Clark experience is now 20 years ago. It is hard to believe.

The paradigm for rejection in xenotransplantation, which of course is the principle topic of my discussion this morning, has been this paradigm of hyperacute rejection, vascular rejection, cell mediated rejection, and chronic. Dr. Logan, my colleague from Nextran, is going to focus on the immunological aspects, but I would simply bring out one point here, and that is that hyperacute rejection doesn't really come on our radar screen at all now in the preclinical program. We just don't see it anymore.

Even more interesting is that despite five years of work, and as I'll show you many cases of prolonged survival, we do not see cell-mediated rejection in long-term xenotransplantation. I believe we have about 90 percent of the long-term survivors, and we have not seen cell-mediated rejection in any of these transplants, transgenic pig transplanted hearts in non-human primates. So I am not sure this is the correct paradigm. We clearly have to do a lot of work, and most of our work, of course, is focusing and overcoming vascular rejection. But I simply raise the point about whether or not cell-mediated rejection will turn out to be the big issue that we thought it was going to be.

Hyperacute rejection, all I will say is that expression of human complement regulating proteins in transgenic pigs protect the heart and kidney from hyperacute rejection, however, transgenic grafts eventually succumb to vascular rejection, and as I said, rejected xenografts show no evidence of a cellular infiltrate.

Vascular rejection, or delayed xenograft rejection, is mediated by alpha-Gal antibodies, in part, in that alpha-Gal antibody removal significantly delays vascular rejection. The alpha-Gal antibody responds to a transplant is dominant with a 20 to 50-fold induction of anti-pig anti-Gal antibodies after removal of the graft. Now our protocol for the treatment of vascular rejection is to use the transgenic organ, therapy to control alpha-Gal antibodies, and we have tried immunoapheresis, both non-specific and specific, drugs both non-specific and more specific. And Dr. Logan will talk about the development of TPC, or therapeutic patalated (phonetic) compound, which has been critical in the success we've achieved in the laboratory, and obviously a general background in the suppressive regimen.

Now preclinical studies using the non-human primate is highly resource demanding and very time-consuming and expensive. We have been performing this for now more than five years. Essentially it is like running a clinical transplant program. One is not going to achieve success in these preclinical

studies unless the recipients of these grafts are treated essentially with the same degree of care and effort as patients. This is our lab with both a donor and recipient operating procedures simultaneously. I show this because of the need for long in-dwelling lines in our non-human primates, and of course we cannot change these lines as we do in humans every week, and it raises all sorts of collateral infectious disease issues that we will not see in humans. And it is clear to me, as someone who has been performing clinical heart transplantation now for 23 years, that managing humans will be much easier than managing the non-human primate.

I should also say that in our studies, we made a decision from the beginning that we would only use an immunosuppressive regimen that would be tolerated by a human patient. We were not interested in immunosuppressive regimens that were so toxic that they would have no clinical applicability. So philosophically at the beginning of this program, we pursued only regimens that we felt we could use safely in human recipients. We have had to develop our own baboon blood bank, and to give you an idea of the degree of the sophistication that is necessary to have success in this work.

In southern Minnesota, where of course Mayo Clinic Rochester is located, we have also built sophisticated transgenic buyer facility which I think is the only functioning buyer facility of its type in the world that was developed with criteria hopefully where the -- the transgenic pig donor organs could be used for potential clinical transplantation.

This is just the rough space of the facility, to give you an idea of the complexity. The -- The food is irradiated, the water is chlorinated, the air is changed frequently. This is a highly controlled environment for the production, hopefully, of safe transgenic pigs.

This is the finder of piglets being developed in an aseptic bubble by cesarean section prior to opening the facility. These are the piglets being born and they are then passed into the facility. These are the finder animals in this facility, so their bacteriology is completely monitored, controlled, and understood.

These are the first group of piglets we had from the finder animals in this transgenic facility. Now what has been our experience in this preclinical program of cardiac xeno? First of all, I would emphasize that the results I am presenting are on the heterotopic model. This is not a life-sustaining model. If we look at the longest duration of surviving, functioning transplanted transgenic pig hearts and baboons at Mayo, we have gone from a longest survival in 1998 of 15 days, to 113 days, nearly four months in 2002.

This recipient, who is 113 days out, died of medical misadventure due to a drug -- a drug error, but this was a very healthy animal, with a well-functioning heart. That is this heart removed after 113 days, and those of you whoever look at hearts, this is healthy heart muscle that looks much the same as our own. Histologically there is the vast majority of the heart shows excellent histological preservation. So this tells us what can be achieved.

More importantly, are what are the median times of these functioning transplanted transgenic pig hearts. That is by -- These are in defined groups, prospectively planned from the point of view of immunosuppressive regimen. We have gone from a median survival in 1998 of 15 days, doubled it by 2001, and more than doubled it again in 2002. So that prospectively, in a group of 10 consecutive animals in whom the immunosuppressive regimen was planned ahead of time, our median survival is now 76 days.

Of some considerable interest is that of these 10 animals, three or four, that the heart did not stop beating, but was beating normally, but the recipient animals died of CMV infection, or pneumonitis in at least three or four of these 10 animals. This is a section of lung showing a CMV inclusion. I would like to acknowledge the collaboration and very valued help from Dr. Marion Michaels on this panel, who is our

infectious disease collaborator in this preclinical program.

So indeed this median of 76 days would have been considerably higher had it not been for loss of recipients due to CMV disease. I believe we have good strategies going forward to control this problem.

Where are these results in the overall context of the literature? To the best of my knowledge, and if anyone knows of any updated results, please let me know at the break. But 99 days is the longest survivor from the Novartis and Immutran program. We, of course, as I've said, have exceeded that, but really more importantly is that we now have nearly two dozen animals going greater than 50 days, and seven animals that have gone greater than three months. When we do one of these transplants now, we have every expectation that these hearts will beat for three months.

Now what is the appropriate requirement for preclinical application? A couple of suggestions, one has come from CBER, which suggests that a reasonable expectation for success is required. I think that that committee are very prudent in not making a formal exact standard. However, a suggestion was a 50 percent survival at 90 days. This is a median of 90 days. This, of course, would be in the orthotopic physician, and the life-sustaining physician. But a range of alternative views were expressed.

The International Society of Heart and Lung Transplantation suggested 60 percent survival of life-supporting grafts at three months, saying some animals had to survive longer, and that the above had to be achieved in the absence of life-threatening complications from immunosuppressive therapy. These recipients that I am describing are healthy, well animals, who of course are supervised by an independent veterinary medicine group.

There are serious challenges in this model that we really have to be aware of, and that is that the management of complex medical and surgical protocols in non-human primates is extraordinarily more difficult than in clinical practice. You cannot do your daily chest x-ray, take your daily blood tests, have a discussion about symptomatology.

Some human reagents may not be testable, and there is no guarantee, of course, that results in the non-human primate will be directly transferable to the clinic. Now, we shouldn't assume they will be worse. I actually think they are going to be a lot better, but we don't know. However, the non-human primate remains the best source of preclinical data at the present time.

The potential initial clinical indications for xenotransplantation, really the goal is to provide additional treatment alternatives for patients with end stage organ failure, and the comparison on outcomes will be with other available treatments, and not with allotransplantation. It is not reasonable to compare it to allotransplantation in early application, but rather compare it to what are the alternatives for that individual sick patient at that time.

Potential clinical strategies include a bridge to allotransplantation in the heart context, or heart or kidney transplantation in non-allotransplant candidates where controls would be the best medical treatment, and of course progressing hopefully to trials with other organs and definitive therapy for end stage organ failure.

The challenges clearly are, first of all, to overcome vascular rejection. I think it is clear from what I have presented today that we are making substantial and ongoing progress in this area, and other challenges that were overtaken by alternative technologies: Unforeseen infectious disease issues are a prohibitive regulator environment. Any of these things, I think, could provide serious challenges to the eventual clinical application of xenotransplantation.

In summary, we have the longest survival of heterotopic cardiac xenografts to date of 113 days, the longest median survival to date of 76 days, which is triple what is in the current literature. More cardiac xenografts are functioning for longer periods with nearly two dozen surviving more than 50 days, and 16 recipients now surviving greater than two months.

Current results do not yet justify clinical application, because we need to establish results in the life-sustaining model. And in fact, all of our work beginning now is focused on transferring to the orthotopic life-supporting model. There are intrinsic limitations to the primate model, and we may have to re-visit some of these issues as we decide what the preclinical requirements will be.

We need time and support to develop this work as industry funding may diminish. It is no secret in this room, the industry funding is going away. If there are no alternatives to industry funding, xenotransplantation will die. There is no question about that. And I think most people in this room are very aware of that situation. Clearly we have strategies in place for future progress, in terms of pig cloning, and knockout technology, additional gene therapy, additional transgenesis in pigs.

My final comment would be that the advantages of biological replacement, including the personalizing of donors physiologically and genetically remain powerful. With the xenograft heart, there is likely to be no need for anticoagulation. Even the latest small rotor pumps are running into thromboembolic programs, whether it is the Jarvik 2000, or the DeBakey pump. Thromboembolism has been the challenge of artificial devices for 40 years, and it continues to be. Xenotransplantation would likely avoid the need for anticoagulation.

The xenograft has an intrinsic power source, as opposed to the requirement of artificial devices to have power sources constantly. As a result, the xenograft is totally implantable and has a biological interface, as opposed to a metal or plastic interface.

There is the ongoing possibility of adding or deleting whatever genes we need to produce a better donor for the number of sick patients who need it. So these advantages to me make xenotransplantation a compelling technology for the future care of the sick.

And my last slide is just a little bit of personal reflection. These are calendar years beginning in 1968, this is 1984, this is one year patient survival and percentage in clinical heart transplantation at Stanford University. I would simply say that it took 15 years from the first clinical heart transplant until one year survival reached 80 percent, and Medicare approval was achieved, 15 hard years of one year survival beginning at 20 percent to get to 80 percent. This is a long and a difficult road. But I see nothing in our research effort that tells me that this is not an achievable goal. Thank you very much.

Agenda Item: Pre-clinical Graft Survival in Pig-to-Primate Models of Heart Transplant

DR. SALOMON: Thank you, Chris. We'll have the second presentation now. This reminds me of when I was a fellow between 1980 and 1994 and woke up to the headlines being that the Mass General had announced that, after a careful review of human transplantation, that it was a failed proposition and that it shouldn't go forward in any way, shape, or form in clinical practice. And it was only a couple of years later that the Mass General basically ate those words and started the heart transplant program. And I think we all know the position that heart transplantation has right now. So I think these cautions about this are well taken.

The next speaker is John Logan. He's Vice President of Research and Development for Nextran. And the topic of his presentation today is Pig To Primate Models of Heart Transplant, the Immunological Aspects.

DR. LOGAN: Thank you again to the committee members for inviting us to speak today concerning pig to primate xenotransplantation. What I thought I would do is review our immunological experiences and our thoughts in terms of the immunological problems associated with xenotransplantation and the strategies that we've utilized to try and overcome those problems.

In doing so, I'll probably tend to start at the beginning of hyperacute rejection and move through the process. Some of this work, clearly, is repetitive of what you have heard in previous meetings but, I think, worthwhile in setting the stage for our understanding of later rejection processes. If you look at the picture of xenograft rejection as we see it, obviously we try to separate it into stages which may not necessarily be accurate neurological stages but are helpful in thinking about the process.

The initial phase of rejection is hyperacute rejection, in which the grafts are lost immediately post-transplant. And this is very well understood, and it can be routinely overcome by a number of strategies. If it is overcome, this occurs in minutes to hours. And in days to weeks, we get a process of acute vascular rejection.

There appears to be largely an antibody mediated process, primarily probably anti-gal antibodies, but also antibodies of other specificities. If we can mitigate the effects of these anti-gal antibodies, we clearly get an anti-nongal or just general anti-pig antibody response, which is obviously not surprising in this system and has really been a challenge to try and overcome.

In addition, we anticipated early on that we would see acute cellular rejection that may, in some ways, be stronger than an allograft. However, in four or five years worth of research, we have not yet seen any significant evidence of acute cellular rejection or indeed, any evidence of cellular infiltrates, even under conditions in which the regime is immunosuppressor less than optimal.

So if you look at our process to try and overcome these immunological challenges in terms of hyperacute rejection, we've utilized transgenic animals. In terms of acute vascular rejections, we've used a combination of therapies associated with mitigating the effects of anti-gal antibodies, either a pegulated (phonetic) carbohydrate molecule which we call Nex1285, or in the use of Gal knockout animals.

I won't speak about our transgenic animals today since there are two other groups which will speak in detail about these. And then also the control of these anti-pig non-gal antibodies and how we've used immunosuppressant agents to try and control that.

I've focused my talk largely on immunological aspects of rejection, but clearly there are other non-immunological factors that can contribute. We know of a number of incompatibilities between the pig system and primates, in particular with regard to the coagulation cascade. So there are likely to be some non-immunological factors. Although, in our transplant we've seen little evidence of that. So we suspect that the majority of challenge that we've seen in the cardiac xenotransplantation really has been immunological in nature. And lastly, is the aspect of cellular rejection.

Let me just take you through each of those stages step by step and show you some of the data that we believe supports these notions. The hyperacute rejection process is immediate. It's clear that it's immediate by preexisting antibodies of an anti-gal specificity. Those anti-gal antibodies bind to the endothelium, activate the complement cascade, and the organ is destroyed.

There are many ways to overcome hyperacute rejection. And I think today that is not viewed as a significant problem in xenotransplantation. These include the use of transgenic animals with human regulatory proteins, the physical removal of antibody, the systemic complement, or systemic complement inactivation, or a combination thereof. And clearly, in a preclinical setting, one can routinely abrogate the

effects of hyperacute rejection.

This is one example that was published now many years ago which is showing the benefit of having complementary regulatory proteins present. These are just either a combination of either CD-59 or CD-55 or CD-46 alone. In either combination, if we just focus on the use of kidneys for example, these are four nontransgenic transplanted kidneys into baboons, and all of them underwent hyperacute rejection.

In the case of transgenic kidneys expressing complementary regulatory proteins -- in this case it's a combination of CD-59 and CD-55 -- hyperacute rejection was overcome, but these grafts were lost within a week to two weeks post transplant.

We see a similar situation in the heart, although a little more variable. We saw one hyperacute rejection, for example, but the rest were largely overcome. Hyperacute rejection as opposed to a nontransgenic controls.

However, routinely in the presence of immunosuppressive regimes that we thought would be compatible with clinical transplantation, we consistently saw a graft loss of these transgenic organs. That graft loss, we attributed to the induction of anti-gal antibodies post-transplant. And this is two pieces of data that suggest that that's the case.

If we look at the response of the primate to these organs, what we see is, if we tied the anti-gal antibody levels to one or arbitrarily pretransplant, the graft is rejected here somewhere around 12-14 days. We remove the organ and continue immunosuppression. What we see is this large induction of anti-gal antibodies, both of IgG and IgM in this case. Although more routinely, it's an induction of IgG and not an induction of IgM. And this is seen consistently in all of our transplanted transgenic organs into baboons with a normal immunosuppressant regime.

If you look at the antibodies that are present on the graphs and look at their specificity, what we see is that the antibodies eluted from the graft contain anti-gal activity. And this is just showing that anti-gal antibodies are eluted from the grafts.

In terms of cytotoxicity, the cytotoxicity of these antibodies, again, is all Gal. And there's no contribution from non-gal antibodies. If you look by other means, such as facts analysis, to look for non-gal specificities, we see little evidence. So the vast majority of antibodies that bind to these grafts are Gal in nature.

In addition previous published data from our group and other groups have shown that the physical removal of anti-gal antibodies in the serum of these animals can prolong graft survivals. Again, pointing to the role of anti-gal antibodies in acute vascular rejection.

So acute vascular rejection, which occurs somewhere between one and three weeks post transplant, we think, is largely motivated by anti-gal antibodies. We see again, binding of antibodies to the grafts. We see a vascular rejection process characterized by thrombosis and ischemia, no evidence of consistent cellular infiltrate, induction of anti-gal antibodies, and the removal of these antibodies can prolong survival.

The induction of these 90 Gal antibodies is largely resistant to the action classic immunosuppressive agents. We found no agents that could control this antibody response effectively. That led us to the development of Nex1285, which is a combination of polyethylene glycol linked to synthetic alpha Gal containing trisaccharide. So this is a polymer, a polyethylene glycol backbone linked to the trisaccharide.

If you look at the effects of Nex1285 -- this is data that's been published in the last couple of years so I'll go through it relatively quickly. If we contain nontransplanted animals, there's three baboons in each group, and each baboon is either treated by specific immunoapheresis in which we physically remove the antibody from the animals or treated with Nex1285. And they're treated five times, and then treatment is stopped. And then we monitor the animals in a recovery period. So there's no immunosuppression, there's no transplant. What we see in the physical removal of the antibody -- and this is looking at IgM anti-gal antibodies, we see the same thing with IgG. We see there's ratcheting with immunoapheresis. Then when immunoapheresis is stopped, the antibodies return relatively quickly to pretransplant levels. However, in the case of the Nex1285, antibody levels go down and remain down during this fifteen day period and don't really recover. This is a thirty day period where they're back to about 10% of their preexisting levels.

And even three months later, they're still substantially reduced. The half life of this molecule and blood is such that by three days essentially all of the initial dose is removed.

If you look not just at the antibodies themselves but look at the antibody secreting cells -- and this is peripheral antibody secreting cells. If you look at immunoapheresis, this is anti-gal antibody secreting cells, we see immunoapheresis has no effect as we would anticipate, on antibody secreting cells, against Gal, either IGM, or IGG.

However, Nex1285 causes a rapid reduction of peripheral antibody secreting cells, although, after removal, they do recover. And this recovery occurs, though even at the same time, there are still very low serum levels of antibodies. So this molecule not only binds to the antibody itself and probably removes it from the circulation, but also appears to have some effect at least on peripheral antibody secreting cells.

If we looked at the effects of Nex1285 on graft survival, these are two sets of transplants. One is a set of transgenics, and then the second set is a set of transgenics with the addition of Nex1285. What we see here is, in the case of the transgenic animals, we see a graft survival of somewhere around five to six days which is fairly consistent in the model with our previous results. We add Nex1285 and push that survival out to a median survival of around three weeks, so around 21 days.

If you look at the affects on anti-gal and antibody induction with no Nex1285 present, if you look at anti-gal here what we see is, again, standardized to one pretransplant. The organ comes out of this induction of anti-gal IgG. In the case of Nex1285, immunosuppression continued as it is here, post-transplant. The next 1285 is stopped after rejection. We see no induction of anti-gal antibodies. Rejection of this system is typical of what we see, which is large areas of ischemic damage, some areas of thrombosis, but no cellular infiltrates. If you look at what comes off these grafts in general, in the vast majority of these graphs, if you look at anti-gal antibodies, we see no evidence of anti-gal antibody. In one case we did see evidence of anti-gal antibody even in the presence of Nex1285. But this is one out of somewhere around 20-30.

If you look for other specificities, apart from Gal, we see quite a different pattern of activity. If you look here there are two targets. These are antibodies eluding from the graft. We see the same picture with antibodies in the serum. If we look at binding to pig splenocytes or baboon splenocytes, what we see in the case of a rejected transplant, which is here, versus a nonrejected, which is here -- so this graft was lost due to a non-immunological reason. We see binding of antibody to splenocytes in the green line. We try to compete it off with either free sugar or treatment of the splenocytes with alpha galactosidase. And we see no difference in the binding. So as antibody, which binds quite well to the splenocytes, is now competed off with Gal sugar, suggesting a non-gal response, that antibody doesn't bind to the baboon splenocytes.

In the case of nonrejected grafts, we see no evidence of binding. If we do that in a larger scale, these are a series of four transplants. One transplant we lost for technical reasons at day zero, and the other three transplants were lost for immunological reasons at various time points post-transplants ranging from 24 days on the short end to 62 days on the long end. Again, this is a facts analysis looking at pig splenocytes as a target. And the animal from day zero, we see no binding. In these rejected grafts at various time points, we see binding in the green line to the splenocytes. And that binding is not competitive with either free sugar or alpha galactosidase treatments, suggesting a non-gal specificity.

If we look by western blot analysis -- and this target antigen here is endothelial cells, or it can also be pig splenocytes because the molecular weights are slightly different. In endothelial cells we see, essentially, a background binding at day zero transplants. And what we see here with these three transplants at various time points, is we see bindings of major bands at somewhere around 60 kilodaltons with a minor of band at somewhere around 70 kilodaltons. And this is fairly consistent in the grafts that undergo rejection.

So what we think is going on is that in the case of transgenic animals with Nex1285 present, we overcome hyperacute rejection, we control induced anti-gal antibody response, but we haven't optimized the immunosuppressive regime. So we still get a significant induced anti-pig antibody response. Again, in these cases, we don't see any evidence of a cellular infiltrate.

This slide is a series of ten transplants in which we try to optimize the immunosuppressive regime. These were heterotopic heart transplants to baboon. We utilized the transgenic pig. We utilized Nex1285, and we utilized an immunosuppressive regime that consisted of rapamycin FK-506, and induction therapy with anti-C 20 monoclonal antibody, which is an anti-B cell monoclonal.

What we saw was a median survival of 76 days with a range from 55 days to 113 days. Three out of ten of these graphs survived for greater than 90 days. Our survival in this study was limited largely by non-immunological factors, including CMV infection. We lost three or four of the animals to CMV infection in what looked like baboon CMV, not pig CMV. And we also had various other technical reasons for losing these grafts.

Only three of these animals succumbed to a vascular rejection process. So by controlling the immunosuppressive regime, targeting anti-gal antibodies, and utilizing transgenic pigs, we think you can obtain sustained grafts viable.

This is just an H & E of a graft at 103 days. This is an animal that died, I think due to CMV infection. We do see some ischemic damage here, but largely large areas of the graft look normal. In fact, you can look at large pictures of the graft, it's a largely well preserved heart.

If you look at antibody deposition at 103 days, this is IgM. We see a focal deposition of IgM antibody. This would be in contrast to a graft in which we see acute vascular rejection, which would be a widespread distribution of both IgM and IgG antibody.

So in summary then, we believe that if we can control antibody mediated rejection, this can result in prolonged pig to primate graft survival. We clearly have some work to do in terms of protocol optimization, controlling CMV infection, simplifying the protocol a little bit. But clearly one of the limiting factors to this study is that these are heterotopic grafts. And while extremely useful for immunological purposes and point to a pathway to obtain long-term graft survival, clearly we need to repeat these results in the life supporting position. Thank you very much.

DR. SALOMON: Thank you, John and Chris, both for just beautiful presentations and also for being on

time and concise. Well done. So I think at this point we can have some questions on these two. There will be more time for questions later. So I see this as a dynamic process. If you don't get your question answered in the next five to ten minutes, it doesn't mean there won't be ample time to come back to it again. It's just that I would like to try to stay on time and make up a little bit of time as well. Questions for either people? Megan?

DR. SYKES: Well, I would like to thank both speakers as well for beautiful presentations, encouraging data, and for really putting the problem of xenotransplantation in perspective, compared to the history of allotransplantation and the artificial heart.

I do have a question about the immunosuppression and its efficacy against the T cell response. Although you both pointed out that there were no cellular infiltrates in these grafts, I think the fact that you do get non-gal anti-pig antibody responses is suggestive that there may be a T cell response going on. In our experience, we have implicated T cells in the development of an anti-gal -- a non-gal antibody response. So although you may not see the infiltrates at this point, at the time points that you've been able to follow the animals to, you may still have a T cell response that is limiting survival.

DR. SALOMON: John or Chris, do you want to comment on that?

DR. LOGAN: I think there is probably a T cell component. These are clearly largely antiprotein antibodies, so one would believe that there's T cell help in making these antibodies. What we have consistently seen though is that while one would believe that there should be a T cell component to that rejection based on the nature of the antibodies, those T-cells themselves do not come into the graft. So whatever response there is, it clearly is different than an allograft in that we've done many transplants now, probably 50 or so transplants and haven't seen a single cellular rejection. It's all been an antibody mediated pathology, even under circumstances with very suboptimal levels of calcium inhibitors. So it's quite surprising to us that we don't see that. Although your point related to the induction of these antibodies, I think, is certainly a valid point.

DR. ALLAN: I wanted to get at the virological aspects. And Marian, I guess, has been involved in this. Since baboon CMV was present, there's potentially other baboon viruses that might have been present. So the question I have is, have you looked in the tissues that necropsied to see if, first of all, PERV is present in the baboon tissues and then was any of the baboon viruses present in the pig tissues, such as simian foamy viruses or some of the H Papilloma viruses, things like that.

DR. MICHAELS: The PERV question I can turn back over to John, since I wasn't doing that. But the baboon cytomegalovirus, I was able to find, by PCR obviously, some baboon CMV in the pig hearts. But there was always a fair amount of baboon mitochondria there as well, depending on which assay I was using for finding baboon cells. So I wasn't finding specifically more baboon CMV in the pig hearts compared to the amount of baboon cells that were there.

And I don't believe the histopathology -- we haven't compared all our notes because we're keeping it blinded to which animals and things -- but I don't know that the pathology in the pig heart showed any inclusions from my recollection.

I did not find pig CMV to any great extent. Sometimes, in one or two animals, I believe I was able to amplify some pig CMV. But really there wasn't that much there. And in the vast majority of animals, there was a really overwhelming amount of baboon CMV.

In terms of the lymphotropic viruses, that's an area that I have been investigating and don't have enough of the data done. But I am finding some of the lymphotropic viruses as well, not so surprising, in a very

highly immunosuppressed baboon model. I have not been finding the pig lymphotropic virus to be expressed, but again that's very very preliminary and needs further evaluation. The simian foamy viruses, I wasn't looking for them so I didn't actually do those experiments, but it brings up a good point.

DR. ALLAN: Because it would be nice if you had like a standardized virological program, especially in necropsy because you have these beautiful tissues that you could really look at.

DR. LOGAN: From each of these animals with necropsy, all the tissues are taken. They are all being processed for PERV analysis. The data isn't in yet. So all the samples have been taken. Histologically, in the heart, there's no evidence of inclusion bodies. The inclusion bodies we saw were either in the lung, as you saw today, or in the kidney, I think, in one animal.

So again, this is disseminated CMV. It wasn't specific to the pig organ. Also, all these pigs come from a barrier facility. So there was a full virological and bacteriological analysis to these pigs prior to transplant. So we know what we transplanted. And we can look, obviously post transplant.

DR. MCGREGOR: Perhaps I would just add one point to that. Although CMV has been a challenge here, it's exactly what we would expect. I mean, it's what we see in humans. It's what we would expect. The good news is that it's controllable with currently available therapeutics.

DR. SALOMON: So the question I have is over time, Chris, you saw a significant improvement in your model. What you didn't let us in on is what was it that changed over the several years that gave you such a significant improvement in mean survival time? I ask that only in the context of sort of, so what can we expect next?

DR. MCGREGOR: I think a number of factors come into play. First is the ability to do a substantial number of transplants and study groups prospectively rather than anecdotally in one or two recipients. That's been a tremendous advantage, building up experience over time.

The use of Nex1285, that's clearly made a difference. Better infectious disease management has made a difference, particularly in control of CMV. And I think that we have optimized our basic immunosuppressive regimen. And my own belief is that the erasure of rapamycin to our former regime contributed significantly to these results.

As I eluded to, this is a difficult model. And there isn't a learning curve in terms of the optimal use of the current immunosuppressants. We use FK-506, rapamycin, NTC20, Nex1285, and a brief induction of ATG. So that's basically the regimen. There's really no hidden ingredient here that we're keeping from you. It's basically currently available therapeutics.

DR. SALOMON: I'll just point out, in a theme that's come out already and, I think, more appropriate than all the scientific details for this particular committee, is that the progress you made required an incredible up front investment in the infrastructure in the development of this difficult model. And it sort of underlines how critical maintaining opportunities for these models to develop and how difficult the money aspect of this whole story is going to be, if money continues to drive in the opposite direction from supporting xeno research. Chair?

DR. VANDERPOOL: I'm incredibly appreciative of both of these presentations. And it's fortuitous that you're here. The questions because the questions that will be posed to us from the FDA directly bear on the research that you are doing. And I hope that at the time when we discuss these queries the FDA will put to us that you will feel free to participate and to offer your ideas also about what the committee should decide and should seek to say about these issues.

DR. SALOMON: Richard and then Megan.

DR. KASLOW: Two things about the immunosuppressive regimen. One is, you didn't mention specifically any toxicities that accumulated as a result of that. And the other question, the follow up is, is this regime, do you think, sustainable over a longer period of time?

DR. LOGAN: The toxicities that occurred were what one would expect from the use of these drugs. And they, of course, decreased dramatically as our experience grew in applying these drugs and this model.

The baboon kidney seems relatively resistant to the nephrotoxicity of FK-506. We have learned to target our doses. And indeed after sixty days we are now reducing the targeted levels of FK-506 and rapamycin. So it's the ability to do substantial numbers of recipients that has allowed us to -- in fact, what we've done in the last three months is significantly reduce immunosuppression in this model. So I think that we're using levels that we would use in the clinical practice. Maybe a little bit more in the first six to twelve weeks, but thereafter, standard targeted levels that one would use in humans.

DR. SALOMON: Last question, Megan.

DR. SYKES: I have a question about the translation of this model to a life sustaining orthotopic heart transplant, obviously, a very important goal before you go to the clinic with a xenograft. Am I correct in understanding these are conventional sized pigs that you're using?

DR. MCGREGOR: The size of the donor pigs is dictated by the size of the recipients. The recipients are baboons which weigh anything from 8-16 kilos. So these are very young pigs.

DR. SYKES: But they're standard sized pigs, they have the potential to grow very large, right?

DR. MCGREGOR: Right, they're standard pigs.

DR. SYKES: So what about the growth of these hearts as you start to get longer survival? Do you think that's going to be a problem? Have you seen evidence of growth in the transplants that you've already performed?

DR. MCGREGOR: The model doesn't allow us to answer your question. The model is a beating perfused heart model. The only part of the heart that bears any load is the right ventricle. And it is of interest that you do see right ventricular thickening in these long term grafts because that is the only part of the heart that is ejecting blood under any force. So that would suggest that there be an adaptation. But we need to do the orthotopic experiments to be sure.

Now, in human experience of course, the hearts grow with the recipient. So that if one puts a heart in a three or four kilogram baby, a heart from another donor child who has died, that heart does of course grow to full adult size as the recipient grows. So the human experience would suggest that the heart will grow with the recipient, but we have to do the experiment.

DR. SALOMON: Thank you all very much for that first part of the session here. The next speaker this morning is Julia Greenstein, President and CEO of Immerge BioTherapeutics. The topic of her presentation will be Xenotransplantation: Miniature Swine Genetic Engineering and Preclinical Transplantation. Julia?

Agenda Xenotransplantation: Miniature Swine Genetic Engineering and Preclinical Transplantation

DR. GREENSTEIN: Thank you. I would like to thank the committee for the opportunity to update you on the work that's been going on at Immerge BioTherapeutics and our various collaborators, both industrial and academic. My goal is to update you on the genetic knockout of the Gal transferase which we presented to you at the last committee meeting, to update you on our preclinical work, and also to quickly run through some of our recent work in the area of porcine endogenous retroviruses.

The mission of our company is to generate pigs and treatment paradigms to allow the use of porcine cells, tissues and organs to be used to treat human diseases. I'll go very quickly over this because John Logan really gave a very elegant description of immune reactivity of discordant xenografting, in that the first step needed by anti-gal antibodies is hyperacute rejection, the subsequent antibody driven delayed vascular rejection, which we feel very strongly is also involved in the anti-gal antibody, and then finally what we're doing to mediate the cell mediated rejection we expect to see, and also the T cell mediated events that generate anti-nongal antibodies. And I will skip the more detailed slides since we have already discussed them today.

Suffice it to say, that the initial antibody mediated reactivity is all pointing at that Gal alpha (1,3) Gal sugar modification that pigs make that humans and old world monkeys do not. And because of that, we felt it would be very important to knockout the alpha Gal transferase from the porcine genome in order to move the transplant survival times out to approach acceptable clinical time frames.

We were encouraged to produce the knockout because we thought it would give us a permanent solution to the natural antibody problem and would avoid any unnecessary recipient treatment. It would leave the recipient anti-gal antibody response in tact. And, at least in the early phases of the work, we were worried about biological feasibility. We felt somewhat comforted by the fact that Gal knockout, per say, was demonstrated biologically feasible by old world primates and man, and also by the production of the Gal knockout mouse.

We reported to you last time that the production of one gene alpha Gal transferase removed piglets in work that was accomplished at the University of Missouri by Dr. Randy Prather. Three of those female pigs are still living. And we have just gotten the first generation of offspring from those animals.

So we went on in our drive to make a two allele targeted Gal knockout. The first step was that we had both female and male, one allele target in animals born. Pigs reach sexual maturity at about six to eight months. The one allele knocked out pigs were shown genetically to miss that allele, but there was no change in the biological expression of Gal, which is as we had expected.

So we needed to move from the one allele targeted animals to a double knockout. And we did that, are doing that, in two ways. The first is to breed both the initial founders and the secondary, in our case, male founders, together. So updating you there, the females have been bred to normal males. I'll take you through the generations that will take you through the double knockouts. But the females have been bred, and they have resulted in healthy offspring. The second and faster approach is to go through a second round of nuclear transfer cloning with another step of genetic modification. And I'll update you on our process there.

I apologize for this slide. It's actually a mistake. This was meant to show you a half blue and half white, one allele knockout founder animal bred to what should have been shown here as a totally blue normal male. And in that case, you would expect 50% of the offspring to show the one allele targeted expression. That then gave you the opportunity to take the second generation from those animals down here and breed male to female one allele knockout animals, in which case, in the F2 generation, 25% of the offspring

would be double knockout. So by having male and female single knockouts at this point, we're about to start this breeding currently.

But a quicker way, although technologically more challenging, is to take cells from the one allele knockout founders, isolate cells, and then either genetically or physically select cells for the expression, to go from one allele, shown here in the blue and white -- it's hard to see, to a fully knocked out cell line. We did that with a combination of antibody and complement. We also tried a second genetic targeting, which was not successful. And then to take those fully knocked out cell lines and generate new founder animals that would be double knockouts.

We had our first animal born, again in the laboratory of DR. Randy Prather at the University of Missouri on November 18th, 2002. She's a single offspring. The lab named her Goldie. And we have been characterizing the expression of Gal in cells from her tail and also from her blood. This graph shows you IB4 binding which is a lectin that binds to Gal alpha (1,3) Gal. And these were the cells prior to nuclear transfer cloning. And you can see normal pig cell expressed Gal alpha (1,3) Gal is shown from the shift from the negative control to this positive dashed line curve.

The cells that we started the cloning effort here are shown in the green. And you can see that they show no expression of Gal alpha 1,3 Gal on their surface by the lectin binding methodology. You can also see that cells taken from the nuclear transfer clone were analyzed again. And this shows you positive control pig, normal pig expressing Gal in the purple, human cells which do not express Gal shown in the green here, and then cells from the nuclear transfer cloned animal which are actually shown here to be even less bright by the lectin binding cells which are fully negative.

We then went on to do genetic analysis to understand the mutation that we had selected for in the production of this nuclear transfer animal. And as we go backwards through this PCR, you can see that the normal animal has two copies of the wild type Gal transferase gene. The first generation, one allele mutated animals have a wild type gene and a slightly larger, by virtue of the addition of our targeting vector, a slightly larger gene. And you can see that when we shift over here to the first lane that the nuclear transfer double knockout animal has only the targeted allele and no evidence for the wild type gene.

For those of you that are up to the date on the work from PPL, which was recently published in "Science", this genetic mutation is very different than the PPL result where they saw a wild type allele but it was just subtly mutated, presumably to have a nonexpressing gene product. This animal has either one copy of the targeted allele and a copy of it by genetic crossover, or we have deleted that part of the chromosome and only have our initial targeted allele.

Just after that, our colleagues at Infigen, using a second generated male cell line generated in the same way, with antibody and complement selection, had three male pigs that were born just in January, on the 13th. So we now have four founder double knockout animals, one female and three males. So we're obviously very excited about taking that work further and beginning to transplant organs that are fully negative for Gal alpha 1,3 Gal.

What I would like to do now is update you on the rest of our programs, both looking at safety and the control of the immune reactivity against pig antigens. We are using Major Histocompatibility Complex inbred miniature swine derived from the laboratory of Dr. David Sachs at the Massachusetts General Hospital. These pigs grow to about 200 or 300 pounds at full adult weight, as opposed to large outbred swine that can grow up to 1,000 pounds at full weight. They are fully inbred in the Major Histocompatibility Complex, and largely inbred in the rest of the genome. This office has some quality advantages in controlling the variability of the herds. They've also been maintained as research animals

for over thirty years on a fully vegetarian diet which allows us to also control any endogenous infectious disease concerns.

We have been studying the PERV transmission in these miniature swine. And these MHC inbred lines were tested for the expression of both human- and pig-tropic porcine endogenous retroviruses. All the lines produced -- up until our recent publication -- produced pig-tropic porcine endogenous retrovirus.

We identified a subset or a subfamily of pigs that had a very low frequency of human-tropic porcine endogenous retroviruses. And with those low producer lines, we identified families that lack the ability to produce human-tropic PERV. This result has been presented it here as well. And it was recently published in the journal of virology.

We then took this work further and tried to understand the nature of the virus that was effective in some of those strains. And we identified the fact that only recombinant viruses were detected in the human-tropic PERV. The full length genomic PERV A and B, which both can affect human cells when derived from other pigs were defective in the small number of animals that we tested.

And we've shown that any virus that manages to get into the human cells is actually a recombination event between PERV A and PERV C in the inbred miniature swine. So it's possible so far that these miniature swine lack replication competent loci and therefore recombination is a prerequisite.

We've gone further on in identifying families and their expression types. And we've looked at the ability to infect the human indicator cell line, 293, as well as ST IOWA, which is the pig cell line that is infectable by porcine endogenous retrovirus. And in studying a non-transmitting animal that had been bred to a transmitter, we found four offspring from this breeding that lost the ability to infect human cells and, for the first time, were also negative for the infection of the pig indicator line ST IOWA. We're very excited about this subfamily and are in the process of carrying this work further by breeding these animals to each other to see whether we can fix this characteristic in the herd of animals. And if we can, this would offer yet another level of safety protection from the issues about porcine endogenous retrovirus spread due to xenotransplantation.

Another way that porcine endogenous retrovirus could potentially cause a problem in a human recipient of xenotransplantation is recombination between porcine endogenous retrovirus and human endogenous retrovirus. We all have fragments in our genome of human endogenous retrovirus. So we wanted to try and ask this question within the in vitro systems that we had accessible to us. So what Clive Patience and his group did was to take cells that chronically express porcine endogenous retrovirus and mix them with cells that were capable of expressing wills that were capable of expressing human endogenous retrovirus. So he co-cultured both human cells with the pig virus in it and then isolated porcine endogenous retrovirus virions from those chronically infected cells and asked, by PCR, was there any co-packaging of porcine endogenous retrovirus and human endogenous retrovirus.

And the results from an experiment like this are shown here, where you can see that in the area of that sucrose gradient where whole virus would be isolated, we could identify porcine endogenous retrovirus. And then he looked at the expression of a variety of known human endogenous retrovirus to see whether they were co-packaged with the porcine endogenous retrovirus. And you can see to the limit of detection in these assays that none of the human endogenous retroviruses were co-packaged the porcine endogenous retrovirus. So the conclusion from experiments like this is that human endogenous retrovirus co-packaging is extremely rare in its in vitro system, and therefore unlikely to be a significant concern for future xenotransplantation, although this is clearly an in vitro model of something that could happen in an in vivo situation.

We also have a program in collaboration with the laboratories of Megan Sykes and David Sachs on trying to induce tolerance to pig antigens, as John Logan very eloquently presented. If we can get around the expression of hyperacute and delayed xenograft rejection by eliminating the transferase, we see still have a T cell mediated event to worry about, whether it be T cells that induce antibody to the non-gal antibodies or whether it's direct cytotoxicity to a non-gal organ.

And in work that was issued in the laboratory of Megan Sykes, she was able to show that in a mouse model and then in a pig to mouse model, that if you could take pre T-cells that immigrate out of a bone marrow and get them to differentiate in a pig thymic environment, you could accomplish two things. The first is that you could negatively select any pig reactive T cells and they would be clonally eliminated. And you can also generate a very healthy and vigorous normal immune response and populate the periphery in the animal. In the case of the initial experiments in a mouse model, and subsequently in some primate experiments, you could generate active T cells that would be tolerant to self, tolerant to pig because of the pig thymic environment, and also defend against any other pathogenic challenge.

David Sachs' group took that initial work that Megan started in the mouse into the primate model. And I'll just very quickly show you two series of experiments. The first was to form what was called a thymo-kidney. So this is a pig kidney, to which his own thymic tissue was injected the kidney capsule. The thymo-kidney was allowed to vascularize in the pig as an autologous transplant for three more months. That pig thymo-kidney was then translated into a baboon, and we were able to study, a month after that transplant the ability of that pig thymic tissue to allow normal T cell differentiation and ask are those T-cells tolerant to pig.

We knew we would lose the kidney because of the Gal transferase. These were actually human complement inhibitor transgenic animals. So we could get the kidneys to survive on the order of thirty days, we would then remove the transplant. But we could study the immune system and the recipients long term.

What you're looking at here is T cell reactivity pretransplant, in the light purple bars, to third party baboons. So the animal has a normal immune response. Prior to transplant it responded to the hDAF donor as well as unrelated MHC inbred miniature swine.

Thirty days after this transplant -- and the induction therapy for this transplant is to remove all the peripheral T cells with a combination of antibody and cyclophosphamide and then to use doses of immunosuppressive drugs to keep the T-cells down. Thirty days after the transplant, the animal has recovered its ability to respond to third-party baboon and you can see is hyporesponsive to the hDAF donor as well as unrelated third party pigs. So we've reduced, by the transplant of this thymo-kidney, hyporesponsiveness at the level of the T cells to pig antigen challenge.

We wanted to switch that thymo-kidney paradigm over to ask whether we could transplant vascularized thymic lobe. This is a confusing slide, but just let me summarize it by saying that what we're looking at on this side is the vascularized thymic lobe recipient. And this is a control. What we have been able to show in the majority of time points post transplant is that, using vascularized thymic lobe, we see the same hyporesponsiveness to the donor pig challenge that we saw in the thymo-kidney experience, whereas you can still see very good reactivity to the third-party baboon, showing that the animal is immunologically competent.

We were able to show, in these series of animals, the initiation of thymopoiesis in baboon cells going through the pig thymus. We looked at immigrants from the vascularized thymic lobe animals shown in the dark symbols. And you can see the beginnings of expression post-transplant in the periphery of double positive CD4⁺ CD45⁺ cells in control animals that either were given no thymic tissue, a sham, or

were given thymocytes as a control. There was no thymopoiesis detected when looking at the number of CD4+/CD45+ cells in these animals. So we've seen the initial signs of active thymopoiesis in these vascular lobe transplants.

So in summary, we have supported a collaborative effort to generate miniature swine incapable of expressing Gal alpha (1,3) Gal epitopes. We're very excited about, very soon, taking organs from those initial founder animals and putting them into our primate transplant models. We've worked and continue to work on the characterization of porcine endogenous retrovirus in our miniature swine donors. And we have shown that thymic tissue transplantation using complement transgenic pigs can aid in controlling the xenogeneic immune response.

And we feel that the combination of the Gal knockout with the ability to control the T cells in these baboons will allow us to move forward in extending organ survival times in the near future. This work is a huge collaboration, both at the industrial level and academic level. And I've just highlighted the directors and lab managers in each of the areas, and each of our collaborators that have been involved in some of this work. Thank you.

DR. SALOMON: Thank you very much, Julia. Questions? Yes?

DR. SWINDLE: Yes. Frequently, when you're making transgenic and knockout models, unexpected side issues show up, different systems than what you would think would be effected. Has anything like that shown up in this breeding line?

DR. GREENSTEIN: So far, in the single knockouts and the double knockouts, we haven't seen any consistent problems with these pigs. They're growing at normal rates. And they seem very healthy. Their reproductive rate in the first generation appears appropriate.

In the first generation after nuclear transfer cloning, we do see some abnormalities in the flexor limbs in some of the animals. And actually our first animal was born without one eye. But we have found that the subsequent breeding of that animal gets rid of that. So it was probably just a reprogramming insufficiency. And the initial nuclear transfer event doesn't seem to be carried through in the offspring.

DR. SALOMON: Alan?

MR. BERGER: I had two comments and then one question. It's really more to the people speaking so far. The first one had to do with a comment that was made. There was a challenge. And the challenge was whether xenotransplantation would be overcome by other alternatives. It seemed like an odd place to put a challenge. That would be something that we would celebrate, if there was something else that came that was better than xenotransplantation. And that hooks on to the comments that money has not been invested in as large of numbers today, it seems to be going by the wayside. And it might be useful for the committee -- who's really not here to promote xenotransplantation but to report and advise to the Secretary of Health and Human Services -- it might be useful to have someone from the investment community come in and evaluate xenotransplantation because obviously they're not looking at it with the same glowing results that we seem to be hearing here. So there is some conflict that might be interesting to this community to hear. If the investment is not coming in, there may be some reason. And we should all probably hear that.

The second comment has to do with something that was actually recommended before, I didn't make this recommendation. But as I'm watching this and listening as to how pigs are being raised and how they're being cloned and what happens to the pigs. And I'm looking at the baboons and wondering what kind of process they must be going through as they're having these foreign organs being put into their bodies.

And animal welfare is a part of this committee. And it seems to me that at some point, which I thought we were going to have by this point, some presentation that has to do with animal welfare. It might be very useful to the committee.

My third question, my actual question, which is something I had asked before, which really has to do with these knockout and double knockout animals -- we've all heard about the cause and effect of changing the genetic make up of the animals. We see it in breeding all the time, whether it's cows or pigs or turkeys and cats and dogs, that if you're trying to get rid of or to express a particular characteristic, there may be very negative changes that might occur in those very animals, things that may be expressed later on. So that you may be creating a herd of animals that may be expressing something very negative that might actually show up if the animal, the baboon that's being used, or human that's being used, much much later down the road. So the question I have for any of these speakers, are you looking for something like that? Are there any tests being done? Have you observed -- or is it something that you're worried about, that as you're genetically modifying these animals you could be creating something else that might actually be negative or worse. Thank you.

DR. SALOMON: There's a lot there to talk about.

DR. GREENSTEIN: I'll just try to answer the last question in that we've been -- you know, these are obviously very early days. The first animals for us were born in November and the second in January. We're monitoring the animal's health, well being. We'll be looking at the reproductive characteristics as they age, and we'll be studying this as well in the pig and looking at ramifications in the baboon. I think we can, you know, we know at least right now that the double knockout is not a genetic lethal, which was always a concern. We do have the evidence in the mouse and ourselves that the expression of Gal Alpha (1,3) Gal does not seem to be a total requirement for life in other species. So we'll be studying that as these animals get older.

DR. SALOMON: Chris?

DR. MCGREGOR: A brief response to the first part of your question. Those of us who are physicians would be delighted if we didn't need to be here. We would be delighted if there wasn't a need for xenotransplantation. The reason that we are here is because there is such a tremendous unmet need in patients dying with endstage organ failure. So yes, we would be delighted not to be here, but the need is very clear.

DR. SALOMON: Michael, do you have any follow up comments on what kind of things could be done to better monitor transgenically engineered animals for possible development of unexpected problems down the line that my effect the welfare of the animals?

DR. SWINDLE: It's something that's actually being looked at internationally in the mouse world. And it's mainly based on clinical observations, things like she was talking about; do they breed, what is their weight gain, things of that sort. It would actually be easier to clinically monitor pigs than it would be mice. And things that would be related to animal welfare would be more apparent, I would think, in the larger end.

But largely it's going to be clinical observation and monitoring of weight gain, breeding, things of that sort. Any number of biochemical changes, it's possible that you may or may not be able to detect down the line. So it's, generally speaking, a good overall, perhaps clinical, type of evaluation.

DR. SALOMON: Harold?

DR. VANDERPOOL: As we know, in the very recent turmoil over cloning that has been advanced by the aliens -- actually the Raeliens. But since they visit regularly, alien sites, according to their website, I'm not sure what to call the group. But one of the arguments against human cloning for years has been all the problematic results that have occurred to Dolly and others. So I do think that it would be good to see if there's a systematic way to chart the adverse changes that may be occurring as these genetic experiments continue.

I entirely agree with the comment, that it would be better if weren't here because there was not human suffering over these issues. At the same time, it is important for us to ask these types of questions in the hope that we get some type of understanding of what is happening to the animals as they're being genetically engineered.

DR. AYARES: Could I speak to that briefly? I think we need to separate issues related to nuclear transfer and reprogramming in the first generation. And Julia brought up it briefly. In subsequent generations, we now have experience with cloned pigs, and you mentioned Dolly as well, that go by five or six years now, with the pigs just the last three years. One of the things that's important is monitoring their reproductive health. And then also we're keeping a database, internal database, on the health issues related to our pigs. And that's something that the agricultural industry is also looking for, because now we're trying to come to decisions on whether or not we're going to clone livestock for agricultural purposes. So the USDA is also trying to establish a similar collection of data on just body size, on meat quality, on various issues related to the pigs and cows from an agricultural point of view. So I think that database is forthcoming.

And as we breed in subsequent generations, we're losing a lot of those reprogramming areas. We haven't seen any abnormalities in progeny from Dolly, for example. We don't even know if Dolly's arthritis is even related to the cloning process. So we would anticipate that a lot of those things would go away in subsequent generations.

DR. VANDERPOOL: One other quick comment for Julia Greenstein. I think it's exciting to see you going beyond genetic knockouts to the thymus research, which we all know is going to be the next -- that is the next major step in being able to overcome other barriers beyond hyperacute rejection. It's good to see what I would call a visionary degree of anticipation for the new dimensions of modification that will need to be done for truly effective transplants to occur.

DR. SALOMON: Can I make the suggestion to the chair that we change things just a little bit and take a break now and then come back and put DR. Hering's and Ayares' together with one question period to both give the group a break and then to also save some time by putting them together there?

DR. VANDERPOOL: That's an excellent suggestion. I suggest that we should be back here pronto at 11:00 so that we can proceed with all due diligence. Thanks.

<BREAK>

Agenda Item: Islet Cell Xenotransplantation

DR. SALOMON: Welcome back from the break, and some day we'll do research on the most optimal way to get everyone back from a 10-minute break in less than 20 minutes, but I'll look for grant proposals on that later. So the next speaker is Dr. Bernhard Hering, who I guess is one of those who hasn't made it back from break. I don't know if this proves the null hypothesis, or what. Okay.

Well, it's my pleasure to introduce Dr. Bernhard Hering, who is an associate professor of surgery, and he

is Director of the Islet Transplantation Program at the University of Minnesota in Minneapolis, and I think it is easy to say one of really the world's major figures in advancing islet transplantation. Bernhard.

DR. HERING: Thank you, Dan. I would like to thank the committee for giving me the opportunity to present results on islet cell xenotransplantation. The studies have been done at the University of Minnesota and more recently also done in close collaboration, and also funded by Immerge BioTherapeutics. I will cover background and rationale of the present results in the pig to non-human primate model, and I will briefly review future research needs and objectives.

Diabetes is a very prevalent, serious and expensive disease. The data is available, and despite progress that has been made in diabetes therapy, the overall situation has not changed significantly. Diabetes, Type I diabetes results, as well as Type II diabetes, from an inadequate amount of functional pancreatic islets, in Type I islets are destroyed by autoimmunity, and in Type II there is an incomplete compensation of the islets to meet the increased demand imposed by insulin resistance. For this reason, islet replacement has been proposed as a treatment.

Human pancreas transplantation was the very first form of islet replacement, now, the feasibility of human islet transplantation has been demonstrated. Porcine islet transplantation and surrogate islet transplantation are being developed. Dr. Shapiro and his colleagues demonstrated the feasibility of islet transplantation in Type I diabetes using steroid-free immunosuppressive treatment with an IL2 receptor antibody Rapamycin and reduced dose Tacrolimus 85 percent one year survival in terms of insulin independence and 71 percent at two years. And the results have been confirmed at about 10 institutions around the world.

The approach is limited by the number of available donor organs. Two to four pancreata are required per transplant, so with this technology we will never be able to perform more than 2000 transplants per year in the U.S.

Now very briefly, what are the results that have been achieved? Here you see the glucose profile of a Type I diabetic subject. Please note frequent episodes of hypoglycemia in the profile after islet transplantation and discontinuation of insulin. So insulin independence, normoglycemia have been demonstrated. Recent results suggest improved quality of life, and it is conceivable that as we proceed, we will be able to show a beneficial impact on the secondary complications, life expectancy and cost utility.

Porcine islet xenotransplantation clearly has potential to solve donor shortage problems. The function of Porcine islet xenografts in human recipients is unlikely to be compromised by physiologic incompatibilities. Pig insulin has been used very successfully for decades before human insulin became available. The risks of disease transmission remain unknown. Mechanisms underlying rejection and ability of immunosuppressive medication to control xeno islet evoked immune responses have yet to be studied in relevant preclinical models.

There are two notable characteristics of islet xenografts: First, islet xenografts are primarily avascular xenografts, and become revascularized by host endothelium. And the Gal epitope is not expressed on adult pig endocrine cells. Now, we have learned about rejection mechanisms in solid organ transplantation. We face hyperacute, acute, vascular and acute cellular rejection in islet transplantation. It has been hypothesized that islets are only subject to acute cellular rejection, because as I pointed out the Gal epitope is not expressed and islets are revascularized by host endothelium. And the questions therefore are: are islets subject to hyperacute rejection, and if islets are facing cellular rejection, can one prevent cell-mediated islet xenograft rejection using treatment protocols that have proven effective in preventing islet allograft rejection. And we wanted to do these studies in relevant preclinical models, and

those are interportal xenotransplantations of adult porcine islets in diabetic -- in diabetic non-human primates. So the first point we needed to document is that islets are viable, and this was done in an islet allotransplant model in diabetic pigs, and here you see reversal of diabetes and normoglycemia in diabetic pigs immunosuppressed with Cyclosporine Rapamycin, clearly documenting the potency of isolated pig islets to reverse diabetes.

We also wanted to document the ability to immunosuppression to prevent islet allograft rejection, and here in collaboration with the Diabetes Research Institute in Miami and Novartis, we performed transplants in diabetic non-human primates, and were able to show prevention of rejection using Basiliximab Rapamycin derivative, RAD, also known as rapatacolimus, and FTY 720. And we also documented the efficacy of a second immunosuppressive protocol with respect to prevention of human islet allograft rejection. This is a protocol rapid ATG, soluble TNF receptor fusion protein, Daclizumab Rapamycin and reduced dose Tacrolimus, which then is replaced by MMF. So we did those studies in Type I diabetic subjects, 6 to 8,000 islet regulants per kilogram, and all eight patients achieved insulin independence after single donor islet transplantation.

So then we thought we are ready to test our hypothesis and ask in this preclinical model first with the hyperacute rejection, so we transplanted islets into rhesus monkeys, no immunosuppression and protocol necropsies at 12, 24, 48 or 72 hours after transplant. Function survival was studied, and in a second and third study, we tested the ability of immunosuppressive medication that was proven effective in preventing islet allograft rejection. Now, here the first study non-immunosuppressed diabetic rhesus monkeys and you see that Adult porcine islets transplanted intraportally promptly reversed diabetes and normoglycemia is maintained for 72 hours in non-immunosuppressed animals. Porcine C-peptide becomes positive after transplantation and remains positive.

On histology, we see insulin positive islet tissue. We see increasing infiltration with CD3 positive cells and also macrophages. I don't show all the results. I would just like to summarize. Very few B cells, no NK cells and minimal IgM and C5 and C9 deposition on islet surfaces only.

Now in the second study we tested the efficacy of this immunosuppressive protocol in diabetic non-human primate islet xenograft recipients, and as you can see, animals become normoglycemic soon after islet transplantation, and this animal remains normoglycemic for about 20 days. C peptide also remains positive. And on necropsy, insulin positive islet tissue is demonstrated.

Now a second recipient shows different outcome. There is a brief period of normoglycemia and insulin independence. We performed a second transplant, which really didn't change the outcome. Nevertheless, there was positive C-peptides, so we speculated that islets are dysfunctional because on necropsy we see quite a number of intact islets.

Here a third animal was sacrificed around day 10, and again, islet tissue present on necropsy. Now, we wanted to address this question, and we asked whether intra-islet macrophages, Porcine macrophages, become and remain activated. And we did quantitative PCR using liver specimens, and we saw two to four-fold increase in Porcine specific in looking better after transplantation, suggesting that Porcine macrophages are activated.

Now in the final study we tested with Basiliximab, plus Rapamycin, plus RAD, plus FTY 720, a protocol that prevented islet allograft rejection in non-human primates, is effective in preventing islet xenograft rejection.

The first animal showed a very promising outcome. We were able to reverse diabetes. The animal remained normoglycemic through day -- about 40, 45, 47. And at necropsy, we found, as previously in

other studies, a number of intact insulin-positive surviving islets.

Now, in this particular animal, we didn't see any anti-Gal or any anti-non-Gal, anti-pig antibody response. You see here no absorption, and then the titers after absorption using a Gal matrix or a Gal matrix and pig cells. So there were titers present before, but no increase after transplantation. Both were IgG and IgM.

The second animal, the same, sees reversal of diabetes, but then the graft dysfunction, hyperglycemia, we resumed insulin treatment. A second transplant was performed, without achieving normoglycemia. And here a third animal, again, a period of normoglycemia for about three weeks, followed by a period of -- of dysfunction. In this animal, we saw an increase in non-Gal anti-pig antibody titers, both IgG and IgM after transplantation.

No Gal expression on islet endocrine cells in situ and after transplantation, here we look at a native pig pancreas day five after transplantation, and day 21, and the lack of staining in transplanted islets suggests that pig islets are revascularized by host endothelial cells.

What are the lessons from the first three studies? Intraportal pig to non-human primate islet xenografts are not subject to hyperacute rejection and reverse diabetes promptly in non-immunosuppressed recipients. It is possible to restore normoglycemia and insulin independence for up to six to seven weeks in immunosuppressed recipients. The fact that xeno islet rejection is delayed, but not prevented by immunosuppressive protocols that are effective in preventing allograft rejection of islets, clearly suggests that we are dealing with different mechanisms operative in islet allograft and islet xenograft rejection.

Islets may become dysfunctional, possibly due to altered regulation of intra-islet donor macrophages or xeno islet directed innate or adaptive immune responses, and islets facing cell-mediated rejection in immunosuppressed and non-immunosuppressed animals dominated by CD4 and CD8 T-cells and macrophages and islet xenografts elicit an anti-pig, but not an anti-Gal antibody response.

Future research needs and objectives: Clearly limiting the risk of retrovirus transmission is of particular importance. We have now started in collaboration again with Immerge using SLADD miniature swine donors that failed to produce human-tropic replication competent PERV. And we think it is clearly of paramount importance to define with increasing precision the molecular and cellular basis for islet xenograft rejection in the pig to non-human primate model, and evaluating the same model, the safety and efficacy of regimens tailored to the specific needs of islet xenografts once those are defined.

What we do right now, is we try to determine the specificity of xenoreactive non-Gal antibodies, and we perform partial liver lobectomies. Here you see a liver specimen that allows us to continue to monitor the animal, but also allows us to study intergraft events, including immunohistochemistry and also study at the messenger RNA level cytokines, chemokines and T-cell effector molecules.

We also have started in collaboration with Washington University in St. Louis, Dr. Mohanakumar to study graft infiltrating leukocytes to study whether T-cells in particular, whether CD4 T-cells are activated through the indirect pathway of recognition, and whether they respond to SLA Class 1 antigens, as he showed previously in reconstituted scid mouse models. We also need to address the fact that CD8 cells are clearly involved, and whether they are directly activated and recognize SLA Class 1 antigen, and we also need to address the mechanism of islet destruction, whether we are dealing with DTH versus direct cytotoxicity.

Finally, when to consider a clinical trial, clearly safety issues must be addressed. With respect to efficacy, we understand this needs a lot of consideration. We believe that normoglycemia and insulin independence for more than six months after xeno islet transplant in at least 10 of 15 diabetic non-human

primates could present such a benchmark. Those recommendations are adapted from the position paper that was already quoted earlier today and published in the "Journal of Heart and Lung Transplantation."

As I pointed out, this work was performed at the University of Minnesota in close collaboration with Immerge BioTherapeutics and also in collaboration with the Department of Veterinary Pathobiology at our institution, Dr. Mike Murtaugh and Dr. Mohanakumar at Washington University St. Louis and also at Massachusetts General Hospital, Drs. Mueller and J. Fishman. I would like to thank in particular Drs. Martin Wijkshrom and Nicole Kirchhoh for directing and coordinating the non-human primate studies, and also Hank Sherman for his guidance and advice, and also Clive Patience and Michelle Awwad. Thank you for your attention.

DR. SALOMON: Thank you, Bernhard. We're going to go in to the next one and discuss both together, so it is my pleasure to introduce Dr. David Ayares, COO and vice president of research for PPL Therapeutics to talk about genetic modification of pigs for xenotransplantation.

Agenda Item: Genetic Modification of Pigs for Xenotransplantation

DR. AYARES: All right. Thank you. I'd like to thank Mary Groesch and the organizers for inviting me today and to be able to round out the pig cloning story for the three groups that are represented today.

I'd also like to thank the Advanced Technology Program, which is a division of NIST, which funded a large part of our pig cloning efforts and the Gal knockout efforts, and as the xeno field is facing its own monetary challenges, so is the Advanced Technology Program, so a little plug in there for trying to keep that federal program alive as a funding source.

What I want to do today is just talk about where we are with the genetic modification of pigs, our cloning program, PPL Therapeutics, many of you know a lot of us from the Dolly work, but the company has actually been around since 1987, focusing on genetic modification of sheep and cattle to produce therapeutic proteins for biomedical applications from the milk of those animals, so the company got into the field to make those biomedical protein products more efficiently, but it also allowed us to very quickly enter the xeno field in the area of genetically modifying pigs for xenotransplantation.

We all know the challenges we are facing, whether it is hyperacute rejection, we need to deal with the acute rejection, as well as the cellular rejection and T-cell mediated rejection, the alpha-Gal work, the knockout work, I'm going to be talking about focuses primarily on the hyperacute response, but we are also going to be breeding into our pigs, and I'll touch on it throughout the presentation, strategies for dealing with acute vascular rejection, as well as the more chronic T-cell mediated rejection in order to get to the end here, which is hopefully long-term graft survival from xenografts.

Challenges of pig cloning, and some of these have been addressed, when it went from the Dolly work to then cloning cattle, cloning pigs is not nearly as simple. We had to initially use the best premier oocytes that we could. We are getting them out freshly from in vivo derived pigs. Pig embryo culture systems are not as well-defined as they are for sheep and cattle, we had to overcome that barrier as well. The protocols that worked very good for sheep and cattle did not translate well at all to pigs for a number of reasons. And then because pigs are litter bearing, you also have the issues that you've got to have four successful nuclear transfer embryos, at least in the earlier stages of implantation, in order to maintain that pregnancy. In the absence of that, you may actually lose the pregnancy very early on. So we developed strategies for maintaining the pregnancy with very low embryo numbers. These are hormonal treatment to the foster mothers before you implant the embryos.

Despite those challenges, after about two years of hard work, we were able to report now, almost three

years ago, the first cloned pigs, and they were named for various -- after various transplant surgeons, and as well as the dot com, because at that time it was a good thing to affiliate yourself with a dot com, hopefully trying to bring the valuation of your company up. That was our CEO's idea. Now, of course, dot com is not where we want to be. I don't know where we want to be, actually. You tell me.

This is just a summary of our current nuclear transfer efficiency, so we've gone now to where cloning is really a reproducible tool. It is no longer a research endeavor for us. We typically reconstruct about 800 embryos a week, do up to six embryo transfer surgeries because we are not able to culture embryos very efficiently, what we do is we just put about 150 of them into one recipient in hope that we get litters of anywhere from three to five animals at the end of the gestation period.

Our pregnancy to term rate is about 50 percent. So if we put them into six recipients, we expect to get about three of them giving birth to litters, so pretty much every day we do nuclear transfer now, and we do it two days a week, on Wednesday and Thursday, we would expect to have pregnancy and live piglets at the end, so it has become a very efficient procedure for us.

Now I'm just going to touch on the next step. Once we solved the cloning issue is the Gal knockout and where we are, again, we had significant challenges to overcome with gene targeting in a primary fetal fibroblast cell line. We all know that you can target in mouse SES cells very efficiently, about two logs more efficiently than you can in primary somatic cells, so we had to overcome the numbers game and the efficiency, or poor efficiency of homologous recombination in the primary fibroblasts.

Also because they are a primary cell line, they have what is called a Hayflick limit, which limits the number of population doublings that these cells have. So you've got to be able to do a number of genetic modifications to them, transfecting your knockout vector, select for those cells that have that rare recombination event, expand those cells to actually do the genetic characterization that says yes, we have a knockout, and you don't need many of them for PCR, but you can get fooled by a positive PCR results, so you have got to be able to get up to about 2 million cells, that is really pushing the limit of how many population doublings a primary cell has, so we needed to optimize the number of population doublings to allow all this. In the end, we were selecting for these targeted modifications with antibiotic resistance genes, like Neomycin and Hydromycin, and primary cells, especially pig cells, really don't like to these cells, so you really have to tweak the conditions for finding your rare homologous recombinant. Obviously you know now that that is very feasible.

This is just the structure of the alpha GT gene. It starts out with exon 4, 5, 6, 7, the business end of the molecule is really in exon 8 and 9. Most of it in 9, and there are a number of spliced products which can give rise to a functional GT gene product. I'm not go to go into the targeting vector, but if this is the endogenous gene, what we've done is we've gone in and inserted a selectable marker gene into the beginning of exon 9, so inactivating the primary business exon, the coding, the primary coding region of that gene. So you use the neogene not only to find your rare homologous recombination event, but also to interrupt, or disrupt that gene so it won't have any functional activity. You need to do that twice, because we have two copies of each genes. We need to knock out the first and then the second. This just goes through that procedure, where you actually then are starting out with wild type pig cells, so plus, plus pig cells, you are electroporating your vector, you played out your cells anywhere from 2 to 10 million cells in any given experiment, you isolate colonies, you expand them through a process that allows you to do a PCR analysis initially. Once you identify a PCR positive knockout cell, we freeze those cells away, because we don't want to expose them to more population doublings, because we have to clone a whole animal from this cell. So we wanted to have a stable karyotype and normal chromosomal makeup so we won't have problems with the animal later on. Then we also have to expand another population, or the same population, but not the one we froze down, in order to do the Southern blot analysis to confirm that we have the knockout.

This is a summary, and you probably can't read that, because I know when I was sitting in the corner I couldn't read the slides that were this size. We have four primary cell lines, this is work that has been published, so you can look this up in "Nature Biotechnology." We had three male cell lines and one female cell line from which we ultimately isolated three male single knockout cell clones and 14 female single knockout cell clones that we used for nuclear transfer.

We've gotten away from the laborious double nuclear transfer method, which is how we cloned the first pigs, to now an efficient single nuclear transfer procedure by sucking out the nucleus, or the nuclear DNA of that egg and putting in your genetically modified cell that has in this case a single gene knockout right into the perivitelline space adjacent to the oocytes' membrane. You give it a mild electric shock, which causes those two membranes to fuse, and the cell, the genetically modified knockout cell now dumps its nucleus into that egg, and that is what then develops after implantation of the pig into a single knockout pig derived from that cell that you put into the oocyte.

These were my Christmas present two years ago, a year and-a-half ago, and these were the Christmas pigs that had the single gene knockout of alpha-Gal, and now we've gone on, now, of course, to inactivate the second gene. This is just a confirmation that we indeed knocked out the first allele, so a Southern Blot analysis where you see a 7 kD band, which is indicative of the endogenous, or non-knockout gene that is still present in these pigs, and a 79 kD band, which is the knockout band that contains the 2 kD neogene insertion. Where are we now with our heterozygous knockout piglets? As I said we have both male and female cell lines. We have 27 male single knockouts, 37 female knockout piglets, all of them are Southern Blot confirmed healthy and normal animals. We also, as in Immerge's program has seen some abnormalities that have been attributed to the reprogramming process. A couple of them have had a syndrome with a large tongue, and that is similar to a human syndrome called macroglossia, which is an imprinting error, which one could expect as reprogramming errors associated with the cloning process.

Before we got into our gal program, we also had been generating transgenic pigs, transgenic for a marker gene, a GFP transgene. We also saw similar abnormalities in those pigs, albeit at very low frequency, so we don't attribute those abnormalities to the knockout, per se, but to the cloning process itself. In pigs it is actually a much lower frequency of abnormality than in sheep or in cattle, the highest abnormality rate being sheep, at least in our hands. The animals you see up there, the 20 or more males, and the 30-plus females are all healthy and normal. And we need to use those to breed up our herd of double knockout animals.

So there is really two strategies we are going about similar to what Julia described in getting these double knockout pigs, which are really going to be the pigs that we need for the primate work to test whether or not this actually works or not.

The youngest males were born around March -- the oldest males around March time frame, they became sexually mature in -- this past December, and so we could expect the earliest double knockouts from just standard breeding around April or May time frame of 2003. By standard mammalian genetics you would expect 25 percent of the offspring to have double knockout just by breeding two single knockouts together, so that is one way of getting there.

This being a very competitive environment, and our need to get the data out as quickly as we can in order to bring in funding as well, we have tried to accelerate the process, and that is to knock the second gene out in fibroblast cells. And similar to what was done in the other program that was described earlier today. So we already knew we had heterozygous knockout cells, fetal-derived cells that came from the first generation, first trimester fetus. That was the starting material. We incorporated a unique selection method. We identified a toxin, Toxin A, from clostridium difficile that bind specifically to the alpha-Gal

and alpha GT receptor and kills those cells that have that receptor, and so a way of selecting for double knockout cells would be to expose these cells to this toxin. Only those cells that were alpha-Gal deficient would actually survive. That is how we then identified our double knockout cells, and then used those for the second round of nuclear transfer to generate double knockout animals. And this really saved about nine months in the program.

And this is outlined on this slide. So what we did, the toxin A selection on single knockout cells, we obtained one colony. You only need one. 6ADB1 was the name of the colony, and it was selected on the basis of surviving in toxin A, and having no cell surface expression, as identified with a Gal-specific lectin called GSIB4.

When we looked at the lectin staining, though, we saw this was a mixed colony often because you are dealing with colonies of cells growing in a petri dish, they can be contaminated with non-knockout cells. About 80 percent of the cells looked to be double knockout, so rather than going ahead and cloning with those cells, which were a mixed population to put animals on the ground, we did a second round of nuclear transfer. We took another fetal rederivation, we found that of the four fetuses that we took, three of them were double knockout again by cell surface lectin staining, and those are the ones we used for a third round of nuclear transfer to produce the double knockout pigs that I am going to talk about in a second.

So the key there was that we wanted to be able to generate animals that were double knockout right out of the gate, and the other thing is that we can do three rounds of nuclear transfer, actually now we know we can do four rounds of nuclear transfer, so you can clone from a clone from a clone from a clone and still get healthy animals at the end of the process.

So these are the fetal cells. So 6ADB1 is the primary colony, B1 through 4 are the four fetal derivatives. As I said, three of those four cell lines were actually identified to be negative for cell surface alpha-Gal, that is 1, 2, and 4. So they didn't show any lectin staining. They are also resistant in a complement lysis assay to human complement media lysis, indicating that they were not being seen as having alpha-Gal on the surface, as recognized by human complement.

The odd thing, though, is when we did the Northern and Southern Blot analysis to prove that we'd knocked out the second copy of the gene, it didn't look like it was knocked out by the analysis that we looked at. We did both Northern analysis and Southern analysis, and we didn't see what we were expecting to see. So they didn't appear to have any cell surface alpha-Gal, so we did DNA sequence analysis of the second GT allele, and we found that the reason for the absence of Gal on the surface of these cells was that we'd had a novel point mutation, a fortuitous event, which in science you know occurs and we all try to take advantage of it as often as we can. Because we did the Toxin A selection, rather than trying to select by the Neomycin resistance again, we identified this tyrosine to asparagine mutation. We believe this is a natural point mutation, that it was not induced by the process, it is a transversion event, which makes a change in the second base of the business part of the molecule, which is exon 9, which is right in the middle of the catalytic domain for Gal transferase. As such, it is a complete functional inactivation of Gal transferase. From a regulatory point of view, we would see this as an advantage, because products that have antibiotic resistant genes are probably going to have a little higher hurdle rate for getting through the regulatory process, so what our goal would be is to breed animals that are homozygous, double knockout, where both alleles have this point mutation in them.

And that way we wouldn't have the Neomycin resistance genes going forward in our product. These are the double knockout piglets, the first ones are a litter of five, four of which survived, we have two subsequent litters of one, and three double knockout animals, so that it is definitely not a lethal, as Julia indicated. This was just recently published in "Science" on January 17th.

Just to confirm that the tissues from these pigs are completely negative for alpha-Gal by the criteria we used, we looked at a variety of tissue sections. You can see there heart, skin, pancreas, intestine, a whole variety of tissues from one of the piglets, from the first litter that died, and also then compared those to a wild type age matched newborn piglet, and with both the GSIB4 lectin, as well as a commercially available monoclonal antibody against gal that was described by Galili, these tissue sections from the knockout piglet were completely absent for cell surface gal expression with those two antibody tests, and the wild type pigs, of course, were positive. We confirmed that on cells from the subsequent two double knockout litters as well.

This is just staining, this is GSIB4 staining of one of those tissues we looked at. This is a vessel in a liver. You can see there is a lot of endothelial cells, which we do expect to be gal positive in a wild type animal, and is completely negative in one of the animals, the double knockout pigs that we looked at. And this is just one section. You can see a very similar result with whatever tissue section you wanted to observe.

We wanted in vivo confirmation that these things appeared to be gal negative. We don't want to just rely on the cell surface characterization of these pigs, so we did an in vivo experiment. That same pig that died, we took islets from that, and in collaboration with the University of Pittsburgh and Tom Starzl's group with the Starzl Transplantation Institute, we isolated islets from this pig very soon after it had died. They were purified at the University of Pittsburgh and they were transplanted into double knockout mice. So double knockout mice have a very low titer against gal, because they don't have a gal gene themselves, and we compared islets from double knockout pigs going into double knockout mice with cells, islet cells coming from normal wild type pigs going into the same model. So there were three transplants done with wild type pig cells into these knockout mice, and there were three transplants, sorry, with wild type cells up here, and double knockout cells down here. There was no induction of an anti-Gal response in vivo when transplanted with double knockout pig islets. There was an induction in all three cases, as you would expect, upon transplantation of islets from wild type pigs. So it is an in vivo confirmation that they are not seeing gal in the surface of these pig tissues.

We also then looked at the double knockout pigs at anti-Gal levels, because, again, the pigs don't have a gal gene, they shouldn't be making gal enzyme. As they are exposed to this particular sugar in their normal daily life through eating, and exposure to microorganisms, they should develop an anti-Gal response. And you can see the bars here are the gal anti-Gal antibody present in a one-month-old double knockout pig, a two-month-old double knockout pig, three and four-month-old double knockout pig. So as they are getting older, they are getting an increased titer against gal, as you would expect from gal an animal that was gal negative.

We did age match controls. You could see a little blip in two of these animals, as far as their level of anti-Gal. Of course, if they were making a significant amount of gal, and they were expressing this anti-Gal response, if the gal is an issue, they would be getting autoimmune disease, which they are not.

As far as future directions, we are going to go ahead, as I said, with the natural breeding up of these animals. So in April, May time frame, we should have anywhere from 20 to 30 double knockout pigs available for preclinical and clinical studies. So I'm not going to talk to you about primate studies here today because we haven't started those yet. Those are to begin in the April, May time frame. We are going to be looking at two primary focus areas: One would be organs, primarily kidney and heart. Initially that work will be in collaboration with Starzl Transplant Institute, also with additional collaborators at other institutions. Also islets from these double knockout pigs, the goal looking not only at long-term survival, but of course function in these model systems.

We are also going to be proceeding with natural breeding of double knockout pigs that have this point

mutation, so a phase two product is going to be an animal that does not contain antibiotic resistance genes in the final product animal. We are just now looking at designs for building out our SPF pig facilities. Most likely they are going to be adjacent to the primary transplant hospital. We envision at these facilities there may be two or three in North America, another one in Europe, another one in Asia or the Far East, adjacent to the primary transplant center. So we, as you saw earlier, you need cesarean rederive our pig lines, which I would call dirty at this point, not a very nice word, but they are from an infectious disease point of view, into an SPF, or clean facility.

We will be looking, then, assuming we get favorable outcome from the primate trials to going to IND for human clinical work in 2005. As I mentioned at the beginning of the talk, we are not only focused on alpha-Gal knockout, we also, through a collaboration that we have with Robert Lechler at the Hammersmith Hospital at Imperial College of London, have developed strategies where we are overexpressing anticoagulant gene, such as TFPI and Hirudin, to address the loss of anticoagulant associated with acute vascular rejection, also a down-modulation of VCAM-1 adhesion molecule, which induces an inflammatory response. Again, some of these delayed xenograft responses we are also going to be breeding in complement regulatory genes, DAF, CD59, possibly other complement inhibitor genes to mop up any residual Gal sugars which could be an issue in transplantation. And we have a T-cell tolerance program, where we will be pretreating the recipient with a tolerogenic cell such as a dendritic cell to induce T-cell mediated tolerance. So it's a strategy where initially we have to start with gal the Gal knockout animal, our platform animal, that will breed in, or clone in these additional gene modifications to deal with the later stage rejection processes.

As far as PERV elimination and reduction, that is going to be a big part of our program going forward. It has not been a big part of our program to date. We have been focusing on the embryology aspects, on the molecular biology aspects. We have very limited financial resources which we are hoping that scenario is going to be changing for us, so we are going to be starting to look at, and are starting to look at the issues of PERV in our population, and this is just Southern Blots of looking at PERV A, and PERV B, PERV C is not on here. This is actually from a paper by Stoy et al., in 1997, and this one as well looking at PERV B, and in the first lane is a mini pig. No. The first lane of this one is a large white pig, which we are using. Lane two is the mini pig. Lane 3, where you see fewer copied genomic copies of PERV, is the Meishan pig. And the last lane is something, a Pietrain pig, a double muscle pig.

You can see both the pigs we are talking about, large whites, and Nextran was talking about, as well as the mini pigs that have large numbers of copies of these PERVs at a genomic level, most of these are defective and not expressed. In the case of the Immerge pigs, they have been able to identify lines that do not transmit, so that is obviously a regulatory benefit. But with our experience in genetic modification of livestock, knocking out genes, and in sheep and in cattle and pigs, we are going to be moving towards systematically inactivating the PERV from our population of pigs, and that is going to be our goal over the next two to three years, is to actually eliminate that risk to our best degree.

I won't really go through this. This is just a list of organisms we are going to be screening from an infectious disease point of view. First, our initial pigs we have now, and then of course going into the SPF facility. So that is it. Thank you.

DR. SALOMON: Thank you. So a couple questions, and then we'll go on to sort of the penultimate thing of this, which is to get to the FDA's questions, so any pressing questions for either Dr. Hering or Dr. Ayares?

I think that reflects the time, as well as the excellent presentation. I'm sorry, Megan.

DR. SYKES: I have one question for Dr. Hering. When you mentioned the six month normoglycemia

time as a -- what you would consider an acceptable duration before going to a clinical trial, would you require that to be from an initial islet transplant, or would you include repeat islet transplants? I mean one of the advantages of the pig is that you can get repeated tissue as needed, and that is potentially an advantage with the inbred swine, or potentially a disadvantage, if you have an immune response to it, but if there are other factors, such as dysfunction for other reasons that are contributing to graft loss, repeat transplantation might be particularly valuable in that setting. So where would that fit into the equation?

DR. HERING: Thank you. This is a very, very important question. I think if you review the rationale for doing a second transplant, in islet allotransplantation, this is predominantly an islet mass point, so additional islet mass was added to reverse diabetes.

In islet xenotransplantation, one would assume you can transplant a sufficient islet mass with the very first transplant, so you would not need to repeat the transplant. At the very same time, I think, in islet xenotransplantation, of course, you know your donor tissue, this is very well-defined, and you would not bring in a different antigen at this point in time. I think it will all really depend on improved understanding of the immunology that is currently limiting islet xenotransplantation. We have to understand really what are the mechanisms that will really contribute to islet dysfunction or islet rejection six, seven, eight weeks after transplantation using the protocols that we have tested. Once we understand this better, I think one would know whether a second islet transplant from the very same donor strain would help address this problem of whether you are dealing with an immune response that would clearly target the second dose of islets as well. I think I understand the importance of your question, but I am not sure I have a good answer at this point in time. I think it is just dependent on better understanding of the problems that we are facing at this point in time.

DR. SALOMON: Harold.

DR. VANDERPOOL: The competition between the two of you at that corner of the table seems to be keen. I hope there is further competition, too, and wish you well on the successes. My one question is, and it may be a naive question, but what are the means of transplantation you have in mind? We have had former presentations on the use of encapsulated islet cells, and so on. Are you talking about just direct injections, or could you just say a word about that for someone who doesn't know the techniques you have in mind for the islet transplants?

DR. HERING: Yes. I think I just reported on non-encapsulated islet transplants here. There clearly has been progress in the field of encapsulation, and it is conceivable that with further refinements, one could probably use the immunosuppressive requirements in xeno islet recipients. This technology clearly needs also to be tested in adequate preclinical models. I am not aware of many studies in the academic setting that test encapsulated islet xenotransplantation in non-human primate models at this point in time. There is work being performed in industry, but I just don't know the results at this point in time, but I think clearly there has been progress, and it is conceivable that one will see proposals in the area of islet transplantation using encapsulation.

DR. SALOMON: Megan.

DR. SYKES: Just a quick question. There is some evidence that nonantibody dependent complement mediated destruction can affect initial islet function. Were your source animals modified -- genetically modified with complement inhibitors?

DR. HERING: No. Those are completely nonmodified pigs.

DR. SALOMON: Okay, thank you. So I think this morning leaves us with a nice update from everyone,

and I want to thank all the speakers on behalf of the committee for a series of excellent presentations that are, I think, very useful to the deliberations of the committee. Certainly they are left with lots of very interesting scientific questions, and I wouldn't begin to try and make a summary of what we've heard this morning, but I think that one theme is really where the next big step is going to catapult us, and that is the double knockout animals. There is no doubt, I think, from everyone's fine work presented today, that this is a major barrier to xenotransplantation, and the question next is sort of how far the field will get jumped forward as the first experiments go forward in non-human primates, and then hopefully I certainly would like to hope that they will be substantial enough to warrant clinical trials at some point. And that certainly focuses the committee, again, I mean we've stayed a course for xenotransplantation, and one never can read the future accurately, but I think as we step up to the next part here, which is the FDA's questions, it is perfectly reasonable for the committee to think that the path just continues to stay open for clinical trials. And so it makes our job and everything that we are doing very relevant, I believe.

So with that, I would like to introduce Eda Bloom. Eda is the chief of the Laboratory of Immunology and Virology for the Center for Biologic Evaluation and Research of the FDA and chair of the Xenotransplantation -- I want to get this right, Xenotransplantation Action Plan. Eda.

Agenda Item: Discussion of Presentations and Specific Questions Posed by the FDA

DR. BLOOM: Thank you, Dan and thank you, Mary, for keeping us so well in the loop and allowing this opportunity for us to be able to gain information from the committee based on the talks we've heard today.

Since, as Dan has so eloquently put it, the creation of these double knockout pigs make the field -- perhaps will make the field of xenotransplantation take quantum leaps forward, FDA needs to be in the position of being able to review the novel protocols as they come forward.

Today we have with us Dr. Richard McFarland and Mercedes Serabian of the Pharmacology and Toxicology Branch of the Division of Cellular Evaluation and Pharmacology/Toxicology Review of the new Office of Cellular Tissue and Gene Therapies. And Mercedes Serabian, the Acting Branch Chief, is going to present the FDA questions.

DR. SERABIAN: I know we are supposed to end in about an hour. I'll try to keep it moving, so hopefully we can stay on time with it.

Basically, as regulators and reviewers of the INDs, or investigational new drugs, that people will be submitting to FDA, we have the responsibility for determining the adequacy of the data that are submitted, thank you, to support the overall safety, if you will, of your proposed product, and your proposed indication. And by safety, I mean toxicity, as well as efficacy, or activity, or proof of concept. You may have heard those terms before. So basically the primary question we have relevant to today's meeting is please comment on the relevancy of the use of non-human primates as an appropriate preclinical model for predicting the safety and efficacy of Porcine xenotransplantation products for future clinical trials. And notice we've said "xenotransplantation products," which could mean whole organ, cell, or tissues.

I just broke it down real quickly to make it a little easier to read, and we can go back to, I have got about six various subheadings, if you will. The first is to consider things such as the transplantation procedure itself, and any associated risks. For example, in a non-human primate model how sufficient will the information on the sick animal mimic the relevancy to humans, and will the information on immune rejection be relevant to humans.

Okay. The intended function of the xenotransplantation product, such things as interspecies differences, size, we've heard hormone cytokines, various differences between the species, how will that preclude or inhibit the function of your particular product. One thing comes to mind for me for cell and tissue transplants and with whole organ, you are looking at the anatomical and functional integration of that particular implant or transplant in the species that you are using, and how will the local environment -- the environmental cues, if you will, affect the function or integrity of that particular tissue or organ.

Infectious disease risks, which we've heard a bit about, for example PERV primarily. How does the difficulty in achieving PERV infection of many non-human primates affect the utility of the model? For example, Dr. Carolyn Wilson from the FDA, as well as others, has concluded based on their in vitro work that non-human primate cells in vitro may not be productively infected by PERV. Where do we stand with the safety of that particular issue if non-human primates are used? Okay.

Okay, the potential for the use of immunosuppressive regimens. Again, we've heard a bit about that today. Again, optimal or different regimens developed for each non-human primate model. We've heard quite a bit about that today. And how relevant are they to the proposed human scenario. Will differences in human and non-human primate responses to pharmacodynamic affects, susceptibilities to the chemicals being used, or other immunosuppression, how will that affect the response in animals, and what is the relevancy to humans? The potential need for periodic and/or retransplantation for some xenotransplant products. For example, if it is going to be used as a bridge to allotransplantation, does that, for some, how that prior xenotransplantation study affects the ability to accept subsequent allografts.

And for cell or tissue implants, if for some down the road you do repeated dosing, repeat implantation of cells, how will that affect what you did earlier. You have the concerns such concentration of cells, volume of cells, cell dose, et cetera.

Okay, last but not least, which I think is very important, is the worldwide shortage of most non-human primate species for research use. For example, the certain species of non-human primate cannot be used in preclinical studies, even if their use is scientifically justified, where do we go? To non-human primate? To other -- to other non -- to non-primate species, or to other non-human primate species, okay.

Okay, what I am going to do is leave the list up here so everyone can take a look at it and keep it in mind. Maybe ideally we'd like to go down the list and potentially around 10 minutes a topic just because to try to keep on track. And, Eda, I don't know if you want to, or Dr. Vanderpool, if you want to control who lights up with comments or questions, however. Okay.

DR. VANDERPOOL: Sure. I think that the topics may end up overlapping.

DR. SERABIAN: Right.

DR. VANDERPOOL: My initial response is it is an incredibly important set of topics. We can only begin to make suggestions. In a sense, this entire set of topics presents this committee with a -- with a real agenda. Fortunately, as you said, the presentations we've had prepare us for that. Many of these questions are fundamentally scientific in terms of their assumptions and the degree of expertise with which these can be dealt with competently. So I hope that not only our own scientific members add freely, but also those who have made presentations that impinge on these questions will comment. So, sure, let's begin with, yes, well, I have just gotten a wonderful note from Mary. Dan is going to moderate the discussion. And I think that is the way it should be. I think a nonscientist trying to direct traffic on the freeway should have police training beforehand. So, Dan is going to moderate this discussion also. Thanks, Dan.

DR. SERABIAN: Dan, could I just make one comment? Also to consider, it is not solely a non-human primate study, or a group of non-human primates. It is what we look in toto, it is at a data package, in vitro, as well as in vivo information, which could be rodent and other large animal species, as well as non-human primate. Okay.

DR. SALOMON: Just a point of clarification here. I mean if I took this, up until that last sentence you just made, I would have dealt with this as specifically the relevance of non-human primates, and not dealt with non-human primates versus all kinds of others.

DR. SERABIAN: Actually, that was almost question number two we had, which we didn't put up.

DR. SALOMON: That is the second hour, I think.

DR. SERABIAN: Right.

DR. SALOMON: Eda.

DR. BLOOM: I think you can deal with non-human primates in the context of these other studies, which we'd also be reviewing.

DR. SALOMON: Agreed. So let's deal with the first one, the transplantation procedure itself, and any associated risks, non-human primates.

Chris, do you want to make brief comment here? We are going to have to kind of rock and roll through this, so if everyone can kind of make their key points, and then say there is five other things I could say, we could maybe get through this.

DR. MCGREGOR: In terms of the procedure itself, I, you know, I wouldn't anticipate any untoward or unexpected issues. The one advantage, of course, of xenotransplantation is if you have primary graft failure, you have an immediate backup available, so there are actually some advantages in terms of the primary transplant procedure. As you know, there is a primary failure rate in transplanted organs somewhere between, you know, two and 10 percent, depending on who you read. So that the -- There is added advantage, and I certainly wouldn't think of starting a clinical practice without having, you know, without having backup donors.

DR. SALOMON: That is the positive side of a non-human primate donor, so well taken. In your own talk, and certainly in my own experience doing non-human primate research, I always just remind myself I am a better human doctor than I am a non-human primate doctor, and I think that there are issues here with non-human primate models that we also have to realize. That it is very, very difficult to take good care of these non-human primates. Bradley.

DR. COLLINS: Thanks, Dan. I just wanted to make a quick comment here. In the field of liver transplantation, sicker patients now are getting transplanted, and the results aren't as good, and in the non-human primate models, some of which I have been affiliated with, we are picking the healthiest animals to utilize, and in clinical transplantation, when something as radical as xenotransplantation is done, I have a feeling it is going to be limited to the sickest and they are going to have associated comorbidities, and may not do as well just because of their level of illness.

DR. SALOMON: Bernhard, do you want to comment on your experience with non-human primate for islet transplantation, good model, what are the limitations?

DR. HERING: I think it is absolutely essential to study the non-human primates, because the results that have been obtained in small animal models have clearly not been confirmed in the non-human primate. That is not to say that the non-human primate is a better model, but I think you cannot move on without learning your lessons in this setting. The immunology is to some extent different, clearly, compared to mouse and rat recipients. With respect to the technical aspects and the transplantation procedure, I don't expect any untoward risks or new side effects. But I think it is important to document that there are no problems with respect to all the regulation of coagulation and other aspects that just need to be studied and need to be documented. I think it is important. There is no better model.

DR. SALOMON: Harold.

DR. VANDERPOOL: I would like to ask Dr. Collins to comment a little more. You are saying that surgical procedures with relatively healthy non-human primates are not exactly parallel to surgical procedures with very, very sick human patients. What kinds of connections are there, are they still approximate enough to each other for you also to say that these kinds of procedures need to be done with non-human primates in preparation for human procedures?

DR. COLLINS: Certainly. Excuse me. You certainly can't underestimate the importance of the non-human primate preclinical trials. The point I was trying to make is that in humans, the technical procedure may go great, but the sicker the patient, the outcome -- the sicker patients just don't have as good an outcome, because they have other co-morbidity that contribute to their not doing as well. You know, technically these things are equivalent, the transplant that is done by Dr. McGregor is equivalent to what would be done to humans in the orthotopic situation, and what Dr. Hering described, the transportal injection would be the same, but the level of illness of the animal compared to the level of illness of a human in whom you'd do a transplant have diabetes induced in the baboons isn't exactly the same as a person who has Type I diabetes, you know, it's just a different disease process. That is the point.

DR. MENDEZ: Dan, I'd like to just comment on Dr. Hering's comment. I think it is imperative to have a non-human primate as a model for the surgical technique because not only because of these factors mentioned, but because we haven't absolutely determined that portal vein infusion is the best methodology for delivery of these cells. It may be encapsulation into the peritoneum. There may be other methodologies that are more efficient and less morbid than the actual portal infusion. And this can be studied much better in a non-human primate.

DR. SALOMON: Chris, is there any difficulty in doing the orthotopic cardiac transplants in the non-human primate, specifically, in terms of bypass equipment, and anesthesia?

DR. MCGREGOR: Not really. There are established orthotopic -- There have been two or three studies using the orthotopic model in which the transgenic pig heart has borne the circulation for, in isolated animals, for up to a month. So the feasibility is proven, it's just the level of detail and care that needs to be taken. But it is feasible.

DR. SALOMON: Does anyone else have any specific comments, including the audience, on this first question of the non-human primate as a model?

DR. SYKES: I have one comment. I think it is important for us to see, if at all feasible, you are talking about healthy versus disease. I know it doesn't necessarily mimic the clinical disease, but it is at best better than a healthy model at times, so if at all possible, we do ask to see, like a diabetic, a diseased model, if you will, to attempt to try to mimic some of the pathology at least that you are seeing clinically. It is not the best, but it's step a little better towards extrapolation.

One thing, I know the content of the presentations this morning, but just curious, considering cell therapy. You talked about islet cells. There is neural cells. There is other cell therapies. I don't know if it is to be discussed today, considering the group that presented. But in terms of using non-human primates versus other smaller animal models, I'm just curious if there is any thought with regard to that?

DR. SALOMON: Well, I, you know, my comment to that comes out, not only of my own experience dealing with both, but doing non-small animal models of cell transplantation and non-human primate models of the same. I think all of us agree that before one goes forward to a non-human primate model, you better have damn good data that supports the reasonableness of your basic trial before you go to such a precious animal. So I don't think there is any threat here to small animal models of transplantation. And I think not only there is no threat to them, but I think they are critical in the development path. Megan, do you want to comment?

DR. SYKES: I would agree with that wholeheartedly. I'd also like to throw something out that is maybe a couple years in the future, but when the two allele gal knockout pigs become widely available, when there are enough of them, those could potentially be used as a large animal model of a xenograft recipient. As you saw from Dr. Ayares, those animals do have anti-Gal natural antibodies, and the pig has been used as an excellent large animal transplantation model for allografting, and this new modification could in fact make it a very good model for xenotransplantation?

DR. SALOMON: That is a really good comment. I was kind of saving that for question F, when we start talking about the worldwide shortage of non-human primates, but that is perfect. I would summarize -- Oh, Harold.

DR. VANDERPOOL: So, Dan, what you are proposing, which I think is really, really good, is that, you know, in the classic codes of research, animal research must precede human subject research, and what you are suggesting is really a kind of expansion of the code, namely, small animal research must -- must precede and prove the possibility of efficaciousness before non-primate research. At that point, you move forward toward humans.

DR. SALOMON: Yes.

DR. VANDERPOOL: So you are minimizing as much as possible the degree to which non-primate research should occur, only after proof of process in earlier models, non-primate models.

DR. SALOMON: And I think that is beautifully stated. The only thing I would do is I wouldn't be able to take any credit for that, though. That is a thought process that has evolved, you know, I didn't personally come up with that today, but, yes, everything you said. Yes. I think that is right. So I mean I think that the consensus here, and I put this out, you can respond with no, it's not the consensus here, is that though we are not obviously in a situation where we can give you any kind of details, it is clear that I haven't heard a single person make a case that at some point in the preclinical development of the xeno trial, that there shouldn't be appropriate large animal research done, that right now, the non-human primate is probably the best accepted large animal model for this, and I think we'll get back to pick up the thread that Megan very appropriately brought up, and Dr. Ayares actually set us up for later, but I think there is non-human primate work that can be done and should be done.

DR. SERABIAN: I guess I'd like to stress, too, knowing all the experts and your products, what you do, but to minimize as much as possible the use of non-human primates. When you do eventually decide you are at a point where you can come to FDA, please come early before you do a 30 monkey study, or some huge study that you think is what we want to see, and use all those animals that may or may not be necessary.

DR. SALOMON: Yes, Harold.

DR. VANDERPOOL: I think that given the preciousness of non-human primates, that this minimization question is a very serious one, and I don't know the degree of which presently that is uppermost in the minds of those in the Food and Drug Administration who are responsible for new drug and xenotransplant development, but I would assume that the committee would also agree that the minimization question should always be kept in mind as xenotransplant science proceeds.

DR. SALOMON: To the second question, then, the second question is the non-human primate model in the context of the intended function of the xenotransplantation product, so there I'd like to kind of bring us to a couple threads that have already been brought up. As Bradley starts us with, you know, can you start with a model in which you have an absolutely healthy non-human primate and use that as a preclinical model for a sick patient? And clearly there are some problems with that, as has already been well said. So then the question is to what extent can we reproduce illnesses in non-human primates that would better reflect the preclinical, or intended use of the xenotransplant product? And a good example there, and Bernhard might want to comment, is on streptozotocin-induced diabetes. Streptozotocin, for those of you who are not familiar, is a toxin that is used to select -- that seems to be more or less selectively taken up by the beta cells, the insulin-producing cells in the pancreas, not only, though, and it kills them promptly, so you end up with diabetic animals, and so that is one example, but everybody has beaten up scientists in basic NIH study sections because that is not the same as a Type I diabetic who has an autoimmune response against their islet, so I just want to point out here that there are possibilities of recreating diseases and weaknesses in them, so we should probably have some consideration of that under this second topic.

Bernhard, do you want to make any comment about that?

DR. HERING: I can only echo what you have said. I think it is not a perfect model, but I think it is also important to emphasize that you have to do those studies in disease models at least in streptozotocin diabetic recipients. It can be very misleading to look at very nice histology and show surviving islet tissue, and yet you have no function in your animal, and the animal is frankly diabetic. So I think at least at some point in time studies must be done in animals with diabetes. And of course we don't have an autoimmune Type I diabetic model, and we probably will not be available, and it is unclear to what extent the reactive T-cells will target xenogeneic islets. There is some controversial data in the literature. It is just not known and cannot be studied in that model.

DR. SALOMON: Any comments about -- I'm sorry. I was going to say about generating heart disease, liver disease, and kidney disease models in non-human primates, feasible, not appropriate --

DR. MCGREGOR: I'd like to point out that I agree completely with Dr. Collins that it will be very difficult to reproduce exactly the clinical situation in terms of recipient illness, but I would also add that there are some potential inherent advantages to the xeno approach, in the sense that one would hopefully have a donor organ that has a short ischemic time. In the heart, as you know, the mortality of transplant rises with each hour of ischemia, and as you approach four hours of ischemia, there is a significant donor heart failure. One could eliminate that ischemic time by having a controlled donor situation. A second circumstance in which xenotransplantation could provide a potential advantage for a sick recipient, is that one, to a certain extent, could choose appropriate sizing. In other words, there are many recipients who are waiting for heart transplantation who are unable to take certain hearts because of size, or because they have an elevated pulmonary vascular resistance. And the ability to place and select a xenograft heart that is chosen to be larger to compensate for that is again a second advantage. So I agree with Dr. Collins. We cannot always reproduce human disease, but that is -- That is balanced to a certain extent by the being

able to compensate with xeno in a positive way.

DR. SALOMON: Megan.

DR. SYKES: Just to extend further the points that have already been made, I think it really is very important that even if you don't have the exact disease model in your non-human primate, in fact the animal is a healthy animal, that nevertheless, the graft be life-sustaining in the case of a heart transplant, or a kidney transplant, or be treating a hyperdiabetic animal in the case of an islet transplant. Without that, we'll never get a proper awareness of the potential physiologic incompatibilities and potential physiologic function that could be achieved. So --

DR. SALOMON: Eda, I know you were --

DR. BLOOM: Yes, actually I think Megan's comment leads well into what I was going to ask, is that one of the things we were interested in, in asking this question, is not only the issue of a disease -- appropriate disease model, but let's say you can optimize your system for a non-human primate, you can show that the non-human primate responds well to Porcine islet cells, that the insulin works fine, I don't know, I'm not a medical doctor, nor am I an endocrinologist, but glucagon, whatever else comes along with the package, is not adverse. It doesn't cause problems, and you've optimized that now in a non-human primate model. Can that be generalized? Can you use that information then you your clinical study? Is that useful in the clinical study, for example, but extend that to other xenotransplantation products as well?

DR. SALOMON: Right, Marian.

DR. MICHAELS: I was going to further what Megan had said and what Eda was saying as well. I think we have to recognize the limitations, but I don't see at this point in time still a better model that we can use, and when we think about taking the non-human primate model, and trying to mimic the human as much as possible, that might be sick, as Bradley was saying, perhaps -- again, I think it has to be a step by step. Each point it has to be what are the questions we are asking at what point? So do we take an animal, and go straight to the orthotopic? I think what Chris is doing where you do the heterotopic at that functioning, ask the questions immunologically that you can answer from the heterotopic before going to the orthotopic is the way, but you have to go, as he said to the orthotopic, and as Megan pointed out, before you would go to the human trial.

DR. SALOMON: I'd like to put my personal view, too, I'm not comfortable actually with the idea of making a non-human primate sick purposely, and I was really bringing that up to make sure that the committee discussed it. My feeling is that we do have to set a functional outcome parameter for all our xeno studies, so whether it be islet transplantation, or heart transplantation, or kidney transplantation, or other neural cell transplantation, for example, if those outcome parameters are clearly established within the physiology of the non-human primate, then I think that we've done our job as a preclinical model, and I think that the non-human primate model doesn't have to be the perfect model for a sick and dying human patient. There is plenty of compelling reasons to go from a good non-human primate preclinical model at that point to the humans, if we can get that far.

DR. COLLINS: I just want the record to state that I was not favoring making animals sick or anything like that.

DR. SALOMON: We weren't trying to get you into trouble, Bradley.

DR. COLLINS: Thank you.

DR. SYKES: I think one way to look at it is that -- The primate should be used for -- for two reasons: One, is to try and obtain enough success that within the limitations of the model, and knowing that you are using the best model available, there is reason to hope that there will be success in the human. And we could talk about how you define "success." But secondly, the non-human primate has to be used as a way of looking for problems that you might not otherwise know about until you went to a human. And just as an example of -- if an organ shows a physiologic incompatibility in a non-human primate, you won't know for sure that that same incompatibility will exist within a human recipient, but nevertheless, it should raise a red flag that should lead to further research, even if it is in vitro. If you can identify what the molecular incompatibility is, for example, glucagon is not regulated, and you have excessive glucagon levels in your islet recipient, what is the molecular incompatibility there that is causing that? If you know that, then you can go in vitro, or go to the molecular level to understand the corresponding pig/human interaction before you would take that to the clinic. So it has to be used as a way of identifying potential problems that should spur further research to find out if these are going to limit human transplantation.

DR. SALOMON: Harold.

DR. VANDERPOOL: To quote from page 17 of the "State of Science Report," there is an assertion that non-human primate models closely approximate conditions in humans, but significant gaps in clinically relevant knowledge of non-human primate biology currently limit the value of these models. It seems to me that insofar as that statement is true, that part of what this question is being put to us should entail is greater encouragement of an understanding of the differences between non-human primates and human beings. So it is more exact, so that more exact understanding of problems that come up can be made between what happens with the primates and what is likely to happen with the humans. And in a sense, these questions commission us to encourage more research in the understanding of the two separate sets of systems, or the mini sets of separate systems, depending on which non-primates are used.

DR. LUBINIECKI: Following up on those comments, I'd like to add I'm a little concerned about the use of the word "predictive" and "preclinical model" in the same sentence. As we've discussed, there is a number of differences in the PK/PD of these various drugs. There are differences in the diseases and the disease models in terms of their severity and etiology and a number of other things. There are certainly differences in viral susceptibility of different hosts. There are differences in the physiology of the complement system and the coagulation system, and so on and so forth. And all of these are going to now interact in these models in unknown ways. And to think that this will lead us to something which gives us predictability, I think may be overreaching. As Harold said, these studies need to be done. It is certainly probably more ethical to do these in non-human primates than in humans, but to think the outcome of non-human studies is going to accurately predict what will happen in humans, I think is probably not the way to go. Definitely you'll yield data. The data should be examined. The data should make us think about what might happen in humans. The data should make us think about what might be relevant to humans. The data should force us to examine what additional data we should gather before we take it to humans. But just because we find something in a non-human primate doesn't a priori mean it will happen in humans. The "Annals of Toxicology" to date in development of human drugs has shown that probably as many things are really not likely to happen in humans as are. So it should be not interpreted as something which gives rise to prediction, but rather should give rise to further thought, to examine the relevance.

DR. SERABIAN: Can I make a comment? Agreed, I'd almost rather have the models on the side of toxicity not be predictive of the human scenario, because we don't want to see the toxicity. So agreed. I do agree with Dr. Sykes' initial comment about, you know, the models, the various animal species models are to look for problems, i.e., what potentially could occur clinically, and it can raise red flags, and those flags could be high enough that if you came to FDA we would say, "Whoa, stop, we have a problem, an

issue. You have to go back and figure out what is going on, be it in vitro, or another way, in vivo, and come to us with a logical data driven explanation for the results you are getting," and go from there. So agreed, it is a step in the process, and it is safety, which I said at the beginning, it is toxicity as well as functionality and activity. Yes.

DR. SALOMON: So I think just again to try and get through this, to kind of come to some sense of the committee on the second question, I think what I am hearing consistently, again, is that we can define biological function of many of these, heart transplant, kidney transplant, an islet transplant, a neural cell transplant, in non-human primates. I think what I've heard is that everyone agrees that demonstrating that in an appropriate model is very important as a preclinical step. However, I think the two themes that come out very clearly, again, please comment if you disagree, is number one, the, what I think Tony's point is that this is a limited model. And so sitting there and doing a hundred non-human primates and supposedly refining this all down, with the idea that one is going to start a clinical trial with the exact milligram per kilogram dose and a list of toxicities, that is going to be applicable to humans is not probably way overreaching the non-human primate model. And that then picks up the theme that Harold gave us, and that we all, I think, commented, is that we don't see making animals purposely sick just to mimic the disease better, nor do we think that we have, to put it in a positive way, that we have to limit the number of non-human primates done by very clearly understanding the limitations of the model. And so that you achieve functional parameters, you make your preclinical point, present it to the FDA, and then hopefully, if they are indicating, move on to the human trial.

Any further discussion on that? Yes, Megan.

DR. SYKES: Yes, as I mentioned earlier, I see the non-human primate model as having two purposes: One is what you just summarized, and the other is to give enough indication of efficacy, that there should be hope for success in the human. I think that is an unusual requirement for preclinical study, perhaps, and that we have a higher burden to have that expectation in the setting of xenotransplantation because of the risk associated with xenotransplantation to society. And I am speaking now for myself, and also for the Ethics Committee of the International Xenotransplantation Association, we've just put together a paper on this issue that will be coming out soon in "Xenotransplantation." We feel that there does need to be that standard, that there has to be some reasonable expectation of efficacy before going to the human.

DR. SERABIAN: One thing we always consider is benefit to risk ratio. It's not a mathematical formula, but that is always a valid consideration.

DR. SALOMON: The third question, infectious disease risks. Non-human primate model, preclinical model as a model for infectious disease risks. John.

DR. ALLAN: See if I can get this to work. I think it is sort of interesting, because when we had these discussions earlier about infectious disease risk versus, efficacy, I mean one of the things that was said, well, it is an infectious disease risk which seems to be most important. That is taking a second -- it is taking a back seat to efficacy, and we've seen a lot of really interesting data now that is moving us closer towards some level of efficacy that may be at some point be able to go to humans.

I don't know that the infectious disease area has kept pace in terms of the research, and that is one of the things that I, that struck me is we didn't see very much on infectious disease amongst these. I'm not saying that there should have been a lot of that, I'm just saying that that was just something that I saw. So I guess the issue is, and I mean I've heard several other things, one is that -- well, there is two things, one is Carolyn Wilson's paper that says, well, maybe a non-human primate is not so a good model for infectious disease risk. Dan is on this paper, too. But there is other data from Denner's group that suggested that PERV can replicate in non-human primate cells. I think you are not going to get at that

issue by some in vitro assays with restricted cell types with restricted viruses, potentially restricted viruses. So the jury is still out as to whether non-human primate model would be a good one for infectious disease risk, for PERV in particular. There are a lot of other viruses out there. So that is an important point. So you still need to use a non-human primate to understand infectious disease risk. I think to say otherwise I think is -- you are going to miss the boat.

Second one was with Julia and Clive, and I think they've got a nice mini pig model. It suggests that it may be safer. It doesn't suggest that that particular pig is therefore safe for PERV. It just means it is likely to be safer. We still don't know what might happen in vivo. If you did the non-human primate infection studies, or transplant studies, you may find more convincing data in terms of infectious disease risks. Along that line -- I need to get this out, so sorry about the time. The other thing is in terms of how I am going to carry the monkeys out. Like in the islet cell, which is a beautiful study, you take about six or seven weeks, and then you end the study. It makes it very difficult to understand infectious disease risk if you stop the study at six to seven weeks, especially in a case where you could actually keep the animal alive longer. It may be a year or longer before you could actually really come to understand that infectious disease risk in the primate. So one of the things I think you really need to consider is if you are trying to get at infectious disease risks, the way you construct your experiment may be a little bit -- a little bit different than the experiment you are trying to conduct to figure out whether the organ is going to function or not. You may need to take the animals out longer. I'm not saying that is something you have to do, but in order to really get at the infectious disease risk, you may have to take the animals out longer.

The only other thing that comes to mind for me is the economic, and I'd hate to see us pushing into human clinical trials, simply push aside infectious disease risk somewhat because of the economics, and the somewhat limited amount of resources to be able to do sufficient non-human primate studies, and then the push to try and do humans because of an underlying economic problem, and I want to make sure you have to be very sensitive to that, so --

DR. SALOMON: Marian.

DR. MICHAELS: I think that the non-human primate models, as Jonathan has brought up, and as everyone stated before, really can give a lot of information in terms of the broad strokes of the types of infections that may arise. But the non-human primate viruses are not the human viruses, and vice versa. And likewise, the pig virus, and what it does in the non-human primate is not completely analogous to what we will end up finding in the human. But I think it will lead us to at least have some concept that if the pig cytomegalovirus was overwhelmingly found to be the pathogen that ended up causing the heart transplant recipients or the kidney recipients to expire, then that would be critical to know. But the baboon virus being the one, while it is important to make the preclinical model work, I'm not sure that it really tells us everything that we'll need to know in the human trial that ultimately will happen. So I think it has to be looked at with broad strokes. But one has to recognize its limitations as well. I think that the immunosuppression that is used will help us also be able to predict, or at least hypothesize what types of human viruses might become a problem, more or less in the xenotransplant world of using a similar kind of immunosuppression. So I think again, just recognizing the limitations, just because it is cytomegalovirus, if it is a baboon, it is not the same as a human. If it is a human, it is not the same as the pig.

DR. SALOMON: I think another thing coming here, in the context of gal the Gal knockout animals, is that the budding of the porcine endogenous retrovirus variant without the gal residues in its envelope removes a major infectious disease barrier, because given that we all have high titers of anti-gal-Gal antibodies right now, if we encountered a PERV virus from a wild type pig, we would quickly wipe that PERV virus out with the antibody, just like we hyperacutely reject the kidney, we'd wipe out the virus. I say that because I know there are people here that know this backwards and forwards, but some might

not. Once we do the gal knockout, of course you don't have that. The non-human primate would be a very good place to test that, before you put it into a human. So I think that is one really big example where the non-human primate model, you don't need a hundred animals, though, you need just several. I think it could be done well there. Tony.

DR. LUBINIECKI: Just to amplify Marian's point. It should be remembered that there probably is an ability of susceptibility and immunosuppression to interact, and that we shouldn't draw conclusions about risks and susceptibilities under one condition in immunosuppression and try and generalize them to a different set of assumptions. More profoundly immunosuppressed animals might have a different level of susceptibility. We certainly see evidence in monkeys and perhaps humans to that effect.

DR. SALOMON: I wonder, I'm not seeing her, but I know she is here. Carolyn, can you make a comment about what you think in terms of infectious disease issues with what we learned in our studies in the non-human primate?

DR. WILSON: I think John Allan made the point that certainly there is conflicting data that has been published, and there are limitations to in vitro studies, but I would just urge the committee to consider that when you see a negative result in an in vivo study, to not necessarily take that as a reassurance, given that in vivo data suggests it may not be a permissive model for PERV replication. The other point being made by both Marion and John is that there are of course a lot of other viruses that could and should be studied in these models, but with the caveats that Marion mentioned, that they may or may not be predictive of what would happen in a human, so nothing really different than what has already been said.

DR. SALOMON: Thank you, Carolyn.

Okay. So with respect to the third question, again, I think the principles that are coming out is that with the appropriate recognition of the limitations of the model, that there are some very important features of non-human primate preclinical work for ensuring the safety of a clinical trial. However, one has to be very careful about a couple key points that different people made. John makes the point of how long you carry the animal is critical in determining how well you have assessed the risk.

DR. SERABIAN: For a six or eight-week study, we would not accept that.

DR. SALOMON: No. But also there, I think there the FDA, and I'm going to step back and make a personal comment, but I think we have to be a little careful, because I would not advise the FDA to say, okay, fine, well, then, you've got to keep these animals alive for three to four years while you look for retroviral infection, and you'll quickly find yourself there if you kind of take that tack. There is going to have to be some uncertainty in order to regulate xenotransplantation, or some other similar field out of any chance to succeed.

DR. SERABIAN: Again, a key thing with that is when we use the word "long-term," what does long-term mean? But it doesn't necessarily mean that a clinical trial cannot be initiated depending on the data that are submitted. You could have an ongoing study in parallel, which you should be doing that, just for you wanting to know what is going on in parallel. Again, there is the risk/benefit, there are a lot of things that should be done, but may not be absolutely required.

DR. SALOMON: That is a key point. Harold.

DR. VANDERPOOL: I hope I'm hearing this. With respect to number three, "Investigate the infectious disease risk vis-a-vis humans, by using non-human primates for humans" in very targeted ways, but re-think what these investigations ought to be in terms of longevity, for example.

DR. SALOMON: Yeah, again, I think that the theme that the committee is sort of putting forward is that there is a place for non-human primate models. These models have their significant advantages for the intended purpose, but they also have significant limitations. And that, if any plan gets put forward to use preclinical trial in preclinical data, rather, in a non-human primate model to support a clinical trial, it just has to take a practical view of both the advantages and limitations. Megan.

DR. SYKES: I just want to bring up the efficacy issue in the context of the infectious disease issue, because there is not that much point in keeping your animal alive if the graft is long gone. The risk there, there may be some microfibers (?), and what have you, but the risk there is probably not equal to the risk associated with an intact surviving graft. And so I think that is another reason to have a relatively high standard of having to demonstrate efficacy, not only because that justifies the clinical trial, but also because it will give you a better measure of infectious disease risk on the immunosuppression you are planning to use than you would ever get from a shorter study, or from a short-term graft survival with a longer study.

DR. SALOMON: I think that is a key point. I would just answer back that I agree with about 80 percent of it. But the 20 percent of my disagreement is that if a small amount of viral transmission, I'm not talking about just PERV, occurred to the host animal, even if you still could foresee a possibility where even though the pig tissue was destroyed by an immune response, whatever, that it might take a year or two, but there could be amplification of the viral pathogen in the host tissue. And that would be an argument independent of the survival of the pig cells.

DR. SYKES: Sure. I'm just saying that the failure to see transmission of any virus under those conditions wouldn't be very reassuring about what might happen if you had a graft surviving for that period.

DR. SALOMON: Yes, absolutely. John.

DR. ALLAN: To beat a dead horse, or whatever, the only thing that I see is, is that there is a nuance, and the nuance is I mean like if you got a heart, or you do an orthotopic heart, or something, you are not going to keep the monkey alive because he may only go out a hundred days or 120 days, so you can't follow them after that. On the other hand, there is some types of treatments that you could follow them after -- after the end of the transplant. And the concern I would have is, is that, well, we'll just do what we need to do, which is we'll just follow the animal, and when we are done, euthanize, and then we'll do whatever we are expected to do in terms of our virology, and then we'll go into the clinics, and so I think maybe you need to think about more than that, that it has to be a little bit more than that. Now, the issue is how much more. You are not going to keep the animals alive three or four years.

DR. SALOMON: I think the way Mercedes dealt with it is fair enough, that is that they would encourage that in the right circumstances with the right models that there be parallel longer term studies done where possible, and I think that is fair enough.

DR. SERABIAN: These are extremely expensive studies, we are well aware of it. There is a lot going into it. It is important to get as much information out of that model, both in terms of efficacy, as well as toxicity, as well as viral issues, and not to aid more animals to the issue, but, you know, sometimes some are taken down early, others can be followed a little longer. But, again, this is non-human primate, you run into this issue of numbers, which is a big problem.

DR. SALOMON: Okay, so I think the infectious disease risk issue is dealt with, and left with, you know, again, this balance between the advantage and limitation. That is going to be very important to

consider.

Okay, potential for use of immunosuppressive regimes in the non-human primate. Clearly we've heard data today from several groups that have successfully used immunosuppression in non-human primates successfully, as defined by a significant prolongation of xenograft survival, and for that matter allograft survival in the case of some data Bernhard showed us. I've also done some studies with pig islets into non-human primates and again we saw significant reductions in immunity that were appropriate for the types of drugs, doses and levels we achieved. So again, I would support the idea that the immunosuppressive regimes can be used with some limitations. Bernhard, do you want to comment anything on that?

DR. HERING: Yeah I would agree that we always have to make compromises. We clearly understand and this was emphasized before. The pharmacokinetics are completely different. We also understand when we are using biologics or when we are using monoclonal antibodies like you just mentioned, you may have different epitopes that are targeted. I think we just have to be very careful with our conclusions, but again, there is no model that would replace the non-human primate. But I think the model clearly has its limitations.

DR. SALOMON: Julia, do you want to add anything to that? I know you guys have also had a good experience.

DR. GREENSTEIN: I think that we just have to be aware, when we design experiments, what the compromises are we are making. We have certain monoclonal antibodies that work well in non-human primates, and certainly would prefer to use when we potentially get to clinical trials, and they may not be exactly parallel to what we can test in the non-human primate, so we try to put together the best pieces when we get to the clinic, and some of those pieces may not be the reagents that happen while tested in the same non-human primates.

DR. SALOMON: Megan, do you want to comment? I know you also have done --

DR. SYKES: Well, I sort of want to throw out a question. So what I got from your talk this morning, Bernhard, was that the regimen, the FTY triple therapy regimen was quite effective for allotransplantation in the non-human primate, and caused impressive prolongation of islet xenografts, but was not what you would call effective from the point of view, I think, of a clinical transplant. I mean, those are non-human primates. I think you've done the right control, allo and xeno, because you can't make the argument that the drugs were more efficacious in one setting than the other. So I think that is an important lesson. And I mean my take on that is that is not a regimen that one would go to the clinic with at this point. Is that yours as well?

DR. HERING: I agree with you. This is a very important observation, I think, clearly suggesting that the xeno directed immune response is fundamentally different from the allo directed immune response. I think this is the lesson we take from those studies.

DR. SALOMON: I think the key point there, though, is that there are differences between the xeno and allo immune response that could reflect different drug needs, and that could be true in the non-human primate and in the human. Those are important issues to answer, don't you think?

DR. SYKES: They are, but I think that the way this study was done really points out how much one can learn by developing an efficacious regimen for allo transplantation. And then once you have that, and you try it in xeno, and if it doesn't work, then you have to start asking questions. And then you are asking the real question, you are asking can I build an immunosuppressive regimen here that is tolerable, and that

I could then go to the clinic with?

DR. SALOMON: I agree. My only point was that would be an advantage of the non-human primate model, so that one wouldn't go forward to a clinical trial with a regimen not expected to immunosuppress adequately a xeno response. I think the other thing, to put it in balance, is there is a lot of experience with these regimens in human patients, so that to the extent that we would use an immunosuppressed regimen that was generally made of therapeutics that were already FDA approved for use in human transplants, I don't think the non-human primate model necessarily has to be that good a model for those, in that I would be comfortable, based on the experience I've already had, let's say using Rapamycin or Tacrolimus. Richard.

DR. KASLOW: I was just going to say you said it would be an advantage, but I think one of the other questions would be whether it is a requirement. You sort of answered it by saying you don't think it ought to be. It seems like somewhere in between there might be an appropriate compromise. There may be situations in which it is important enough to actually require that the setting in non-human primates be as comparable as it could be to humans before you would go ahead to clinical trial. I can't cite what that would be exactly, but you may want to think about it in those terms.

DR. SALOMON: Fair enough. I guess for clarity, what I meant was I wouldn't really be uptight about a clinical drug-related toxicity in a non-human primate that otherwise was part of a functioning regimen, if I knew that in a human patient that drug was well-tolerated in equivalent doses, I would then say, "Hey, that is a non-human primate issue, not an issue for going forward in a clinical trial." Harold.

DR. VANDERPOOL: It strikes me that as worded in D it says "The potential for use of immunosuppressive regimens," I don't think of any question non-human primate models talk about not only the potential, but the efficaciousness of immunosuppressives. The question is which immunosuppressives, and that is a different question, because you can show the potential and efficaciousness in non-human primates, but that doesn't mean that those particular forms of immunosuppression will be the ones that will work in humans. You see what I mean? I think we are answering the question possibly yes. The potential immunosuppressive have shown great potential and efficaciousness in various ways. Now, what types of immunosuppressives is another question.

DR. SALOMON: I think, getting back to something Megan said, I would repeat, because your point is very well taken, Harold. That is a perfect system would be where you had a non-human primate model, and you did an allotransplantation. I think Bernhard is pointing us in those kind of directions. You showed that you had a perfect immunosuppressive regimen in that model for allo. And then you went ahead and did xeno and showed it wasn't adequate, and then you changed it and it now worked for xeno. If you could -- If that was in place for you, as you stepped up to say no, I want to go forward to a clinical trial, that would be ideal. I think then you could have a pretty high level of confidence in the rigor of that preclinical process, you know.

DR. SERABIAN: Just one regulatory hurdle to throw out, again, if it is a different dose of immunosuppressive agent, or one that is not approved yet, that is another issue that has to be considered, and it is center cross. You might end up at the Center for Drugs, because they handle most of the immunosuppressive agents. So if it is one that is ten-fold higher than what it has been approved for, then that may be another issue that has to be dealt with in itself.

DR. SALOMON: Bob.

DR. MENDEZ: I was just going to comment that I think Dr. McGregor answered it partially by saying they were trying to get the levels of whatever medications they were down to those in which humans were

tolerant of. And I think that would definitely need to be done, otherwise you are going to have to have a whole new trial.

DR. SALOMON: Yeah, I think partly, here, we don't want to lose sight of the fact that there is quite a lot of experience already in using immunosuppressive drugs in non-human primates. And in general, to date, there have been some products, particularly engineered products, like antibodies, for example, that may not work as well because the epitopes are different, as Julia correctly points out. But in general, when you are talking about the drugs themselves, it is not -- there haven't been any spectacular, oh my gosh, differences in dose or toxicities. The animals get sick, they get CMV infections, fungal infections, they get renal toxicity, and it is pretty much predictable along the lines of our human experience. Bob, did you --

DR. MENDEZ: No.

DR. SALOMON: Sorry, you still have your light on. So I think that we, again, I don't think we need to repeat. I think we've got a pretty clear message on the -- on the immunosuppressive drugs. The fifth question, the potential need for periodic and/or retransplantation for some xenotransplantation products, any discussion on that? I don't see that as being a really big deal for the non-human primate specifically.

DR. LUBINIECKI: Is there an intention on the agency's part to request preclinical models of retransplantation?

DR. SERABIAN: Again, I think it depends on what the clinical indication is. Again, if it is a cell therapy, for example, potentially the intent is to repeat dose down the road, then you would have to do something like that down the road, yeah.

DR. SALOMON: Harold.

DR. VANDERPOOL: There is some regulatory concern with respect to the actual regulations regarding the use of animals, that they not be used again and again and again for multiple experiments. So I think that -- I think the retransplantation issue would raise that, and so that is maybe something that deserves a separate level of analysis to see the degree to which retransplantation of some xeno -- xenotransplantation products in animals might represent a new level of experimentation. I mean you could define it either way, I mean we could cut angels off the edge and have it a pin with this one. Nevertheless, I do think that issue is -- is raised in terms of present regulations regarding animal research.

DR. LUBINIECKI: I think there might possibly end up being some conflict between the sample size required to allow for subsequent reoperation, and the need to preserve the animal. So there would probably need to be some further thought about where the balance lies.

DR. SALOMON: Then the last question -- Oh, Eda.

DR. BLOOM: I'm sorry, I know we are all ready for lunch, but one of the examples where transplantation might be important, as Mercedes said, would be redosing. Another example might be if you are using a heart as a bridge to a human heart. Does the committee -- Could the committee consider whether or not that would be something we'd want to have done in non-human primates? Would you want to do a xenogeneic heart and then follow it with an allogeneic heart, because you know -- well --

DR. SYKES: I mean --

DR. SALOMON: No, I wouldn't want to do that. That doesn't mean it was an answer for the committee,

sure. In a specific example like that, given that there may be immune activation or sensitization of gal antibodies, I mean, various aspects to the first transplant with the pig graft, would we want to insist, then, that an allograft be done to solve that, or to address that issue? Megan.

DR. SYKES: Well, these are things that have to be addressed in non-human primate models, and the -- those will allow you to develop parameters to monitor in the patients, because clearly, if you have evidence of immunological sensitization to your porcine donor, you are not going to want to give another transplant from that same pig, or from a genetically identical pig, or perhaps from any other pig, if it is a pan pig reactive response.

Likewise, there has been a question out there that has already undergone some investigation in non-human primate models as to whether sensitization by xenograft will then cross-react on an allograft, and that is a very important question. That probably does need further investigation.

DR. SALOMON: Marian.

DR. MICHAELS: So taking that in conjunction with the comments that Harold made, where he pointed out that the IACUC at the institutions at the moment don't allow for a second surgical procedure, keeping in mind that the animal wasn't sick to start, and was being used in the procedure, and could be trying to balance that out with the questions. I think that the questions have to be posed. This is what we need to answer. And if there is a specific scientific question that can only be answered in that fashion, then it should go forward with the smallest numbers of animals possible, but if it was that pig heart was placed, and the pig heart failed, it wouldn't make sense to then do a retransplant for a second surgical procedure in that kind of situation, putting the animal through a second procedure that otherwise wouldn't have been necessary. But with a specific question in mind, will the xeno antigens then go on to cause problems with a bridge transplanted into an allo? I think you have to do it.

DR. SALOMON: I think the other thing that Megan points out is it's really a serious issue if we go forward with the first set of clinical trials in kidney transplants, for example, with the idea that well, they're on dialysis, it is a relatively safe procedure, et cetera, to those patients, and I've made those arguments myself, but if putting the pig kidney in, and then, say, it lasts four weeks, and that patient is now sensitized for a subsequent human kidney transplant, we sure as heck better know that before, because that is a critical piece of the informed consent for that patient and for guaranteeing the safety. So in that situation, those, as Megan points out, those questions are not trivial at all, and they have to be modeled. Harold.

DR. VANDERPOOL: Those are excellent discussion. We -- I have learned to expect that Eda can always ask specific questions that bend your mind in new directions. Yes, indeed, if it becomes reasonable and somewhat common to go from an allo to a xeno, or a xeno to an allo, and there is essential bodies of information that have to be known in order to assess the safety of that, then the door is open for the necessity of non-primate models. Maybe FDA needs to tell us when -- when the proposals for those -- for those types of contingencies arise so that we could think about this issue further.

DR. SYKES: There should be data, that, you know, not all of these data will require retransplantation. You can look at the cross-reactive antibodies in vitro without having to do a retransplant. Also there should be data on people who undergo bridge transplants with a pig liver, what happens to their alloimmune response. I believe those sorts of things are ongoing.

DR. SALOMON: Eda.

DR. BLOOM: I'm sorry. I certainly understand the concerns about the immune response, that is one that

is paramount to me personally, but what about if you take, if you put a pig heart into a human being and you have done the suturing, and you've done all the connecting up of all the vessels, can you then come back and put a human heart in there? And that is the question.

DR. SALOMON: Well, I mean there I think we could answer you in the sense that there is plenty of experience doing retransplants of every organ: Heart, kidney, liver, lung, small intestine in humans. And there are difficulties associated with each. I don't think any surgeon wakes up in the morning praying for a retransplant. But Bob or Bradley might want to comment, since they are the ones more on the line. I usually send them their direction and pray.

DR. SALOMON: The last question, the worldwide shortage of non-human primate species for research use, and the way, I think we come back, then, to something that Megan said earlier, and that was are there other large animal models that are equally -- You can take this a couple different ways. We could go back to the beginning and say, "Do this all in small animal models, and not on the non-human primate." I'm not sure the committee really wants to go back to question one again, though anyone, you are welcome to take us back there. The other way to look at this is are there other large animal models that might not have some of the ethical issues associated with them as non-human primate, and the pig was brought up as one large animal model. So I leave that to discussion. Comments? Bob, you look like --

DR. MENDEZ: I was just going to comment in terms of the -- We definitely want to limit the use of non-human primates. And one of the ways I think to do is why are we doing so much work on heterotopic transplantation. Why don't we just go directly to orthotopic, at least minimize significantly the heterotopic model?

DR. VANDERPOOL: I would just, for the sake of conceptual questions, say that the -- the phrase "worldwide shortage" doesn't exactly capture the reason why use of non-human primate species should be minimized for the research. It is not just the question of rarity, it is the question of their quality of consciousness and so. So it is a very rich set of issues that involve why non-human primate species should be restricted in research use, and it raises -- obviously we are all aware of the degree to which this raises controversy with respect to people who want to protect not only non-human primates, but animals of a lesser level of consciousness and genetic and mental similarity to human beings.

DR. SALOMON: Allan.

MR. BERGER: I'll probably add a couple things from before, although I appreciate the committee wanting to limit the use of non-human primates. It does seem kind of the ethical issues that I mentioned before were not brought up on the FDA sheet here, so I'll kind of add to it a little bit. It does seem for ethical and practical reasons, along with some of the questions about xenotransplantation as a solution and the limited use of baboons, that I would kind of differ with the committee and not using non-human primates. To go one step further with that, I do think that there is a large proportion of the public that would not only like to see the use of non-human primates in research reduced, but eliminated. And I would appreciate that the FDA to take that into consideration and move towards that direction. I wanted to combine those comments with this one because my own organization is very involved with the primate trade. Any use of non-human primates encourages the primate trade in this country. We use about 55 thousand non-human primates in research. We import about 12 thousand non-human primates a year, which are both well caught and captive bred. I think the term "captive bred" from animals coming from overseas is questionable. Thousands and thousands of animals die in the process before they ever get over into this country by being part of that importation program. And as some people know here, there is not one U.S. airline that will bring non-human primates directly into this country. So it seems to me that we should be looking at ways not to just to reduce, but to eliminate their use, period.

DR. MENDEZ: To perhaps go halfway on that point, I agree with you on that, is that many of the most important problems we are trying to solve for successful xenograft transplantation is the immunological aspects of the infectious disease aspects of it. With these types of models I don't see the excessive need to use life-saving organs such as heart and liver in solving many of these problems. Whereas I think the preliminary work with xenograft transplantation with non-human primates could be done with kidney, with islet cells, with other types of organs that would not necessarily cause the demise of a primate, nor subject him to undue pain and suffering or death.

DR. SERABIAN: I just want to say that I agree with your statement, and that is why some of these questions were brought up, as well as we talked about a total package, i.e., in vitro, as well as small animal data to again minimize as much as possible the use of non-human primates, and that is something FDA is very much aware of. That is why we encourage people to come talk to us before they go off to do these large studies that, as I said, may not be necessary at all.

DR. SYKES: Sorry, but I have to disagree. I think we heard two examples this morning of xenografts in non-human primates that on immunosuppression got rejected by what appeared to be very different mechanisms. We saw cellular infiltrates, T-cells, in one type of graft, and absolutely none in the other, and so from an immunological standpoint, I think that you can't extrapolate what you learn from one graph with one type of immunosuppression to another graft, or even to another type of immunosuppression, and go into humans from there. And secondly, we made the point this morning, that the physiologic incompatibilities can only be identified, or at least one can only start to get a clue about them by transplanting functioning organs in non-human primates.

DR. MENDEZ: I understand those particular statements, but I would say perhaps we can do it in a step-wise basis. I think many of the problems initially can initially be solved, perhaps, in nonlife-saving xenografts, and then progress on as we understand more and more about it, thus limiting the exposure or the utilization of non-human primates.

DR. ALLAN: What Megan said and Bob said sort of brings to mind what has sort of happened in the AIDS field in using non-human primates, and that is that each of the investigators, or each of the groups has their own pet virus. They have their own pet vaccine protocol. They have their own pet adjuvant, and then they use groups of monkeys to test each one of these things. You can't extrapolate from this experiment to this experiment to this experiment, so they use a lot of monkeys, and you may not get the kind of results you need, so you might want to think about uniformity prior to developing a lot of these, especially when there are different companies involved, and different protocols involved, and thinking beforehand, maybe, about the immunosuppressive protocols you are using, and whether you could, you know, get some sort of uniformity so you don't have to say: Well, mine worked. Yours didn't work because you used the soluble TNF, and we used X, Y and Z, and you can't figure out exactly why this worked for the other. I'm just thinking off the top of my head, but that may be one way to sort of limit excessive use of non-human primates.

DR. SALOMON: I think we need to close, but I think that the theme that I think is most consistent through all six questions is a sensitivity on the part of the committee to the issue of using non-human primates on one hand, and I think we all see the significant advantages, to preclinical studies as a way of improving the safety -- our understanding of the safety and the efficacy of the xenotransplants before going on into human patients, many of whom could die if the therapy that was proposed into a clinical trial had not been appropriately tested and shown efficacy. So I think the positive aspect of the non-human primate in the context of improving the safety for human patients is clear. On the other hand, I think the committee has tried as best as possible to also be sensitive to the other side of it, and that is what the non-human primates are getting out of this, and the significant ethical issues that we are all very well aware of about non human primate research. It comes down to, we said again and again, almost with

every question, it's okay, but it has to be limited. It's okay, but it has to be a very clear understanding of the limitations in order to limit the numbers. So everything comes down to a sense of wanting to control the progress of doing these studies such that one would really be assured that one could say, all right, I know it's not great that we are doing non-human primate studies, but at least we are doing only the right number properly designed with appropriate small animal model data to show that it is worth even going forward.

But with that said, that is what we'd all like. I just have no clue how we could ever have any significant impact on that, and that should probably be the last thing we talk about for a second, and then close.
Harold.

DR. VANDERPOOL: One thing that perhaps is already being done, is for the FDA to have a very clear grasp of where all non-human primates are being used, and then when people come in and make FDA applications to use X number of non-human primates, that they scrutinize the degree to which this is repetitious, or that other researchers have been doing this, or that too many primates are to be used, or more than seems to be warranted, and so on.

And I think the FDA is bringing us questions, and I think the FDA is ultimately the agency that will be able to hopefully put into effect our desire on the one hand to see this experiment continue as needed, but to be delimited when possible.

DR. SALOMON: I hate to put Amy on the spot, she probably isn't expecting, of all people, to be called on, but at the level of OBA, or at the NIH level here, I would also turn to Dan Rotrosen, is there any overarching authority over animal review boards for non-human primate studies that we could address in a way to try and limit the use of non-human primates so you didn't have 20 different academic centers doing their own pet study?

DR. PATTERSON: Well, certainly at NIH there is the Office of Laboratory Animal Review, which could help coordinate some of the institutional animal use and committee reviews as well. So I think one of the issues here is that if there are fundamental principles, and indeed there are, of looking out for animal welfare in structuring these studies to maximize knowledge and minimize harm, that some type of coordinated review, or coordinated principles of review could be developed so that each institution didn't have to reinvent the wheel, or recapitulate the wheel. Dan, would you like to add anything to that?

DR. ROTROSEN: Yeah, I think what you said is absolutely true and important. At the NIH level, though, in terms of institute funding of non-human primate research, we try to take all of these issues, and I think we do quite well, in terms of animal safety and availability into mind. But that is on an institute -- that is on an institute by institute basis, usually, and there is little authority that we as a funding agency have to restrict the use of any animal. Also, I think in terms of non-human primate animal research, in terms of transplantation research, this comprises a very small percentage of non-human primates that are used either by NIH, in general, or by everybody else throughout the industry.

DR. SERABIAN: I would like to just say from FDA or from CBER, we understand, we preach this all the time, we go out giving public presentations that non-human primates are not the default species to use by any means. We only know what people come into us with, you know, we could have sponsors that already utilized a hundred monkeys for something we think that was just not worthwhile, but it is a moot point, so we only know what we receive and can respond appropriately. Again, to bring up the issue with CBER, a lot of the therapeutic proteins, specifically many are species specific, and can only be used with non-human primates. Sometimes sponsors will create an homologous protein. Again, with conversation with us and other data, that potentially can fly, and that you can use -- I mean you don't have to use non-human primates in order to complete your preclinical package, if you will. So there are -- you know,

it is not a default, by any means. There are scientific logical ways to deal with the issue. Sometimes that is the species that has to be used, but then again, it is judicious use of that particular group of animals.

DR. SALOMON: Okay, so I think with that, we are done, and I think everybody's participation this morning, from the speakers, to the FDA, and to the discussion that followed, certainly we haven't answered everything definitively, obviously, and there will be a lot more discussion. But is there anybody who has some last key point that if I close this session without hearing it, that we'll have done a disservice? Harold.

DR. VANDERPOOL: Yes, I have a last key point about lunch. We are to be back here at, instead of 12:55, at 1:15, to begin our deliberations. I'm sorry, 2:15, I have Texas time, sorry. And so let's come back by 2:15. Mary tells me that there are no other meetings that are going on in this hotel today, so the restaurant should be able to accommodate us in due time in order for us to get back here by 2:15. Thanks.

DR. SERABIAN: Again, thank you for your input.

[Lunch Break]

DR. VANDERPOOL: Now, we're already significantly behind, but we'll seek to catch up. Before we begin the overview of the draft report on informed consent and clinical research involving xenotransplantation, I want to recognize Dr. Margaret Snyder, the director of the office of scientific affairs at the office of intramural research for the National Institute of Health to say a word about the last set of topics we were talking about vis-a-vis responses to the FDA's queries over the use of primates in research. We talked a while; she has excellent points to make. Many of us have no real knowledge of the depth to which this has been a concern over the years, and so I welcome Dr. Snyder's comments to the committee on those questions.

DR. SNYDER: Thank you, Mr. Chairman. Number one, I want to say I am not speaking for the Office of Laboratory Animal Welfare. Any discussion with regard to their policies and regs should come directly from them. But in my position I try and clarify to the public the need for the use of animals in research, but humane, responsible use.

One of the points was made that you cannot do multiple surgeries, and clearly that's not the case. You can do multiple surgeries when it is part and parcel of a protocol. That is clearly what happens in the neurosciences. We're looking at vision research, we're trying to understand the whole dynamics of vision systems, and so there will be eye implants, lid implants, as well as probes within the brain that will be multiple surgeries will be conducted. It is approved, it is somewhat a standard procedure for the variety of scientists doing that.

And so when an activity involves multiple surgeries, it needs to be approved in advance. So if you're doing multiple transplantation of eyelet cells, you would have that in your protocol. You can't do an "oh, by the way" midway into the research unless you go through an amendment. But it would be much better to have it laid out in advance and say, given these contingencies, we would wish to do multiple transplants, and define how many attempts you would make at multiple transplants. An IACUC that is being responsible in their review will take the different factors into consideration and look at the ethics of it.

I think also any committee that's looking at your procedures will look at the optimism for success within the research. You're not going to start off with primates, again. One would expect that you would have rodent models or other models that would lead to an expectation of success that would justify the use of this very limited and valuable resource.

Another suggestion that I heard, maybe misinterpreted, was that there should be limited protocols going forward with regard to the different efforts. There was a comment about how, with AIDS research, people have their pet peeves, their pet reagents, et cetera. I think that's a disservice to science. We do not know where the answers will come from. We have to use good judgment, and that's what IACUCs are all about.

We need to pursue those avenues that look potentially fruitful, and we need to not expect that one track, one protocol will necessarily lead to success. Clearly we wouldn't expect one mouse to give us a cure for cancer. We do expect variations of protocols, and it's within those variations that we learn additional pieces of information that add to the total picture.

And the last point is clearly the Rhesus, the Indian Rhesus, are in short supply. Yes, the transportation of primates into the U.S. Has now become very restricted, but I think to have a global impression that primates are not available in general is not correct. There are breeding programs, there are efforts to make animals available to the scientific community, but clearly it's going to be a prioritized effort to see that those activities that have merit and have strong potential for success are going to be the ones to achieve them first. The USDA has a good handle on the number of primates, and I think we can look at different species' availability. Clearly the baboon, I don't believe, is as restricted as the Indian Rhesus. So thank you.

Agenda Item: Overview of Draft Report on Informed Consent in Clinical Research Involving Xenotransplantation

DR. VANDERPOOL: Thank you. Now let's move to an overview of the draft report on informed consent. This overview will consist of four brief, very brief presentations. I will be talking about the first sections that deal with from the background through the components of informed consent, then Dr. Cathy Crone will deal with the informed consent process, then I'll return to give an overview of the informed consent forms. And then Professor Shapiro will review the sections on special problems and concerns raised by xenotransplantation, after which we will have our plenary discussion of this report.

The first section on the background is very brief and talks about SACX, why it was formed and what our particular charges are, and then the second section under introduction points out that there are a number of ethical issues raised by xenotransplantation, but a particularly pressing one is a need to deal with the unique and complex issues pertaining to informed consent for prospective research subjects.

And then, after giving us a brief road map of the things to come, we begin traveling down the road, with the first section being ethical foundations and functions of informed consent. This section indicates how the process of informed consent upholds an essential and profound set of ethical and legal values. To quote from page three of our report, "the ethical foundations of informed consent emerge when we ask why the process of securing consent is required before research involving human subjects can be initiated."

The short, far from vague answer is that consent is mandated by federal regulation; the longer, far from bland answer is that informed consent preserves the values of self-determination, freedom of choice, and protection from harm, abuse, and deception. These values are rooted in the basic ethical principles of beneficence, "do no harm," and respect for human beings as autonomous agents.

Then we move to the components of informed consent, and these components are clearly spelled out and outlined in the Belmont report, which became the benchmark statement about the ethics of research involving human subjects when it was first published by the National Commission in 1979. And, of

course, this section is not merely drawn from the Belmont report, but from the literature in the area.

The three components of informed consent include disclosure of information, comprehension of information, and voluntariness. To quote from the bottom of page three of our report, "the disclosure of information occurs through discussions and dialogue with prospective research participants about material information concerning the trial, in which questions are asked and answered through consent forms and accompanying materials. Comprehension is facilitated through careful attention to the process of communication between research participants and investigators, as well as other knowledgeable persons. Voluntariness is assured if the conditions under which the research subject's agreement to participate are free from coercion and undue influence.

Our report then details what these three components are. With respect to disclosure, the forthright and sufficient disclosure of information so that persons can decide whether they wish to participate or not in all phases of the research in question.

Comprehension involves the process that involves adapting the information to the participant's mental capacity, to level of education, to language skills, emotional needs, and social situations, and this means that participants need to be able to ask questions about the details of the trial and about his or her physical, emotional, social and spiritual concerns related to the trial.

Voluntariness involves, in terms of the Belmont report, the need to secure informed consent free from conditions of coercion, undue influence, and unjust pressures. We also recognize in this report, however, that voluntariness can be affected by the levels of pain and personal suffering and desperation in the face of overwhelming illness. So we say at the end of page four, "when risks are high, when uncertainty exists, when procedures are complex, and when patients are desperate, researchers should make an extra effort to determine whether prospective research participants have in fact comprehended the disclosed information and made a voluntary choice to enroll in the research. The best way to ensure comprehension and voluntariness is to develop and follow an effective consent process."

And Dr. Crone will tell us some about what we have stated and set forth regarding this process.

DR. CRONE: I guess what I can start off with is saying what some of the problems that we recognized with what happens when informed consent is requested of subjects of studies. Some of the problems are that there's oftentimes an excessive focus on simply obtaining a signature on the form, also that there's focus on the medical/legal aspects of informed consent rather than the subject who is actually going to be signing it. There's also a tendency oftentimes to use excessive jargon, medical jargon, scientific jargon, and some subjects don't necessarily know what's being explained to them.

Also one of the problems is that informed consent oftentimes is only a one-time meeting, so it's not really an opportunity for a subject to reflect and ask questions. Even if that one meeting they may be encouraged to, but sometimes people don't have questions until they step a way and think about and weigh their options.

Some of these concerns, as well as recognition about the fact that xenotransplantation, any subject to undergo this is going to be signing on to a very complex process with very long-term ramifications, led our subcommittee to feel that there was a need to not just focus on the informed consent form, but the actual process. And with that in mind, we were trying to figure out a way to set up the informed consent process in a way that would facilitate a subject patient to have the best opportunity to understand what it is that they're deciding on and whether or not they want to pursue the procedure or not.

Part of what we had recommended was that the informed consent process, that the participants in this

process should involve an actual informed consent -- it's a team of people. For it not just to be the principal investigator, but for it to involve more than that; for it to involve individuals who could be a coordinator or a nurse, it could be somebody who is a psychologist or a social worker, people to address other issues beyond just the medical facts, or another group that would be approachable if someone has questions.

And that we were encouraging that this team of individuals actually meet individually, and they should be separate meetings for the subject. Meaning the principal investigator should meet with the subject, so should each of these different members, so that there's time for repetition of the information, for encouraging discussion and questions, and really for there to be a two-way discussion, not just one person talking to the subject and going through the same material over and over again.

Also we had talked about in this way it being a step-wise process so that you didn't overwhelm a subject with too much information by just giving them everything all at once. So that this would give a chance, again, for the person to take it in, to absorb it, to develop questions, or if they raise concerns. And also we wanted to offer the possibility of even additional consultants being pulled in as needed, like if there were religious concerns, if there were psychological concerns, if there were other particular concerns. And also to encourage that the subject bring in those close to them, a family member, a significant other, because that may also facilitate their ability to take in the information and to manipulate the information to make it really informed consent.

And we had also felt that it was important to recognize the setting, the format, and pacing. Setting meaning for the informed consent process to not be done like at bedside at a busy hospital, but for it to be in a location where it's quiet, where there's not going to be a lot of disturbances, where somebody can really take in and focus on what they're learning.

And again, when we talk about pacing, again, that's sort of the emphasis on the step-wise process of all of this, and also for us to use more than just simply written information; also if we need to, provide visual aids, use other different methods in order to get across the point. Because not everybody learns through the same medium.

And lastly, we had also mentioned, besides kind of going beyond what's kind of mandatory for what needs to be included in the informed consent form, we also felt that there were some additional points that we wanted to stress or to add that should be covered. That included issues about the background and history of the procedure they were going to go through so that they could understand not just that procedure, but what's the history of it, what are other trials that have been put forth, what success or complications have happened. And so what are the results, so that they have some history to it and they can kind of weigh this out.

And a description of the procedure, focusing on it coming from the patient's point of view, which is sometimes difficult to focus on, being a health care provider or researcher; a realistic estimate of the potential risks and benefits that this patient is going to be facing; also to make sure that available alternatives are discussed, and include discussion of the comparative risks and benefits.

And also lastly, social consequences, because this is some of the unique issues about xenotransplantation; the fact that there might be issues with media attention, that there will be concerns about transmission of infectious diseases that are added in long-term issues, complicated issues that make xenotransplant sort of a unique procedure. And those were sort of the things we felt were important to focus on besides just the content of the actual form.

DR. VANDERPOOL: One thing is for sure, those of us who are reviewing this report are by no means

those who did all the contributing. There are a number of people sitting around this table who made extremely important contributions to this entire document. We spent a lot of time together, got to know each other better in the process. But Sharon and Brad, Jim, Karren, Louisa, Eda and others were there and contributed, so it's really a document with the input of many.

Now, with respect to our understanding of the relationship between the consent process and the informed consent form, we commented on page seven, "Placed in this perspective, consent forms can and should play important roles in the overall consent process. Its roles include disclosing potential information to prospective subjects and assisting them to comprehend this information."

Now, instead of just giving all the paragraph after paragraph of what needed to be included, we decided instead to give what we considered a model consent form. And I'll say a few things about the model we set forth. We wanted it to be in a different form than the actual full document, but not exactly in the form here; here the lettering is too large and so on. But it gives you the sense that we wanted the presentation of the consent form in our document to look a little bit like a consent form or a good bit like a consent form, and therefore to have it stand out somewhat from the rest of the text.

Now, in this model consent form we sought to give, we definitely did several things. For one thing, we included, insofar as I can tell - all of the topics the federal regulations and the guidance documents from the PHS, DHHS, and FDA would have us adhere to. They tell a great deal about what needs to be in a consent form, and all of that, as far as I can tell, is within this model form.

This model form also seeks to convey the information in ways that maximize understanding, and to that end, we did some real research in the type of wording that needs to be used that can be understood by ordinary American citizens from all walks of life. And to be readily and easily understood, we talked about easily read print, print size, lower case letters, simple and frequent headings and subheadings, and certainly not the use of overly technical language.

And so with respect to that language, we tried to say what this language should be in light of the real studies of understandable language. You'll see on page eight of the form, and I'll quote from these last few lines, "The following outline reflects the influence of the article on consent forms by Hochhauser, who showed that many of the words that are familiar to investigators and IRB members, such as clinically, orally, placebo, protocol, and regimen, are, in fact, rarely used and unfamiliar to many persons and prospective research subjects." that may be a surprise to those of us who work on IRB's and in medicine, but it's true with respect to ordinary American citizens.

Hochhauser and others also recommend replacing often used terms by medical professionals such as abstain, discontinue, new indication, uncommonly, and specimens - we hear these all the time - with more familiar terms such as a void, stop, a new use, rarely, and samples.

So in the outline that we give, we do the following: Instead of giving the technical word and in parentheses putting in the commonsensical word, we give the commonsensical word and in parentheses put in the technical terms or the less understood terms we often use.

Now, you can see on the slide, under Adult Consent Forms, the different categories we discuss, and I won't review most of these. Some things about the protocol itself, a clear statement of the purposes; we try to make these as clearly and succinctly, and in as ordinary language as we can. Treatment choices we thought ought to come early rather than late in the consent form. This suggestion came from Brad Collins, because Brad felt and feels that you should hear about the alternatives to treatment - we call them treatment choices in this document - so that you can be thinking about what these are as you listen to what the research is.

Participation. Instead of saying "entry criteria," we just simply use the words "who can enroll." instead of "exclusion criteria," we use the words "who cannot enroll." we talked about duration of involvement, chance division of groups that enroll - obviously that has to do with placebo groups - and a whole host of study procedures. We discussed each of these as straightforwardly as we can.

The risks, we try to give, again, a straightforward, honest description of the risks, that include rejection, failure, immunosuppression. We suggested forms with long discussions of immunosuppression may belong in indexes, and animal and human infections and so on. You can see the wording regarding animal and human infections on page 14 near the top. We give some wording that might be used; "While precautions against your developing this type of disease have been and are being taken, the risk of your becoming infected is possible but presently unknown. Beyond your personal health, there is the potential risk that you could transmit an infectious disease to family members, health professionals, and the public."

So we go on with the risks and then we come to the responsibilities. You may think the list of responsibilities on pages 15 and 16 are overly long. If you do, you need to revise the guidance documents we are now counseled to follow. These responsibilities include, on page 15, regular checkups, enlistment in databases, the necessity of informing researchers of changes of address, timely reporting of all unexplained illnesses, practices that limit the exchange of bodily fluids with intimate personal contacts, no future blood, sperm, et cetera, donations. Autopsy at death, education of family members, we talk about that. Then we say on page 16 this section should include assurances that a counselor and/or other members of the research team will assist those who volunteer to enroll with these educational responsibilities.

The final comment to make is that after we go on with the benefits, costs, compensation, and so on that Mary has on the screen, we try to capture a dynamic that Robyn will certainly comment at greater length on, the dynamic between voluntary enrollment accompanied by agreement to follow responsibilities. And that wording is at the bottom of page 16 of the report. Suggested language for this section is as follows: "your enrollment in this research is completely voluntary; that is, enrolling is something you want to do a part from any pressure from anyone else. Refusal to participate will involve no penalty or loss of benefits to which you are entitled," and so forth. "unlike many other kinds of medical research, however, your voluntary decision to enroll in this study should be based on the recognition that once enrolled, you are expected to fulfill future responsibilities that are a part of or accompany this research as outlined above. Your dropping out or withdrawing from this study may result in stopping financial support of lifetime checkups and other responsibilities. Your dropping out could also lead to imposing public health measures against you and your intimate contacts."

So that covers the many topics on the consent form in as simple language and as understandable format as we could come up with for recommendations to the entire committee.

MS. SHAPIRO: And that brings us to special problems and concerns raised by xenotransplantation, and we, in the document, categorize them in three different groupings. The first involves public safety measures vis-a-vis the participant himself or herself. And clearly, because of the potential infectious disease risks, informed consent is different in this type of research than in any other in that it requires the participant to be fully informed of and to agree to lifetime monitoring, including routine physical evaluations, laboratory testing, archiving and future testing of tissue or body fluids, and autopsy.

And since, as I mentioned before, currently there is a requirement in federal regulations governing this type of research, that participants be allowed to withdraw, there's no direct hammer to enforce those requirements. And that's why it's so critical for people who are conducting this research to be thorough in

the informed consent process about the nature of this responsibility and thorough in their evaluation about the extent to which the prospective participant is agreeing to that.

In cases of non-compliance, we kind of again have two different categories, one of which has an answer and the other doesn't. It's clear that states can have and do have public health laws that may adequately address the situation where there's a non-compliant recipient of a xenotransplant product who has acquired an infection that's imminently dangerous to the public. Our public health laws currently on the books will address that set of circumstances. These must be reported, and, once reported, state laws give health departments broad discretion to take whatever steps are necessary to prevent and control the spread of communicable diseases. Legal compulsion actually is really needed in this kind of set of circumstances, because people are willing to voluntarily comply with testing and control measures, but if not, there is redress in state law in this set of circumstances.

So a xenotransplant recipient's doctor would be on the front line and required to report an unidentified disease if there were reason to believe that it could be caused by a transmissible infectious agent and pose a threat to the public, and then the health department would and could step in and exert its authority to do what it had to do.

On account of this, on account of the primary care physicians being on the front line, one of our recommendations I think at the end of the document was that there has to be good communication between physicians and public health departments about looking out for and reporting disease in this set of circumstances.

Where we don't have as easy answer, and we talked about this some at past sessions, is when there's a xenotransplant recipient who is asymptomatic, manifests no sign of infectious disease but simply stops complying with the lifetime monitoring requirements. Under current public health laws, mandatory periodic monitoring of these kinds of individuals and their intimate contacts - that is, before any evidence of a communicable disease - probably would not be possible. We are undertaking a comprehensive review of the public health laws in all the 50 states to see what they could do and where they might fall short, and perhaps we'll make recommendations about the need to take another look at our public health laws in the states on account of this and analogous situations involving other situations, other disease risks.

The second set of special problems, also involving infectious disease risks but focusing not as much on the recipient of the xenotransplant product but on third parties, the intimate contacts of recipients, health care workers, and ultimately the community at large. We currently don't have any legal requirement or opportunity to get the consent of third parties for research being conducted on the direct participant. Nonetheless, because there is a risk of infectious disease transmission to intimate contacts, we recommend in the document that we, in the informed consent process again, inform the prospective participant of his or her obligation to fully educate not only current but future intimate contacts about this risk, as well as about how infectious -- the risks come about, the methods that can be undertaken to reduce that risk, the need for intimate contacts to report significant unexplained illnesses, and so forth.

We recommend that this education could be done with the help of people on the xenotransplant team, and that the recipients be informed of that fully during the consent process. Health care professionals also face some risk of transmission of infectious disease, and so we recommend that they too should be informed in advance about what the procedure is going to involve, about the known and the potential risks of xenogeneic infections posed by the procedure, behaviors known to transmit infectious agents, how to minimize the risk of that transmission, and the need, again, to report significant unexplained illnesses.

We also recommend that each institution where this is going to be performed have a plan for monitoring

their health care personnel who are involved, that that too be explained pre-procedure to the health care worker - and there are some recommendations put out by PHS about how to do this, how to collect specimens pre and post exposure in case there is an exposure - and that there be monitoring of adherence to infection control measures, which should always happen.

And then we get to the community. And as I explained briefly before and as we have discussed briefly before, and as is discussed in this document, is there a risk potentially posed to the community? Yes. Is this easy to deal with in this document? No. The first problem is defining the community; we kind of conclude that you really can't do it without including the entire global population in light of the highly mobile society in which we live. We can't get consent from the whole global community, but we can involve the community.

And then we look in this document on page 21 about different ways to do that and the shortcomings of some of the methods that have been attempted, and conclude that really this committee itself could do a lot to involve the community by continuing to have open public meetings like this, by being available as members of this committee for interviews, by reviewing the protocols themselves so that we can give input in the evaluation and be informed about what actually is going on in the research community, by developing and making available informational resources on the scientific and medical, social, ethical, and public health issues posed by xenotransplantation, providing a forum for public discussion of these issues when appropriate, making recommendations to the secretary when appropriate, and developing closer collaborative relationships with private and public agencies that are conducting xenotransplant research in other nations. More on this later, I think.

The last group of special problems and concerns raised by xenotransplant research has to do with obtaining informed consent for research involving incapacitated adults or children. This is a real problem. We have, as I said before, very little if any guidance in the federal regulations about criteria that should be used by surrogate or legal representatives of prospective research participants who are incapacitated, criteria that should be used for enrolling them exerted by a legal representative.

We also don't have terribly helpful information from more general case law or statutes about how surrogate decision-makers should make any health care decisions on behalf of incapacitated patients. We also have a wide variety of incapacity, potentially, in prospective research participants.

And the group that we found to be most compelling with respect to should incapacitated adults ever be allowed to enroll in these sorts of protocols are those for whom the procedure is likely to reverse the incapacity. It's discussed some on page 22, "Patients with fulminant hepatic failure, often as a result of viral exposure or drug reaction, frequently experience altered mental status or hepatic coma due to circulating toxins in the later stages of their disease, and patients with chronic liver failure also are at risk for mental status changes as their disease process progresses."

So for both of those, I'm told - I'm not a physician - liver transplantation from a human donor, a period of mental competency returns. But because of the organ shortage, of course they may be good candidates for a xenotransplant as a bridge, and so that we can anticipate that with this help, their mental capacity would return.

If we're dealing with that sort of a patient, and if the surrogate decision-maker has information either that the person likely would agree to enroll in this kind of research or that enrollment would serve his or her best interests - and this is borrowing from general guidance that we have about how to make decisions concerning health for incapacitated patients - and if we have evidence from the surrogate who is speaking on behalf of the incapacitated patient that this person is generally responsible, and we would expect that once capacity was restored, he or she would comply with the lifelong monitoring requirements, and if we

have a surrogate who has an established relationship with this person, who we think will help to assure compliance with the lifelong monitoring requirements, then we were persuaded that inclusion of that incapacitated adult in a xenotransplant research protocol might be permissible.

And then we get to children, as if it wasn't hard enough. And this clearly also raises huge problems because of the lack of guidance in general and the special problems involving this sort of research where the risks are high and the lifelong requirements are onerous. And those considerations led us to recommend that as a general matter, children should not participate in these protocols.

And there may be a question when we're dealing with adolescents who are close to the age of majority, which varies some from state to state, about whether they're sufficiently mature to understand the risks and the benefits and the scope of commitment and compliance that's demanded of them. And we end up by saying that this is certainly a topic that deserves further reflection.

Agenda Item: Plenary Discussion of Draft Report on Informed Consent in Clinical Research Involving Xenotransplantation

MS. SHAPIRO: And now I think it's open for discussion. And I'm going to be moderating this part of the discussion, and Harold, tell me where I'm wrong here, but I think that what we want to do is to ask for comments on all sections, on what Harold talked about, what I talked about, what Cathy talked about.

DR. SALOMON: I have a couple of questions. I think you guys have done a spectacular job, by the way. This is a very, very difficult area, and a lot to be proud of here. I won't ask all of them at once. We'll see how the discussion goes. Let me start with one, and that is this ending study clause. I realize that's not just for xenotransplantation, but I think it's appropriate to bring up here because there are some issues with long-term follow-up for xenotransplantation. This may be unique with respect, perhaps, maybe also to gene therapy.

The question is, is it really ethical or legal to have somebody in an informed consent sign off the statement saying that for whatever reasons, anyone can decide to end the study; the PI can end it, the company can end it, the university can end it, or the grant can run out and you're stuck with any costs as well as follow-up? I don't buy that.

MS. SHAPIRO: You're on page 15, right? Just so people can follow you, you're on page 15, paragraph 7?

DR. SALOMON: 15, 7, "possibility that this study will be ended early." I'm not comfortable with the way that was written. On the other hand, I think you need to point out that a study can end, but I think it's another step further to go, now you're going to receive lifelong care from the sponsor and you could be responsible for the health care costs.

MS. SHAPIRO: As I recall, we really got a lot of information from Eda about how this sometimes happens, right, and how this sometimes happens --

DR. SALOMON: Well, blank happens, but it's not necessarily something that you can ask someone to sign away on.

MS. SHAPIRO: On the other hand, people should go in with their eyes open that this could happen. I mean, there's no law that makes you stay in business if you can't. Right?

So we talked about this for a while, and it feels kind of yucky, but again, if it is a risk ...

DR. VANDERPOOL: Dan, you're absolutely correct. What we're trying to do here is informed consent. If they're caught between a rock and a hard place on this, then they need to be told up front that this could be ended early and you could be left holding the bag. If there's a way to avoid that, then we believe they ought to be informed how to avoid it. But it is a dilemma, but what we're after is to tell the patients what's likely the situation.

DR. SALOMON: Well, there's other people who want to talk about this, but let me just point out that we dealt with part of this in the BRMAC for gene therapy, and there are ways to insist that sponsors cover this. It can be done through insurance, it can be done through bonds, it can be done through other agreements.

Yes, after everything is said and done, everything can go wrong and you would be stuck. But at that point, if I were the patient, I'm not responsible for reporting myself every year and having X and XY blood test done because the FDA decided me to do it. Forget it. I'm not signing it.

So that's a problem, I think. That's kind of what I'm thinking here. There's a limit here of what you can ask someone to sign a way.

DR. KASLOW: I guess the question to me is one more of a matter of degree than of kind or complexity, because there are lots of surgical procedures I could imagine that have taken place over the years - let's say implantation of a heart valve that was made by a particular company - that basically if you had that put in, you could never have any kind of heart valve put in or whatever and then that company goes out of business and so on.

To me it would sound like the issue is more what is distinctive about xenotransplantation from any other procedure, and I have a feeling it's more the longevity and the complexity than it is the principle, per se, that they go out of business and there's nobody there. Maybe we need to address it.

DR. ALLAN: I just think maybe if you just rewrote it a little bit so it's not like in your face, so it's more that there is an unlikely possibility or a remote possibility of X, Y, and Z. You know, because the way it looks now - and I agree with Dan to some degree - it's like, well, heck, I'm not going to sign up for this if I have to commit, and it sounds to me like the company doesn't have to commit, so I don't know if I want to sign up for this.

MS. SHAPIRO: If we analogize this to general informed consent principles, remote risks don't have to be exposed. And I don't know if this is a remote risk. I really don't.

DR. VANDERPOOL: Well, I think John has an excellent point, that we can moderate some of the language of that section seven.

DR. CHAPMAN: Perhaps I'm misreading this, but Dan, I have a question about your question. Because you're talking about section seven on page 15, right, possibility the study will be ended early, and it explains that the study may be ended before the study plan was complete for whatever reason, and if that happened, there would be some potential implications for the subjects.

And then my reading of this was that you're going on to give an example, and the example was perhaps participants receiving lifelong care from the sponsor had been one of the things that were problems when they enrolled in the trial, but if the trial ended early, the patient would not receive that and they would

then be responsible for their own health care costs that arose from the research project.

Maybe I'm misunderstanding this, but my reading of this, the note I made, was use a more realistic example. Because I don't know of one clinical trial in which a sponsor says, if you participate in my clinical trial, your health care is covered for life.

So I guess I'm not certain if the discussion here is revolving around the issue of whether it needs to be disclosed to patients quite clearly that the trial they're choosing to enroll in may not go to termination, and if it doesn't go to termination, their expectations from the trial may not be met, or if we're getting into discussion about something that may not, in the end, be relevant, which is a loss of benefits that in reality no sponsor would ever promise.

DR. SALOMON: Okay. So in response to that, there's two specific things that bother me. You're going to have to have a clause like this in here. I mean, you realize that's not what I'm objecting to, it's just the specifics.

So situation one of two is the FDA is going to say, if we follow what we've done with gene therapy as a guide and what's been done up until now with xeno, that you are going to follow these people lifelong. That's going to be in the -- that's going to be in black and white somewhere, even, let's say, if it's 10 years. So point number one is that what this is saying is that you are responsible for the medical costs of all monitoring for the next 10 years or forever. And that's not acceptable. That's all I'm saying.

The second option here that's also equally unacceptable is that I go and I have a pig kidney transplant and this and this goes on, and in the middle of my recovery, the company or something decides we're going out of business and I get a \$200,000 bill from the university hospital saying, guess what, you signed it.

MS. SHAPIRO: So what's the answer, then?

DR. SALOMON: I don't think that any trial ought to be allowed that doesn't deal with these issues up front in the process of the approval for doing the trial. These shouldn't be the -- this is a cheap way of sticking it on the patient, and I don't buy it. I mean, if I'm going to do the trial, then I have to account for the fact that either of the two instances that I just outlined are not going to happen.

MR. BERGER: I don't think this covers the first example, Dan. That's not my reading at all that anything to do with trial cost. I don't think that was the intention. Maybe it needs to be written slightly differently, but that was certainly not the intent.

But let's use maybe another example. Let's say someone has a kidney transplant and there are some problems that occur later on; the sponsor stops their trial and the patient is stuck with some new condition that developed because of that transplant. Would that be an example that we're talking about, that then the patient is in a situation, the sponsor is gone, they have some new condition, and they should be a ware of that?

MS. SHAPIRO: So is that objectionable, too?

DR. SALOMON: No. Because that falls into -- that could happen in a lot of ways, so I'm not as concerned about that.

DR. VANDERPOOL: In keeping with my suggestion -- I think we've got the issue out there, and in keeping with my letter to all of us on January the 17th, make changes in the margins. You know, suggest

what analogies should be used. We'll fix this. We'll fix it. And we agree with not getting stuck with something, et cetera, as you said, Dan. Alan has pointed out that was not the intent in this paragraph, so let's fix it. But let's move on to other issues, as we recognize them.

DR. SYKES: I have a question about section three on page 14 of the informed consent form. It says in the second paragraph, "to restrict these risks, volunteers for this study as well as family members and intimate contacts are required to follow safety precautions," and then it describes the lifelong medical checkups and refraining from donating blood, sperm, et cetera. That seems a bit Draconian for the intimate contacts in all xenotransplant trials at this point. Was that really the intention of this, that you feel that intimate contacts should definitely be followed in this way and refrain from these practices in all cases?

MS. SHAPIRO: The guidance -- Eda, clarify for us what that guidance says currently.

DR. BLOOM: I'd like to, but I'm not sure exactly. I'm trying to figure out where it is.

MS. SHAPIRO: Second paragraph, section three.

DR. BLOOM: Oh, I see. Yes. I don't believe actually that the guidance says that the contacts will be followed by checkups, that the contacts will be followed only if there is reason to follow them. But they will be educated.

MS. SHAPIRO: And educated about refraining from donating. Isn't that part of it? Yeah, so I think it's miswritten, Megan. So we can change that.

DR. VANDERPOOL: Let's scratch the phrase, "as well as family members and intimate contacts, volunteers for this study are required." I will have to recheck the regulatory guidance --

MS. SHAPIRO: Yeah, it would require more changes than that.

DR. VANDERPOOL: -- to see what intimate contacts have to do.

DR. MICHAELS: Actually, that was a big question that came up from the last meeting or the meeting before from the blood bank community in terms of what we were going to put down as restrictions of the intimate contacts, and whether we were going to have that. And I know we had discussion, but I didn't think we had actually come up with a resolution. We certainly had said that any recipients of a xenotransplant should refrain from any donation, but I didn't think we had actually come to a conclusion on the contacts.

MS. SHAPIRO: Well, if we were to rewrite this paragraph so that the volunteers are required to do the whole laundry list and the intimate contacts only were required to do the refraining from donating blood, sperm, other bodily fluids, how would people feel about that recommendation coming out of our group?

DR. SYKES: Well, I mean, first of all, it's pretty hard to ask somebody to make commitments for somebody else, and also not only current somebody else but future somebody else. All future intimate contacts would be subject to the same restrictions.

MS. SHAPIRO: Well, and it's more asking the participants to educate their future and current contacts that they shouldn't do this. Not making them sign in blood on behalf of, but educating them that they probably shouldn't, I think.

DR. VANDERPOOL: If we removed "as well as family members and intimate contacts," we don't have that problem at all. But what we do have to do is check the regulatory guidance to see what they're supposed to do, and if they're supposed to do things that this committee has a problem with, then what we need to do is go ahead and state what needs to be in the consent form at this point but make a recommendation that that guidance be changed.

But this consent form is meant to be a guide for present researchers, and they need to follow the guidance that is now out there. I think you're right that right now this whole list of things is not required of family members and intimate contacts, but I'm not sure it's not. I have all the guidance upstairs in a briefcase, and so I can check on that tonight.

MS. SHAPIRO: We also have to be sure that it's consistent with what we see in the body of the document on page 20. And so what we see in the body of the document on page 20 is what I just said, which is that they have to educate about behaviors known to transmit.

DR. VANDERPOOL: And that's in the form, too.

MS. SHAPIRO: Well, it's in the form, but we've got to fix it. Yeah.

DR. SALOMON: Well, just as a point of information, the time before that this was brought up, so the last time we dealt with it, was when the blood banking community came to us. The time before that, by my recollection, was not in this committee, it was when I was on the FDA's xenotransplantation advisory committee, representing that committee at a meeting in Gaithersburg of the advisory committee for blood products. Right, Eda? And that was the time when -- it was Hugh Auchincloss and myself, and it was Hugh who got into this concept of intimate contacts to try and get us around the problem of all contacts.

And so it's my understanding, at least in the spirit of the current FDA guidances for this, is that there is a stipulation that intimate contacts of subjects having received a xenotransplant are not to give blood, sperm, or tissues, so that in that spirit, it's not unreasonable that you would want some statement that the subject acknowledges some responsibility for communicating to the intimate contacts. And I think you could probably fashion something from that without quite using the words that Megan objected to.

MS. SHAPIRO: That's actually just what I had in mind.

DR. KASLOW: I would also suggest you take another look at the wording about family members, because that seems pretty vague to me, the more I think about it. What's a family member? How many degrees of relativity do you follow that, and is it intimate contact that you're really concerned about? Is it family members or intimate contact?

DR. VANDERPOOL: Dick, we've already scratched that phrase. But I do think when we meet tomorrow in our breakout session we're going to have to fix this, and I'll get the regs. Dan's memory, I think, is right on target, that intimate contacts can't give blood and other things, can't donate blood and so on, but we'll have to see what else they're required to do.

DR. CHAPMAN: I just want to suggest that in addition to the guidances that have been issued, you may want to also review the transcripts of the various advisory committee meetings that have discussed this, the FDA xeno subcommittee and the BPAC, the blood products advisory committee, for the issues that Dan has said. Because there have been discussions that have gone on without a reissuing of some of the draft guidances that were initially issued for public comment and for review, and so just the guidances

may not give the final comment. Is that correct, Eda? If you're talking about the FDA blood donor guidance, has that come back out in final?

DR. BLOOM: It came out in a second draft and it's being rewritten.

DR. CHAPMAN: And there's been discussion since then?

DR. BLOOM: What was presented to this committee -- what's been presented at this committee was the second draft. Comment has been received on the second draft. There's a rewrite in progress.

MS. SHAPIRO: And when is that due? Bad question.

DR. BLOOM: I've been telling you for, what, a year and a half that our big guidance is about to come out in final. Don't make me go there again.

MS. SHAPIRO: Okay. Other comments?

DR. SYKES: Just one thing I didn't see was any explicit statement that the subject is responsible for informing future health care providers of his or her xenotransplant, and I think that is an important thing since those individuals may come in contact with blood and bodily fluids and so on.

And also, I don't know if it's ever explicitly stated that future intimate contacts as well should be informed. Maybe that one is in there.

MS. SHAPIRO: Family members, but the health care providers isn't. Thank you for that.

DR. ROTROSEN: I was also struck by the absence of any explicit mention of risks to a fetus or a neonate through intimate contact or breast feeding, the birth process, and wondered whether that was an intentional area that authors a voided or an omission. And if the latter, should there be mention of contraception or education about contraception to participants?

MS. SHAPIRO: It didn't come up and it should have, and we'll talk about it. Excellent point. Yes?

DR. MENDEZ: Just a few comments. First of all, I thought it was a very comprehensive and beautiful article. There are two things that I not object to but have some concern about, and that is the consent of the children and the consent of the disabled.

First of all, as you may all well know, children are given the highest priority for human organ transplantation, thus theoretically they would hopefully not need to have a xenograft transplant. It is not inappropriate to have contraindications to any types of surgery, and in transplantation, historically there have been significant contraindications to transplantation, with children getting the highest priority. I'm not actually sure that we even need to have children receiving xenotransplants. The same thing perhaps would go for the disabled individuals.

One comment with regard to the consent, the generalized consent form. It's been our experience in California that informed consent, no matter how precise and how intense it is and how accurate it is, is not an informed consent unless you document backwards that the individual receiving the consent understands the consent, and thus you have to have some sort of a verbal or written statement from them in terms of their understanding of the informed consent. We do it in two ways; by actual video presentations and then by an examination that they must take afterwards. And thirdly, by talking with

previous individuals who have been involved in the protocols.

MS. SHAPIRO: And Harold can touch on the latter point. We talked about it some. Let me just ask you, Dr. Mendez, with respect to your first comment. In the document we do kind of say with respect to children, we don't think they should get them now. We could bolster that with your comment that since they are likely to get human organ -- no, we can't say that, can we?

DR. BLOOM: Everybody keeps forgetting that organs aren't the only things in xenotransplantation. You've got eyelet cells for diabetes, you've got skin cells for burns. And in fact, I was going to suggest that you might want to put exceptions to the no treatment for children, because there are some that are intended explicitly for children, specifically for children.

MS. SHAPIRO: I think what we're going to be faced with is we have not given this its due. Now we make a couple of cursory comments and we say we really need to think about this more. So I think our question will be do we give it some more thought now or do we just kind of say this really deserves so much more attention than we can give it at this point that we can't develop this section well. And maybe we'll decide that tomorrow. Yes, Harold?

DR. VANDERPOOL: The question of children really is a complex question. I suspect as soon as more -- assuming a resumption organ transplants occurs, the question of children will come up rather quickly, and it seems to me maybe that's the time to let children do it, but let adults go first. I mean, there was so much -- there was so much turmoil over Baby Faye, that I think to step into any sort of a recommendation mode at this point is to call into play a set of criticisms we shouldn't have and really, in a sense, can't afford to have.

Now, on your very good point about prospective subjects making statements to the effect that, "I understand what's going on and I'm ready to sign," I think that makes a lot of sense in non-complex research settings where the subjects aren't as likely to be as physically compromised. Jim Finn won the day with us on a couple of points. He doesn't speak very often, but when he speaks, it's sort of like Moses coming down from Sinai. He made the point that he didn't understand his consent form; he knew he was going to die if he didn't do something, and he found out about his consent form after everything started.

It seems to me that the decision -- this paper rests on the assumption that, pardon my language, we're going to do our damndest to make sure that prospective subjects understand, through the consent process and through the form and all kinds of things, what they're getting into. But to sort of give them a test and make them prove that they understood things or to make them say that they understand it when they might well, if they're desperate, be lying about it, is not something we're ready to go to.

So I'm saying two things; I'm saying on the one hand I can understand why ideally it would be good for them to say I understand and to mean it. On the other hand, realism says there are going to be a lot of people who are not going to be able to go there.

DR. MENDEZ: They'll never fully understand. None of us will. I was just trying to avoid what's happening with AbioCor and the artificial heart, and the huge lawsuit that is pending now because, quote, they were not given, quote, the informed consent. You can imagine the informed consent they had, but they didn't, quote, understand what the life-style would really be like.

MS. SHAPIRO: One second. I just want to go back to Eda for one second. Eda, I hope that you'll come to our work group tomorrow so that we can perhaps have further conversation. I would like to hear your list about the children and the non- whole organ procedures that may be different.

DR. KIELY: Just a couple of things. Insofar as the section on incapacitated adults, I was wondering if we shouldn't clarify a little bit. And I'm not maybe completely understanding where we were going with this insofar as, for example, if you had a person who was -- had some mental limitations and became further incapacitated by their fulminant hepatic failure, would you be saying, then, that that person -- because the anticipation, at least, would be that they would go back to their baseline mental functioning, which might not, in fact, be full adult capacity as we might define it, but it's clearly their capacity. And I think we need to clarify what the sense of the committee is in that regard.

The second issue I wanted to mention is related to children. We will talk more about that tomorrow, but I think there was always a sense in the committee that if there was no reasonable expectation of benefit to a child, none of us would get behind that. But we recognize that this is not what you would call standard procedure in any sense.

And then finally, I just bring up maybe we need to do a little bit of research related to the HIPPA requirements, the privacy requirements on future needs of research. Now, this is starting to come out where all the IRB's are being educated on HIPPA requirements, particularly related to future undefined and unknown outcomes of surgery, on transplantation research, what have you. And so I think we really need to get a sense of that to make this report a little bit more timely.

MS. SHAPIRO: Thank you. I don't know, Sharon, tell me what you remember and we'll talk about it more tomorrow. But my sense was that if one did not have the capacity to consent at the initiation of the protocol, then one wasn't going to be enrollable unless we could get back to decisionality. So I think in your hypothetical under what we had talked about so far, that person would be excluded.

DR. KIELY: And I think if that's the sense of the committee, then we need to be clear about that.

MS. SHAPIRO: You're right. Yeah, I think you're right. Ellen?

DR. GADBOIS: I just had a few minor comments to what I found to be a very thoughtful report, draft report. I noticed there were a few places in the draft informed consent document where language a long the lines of treatment, patient, doctor was used, and I just wanted to suggest to the group as you're doing your editing that you think about whether you would rather choose terms that wouldn't invoke possible therapeutic misconceptions.

MS. SHAPIRO: I have the same scruples.

DR. GADBOIS: Okay. And one other suggestion with regard to the earlier comments about the provision on disclosing costs and compensation, you may want to check the required elements of disclosure in the common rule and the equivalent FDA regulations. I don't have them with me, but that's addressed fairly explicitly as a requirement in HHS and FDA regulations.

MS. SHAPIRO: Okay. Thank you. Dan?

DR. SALOMON: I'm uncomfortable with the verbiage about nurses and laboratory workers, et cetera. Now, I realize we're not talking about the informed consent any longer, but to the extent that this becomes a guidance document, and it will, these patients are not going to be quarantined. I mean, we've been through that. These patients' infectious disease risks to these laboratory workers is, for all we know right now, based on all the research that's been done, a fragment of what it is for an HIV patient, a Hepatitis C patient, a Hepatitis B patient.

So given the fact that what we're trying to do is have a reasonable implementation pathway for a clinical trial, if you put this in, the hospitals that are going to look at it are going to be scared to death, because your ability to inform every single person who might at some point in the career of your patient, through this trial, come in contact with them, of all these issues, and do it and document it and then leave the hospital open to every blinking lawsuit that could possibly happen, it's just not necessary, I think. Every hospital has to have a whole guide in place to protect their staff and monitor them for infections appropriately that go across the board with universal precautions, and I think we ought to just stay out of that in this kind of a document.

MS. SHAPIRO: PHS does have some guidance on this, you know.

DR. SALOMON: Are you talking about specifically with xeno?

DR. BLOOM: Yeah, it's in the PHS guideline.

DR. SALOMON: Fine. They should leave it in the PHS guideline, but I would leave it out of this for the reasons I just stated.

MS. SHAPIRO: Not that it's going to lessen the onerous burden. I mean, it's there. So if we're talking about third parties, why wouldn't we talk about them?

DR. SALOMON: Well, I'm just saying, I haven't seen what exactly -- I mean, I participated in those conversations, but I'm not exactly clear that we went anywhere beyond just pointing out -- we went through discussions that should we quarantine these people, and that's where these discussions came up. And the guidance was very clearly, no, you should not.

After that, I'm not aware that we demanded that you blood test everyone who was in contact with patients or anything else. So I'm very comfortable just dropping this, just leaving it out of this document.

DR. MICHAELS: I can go after you, Eda.

DR. BLOOM: I was just going to say for clarification - and please correct me if I'm misremembering - the PHS guideline talks about educating health care workers, not about quarantining them and not about testing them, unless, of course, something happens which would otherwise suggest they need to be tested. And health care workers already, as you say, have samples that are stored in the hospital that they work in. They just need to be educated.

As far as quarantining, nobody is talking about quarantining health care workers. If they were to become ill with a xenogeneic infection, that would be a different matter. But that's not what this is about.

DR. MICHAELS: I'm actually glad that Eda spoke up in regard to that. I feel that the education should be there for the health care workers and that it doesn't have to be in a fashion that would be open to all kinds of lawsuits. I think that if an individual had a needle stick from a person who was a xenotransplant recipient who then later was found to have PERV, there might be implications in terms of some anti-retrovirus that might be offered as a post-exposure prophylaxis. I mean, this is a fluid document which is not going to stay the same as more data is gathered, and so I actually think having that education is not quite the same as saying, we're going to test you at times zero of exposure, and then in six months for Hepatitis C, and offer you either testing for HIV as appropriate. I think that there has to be, we will also store blood so that we can look in the future for porcine retroviruses or what have you.

DR. SALOMON: That's a reasonable point. My point is that one of the hospital workers has a needle stick, for example, there are already procedures in place to respond to that. Now, you could go the next step and say that there is some instance that, for example, zidovudine may reduce replication of PERV, and that perhaps these people with finger sticks should then be put on that. I mean, you could put that into the protocol, I wouldn't object to that.

I just think that we have to be really cautious about what areas we get into that aren't already amply covered by existing guidances, and not create additional problems and barriers by creating fears and possible problems. That's where I'm coming from.

MS. SHAPIRO: Maybe we can make this warmer and fuzzier and vaguer.

DR. VANDERPOOL: Dan, if we can ease that section by changing the wording, then great. What I think we will need to do and will be able to do tomorrow because of our access to the guidance documents is to state what we are directed, to let the public and let the research subjects and let the researchers know what needs to be done at this point. If changes are made in the future, great. But we'll find that documentation and make sure that the wording here suits what the FDA and other agencies have told us we need to do.

DR. SYKES: Page 17 of the consent document, the last paragraph about voluntary enrollment accompanied by an agreement to follow responsibilities, the last part of that is written like a threat, and I think the wording probably needs to be changed. It's written as though it violates a patient's right to withdraw from the treatment, which is not what you mean.

MS. SHAPIRO: I have that marked, too. That has to go.

DR. ALLAN: I guess more than anything, just a clarification as to how you are sort of dealing with this particular issue. It's one that's already been brought up several times, and I think it's on page -- let's see. It's page 23, where you're talking about decision-making capacity, again. And I was using an old copy, so I sort of have to go back and forth.

In the decision-making capacity section, you talked that an investigator may proceed with the best interests of the research participant in those cases where you don't have a surrogate and you don't have a family member and you don't have a guardian. Is that correct?

MS. SHAPIRO: No, I think that's been significantly changed.

DR. ALLAN: It has been?

MS. SHAPIRO: Yes. Do you want to read the new one?

DR. ALLAN: Yes.

MS. SHAPIRO: Really what we say now is that there are three conditions that have to exist in order for an incapacitated adult to be in; one, we're pretty sure that the procedure itself will restore the decision-making capacity, and per Sharon's comments, that is restore it to someone who was decisional right before; two, that the surrogate decision-maker determines either that the person would want to enroll or that it would further his or her best interests; and three, that the surrogate decision-maker has a very close relationship with this person and will help to assure compliance with the monitoring requirements, and

also can let us know that this person, in normal times, was a responsible individual, and so once decision-making capacity is restored, is likely to adhere.

DR. ALLAN: So the surrogate would not be the investigator, it would be --

MS. SHAPIRO: No .

DR. ALLAN: -- someone else?

MS. SHAPIRO: That's correct.

DR. ALLAN: So I guess the question I want to ask is, how does the surrogate make a decision that the patient may have wanted a xenotransplant? Could that be influenced by the investigator? In other words, they won't say, they signed a donor, an organ donor card, so I would say they want to participate in this. Do you see what I'm saying? I mean, it's a stretch.

MS. SHAPIRO: It is, but it's no different than any other --

DR. ALLAN: Because the real issue is that if it is the first clinical trial for xeno, there is no previous history or any ...

MS. SHAPIRO: Well, and what's sad but true is that in almost any other health care decision-making set of circumstances, they're also guessing. So, you know, hopefully it's not going to be recommended unless it's thought to be in the best interests of this person anyway, which is the fall-back criteria for making the decision about enrolling someone else.

DR. ALLAN: So okay, say it restores mental capacity. The thing that I guess that you guys have had to deal with is the fact that if you could restore mental capacity, but let's say then the events that transpired after that were less than desirable - in other words, the patient got sicker and sicker, so they actually suffered by this procedure - how did you sort of work with that?

MS. SHAPIRO: With difficulty. Who knows for sure, you know? But our assumptions were that, A, there are certain circumstances where it's the disease process that's causing the incapacity and that could be alleviated by the procedure, and that the procedure is likely to do more benefit than harm. I mean, that's something we're always guessing and hoping about. Right? Dan?

DR. SALOMON: The irony here is that on one hand we have this thing where you have to have, like, three people explaining it to them and you have to explain to them, like, the side effects of all the drugs and all of that, but by the way, if they can't make any decisions, the doctor gets to do it.

I think at this point I don't think that this should be in here, and I would make the following argument for that: There are experimental procedures that are appropriate as life-saving measures for patients who, for the reasons you already articulated, would not be decisional at the time; however, they're not completely out-of-the-blue procedures, they're refinements and evolutions of things. And so this sort of a clause, for many kinds of research, is very important and very powerful.

In this case, however, I'm arguing that it's not the same thing. You know, we don't have any preknowledge right now that a xenotransplant is going to work. Now, this could change, you know, right after that was done, so this is, of course, dynamic, but right this minute I don't feel the pressure, nor do I think that we should be advising that at this point these first xeno trials would go forward in people that

were non- decisional.

MS. SHAPIRO: Well, I have a question. I mean, no, I don't know of anything like with xeno, but going back to Eda's reminder that we're not just talking about whole organs, I mean, would exposure to a xenotransplant product ever be appropriate to get someone over a hump so that they could regain capacity and get better?

DR. SALOMON: I'm still pointing out that at this point in the early phases of xenotransplantation, we should focus -- this gets back to something that Bob Mendez said. Now, this is a decision that should be made by the committee; I'm just suggesting to you that one way of looking at this is we don't want to close any doors for a possible xenotransplant trial, in which case then you don't want to listen to me, you want to definitely allow for every possibility.

The other part of this is to say, we want to make sure that the first xenotransplant trials are done in a very responsible way with a maximum amount of safety because there's all these unknowns. In that case I'm arguing you don't want to have non-decisional patients involved, and 10 patients later, nobody has got this, that, it's working, oh, maybe you make a change. So that's my argument here.

DR. BLOOM: I'm going to butt in here. We already do have patients under xenotransplantation trials. They already have been treated. There have been 100 and something patients treated with extracorporeal perfusion over liver assist devices that contain the porcine cells, many of which - I can't tell you the proportion, I don't know - but many of which were comatose. These were non- decisional patients, but they're the only patients that have a chance of being helped by this.

So we have such a broad spectrum of xenotransplantation products, that unless you get very specific, you have a problem, I think.

DR. SYKES: Yes, I think having a one-size-fits-all document is really not possible. I mean, when you think about extracorporeal perfusion, that's the short-term exposure to porcine cells or organs. And furthermore, we have an experience with it. We have a group of patients who have had it and who have been followed, and so far haven't shown any signs of infection.

So I think that that is justifiable, to continue with that, whereas if you were thinking of putting in an organ that you expect it to last forever, there are different considerations.

DR. VANDERPOOL: And, in fact, Megan, that's what we had in mind here. In rare instances when -- for example, in the case of hepatic failure, when someone could be brought back with the procedure, those are the people we had in mind. And it did build on precedent rather than trying to create some new possibilities.

DR. CHAPMAN: There were two things I wanted to bring out in the discussion. One was the issue about one of the most common applications, I think, of xenotransplantation in the past, and certainly in the preregulatory days, was hepatic perfusion, where you had, actually, Eda, I think probably 100 percent of those patients, because by definition you have to be at a position where you're expected not to survive, and so the outcome is grim without it. And when you're talking about hepatic failure, encephalopathy occurs pretty often.

The second thing I think might be -- I'm wondering if it would be helpful to the discussion process here to clarify the context in which this surrogate decision-making would occur in a medical setting. John, my perception was one of your concerns was that the wording in this document might give undue power to

the physician who believes strongly in the -- you know, is emotionally committed to the value of the procedure they're doing and influencing the surrogate decision-maker.

But I'm thinking that the guidance in this document about surrogate decision-making is going to occur in a bigger context where there are already laid out, not ethical, I would say legal requirements for when and how one person is allowed to give medical consent for another person. And I presume that these would not supersede those; it would have to occur in addition to those.

And one condition even for a life-threatening situation for a surrogate decision-maker, the person who makes the decision has to have some authority to decide on behalf of the other. If it's a minor, it's a parent or guardian, and if the other person is not a minor, even if they're mentally incapacitated, generally the decision-maker has to have legal power of attorney for medical decision-making purposes. And in the absence of either of those, usually the medical personnel will have to go to a judge or a legal system to get an adjudication that they can proceed with the intention.

So my assumption, and Robyn can maybe clarify this, is that for xenotransplantation, it would still have those requirements, and then in addition, the conditions laid out here would need to be met.

MS. SHAPIRO: Well, you know, the federal regulations talk about the legal representative being able to enroll an incapacitated person, and I would hate to get more specific about that in this document. Because, A, it's variable from state to state, and B, when you get courts involved, it almost always gets worse.

DR. CHAPMAN: But the decision-making in this document would occur in a context in which the uniform requirements for surrogate decision-making and medical care giving have already been met, and those would ensure that someone who has been intentionally given legal status to make decisions -- like I have power of attorney for medical decision-making for my father if he's incapacitated, and that's been laid out with documents with a lawyer in advance. Or in the absence of that, there would have to be a judge or legal representative who would grant that approval.

MS. SHAPIRO: Well, not necessarily. Some states have case law where they acknowledge that a surrogate decision-maker is going to be a family member. Some states have surrogate decision-making acts where they say, if you haven't done a power of attorney for health care, if you don't have a guardian, then here's the pecking order of who has the power to make decisions. So it's very complicated, and I would rather just leave it myself at legal representative, with people figuring out what that means for them in their set of circumstances.

MS. KING: Robyn, I have the same concerns as Louisa. Do we say legal? I think we say surrogate, to my knowledge, or proxy. I think we say proxy or representative. I don't think we ever do say the word "legal." and I had the same issues, that there's legal precedent set, and I think we need to refer back at least to say, at the bare minimum, what you're saying, unless it's already said and I missed it.

MS. SHAPIRO: Yeah, I just hate mixing that word into --

MS. KING: I think otherwise you get into questions of who's to say who's the surrogate. What if one family member says one thing and then another. I think there's a reason to not go into the specific detail, because I think otherwise you leave yourself wide open for issues of who's surrogate and who makes the decision, and what if they don't agree, and on and on and on.

MS. SHAPIRO: On the other hand, if you simply leave it legal representative, they may want to know

more from us about who we think that is. And I don't want to provide that answer

MS. KING: I mean, it's going to vary from state to state, as you said. They're going to have to refer to legal counsel or whatever entity is doing this. But I don't think we need to necessarily say law, but I think we need to at least say there is a legal precedent set to determine who is a surrogate.

DR. CHAPMAN: Maybe a vague introductory statement that acknowledges that there are already existing policies and regulations that are set state by state on when and who has the right to make surrogate decisions for medical care, and in that context, in addition with xenotransplantation, these things should be considered. Not something that vague, but just acknowledging that --

MS. SHAPIRO: We can do that. We can mess with this.

DR. KIELY: Just one quick thing to maybe consider tomorrow in our discussion. The comment regarding the surrogate says, "In all cases involving incapacitated patients, providing consent should imply willingness on the part of the surrogate to assist in compliance with post-procedure medical regimen." If this person does not regain their competency, what I see in this statement is a potential for undue influence, negative influence, on the surrogate to act in the best interests of the individual. I mean, if you're really thinking about the fact that you're going to have to manage this person beyond this illness, it's well beyond what normal surrogacy really implies.

MS. SHAPIRO: Right. So what do you suggest?

DR. KIELY: I suggest we talk about it a little bit tomorrow. It just caught my eye and I haven't had time to think about it.

DR. MICHAELS: Can I just clarify, then? Because I became a bit confused in terms of this discussion. The part that's right above Xenotransplantation for Incapacitated Adults that deals with the surrogate, the part that seems to be discussing having the investigator and another physician make a decision when a legal authorized representative is not available, that part is being deleted?

MS. SHAPIRO: Oh, no. Actually, that's just in emergency situations, it's the generic guidance about when you don't have to go through the legally authorized representative. It's in the federal regulations right now.

DR. MICHAELS: I see. So I guess I would come back, then, to Dan's point that he said earlier, that I think at this early stage of xenotransplantation, where even with the hepatic cellular exposure for short periods of time, where it is really quite a research study and we do not know that it will -- well, we hope and we have reasonable expectation, and that's why it's in the clinical research protocol, that while we don't know that it will work, that I would be uncomfortable having it without a surrogate involved.

MS. SHAPIRO: So that you would suggest that the more generic emergency consent procedures in the federal regulations currently not apply to this kind of research at the moment, where you can get a way without the -- okay. We can talk about that tomorrow.

DR. SALOMON: I mean, the point that was made that if you look at that there's been 100 cases done with recirculation in patients in coma, that's actually not an argument against what I said, Eda. The point there is that, yeah, great, so now you've got 100 patients, you've got some data; if you want to limit it to non compos mentis patients, go for it, because you've got the evidence.

I'm talking about the first 10 or 15. And the first 10 or 15, even in that setting, could be done in patients who have had informed consent ahead of time. Because let's face it, I've got 50 some people on our list right now at Scripps for a liver transplant. It wouldn't be that hard, if I had such a procedure, to inform all of them that if you should -- you know, this and this happened and you end up in the ICU, then this might be one therapy, would you agree with it, and then it would be placed. Now, after I've done 100 of them, then sure, any comers would be appropriate. I think there's a subtlety there.

DR. BLOOM: You're right, there's a subtlety there. But if this first 15 of these people were the first 15 and there weren't any before then -- but my point is that at some point you need to start. And with some indications - and I threw that out as an example because that was one - you may not have the luxury of being able to have a patient that can consult.

DR. CRONE: I think the talk about using the liver, those patients in particular, this is not -- Dan, these are not patients waiting for a liver transplant who then get informed consent, and if you start deteriorating, then you can use this as a bridge. These are oftentimes people who come in emergently; they are already not competent by the time they hit your door at your hospital, and you are making a life and death decision for that person.

DR. SALOMON: No, I understand the group and I understand that point. I guess what I'm -- this is the last comment. I won't argue it anymore. But the point here that's really a decision on the part of the committee is how hard you want to make the first set of studies. We're not talking about studies like this - I mean, we're not grandfathering this in - but the fact is, is that even in that setting, there were patients that the first 15 or 20 could have been done in compos mentis people, or at least consent. Yeah, sure, later the target population is exactly what you say, drug overdoses, idiopathic a cute hepatitis, et cetera.

And that's just a decision to think about. And when you craft this section, you might want to just say that it's very important that for each trial that gets proposed, that there be a fairly -- that it at least be a barrier that you have to get over before you just default to a non compos mentis patient. That we should resist it, maybe would be the best way to put it, but not prohibit it.

DR. VANDERPOOL: I'll bet we can find some wording, Dan, that will say something to the effect that after organ xenotransplantation has resumed, or something like after some experience with the organ transplantation, then something can occur.

There's another reason beyond your arguments that agrees with and is in compatibility with your arguments for not allowing incapacitated patients to be involved at the very first, is a question of public perception. It might look like xenotransplant researchers are seizing these people who don't have any ability to say no.

And so that would be totally antithetical to what we want to see happen here, but you have to worry about public contingencies. So we'll work at it and bring a recommendation to the group after our working session tomorrow.

MS. SHAPIRO: At this time we would welcome any public comment. You have a comment?

DR. SYKES: Sort of. There was this one other issue that I thought we should discuss. Page 21 to 22, the role of SACX is discussed in a way that it might be considerably expanded. And I just thought this is something that SACX probably should discuss as a whole.

MS. SHAPIRO: Good. Why don't we?

DR. SYKES: Well, it's pretty different from what has been mandated.

DR. KASLOW: Isn't that compatible with our charge?

DR. SYKES: No, I think it goes way beyond our charge.

MS. SHAPIRO: The reason we set up here with this set of bullet point recommended activities expanding our role was simply because it seemed at the moment that we could do the involvement with the community better than any other option that was put on the table.

But I don't know if we can make these kind of recommendations, if they would be beyond the current charge, or if they are, recommend an amendment to the charge, or if you like this at all.

DR. KASLOW: It could sound a little self-serving for starters that we're trying to create our perpetuating existence, but I wonder if what you shouldn't do is just outline the principles or the bullet points that should apply to whatever group it is. If it turns out that we're the only group that can do it, then the FDA or the secretary will say so, we shouldn't be saying so.

MS. SHAPIRO: So talk about some public body which is multirepresentative --

DR. KASLOW: Yeah. Something.

MS. SHAPIRO: -- maybe taking on these rules?

DR. VANDERPOOL: Some group similar to SACX?

DR. SYKES: No, I wouldn't even say it that way. Because it sounds to me like that it requires -- what is suggested here requires a different kind of structure. It says, "Developing and making available informational resources on scientific, medical, social, ethical, and public health issues." I mean, that's a big job. Making a web site or whatever kind of informational resources you want, you need people to do that. That's a different type of organization than what we are.

MS. SHAPIRO: Good point. And I think we could modify this to not have our name on it.

DR. ROTROSEN: I had a similar question, I guess, about the first bullet, reviewing clinical xenotransplantation protocols, including research participant enrollment, safety data, annual progress reports, and filing of adverse events. This overlaps quite a bit with the typical responsibilities of DSMB's, which probably are much better equipped to fulfill those responsibilities. And I wonder if that's something we really want in this report or whether it belongs in this report at all.

MS. SHAPIRO: I think the thought was that whatever body is going to do this, advising, evaluating, monitoring, getting out to the public, needs to know what's happening. So I agree with you, I don't think we should replicate the workings of the DSMB, but is there a suggestion for how to assure that this group would be kept up to date?

DR. MICHAELS: We could just change the wording, since already in the charter it is that we are to be informed about current and proposed xenotransplantation clinical trials, and I think that that term "reviewing" as opposed to being informed is probably ...

MS. SHAPIRO: I have deja vu. Okay. Good. Any other committee comments? Any comments from

the public, questions or comments from the public? Yes?

Agenda Item: Public Comment

MR. BRESLIN: I had a couple of questions and comments, but I see that the people to whom I wanted to address them have left.

DR GROESCH: Could you identify yourself, please?

MR. BRESLIN: My name is Andrew Breslin, I'm working with a group called Campaign for Responsible Transplantation, although my comments are mostly mine and I don't necessarily speak on behalf of them. But is Julia Greenstein still in the room or has she left?

MS. SHAPIRO: No, she left.

MR. BRESLIN: And is Bernhard Hering still here? Well, they leave and they lose their opportunity to defend themselves from spurious accusations from the gadfly.

In Dr. Hering's presentation he was discussing eyelet cells, and stated that we would never have enough human eyelets for more than a few thousand transplants per year based on there being three to four pancreases required per transplant.

Now, my understanding is that there are 6,000 people who die in the United States every day. Obviously not all of them are suitable donors for all types of organs and tissues and cells; for example, more people die of heart disease than anything else, so obviously they wouldn't make good potential heart donors. But my understanding - and please correct me if I'm wrong - is that in contrast to whole hearts and livers, for example, quite a lot of people who die would be potential donors of eyelet cells, that that's not nearly as rare that someone who dies would be a perfectly viable donor of eyelet cells. And yet even with 6,000 of them dying per day, he stated - and it's sort of an often quoted figure - that we could only do two to four thousand, something like that, whereas my math would indicate that if we recovered the majority of potential viable eyelet cells from people, it would be more like several hundred thousand per year rather than just a couple of thousand. So I wondered if anyone can comment on that.

MS. SHAPIRO: Dr. Mendez?

DR. MENDEZ: You make a good point; however, if we could have, we probably would have. The sad fact is that human organ donation has been pretty still for the last 10 years, going to approximately 18 or 19 thousand individuals now. 6,000 people may die per day, but they're not -- they have not given informed consent or have they indicated a desire to donate. And that is probably not going to change too greatly in the next five or 10 years, at least, at least if we change our entire governmental structure with regard organ donation.

DR. SALOMON: The other critical issue is that the patients die, but they die in the field or they die at home. These are not suitable donors. Even the closest one could get would be what we're now calling non-heartbeating donors, and that research is really just research right now, that even those are being done only in hospitals under incredibly controlled situations. So there is no such thing that's even close to what would happen if someone died in the field.

And we tried even something as simple in San Diego back in a discussion in the emergency room of ambulance service, at the time they had these machines that automatically pump. And we said, okay,

fine, if you found someone who died in the field, would you put them on this automatic pumping machine and then bring them to the hospital and that sort of thing. And they looked at us like we were totally insane. Who's going to pay for that, the ethical issues, the consent form problems, the infectious disease issues would never even get close to anything that anyone in medicine right now would accept as an organ donor. The reality is that if we knew a better way to get organs, we would definitely do it, and I think the dialogue has to continue. But there aren't 6,000 people dying a day that are being lost as organ donors.

DR. ST. MARTIN: I just wanted to add to that. There's been several methods proposed for estimating the donor potential, and by current estimates, it's only about 12,000 to 15,000 individuals that die under conditions that make them suitable to be organ donors. We're working to try to increase that, but it's really a very small fraction of the number of people that die that are potential organ donors.

DR. CHAPMAN: Could I add one other thing which maybe hasn't been stated explicitly? There are conditions other than disease of the specific organ intended for transplant that can invalidate someone as a donor. Blood-borne persistent viral infection like HIV, Hepatitis B, Hepatitis C, HTLV invalidate a certain proportion of people, but current or a recent history of cancer that metastasizes rapidly can invalidate someone as an organ donor, because there have been instances where metastatic cancer has been transplanted with the organs.

And then in addition, the pancreas is kind of a special organ because pancreatic eyelets are basically -- I mean, the pancreas is basically little sacks of digestive enzymes, and so the circumstances under which you can harvest those while they're still intact and they can be transplanted have to be much more precise and much more careful. And they survive much less well insults of low oxygen or trauma than, say, a heart or a liver or a kidney. It's a problem even with living patients in the hospital. They get shocky and they drop their blood pressure; sometimes you can treat their underlying problem but they get this rip-roaring pancreatitis, which is basically an inflammation of the pancreas which often results from cells breaking down internally, and then the digestive enzymes start digesting themselves and start digesting the pancreas.

So what looks on the surface like the mass that would provide a much larger supply is actually just extremely hard to bring into reality for all the reasons everybody here has described.

DR. KIELY: If I could just say one other thing regarding pancreas transplants. We could do a better job of educating transplant teams and other organizations. For example, if you're going to be transplanting a whole pancreas, there are certain criteria for the pancreas and for the patient, as Dr. Chapman mentioned. However, for eyelets, what we have found is actually that we can get high quality eyelets from relatively fatty pancreases, and so what was considered to be an unacceptable organ for whole organ transplant has actually been an acceptable organ for eyelet transplant.

And so that education is ongoing now nationally for organ procurement organizations as well as transplant teams. And so I think we could do a better job about that. And that research has helped us to understand that those otherwise unusable organs are actually quite valuable.

DR. VANDERPOOL: Another comment from the public?

DR. HAYWARD: My name is Anthony Hayward and I'm from the Division of Research Resources. And I wanted to comment, maybe risk stating the obvious, that in coming up with recommendations for consent forms, we have to bear in mind that for those who are dead, their body is no longer their own, and so we will be relying on the next of kin to agree to the autopsy. I'm not sure there was a general

consensus to specifically agree to that.

The other one, from the point of view, of course, of a practicing physician, it would be extremely difficult to report undefined diseases, because so often patients arrive with things where you're not quite sure what they have. And to report that you're not quite sure what they have would be a clinical challenge.

And finally, speaking personally, I would urge you to be careful in your recommendations about waves of consenters who come one after another. It's difficult always to be ensured that they're all adequately educated, and some may say something different from the principal investigator, who is likely to be much better informed about the procedure than some of the other more peripherally involved individuals.

DR. COLLINS: Sir, I can address that third point that you brought up. The reason we thought that having more than one person -- and it's a process, and it wouldn't be waves coming one after another until you're knocked senseless, but over a period of days, weeks, if you have that luxury, depending on the clinical situation. The reason we didn't want to rely on the clinical or the principal investigator, we thought that that person would not be very objective, and we wanted to add some objectivity to the consent process.

So, of course, as I always tell members of the committee, I can pretty much convince one of my patients to do anything with respect to a surgical procedure that I would like to perform on them, but it may not be the right thing for them. And we wanted to bounce -- although I tell them one thing, we wanted to have other people to explain the procedure in a different way so that they could reflect on that also.

DR. VANDERPOOL: Thank you for your comments. Would you please, if you so desire, write down further comments and inquiries to give to us on this committee? We're concerned about the input of the public. And also to all committee and federal agency members, any particular wording and other suggestions that you have for the subcommittee on informed consent, by all means, hand those to us so that in our working session tomorrow we can take all your suggestions into consideration.

Let's now take a 15-minute break. Let's be back here -- we're going to begin at 15 until 5:00. Okay? So I hope you're in the room. And we're going to review the state of the science paper, which is the other side of our committee's activities.

MS. KING: I just had one comment also to the gentleman about the process, the team. In addition to what Brad said about it would be basically a step-by-step kind of process and we wouldn't all be coming in one after the other, the reason for the multiple members as well is that different people have different expertise. The PI, for example, may not be an expert in the psychological and emotional, social ramifications that could come from participating in a xenotransplantation trial.

So part of it was also bringing in different members with different expertise that they could provide.

[Break]

Agenda Item: Overview of Draft Report on the State of the Science in Xenotransplantation

DR. VANDERPOOL: Shall we take our seats for the final session of the day?

DR. SYKES: Should we get started? Okay. So what we'll do is, I'm just going to say a few words about the product of our working group and then we'll go through the various sections and take you briefly through the contents of each section.

So basically this document is the product of three groups of people who've written different sections. It begins with an introduction that tries to put the xenotransplantation into a public health perspective, starting with the burden of chronic and degenerative diseases and other strategies and disease prevention. And this section was written by Bob Mendez and Bill Scheckler. And Bob will take you through it for a few minutes after I've done my introduction.

I should just say that the document that you have at the moment is really four separate documents in the sense that it has not yet been brought together by the working group into a cohesive document because we were not given several of these sections before you were. So the introduction and the section, the final section on infectious disease risks, were only given out to the rest of the working group at the same time that you got them. And so we're not in as advanced a stage of producing a cohesive document as the other working group was.

The second section, the science of xenotransplantation, was put together by Dan Salomon, Dick Kaslow and myself. And this section was given out in advance. And so the working group has had an opportunity to comment on it. And after Bob, I'll take you through the contents of that section.

And finally, the third section covers the infectious disease risks associated with xenotransplantation. And this was put together by Jon Allan, Marian Michaels, Tony Lubiniecki, and Mike Swindle. And the final section on xenotourism was put together by Dan Solomon. And this section also has been distributed in advance. And so the working group has had a chance to look at this one as well.

So with that, I'll ask Bob to take a few minutes to take us through the introductory section.

DR. MENDEZ: I guess we'll just take a couple, two or three minutes. I would preface it by saying that I would like very much all of your inputs, any help that you can have. The draft that you have is actually the first draft and it's kind of long, laborious, and semantically rather crude. We now are on the second or third draft as of this morning. Unfortunately, Bill and I were unable to get together and I did not get his revisions until last Friday -- actually yesterday. What we have done is trim it down from six pages to about four and improve the semantics to a great extent.

In talking to some individuals, the format of the introduction is somewhat like Gray's anatomy. You know, it goes through the whole vascular tree, and then it goes through the endocrine tree, rather than say, organ specific, and then addressing it as to a particular disease entity and going through the physiology, pathology, therapeutics, et cetera. So there's a lot of repetitiveness in the introduction. And I think we've tried to get rid of some of that repetitiveness.

The other thing that Megan brought up to me last night, which I think was very good, is that she felt it was kind of bland in terms of not focusing and emphasizing greater the significance of the benefits to the individuals and to the extent that the potential xenograft would affect the vast majority of citizens in some specific way, rather than just the selective patients that are on organ transplant lists now. In other words, we're not dealing with a problem for 2,500 diabetics, we're dealing with a problem for 2,000,000 diabetics. And that should be strongly emphasized. And we will try to do that.

One of the things Bill and I, I think, disagreed a little bit on was deleting some of the examples. Some of the examples, I think, should be deleted, such as adult polycystic kidney disease. And we can give one example of that. The verbiage, as I mentioned, has been redone; perhaps only one example of the various organ systems and disease entities that might be affected. Where there was another, perhaps question, was to minimize the content or even the statements regarding cloning or stem cell, and not even to mention that. And to minimize significantly the comparisons with the bioartificial techniques that are available.

I do think that we should leave in the bioartificial techniques as an alternate. That we should talk about. I don't think we should delete it completely.

And then the economic factors, I think, we needed to stress more vividly. I guess, if you don't ask, you don't get. If you don't ask for a lot, you don't get a lot. And so I think we need to perhaps put in a few more facts about the ramifications of the therapy and the treatment from an economic standpoint more vividly. I thought we had done it in certain respects on the last page, but we could perhaps emphasize that a little bit more.

I certainly would like the input of everyone or anyone who has thoughts on it so that we can smooth it out a little bit, and also some indication as to the length of it. We've got it down to four pages. It should probably go down to three pages. Should it be three paragraphs? That was the question Bill wanted to ask.

DR. SYKES: Thanks, Bob. So we'll come back to those issues at the end of the introduction. So the next section is the science of xenotransplantation. And I'll just try to briefly take you through what's in this part of the document. We begin by providing a description of the scope of xenotransplantation, starting with the definition of xenotransplantation. And I see that's redundant with what you have at the beginning of your section. So we can probably take that out.

But we then go through a description of what is solid organ xenotransplantation, what cellular and tissue xenotransplants are and extra extracorporeal perfusion, and finally exposure to animal-derived feeder layers. And we provide explanations for what those are and what some examples are. And we introduce some of the immunological issues related to those.

Next is a section on potential xenograft source animals. We spent a paragraph explaining why the pig is considered to be interesting as a potential source animal. And then we go on to discuss other source animals that have been and are being considered. And we touch on some small animal species like tilapia being considered as islet donors and islet sources, and also the use of animal cells producing viral gene delivery vectors for cancer therapy and the possibility that other types of cells producing biological agents might be injected or introduced into humans. We also mention the issue that cell lines that are being passage on non human cells are also considered xenotransplants. Finally, we end up discussing nonhuman primates as potential sources animals and explain why we don't think these really are worthy of consideration as source animals at this point in time.

The next major section goes through the hurdles of xenotransplantation. And we hope that, with the introduction to the different types of xenotransplants that had already been provided, that the reader would now be able to understand how these different types of barriers affect different types of grafts. So we begin by dividing these hurdles into immunologic hurdles. And we take the reader through hyperacute rejection and its pathophysiology, then delayed vascular rejection, which you've heard about, acute cellular rejection, and chronic rejection. So we try to give explanations of immunology of those process, what's known, and in what context they're relevant.

Then the next major section is the physiologic hurdles to xenotransplantation. And we explain how these are relevant, much greater relevance to xenotransplantation than allotransplantation. And we go through some of the known physiologic compatibilities and incompatibilities, discussing the complement and coagulation systems in which you've heard there are a number of incompatibilities, adhesion molecules, cytokines and growth factors and how those could affect the growth and survival of an organ or tissue and could also effect homing of cells that are being used, for example, hematopoietic cells being used for tolerance induction.

We then go on to more organ specific physiologic considerations. We give some examples of incompatibilities that have been identified, others that really haven't been adequately looked at. And we really point out that there's very little information on this very important area.

The next major section is a discussion of strategies for overcoming these hurdles. We go through source animal genetic modification, discussing the use of transgenic source animals. Moving on then to knockout animals, specifically knockout pigs. Second strategy is encapsulation and other bioartificial isolation devices. And again, an explanation of that. Third strategy, tolerance. And we go through some of the approaches to achieving that and how it works. Gene therapy, and a couple of examples there. And we try to give the scope of where that might be relevant. Finally, a short, broad paragraph on targeted molecular therapies, which some are in existence now and others may develop in the future. And we sort of brought a general section on other treatments, including absorption techniques for anti-gal antibodies and so on.

And now the final part of our section is advances and impediments, where we try to synthesize what has been said in the earlier parts of this section to try to come up with some perspective on where we are and what is needed. And basically we summarize the natural antibody problem and the delayed vascular rejection problem and how there's need for further research into incompatibilities in the innate immune system that may be participating in this delayed xenograft rejection process and how greater understanding is needed of physiologic incompatibilities and how all of this research could lead to new molecular strategies for modifying source animals or treating recipients.

We also spent a paragraph discussing the importance of nonhuman primate models. And this bears somewhat on the discussion we had this morning. We take the same stance that I mentioned we at the IXA had taken, which is the risk to society imposed by xenotransplantation imposes an ethical imperative to demonstrate potential benefit to the recipient, and ultimately society at large, to justify clinical xenotransplant trials. So we have taken a stand on that issue in this section of our report.

We also point out though that while nonhuman primate models most closely approximate conditions in humans, significant gaps and clinically relevant knowledge of nonhuman primate biology currently limit the value of those models.

And we point out that in further information on the function of human trans genes and nonhuman primates in which they may be incomplete, in which their function may be incomplete, would be helpful that we could even consider developing transgenic pigs adapted to nonhuman primate models, and the need for improved methods for monitoring transplants in nonhuman primates. And so there's a suggestion that a significant investment in these nonhuman primate models could extend the knowledge of technical capabilities of human clinical monitoring to the nonhuman primate species most suitable for transplant research.

And this is followed by a paragraph discussing the difficulties in relying on industry to support these advances and also difficulties in relying on nonprofit organizations or academia alone to do this. And some of the reasons for not being able to rely on industry at this point, the short horizons for investment return, disappointment over previous expectations, current structural economy difficulties, problems sharing, proprietary interests, et cetera, all create difficulties for getting an investment from the biotechnology sector. So the feeling is that there's a need for a proof of principle accomplishment in xenotransplantation research.

And I think we, many of us feel that there have been some major advances we've heard about today that are very encouraging and that the public does have a high stake in the products of xenotransplantation. And government may be the logical, if not the only, catalyst for mobilizing the requisite additional

support. And then some possible ways in which this could be achieved, such as a reagent and information repository, core facilities to serve common technical requirements, and then incentives for scientists in alternative career paths, as well as ways to assist industry in negotiating past the regulatory hurdles and stringent safety guidelines are suggested.

DR. ALLAN: I guess I'm up. This section deals with the infectious disease risks associated with xenotransplantation. The thing we didn't want to do was to rehash everything that was already published. There is the PHS Guidelines on Infectious Disease Risks in Xeno. There's the Guide To Industry, and many well written publications out there on disease risks. So we didn't want to just rehash everything, but we also wanted to sort of update people in terms of what the state of the art is in terms of where we're at with what we know about certain infectious diseases, and just to be very brief about it as well.

So what we initially did was we started with a little brief introductory section talking about zoonosis and xenotransplantation. It's only one paragraph. We then went to the infectious disease risks from source animals. So the next step was to say, okay, what's the source animal that's currently being evaluated, and essentially, are there risks associated that animal, again, the pig.

And so we just sort of talked about the nonhuman primate as probably not a good source animal because of infectious disease risks, that the pig initially seemed to be almost an ideal resource from an infectious standpoint until PERV was discovered and what to do about PERV.

We also talked in general, in the next session, on viral persistence as an infectious disease risk factor, again talking about now the difference between acute infections and chronic persistent infections and how that relates to risk from a source animal, that being latent chronic infection could have greater implications to public health then, let's say, an acute infection, example being influenza, Nipah virus, some of these other pig viruses that would blow through the patients and be gone. So we wanted to try and make that distinction. And also give examples such HIV, antivirus infections. So these are the kind of things that, you know are pretty common sense. But we wanted to make sure that we illustrated those and got the message across in as simple of terms as we could.

We also wanted to address what's been known over the last year, two years, three years in terms of what types of studies have addressed porcine endogenous retrovirus risk in humans in particular, because this seems to have gotten the most scrutiny. So we went through and we talked about the different types of studies that have been performed and what the outcome has been from those studies, including the 160 patients, what's happened in PERV cells, cell types, attempts to transmit PERV, and then also what we know about nonhuman primates from past experience in terms of transmission of Simian foamy virus in the liver, the baboon to human liver transplants, and transmission of baboon CMV. Those types of things just to give the foundation that these things could exist and that these types of things could happen.

And we tried to, in some cases, not all cases, to give bullet summaries at the end of each section. We didn't do that for everything, of course. We also talked about infectious disease risks in animal model systems. In other words, okay, so, if there's an infectious disease risk, how do you evaluate it? And we sort of give you up-to-date on what we know about what's been learned, published and unpublished, in the use of animal model systems, whether it's mice or whether it's pig to primate in terms of PERV risk at least.

And we've even included some of the recent studies by Clive Patience in the mini pigs in the possibility that there may be some strains of pigs that may be less infectious or less transmissible than others. We also included a little about Gal knockout pigs and how that will influence infectious disease risks. And we also have a section on porcine infections as potential pathogens to humans. So in other words, we want to get out of the box, get out of the PERV and just mention that there are other viral infections that

one needs to consider in the transplant setting. And we just briefly covered several of these, such as Hepatitis E virus. There's the relatively new porcine lymphotropic herpesvirus 1 and 2.

And in the other area I think what we did was we initially had a separate section on diagnostics and detection. I think we merge it into one into this section. So we also mentioned briefly about having antibody and molecular based genetic testing methods up to date, and stringent diagnostic assays. I think this is a little bit brief. And maybe we want to consider talking about this tomorrow in more detail in terms of uniformity of testing and things of that nature.

And we went from that point to control of infectious disease risks. We talk about cell based xenotransplantation products, primary cells, and what kind of control methods one might use to prevent transmission of infection from a source animal through the product to the recipient.

And essentially, what we've done is we've provided bullets. Mike covered this section actually, did a very good job. Just a series of bullets and the types of control methods one could consider. And we also refer to the published guidelines that are in place by FDA.

We also have another section of husbandry of source animals in terms of how to handle these animals, closed birds, C sections, uniformity of swine operations regulations, impact on safety. All of these things we try and consider.

So this is sort of a broad section. We didn't want to rehash everything that's already been published, but we wanted to just highlight those areas that we thought were important.

We also have a section on regulatory guidelines and regulations. And I think this is an area that also needs greater focus by the SACX. And we may want to address that in a joint committee and or on our working groups. But I think the regulatory end probably has short shrift here. And I think I'll stop there and turn it over to Dan.

DR. SALOMON: The first thing I want to say is when I got this I was a little bit appalled because there were all these underlines in this section which could only mean one of two things; either there's a problem in that section -- and there's not -- or, even worst, that I had resorted to the lowest of low writing tricks which is, in case you don't think it's important, I'm going to underline it for you. And I didn't do that either.

So this is something that happened between Mary and the Word program trying to do tracking changes. So there's nothing about that tracking section that's any different than the others. You can like it or don't like it. But don't like it any more or less.

So xenotourism. Just a couple of key points. First of all, I think one point we want to make is that xenotourism potentially does constitute a real public health risk, and as such, should be considered number one, and also be considered separately from the overall concept of an infectious disease risk with xenotransplantation.

We tried to defined it. I don't think I need to read all of that, but we try and define the idea of traveling to foreign nations to participate in private xenotransplant programs or clinics. A key point is that in almost all cases of xenotourism, these procedures would not be permitted in the U.S. due to lack of compliance with the PHS guideline. And I think there's a really important distinction here. The more I got into it, the more I realized how very important it was. And these came out of dialogues that I had with Eda Bloom, particularly, and Carolyn Wilson, and Megan, and Mary Groesch, and others.

You know, there are going to be two different things, I think, that are going to happen. One are going to be clinical trials in other countries that are going to be presented internationally as a clinical trial. Now, those clinical trials will in most instances, not fulfill the PHS guideline on infectious disease. But that's one kind of a thing. And the current functioning example of that is what's going on in Mexico City where there's a clinical trial that has been reviewed, purportedly, by the institutional review board, et cetera, where they're doing pig islet transplants into children. That would be an example. At least that will come across as a clinical trial.

In contrast, the other form of xenotourism would be these luxury clinics that are essentially treating anything from impotence to autoimmune diseases with unknown kinds of tissues from a whole host of animals. And that's a very different sort of venue and a very different sort of issue. Yet, both would be encompassed under a consideration of xenotourism.

Currently, there's no way to determine how many U.S. citizens are transplanted in any of these types of clinics. There's no systematic way of tracking these people. And there's no systematic way of knowing whether there's any complications or serious health problems emerging from these procedures. In response, we suggest that there should be a systematic effort to identify these programs and assess the activity of U.S. citizens in these programs.

Another point we want to make is that oversight within our country of xenotransplantation, which is what this whole committee is about, and the PHS guideline, and other committees that have weighed into this, and equivalent efforts in many other countries around the world are not going to be sufficient to protect us if the same risks are introduced by individuals reentering all of these countries, including our country, after receiving unregulated xenotransplant exposures abroad. And that's where the potential issues are compounded.

So based on that, we make several different recommendations. Underlying all of this is trying to be overwhelmingly clear and sensitive one was issue. We know that we cannot go to sovereign governments and start telling them what to do, notwithstanding some of the recent events in politics. And the appropriate agency reviews the options to create a policy and communicate this to the public would be a really good start, particularly patient groups that would be most likely to seek these therapies.

When I came out as critical about the pig islet xeno transplants down in New Zealand, I mean, I would be happy to share the emails that I got from patients, particularly parents of patients with diabetes about how dare I prevent their child from access to islets. And as a physician, I'm compassionate to the concept of having a sick child. But I think we can't underestimate how important it would be to reach out to these groups and at least engage them in an educational process about what it really entails; get on an airplane and go to country X, Y, and Z, and get a pink islet xenurus (?), if that's what's going to happen.

At the same time, the same concerns I have with China, where they just recently, within the last year, announced an 80% success rate with pig hepatocytes into the liver for acute liver failure. Now, I have no idea where that was done, and I have no idea what 80% success rate means. But I do have a patient in my clinic who I now see every other week who went to China and got a kidney. So I don't think it's totally impossible that the next group of my liver transplantation patients aren't going to be going there for pig hepatocyte transplants.

So educational materials, reaching out to specific patient groups that might be seeking these sorts of therapies potentially. Consider the development of questions about xenotourism for individuals entering the U.S. I mean right now we have no idea if someone's coming back in. At least sensitizing everyone at that point of entry.

And then in the positive way, internationally, offer U.S. expertise to appropriate government agencies in foreign countries. We've got a lot of expertise here in a non-threatening, non-aggressive way. We could create opportunities. We could make countries around us know that we're willing to consult and provide that expertise.

And lastly, support generally additional efforts to harmonize the international practices of regulating biotechnology, et cetera. Because frankly, it's not just xenotourism, right. I mean the next thing is someone decides that they want to do lentiviral gene therapy research in another country. And again these issues go beyond simply xenotransplantation.

Agenda Item: Plenary Discussion of Draft Report on the State of the Science in Xenotransplantation

DR. SYKES: At this point we should open up this section for discussion. I guess the best way to do it would be to go through it in order, section by section. Would you agree with that Jon?

DR. ALLAN: Yes. We should go through intro first. Then we'll do the state of the science policy. But I don't know if we need to go by subsection.

DR. SYKES: That's what I mean, no. Given that our document is still in a fairly early form, please give us your comments. At this point they should probably be somewhat general since there are many specifics that still remain to be addressed here. Marian?

DR. MICHAELS: Just to answer the question Bob had thrown out in the beginning about the introduction, whether it should be three paragraphs or three pages, I thought it was a very good start and would hope for the more three pages rather than three paragraphs. And I really thought that it was, you know, an extremely good start to it.

DR. VANDERPOOL: I think you were too hard on yourselves too. Bob, I thought the whole document was really educational. Now, I think we're probably going to end up arguing over what level of education, but I found it excellent coverage. Others I've talked to, some on the committee, couldn't fully understand it. So there's going to be some difference on the level at which you are writing. And that raises a further question of who your audience is, who you think your audience is.

But back to the first section, I found it helpful as setting the stage. I have offered a number of suggestions about things to cut, not a lot, but quite a few things. I do think at a couple of points you were a little overly optimistic. You know, such and such was very promising, or artificial organs, which is well on its way to becoming a medical reality. I think some of that could be modified. But I thought it set the stage well. I do think you could cut it down some, but certainly quite a bit of the material here I found helpful. And if we think of this document as one that's going to inform a larger public and not merely xenotransplantation specialists, it seems to me to be helpful to have a good bit of detail, most of the detail that you have here.

DR. MENDEZ: I do think some of my adjectives were a little too flamboyant, and have cut those down -- cut them out, actually. I actually wrote that session after I talked with Bud Fraiser down at the Texas Heart Institute who had just finished his Ambicor and was so excited about it. I probably should have waited a day or two before I went on to write that.

Do you think that, with regard to that mechanical device section, Bill is of the opinion we should just delete it. And I didn't want to delete the whole thing. But perhaps the paragraph on the left ventricular assistive device, the cost; I don't know whether you want to delete it mainly to make sure that that would be an impetus toward the government spending more money on artificial devices.

DR. VANDERPOOL: To me these questions fall at the point editorial innovations. And I think it's for the committee to decide, the subcommittee to decide what you would like to amend and delete. I wouldn't want to suggest any particular point. I've made several editorial suggestions myself. But those are take it or leave it suggestions.

DR. KASLOW: Can I just ask a general question? How much pruning or major surgery depends on how long, I guess, we think the report would be optimally. And maybe there's no logical answer to that. But it's 27 pages now. I don't remember whether we decided we would do an executive summary, and if so, how long that would be. It might be worth our thinking about those sort of metaissues before we decide how we severely we're to start cutting and pasting.

DR. CHAPMAN: I have some comments that I think are really largely editorial but I'll bring them up because of your proposal to go through this section by section. One of the things I would suggest after reading it is that you might want to reorganize the order of the sections.

When I read it, it struck me that we go through this whole background that explains to people why xenotransplantation is being attempted. And then when we get to the science of xenotransplantation, the section scope of xenotransplantation, you tell people what xenotransplantation is. And my suggestion would be that you actually move that section up to introduce the document and then follow it with what is now the introductory section.

It also suggests that your xenotourism is a little artificially stuck in this part of the document because it really deals with sort of broader issues. You've got a document on informed consent issues, and you've got a document on the state of the science. Then suddenly, at the end of that, there's a little thing talking about a specific situation in which concerns are raised about how the science is portrayed versus the actual state of the science and how consent is garnered versus what would be appropriate. Perhaps you want to consider making that a stand alone section that comes after the reader has read both, you know, what's now one document on the state of informed consent issues and the document on the state of the science, and then come to this as sort of a more -- it seems to me what you're doing is describing a situations in which you're trying to describe concerns that arise out of applications of the issues in these two documents to one specific situation.

The other suggestion I would have that, again, is kind editorial, is this issue of how detailed to make the introduction. I think it's often very hard to write an introduction until you have in hand what you're introducing. I know when I write a science paper, often I begin by writing the materials, the methods, and the results. And then I figure out what to say in the introduction. Sometimes I do the discussion and then go back to the the introduction. To my reading here, the introduction goes into much more detail compared to what follows in the state of the science. So my thought would be that you may want to keep all the concepts and the examples here, but somehow try to reduce that, you know, try to work toward an economy of expression that manages to refer to those but in a much more condensed form that's more in keeping with the body of the rest of the document. Just suggestions.

DR. CRONE: I would echo some of the things Louisa said. Bob, you know, you cover a lot in really not in a lot of pages. But I found that, when I was reading it, it's a little too separated. And there are some things that just look like facts that are just thrown in there. burden of fact is in there. Like the burden of chronic and degenerative diseases, as well as the disease prevention; if you want to talk about cutting, a lot of that could be cut. You're trying to make an argument, and when you're talking about ways of knowing what you're trying to introduce, you're trying to make an argument about the high prevalence of, you know, these various problems, diseases that lead to end stage organ disease. And then you're making comments about the burden, you know, the financial burden that this is costing. And then you're also

saying what kind of options we have to see it, and then xeno -- or what our options are to treat these problems. It might flow a little easier.

DR. MENDEZ: That's a very good point. And as Louisa mentioned, how the intro was written without knowing what we were introducing. So it was a generic thing about how xeno my impact transplantation in general.

Your second statement was very correct also, the disjointedness of it. And that's what I mentioned about the Gray's anatomy versus taking an organ and going through each of the things. It was so disjointed, but that was the way it was suggested that we do it. But I agree with you. As I was writing it, I was saying I would like to just put all of this together under one thing and not have it disjointed and then have to come back and restate it.

MR. BERGER: I have a couple of comments and then one question. I like that you did mention some of the disease prevention and organ donations. It's come up today and before. And not that this should be changed necessarily, but I would like to make a recommendation in the final recommendation, that we do put something in there as a recommendation long-term to do something for the need to decrease the need for these organs. You make a comment about healthier lifestyles and the ability to change behavior. On the other hand, something long term has to be done to decrease the need for these organs. And I think we should make a strong recommendation at the end. And there are things the government can do to promote healthier lifestyles.

And secondly, the organ donation part which came up earlier today, it's come up all the time. And you get into organ donations on page six. And even with the comment that was made today, even with all these changes, we may only have 12 to 15,000 extra organs, but that's a lot more than the people who die every year. So it seems to me that we should make some very strong comment as a committee that we should be doing something about it to promote organ donations, including something like a presumed consent law, a mandated choice, or something to do that as a final recommendation.

And third, this is a question. And I'm just interested in the source of the information. But on Page 8, where you did get into cost -- and I've looked at cost for things before and I may not have up-to-date figures. I would just like the source of these because they're a lot different from costs that I've seen. The cost of maintaining these patients is approximately \$73,500 per year on dialysis versus \$800 to \$1,000 per year following transplantation. I've always seen much different numbers. So I'm just interested in that source. \$800 to \$1,000 is dramatically less than what I've seen before.

DR. MENDEZ: That comes from the ESRD Network of costs of dialysis. And you can take that to either the first to three years of dialysis or the first five years after dialysis.

MS. KING: I have a couple of comments related to the quality of life issue. I interrupted you, I'm sorry. did you say that was a typo?

DR. MENDEZ: Yes, it's \$8,000 to \$10,000; not \$800 to \$1,000. That was a typo.

MS. KING: Because we were saying cyclosporine alone would cost more than that.

DR. MENDEZ: That's figuring generics. The \$8,000 to \$10,000 is quite expensive.

MS. KING: I had a couple of comments on the quality of life statements that are made. And I guess I would caution -- on page four we're talking about the implantable heart, and on page five we talk about it as well. On page five we say the quality of life is unknown. So those are contradictory. And I guess I

would caution against saying its satisfactory. I don't know who's to say.

On page six, we talk about quality of life, comparing cost of xenotransplantation with artificial organ replacement and again say the quality of life would be superior, an improvement. Again, I don't know if we know the quality of life with xenotransplantation. So I caution against that statement as well there. The only other thing I had related to the introduction is in the statement on page six, the first paragraph that says basically, when you're looking at the cost of transplantation versus dialysis, specifically hemo, that centers for Medicare and Medicaid services is requiring consultation for every hemo placement. My understanding of the reg, if we're referring to the same one, is that every dialysis patient, not just hemo but everyone with the VSRD has to be informed of all their treatment options. So it should be VSRD I would think. As well, as they don't have to have a consult. They have to be informed of their option and they can refuse to pursue that. So that wording should be clarified if we're talking about the same reg.

DR. MENDEZ: I'm looking, unfortunately, at the second draft here. You're looking at the first one. I did change that. But thank you very much. With regard to the contradictory statements, we'll take them out.

DR. SYKES: Well, I don't think there's anything wrong with pointing out that there's hope that the quality of life with a live organ transplant will be better than that achieved with an artificial organ. I think that's one of the reasons to pursue xenotransplantation. You know, I think the limitations in quality of life that have already been encountered, the coagulation problems, the infectious risks of having an artificial device implanted, the psychological impact of depending on a battery for survival should be mentioned.

MS. KING: What I was saying is, here it says it will be dramatically improved. I don't think we can say it will be. I think there's hope that it will be.

DR. COLLINS: Bob you've got a lot of great information, a lot of great data. On page five where you talk about the direct measure of years in productive life, those data are so good. I wonder how much endstage disease cost, how much money you save with transplantation compared to dialysis. I wonder if that shall go even in that very first section when you have the burden when you're introducing your whole section. Those points are so important, I would recommend that they go there. That's just a personal preference, of course.

Then you talk about the assist devices. I think you do need that section because it is certainly a destination therapy for some patients, and it at least gives the reader an idea that there are alternatives or at least that we've thought about, the alternatives to xeno. Thanks.

DR. MENDEZ: Thank you.

DR. VANDERPOOL: A general comment, and I think this applies to the whole paper. I definitely would like to see references throughout, even A statement to the effect that, you know, this was a seminal paper and we don't have the paper. So I think the -- while I don't doubt the factual basis, I think it would be greatly strengthened by references and also allow the reader to go to whatever references there are in case the reader wants further validation and augmentation.

DR. MENDEZ: Very good point. We were going to do this. I didn't know whether it was going to go in the bibliography.

DR. VANDERPOOL: I didn't mean that just for the first section. I mean it to apply throughout the paper.

MS. SHAPIRO: I have some scribbles, for what they may be worth that I'm happy to share. I think it's a great introduction. There are a couple of statements that I think maybe are too optimistic or too broad or something, one of them being on page six; "Although the current potential cost of xenotransplant strategies are not well documented at this time, xenotransplantation and or artificial organs especially heart are the only mechanisms by which we can address the burden for life saving organs." The only I thing --

DR. MENDEZ: Should be deleted. There are obviously two other ways to do it.

MS. SHAPIRO: I have a general question to both groups actually. And as we get into the next sections -- maybe I can put it out there now and let people give me what their sense of it is. That is, who is our audience for these papers. The next section -- I think I understood most of it. And I probably could, if I read it 5 or 500 more times. But it was difficult for me, and I've been with you guys for awhile. So, I'm not so sure who the audience is going to be. If it's going to be one like me it may have to be toned down a little bit.

DR. SYKES: Well, Dan and I worked on this a little bit. His initial writing of his parts was much more in lay language. And I actually felt that that was not appropriate for what I had envisioned as the audience, which would be an educated health care, you know, either an M.D. or somebody in the health care profession who would be familiar with this terminology. I mean, it is a report to the Secretary of Health. And I just felt it was inappropriate to write as though the secretary had absolutely no medical knowledge whatsoever. But certainly we can discuss that.

DR. KIELY: One of the things I actually found helpful, because I actually learned a lot reading this, was the section where you had the summary points, where you pulled it together. Because as a relative lay person to this, to say the least, I did get lost in a lot of details but found that I got a lot of education in the process. But when we got to the section that had the summary points, I was very, very happy. I sometimes read those over and looked back to see when that point had been made. I think it may be helpful.

Again, it might be useful if we knew we were going to have an executive summary, obviously, we can balance the level they're on.

DR. SALOMON: Actually, I'll embrace that idea. I didn't resist Megan's changes so much. I don't want to sound like we had a big argument about it. I'm more comfortable at writing at the level we are here. I'm also concerned that the audience will be at level with my peers, I'm not worried about that. So I think if we're calling this a series of summaries, then maybe we could play to both audiences really responsibly. So I think that's a pretty good idea.

DR. ALLAN: I like the introduction as well. There's a couple of things that I would want to put out there, and one is to Bob. You said that you had gotten feedback that you should take the stem cell out and you should take some of this other stuff out. I think it's important and ought to be in there, because I think xenotransplantation should be within the context of potential alternatives, and certainly stem cell therapies that are obviously not there yet but that do represent the potential for some technological breakthroughs. I don't think there's a problem with that. And I think that would be very helpful.

DR. MENDEZ: I thought that was perhaps corrected. There's a question I discussed with whether or not we're here to advocate xenotransplantation or put it into the context of what is presently possible or not. Are we the cheerleaders for xeno, and should we diminish perhaps the enthusiasm of the other types of things?

DR. ALLAN: So that's what you meant.

DR. MENDEZ: I was inclined to keep it.

DR. ALLAN: I would say keep the stem cell. If someone was saying you were too hard on that technology, I would maybe amend that. But I would keep the alternative in.

DR. SYKES: I think our job is to tell it as it is, to say what all the alternatives are but where they are, what is the state of the art compared to xenotransplantation. I don't think anyone would argue that stem cell transplantation is anywhere close to solving these public health problems that we have. And that has to be said too. Not that we're here to cheerlead for Xeno, but we're saying it's here and stem cells are here.

DR. MENDEZ: That's why I have no hesitation in putting it in because I think we are ahead. Perhaps in certain biomechanical things, we may not be. It may be a close race, whether or not you're talking about insulin pumps or eyelids. But in the other things, I think, we do have to mention it.

DR. ALLAN: I would like to finish some of the things I had. The other thing was the economic end of it. I raised these once before, but I'm going to raise it again. I'm going to throw this out there. My suggestion is that our committee recommends that a study be done to understand the potential costs or the economic costs of various types of xenotransplantation technologies.

DR. MENDEZ: Should it be a comparative cost to the other modalities?

DR. ALLAN: It may end up being that way because you have to put it in context with something. Let's say, heart transplant, allotransplants or some of these other things. I think that, you know, if you're going to be advocating or even discussing the state of the art for xeno or whether or not it has a strong potential, then it has to be in the context of economics. And we just don't know what those costs are. I think it will be helpful. I'm not saying it should go in here, but it's something that the SACX could look into.

DR. MENDEZ: I would strongly agree. And I would say that should be put into the executive summary also.

DR. SYKES: What data are available on costs of xenotransplantation?

DR. MENDEZ: I'm not quite sure. I think we would have to go to each individual aspect of it and talk to every particular area in which it would be involved to see if we could get a feel for it. That's why we don't have a handle on what the costs are. But I think Jonathan is very correct. Lay people, the first thing they ask me is, what is the cost for this? And I think that as a committee, that's one of our charges, to get that information.

What you recommend is that a study be done so that information is available. If it turns out that it's going to cost five times what it costs to go to Mars, maybe there will be some thought about it. Or if that can cure AIDS, you know, with one-tenth of the cost, maybe they'll think about that.

DR. SYKES: But even a drug is extraordinarily expensive when it's in its development stage. It's a huge projection, to try to imagine the cost of xenotransplantation when it's actually made it to the therapeutic stage, if it has. We can try.

DR. ALLAN: It's not that we're going to say it's going to cost this much. I think we can get information that's going to give you certain predictions and ranges of cost based on allotransplantation, based on the

cost of transgenic pig production, based on all these different instances. I've already heard -- I think Dan who used to say well, it's going to cost -- I think it was Dan that said I think hearts were, \$25,000, human hearts. And somebody said that a transgenic pig heart is going to cost you about \$25,000, these kind of things that are thrown out there.

DR. SALOMON: We were saying one sort way to get a reality check of what this is going to cost is just what we're paying right now for a human heart or a human kidney, or really any organ, is somewhere between 15 to 25 to \$28,000, going rate for procurement. I'm not talking about a profit motive. I want to make sure that no one misunderstands what I'm saying here publicly. But that will be around the target cost, I think, for companies once the field was up and going and practical. And I think if it was significantly more than that, there would be public issues raised, the profit motives question. On the other hand, I just want to comment, if you go to the companies now, these poor biotech companies, and start asking them to commit to the xenotransplantation, what the costs are going to be, they're going to absolutely not accept that. And I agree. I would feel very uncomfortable with that.

MR. FINN: As far as the cost is concerned, we're talking about the overall cost for care, it may be cheaper to give them a heart than put them in the ICU and wait for another heart to come along.

As far as the paper is concerned, I think it's great. There's no one in this room that's more of a proponent of xenotransplantation than I am. I've had the procedure done.

I think the report is a little too forward looking. It's, as you said before, cheerleading for xeno, I don't think should be done quite yet because a lot of things to need to be taken care of before we can get it into full production.

DR. SYKES: Louisa has had her light on for a little while.

DR. CHAPMAN: I think the discussion brought up the points. When I initially put my hand up I was going to ask for clarification on Jon's request for more information on cost, because of exactly the point you've made and some others have made, which is you can come up with cost predictions for experimental therapies still under development not yet brought into existence, but in reality they're going to be relatively meaningless.

But what I've heard the discussion say is you can come up with probably reasonable cost estimates for the current alternatives, and you can make a recommendation that comparative costs of these therapies needs to be borne in mind and studied as development proceeds relative to the cost of current alternatives. And that's what I thought I heard coming out of the discussion. That's why I sort of put my hand down. I think the committee should be very careful about trying to estimate cost in places where, in fact, the field is not far enough developed for those cost estimates to be meaningful in terms of recommendation.

DR. LUBINIECKI: Cost is an interesting topic. But in addition to cost, there's also value. If we're going to estimate one we should estimate the other. Otherwise there's no balance.

I also think that in a world where all technologies compete for finite resources, if we can't make the case that this technology will contribute value despite the cost of developing it, then why are we sitting here? So I would recommend that we actually do attempt to address an estimate of what it will cost and what value would be created.

DR. SYKES: Eda?

DR. BLOOM: Thank you. I was actually going to change the subject away from cost. So if anybody

else wants to -- I was just going to say, be sure that the introduction says what it means or what you mean it to say. For example when you say, we must look to cloning and xenograft techniques, I'm not sure what you mean by cloning, whether you mean cloning animals, cloning cells --

DR. MENDEZ: Cloning cells, human cells.

DR. BLOOM: I think there needs to be some clarification. Like in the other places, when you talk about stem cells, I don't know whether you mean embryonic stem cells or you mean organ specific stem cells. When you talk about --

DR. MENDEZ: Both.

DR. BLOOM: I think clarification is needed. When you talk about adenovirus, when it could be used to incorporate normal CFTR -- of course the results of those studies are pretty publicly known that, yes, maybe they could be used but they haven't yet been able to be used. So just being, you know, -- since this was a rough draft, it feels funny saying that sort of thing --

DR. MENDEZ: No. I'm glad you did. I think we deleted that on the next one. But we'll make sure we do.

DR. SYKES: Okay. If there are no the other pressing points of the introduction, I think we shall probably move on to the next section in the interest of time. So any more comments on the introduction that must be said? Harold?

DR. VANDERPOOL: I thought it was really well organized and very pertinent to what the science is about. My concern, Megan, is that again back to what educational level we want to write on. I fully understand your point of view that if we're writing to the secretary we don't want to treat him as if he can't understand a good level of scientification. On the other hand, there are the other reasons for simplifying it even further, making it easier to understand. In so far as SACX has an educational mission, then I think there's cause for this to be a little more, significantly more successful to common understanding. Bob mentioned a minute ago that we're talking to lay persons.

In so far as our own informed consent document was written, what we had in mind was, of course, researchers, but also IRB members who need to know about the informed consent level. So I don't know what the answer is, but I think it's something we need to talk about and agree on, because I think you can make a case for either way.

Maybe we need, in keeping with Bob Mendez's twin brother and my own twin brother, to make these twins. One of them is more scientifically ordered. One of them is more man of the streets. In the other words, we might need two documents.

DR. SYKES: Yeah. I think that might be a thought. We could consider having a science writer translate it into lay language, to have a separate document. But I think our charge is to write a report to the secretary. And I really don't feel there's anything in here that your average medical professional couldn't understand. We've made attempts -- I mean, I'm embarrassed by some of the definitions that we've provided. I think that it would be almost insulting to go further.

DR. VANDERPOOL: But at the same time, in the federal agency, there are a lot of people who talk more and more common language and who would advise the secretary to play important roles in the deliberations of the department. So again it's a tough issue. I see your point about writing only to the

secretary. We hope it will get to the secretary. But in the meanwhile, I don't know what the culture of the DHHS is, in terms of who will end up reading it and for whom it will end up making a difference. I don't know. I think we need to talk about that a little bit more.

DR. GADBOIS: Just for those of you who don't know me because this is a first meeting here, I'm from the Office of the Assistant Secretary of Planning and Evaluation at HHS, and I see a lot of reports, many of which are written for the secretary. And often when there's concerns about what the mission of a group is, everyone goes back to the charter.

Your charter is quite clear, that first and foremost you advise the department. The secretary is the head of the department, But there are many people who could benefit from this document. Many of those people will be M.D.s or Ph.D.'s. Others are not. They may be in other areas of health expertise. So it's definitely a challenge to put something like this together.

But I would recommend that you try to make this an accessible document. Many documents start out with basic explanations and then get more complex. So they try to address the range of expertise of those who read it. So I don't think it's, you know, dumb it down or make it very technical. I think with some work you can make something that a lot of people can get what they need out of it.

I would also put in a plug for the secretary. There are a lot of people who won't get through the document. Many will, but some could benefit from an executive summary. That's a place you can boil things down in more simple lay language as well.

DR. SYKES: Marian?

DR. MICHAELS: I was just going to come back to Sharon's point of putting the bullet points as well would be really helpful, and perhaps, also the need to have two documents. I appreciate the comments that you just made about the executive summary.

DR. CHAPMAN: I was going to comment on things that both Ellen and Mary have said. Before Ellen spoke up I was thinking that perhaps we should point out that actually our current secretary of Health and Human Services is, by training, a lawyer. His predecessor was, by training an administrator. But your advice is to the department that the secretary heads. And that department is composed of many kinds of training, people who are physicians, scientists, many of whom are lawyers, many administrators. And undoubtedly, those people with the technical background will be asked to review this and advise the secretary on its content. I think you're speaking to both groups.

And the question is, do you want to translation to the nonphysicians, nonscientists, to be done by you or to be done by the scientist and physicians who are members of the department? And you may be able to do both if you incorporate Marion's and Sharon's suggestions about the summaries. You can put those summary bullet points in lay language and leave the broader discussion and more technical language. Then you have retained some ability of your own to speak directly to the policy makers who may not be technically trained in medicine and science instead of turning that completely over to the departmental advisers who are technically trained at medicine and science to make those translations for you.

DR. SYKES: I think those are all good suggestions. These are all really helpful comments. I think trying to translate the entire document and the scientific details into lay language would make it unduly lengthy at this point, explaining every single term. But just distilling the essential points into lay language at the end of each section might be a good compromise. Do you think that would help to make it more accessible?

DR. GADBOIS: I think there's probably different ways to do it. I guess I'm more familiar with documents where definitions are given in the beginning and then it gets more complicated. But I think the concept that you're trying to make is that you can try to make it understandable to everybody.

DR. SYKES: We do try to define the major words. It's just words like thymus we don't define. Not everyone may know what a thymus is. Or murine. Not everyone may know that word. But most people, I think, in the health professions would.

But we could either, every time we encounter a word like that, provide a definition. That would make this thing huge because words like that come up in every line.

DR. GADBOIS: Sharon just mentioned, and I was having the same thought, that a glossary may be helpful. Now, I've read several reports on cloning, which is one of the most technical things to explain, but it was very important that it be understood by multiple people.

DR. SHAPIRO: I would volunteer, Megan, to go through it, because for me it's not so much the terms but the concepts. I'll be happy to go through and tell you where I get lost. Having said that and everything else, I have a problem with really only one sentence in your part. That's the last sentence, "It, (being the Government,) could also explore ways to assist industry at negotiating past the regulatory hurdles and stringent safety guidelines." Well, we believe in those safety guidelines.

DR. SYKES: Well, I think what we were trying to say there deals with them constructively. Perhaps the language needs to be changed a little bit.

DR. VANDERPOOL: Actually, the government guidelines are praised in another section of the report. I think this wording needs to be changed, but I would certainly put a question mark by negotiating. You know, this committee is into slipping people by, Eda and others. But no, that's not what you're trying to say.

DR. SALOMON: I want to know when Megan slipped this one in.

DR. SALOMON: Dick did this?

DR. KASLOW: I wrote that after you guys told me to.

DR. SALOMON: Now we've got the culprit.

DR. SYKES: Shall we move on to the infectious disease section?

DR. ALLAN: Are we done with your section?

DR. SYKES: Are we done? Do we have anymore comments on this section?

DR. CHAPMAN: The one thing -- I thought overall it was beautifully done. But the one advance in science -- it wasn't mentioned here. This was clearly a document that was produced prior to August when the advent of the homozygous pig was announced.

DR. SYKES: Yes, this document was produced in July, as a matter of fact. Harold?

DR. VANDERPOOL: A comment. I do think that one of the neat things about this section is that it's stocked full of recommendations. So I think it would be quite easy to go through and pull out the

different recommendations that are being made as part of the final report. I mean, I have what, maybe eight or nine myself. But you call for a variety of initiatives and places where research can advance the science and also places where there are gaps in the science.

So it seems to me it will be quite easy for the committee to go through and say, okay, now, which of these recommendations do we really want to flag or which do we want to put together and flag as initiatives that belong with each the other and so on?

DR. ALLAN: I have a question on the last section of that -- your section, the Advances in Impediments. I thought it might be easier if it was broken into subsections because it's several paragraphs, and it's not -- I mean what you're trying to say, I think it would be very specific in terms of subsections if you want to give it advances and then impediments or, you know, sort of highlight it and then you can have the bullets at the end.

It's well written. I think it would sort of help to have some subheadings or something to keep your eye to and focus in on certain areas. And then some of the wording, I thought it would probably get changed anyway. But some of the wording in terms of unwise, unrealistic appetite, things like that, I think, we should probably, you know, fine different wording for that. I guess that's it.

DR. SYKES: Anymore comments on this section? If not we'll move on to Jon's section, Infectious Disease Risks Associated With Xenotransplantation.

DR. SHAPIRO: There are two statements that I think raise concerns. One is on Page 25 in the summary "When any organization, regardless of location or funding sources is involved in xenotransplant procedures on U.S. residents, it should be required that U.S. guidelines and regulations be followed." Well, that will be tough to sell. I mean we really can't tell institutions in the other countries what has to be required just because one of our citizens happens to be there.

And then the only the other thing I thought, on the next page, in the second paragraph that this statement, "It's important to note that concern has already been raised by the constituents where they can buy human kidney;" I don't think that we should throw that in there. That's really such a different issue.

DR. ALLAN: Where are you?

DR. SHAPIRO: That's the next section. I'm sorry. Never mind. That's for Dan.

DR. ALLAN: You've already hurt his feelings.

DR. SALOMON: You almost have to vote on that. You know what, I don't agree. I think it's really relevant, but this isn't my report. So if it's felt that that's not relevant, just take it out. I think the point is, how do you make the case in a way that people reading it will understand that this isn't just us, this isn't a fantasy, this is the real thing.

And there's a report in the press that 80% success rate with pig hepatocytes and acute liver failure and then patients are definitely going to China, completely blowing us off in terms of all the ethical and international conventions of transplantation, and then coming back, and the "New York Times" discussions is, that we have to take care of them, which I'm doing. So I don't think that's a big deal. I think it's important to make that point. So that's what I was thinking. But if people aren't comfortable with it, we should delete it.

DR. SYKES: Harold?

DR. VANDERPOOL: One of the issues, I don't think needs to be here because it's really another agenda, is the issue that's somewhat differently stated on page 25 on one hand and 26 on the other, arguing that present guidance is fine. And it's followed by saying that periodic review needs to occur. I can see how those do fit together, but I'm not sure that we need to make that judgment without having -- unless your committee has really combed through the present guidance really carefully and come to a decision that the present guidance is fine.

I don't think it belongs in this report. I'm not saying that the present guidance isn't fine. I'm just saying, unless we've really worked at this as a separate topic, we shouldn't be making recommendations about it.

DR. ALLAN: I mentioned this earlier, but we really didn't tackle the regulatory issues in terms of the guidance as you were just suggesting. This is in here, but we really, I think as a group, need to discuss in more detail the HHS guidelines and regulatory issues because we really haven't discussed that as a group at all.

So I think you're absolutely right. We'll see whether we need to have a joint session to discuss regulatory issues, or whether we should do it in the scientific group. I'm not certain of that.

DR. VANDERPOOL: And that's one of the charges of our committee, to look that over. And we've never done it, never really sat down and done that. I told Eda at break that I happened to have done that over the last several months for a reason different than the demands of this committee, and I learned a whole lot that I didn't know before, because I had read it but I hadn't really really worked with it.

And so I think that's an important part of our charter.

And I mean, when the FDA came to us to ask questions of us then I think at some point it would be certainly important for us to carefully review the guidelines that have been set out, the most recent ones, and to give them, the agencies, the feedback they deserve from this committee on the adequacy of what they've done.

DR. SYKES: Eda?

DR. BLOOM: I just wanted to point out along those lines, actually to remind the committee that guidelines -- or at least the PHS guidelines, infectious disease issues, xenotransplantation, and the FDA guidance documents, are not recommendations, they are requirements. And so when you go over it with your fine toothed comb, please read it with that in mind. And when you talk about being required, as Robin pointed out, required to follow applicable laws and guidelines, we can't require anybody to follow guidelines.

And just a little aside here, well, some of the follow-up guidelines, the thirty years follow up -- well, it's fifty years. I think that makes it much more practical.

DR. SYKES: I have some comments on the section on porcine infections as potential pathogens to humans. I realize your goal for this section was not to include control measures.

There's a section later, controlled infectious disease risks. But in fact when you get to control of infectious disease risks, you don't come back to any of the specific infections that you mentioned in the section porcine infections as potential pathogens to humans. And I felt that as a result of that this section came across as unnecessarily scary and negative. For example, CMV, you mentioned that it can be transmitted in utero, and horizontally in swine well, in fact, we're routinely during transplant from CMV negative pigs. It's really easy to get CMV-negative pigs. You just wean them early. There's no reason

why CMV couldn't be kept out of a closed herd of miniature swine. Likewise, I assume the same would apply to rabies, hepatitis E, and a variety of the other infections mentioned there. So I think that this section should be mitigated by a discussion of how these things can be very easily kept out of human transplants.

DR. SALOMON: It seems like instead of two sections it might be worth doing it in tandem, you know say a risk is this but it's mitigated by that. It's been very helpful in my experience, in dealing with people who are not from this area, to separate those risks that are here and easily handled by appropriate specific pathogen free colonies and good husbandry versus those risks that you can't deal with and then you highlight those.

I still remember, I won't mention the country, but I was doing some consulting for a company and the guy says, oh, there's no problem, the pigs are fine, they're perfectly healthy in the farm where I took them from.

DR. SYKES: In fact, a more specific list of what should be kept out of the herd, I think, would be very valuable. I know such lists are being generated.

DR. SWINDLE: Well, we discussed that at great lengths because it's a really lengthy list, as you're aware of. And we finally ended up not putting it in. I mean, we can put it back in but it's going to be a list of scary things for about six pages.

DR. SYKES: Maybe it could be provided as a reference.

DR. SWINDLE: Yeah. There are references. There are plenty of references. One of the things we totally attempted to do, as we said at the introduction, was not to write and rewrite all the things that are already out there. That's why we referenced the documents for committees who have already studied and made recommendations, and just tried to highlight it and keep it simple. But the infectious disease list -- not only what you were saying about the control of the infectious diseases -- that's all published too. We can reference that without going this and that. Because a lot of the comments I've heard are going to double this document or this section to do that. And I don't think that serves any purpose.

DR. SYKES: You need to, in the body of the document, make the connection for the reader. Because your summary of porcine infections as potential pathogens, a bullet point, "several persistent viral infections of swine may pose a risk in the transplant setting"; well, they might if you didn't keep them out, but you can keep them out. So never do you make the connection in the document. You just, in the next section, say use of specific pathogen free animals. But you don't say which pathogen. You have to refer back to the ones you've just scared everyone about.

DR. SWINDLE: One of things that occur to me is that we've got this broken down into three sections and maybe we should put it all together into one and make a combined recommendation because there is some overlap between it. If we say this list of pathogens is published in depth here with the control measures, and these are general control measures something like that -- but I really, I mean even taking some retroviruses, you can go on and on forever and write a 25 page grant on that.

DR. KASLOW: I don't know if this will work, but go backwards. Start with the message you want to get across about each category of what you would do to prevent this, what's the important thing and here's an example it. There are many others for which this would also apply. There may be two or three other principles of control.

DR. SYKES: And at some point you have to draw the bottom line, this or this category can be contained.

What we're worried about are PERV and unknowns that are already there in swine that are going to be kept in closed herds that we don't know about.

DR. SWINDLE: So stick with categories like viral bacterial? Would you do that or be more specific?

DR. KASLOW: Stick with the categories.

DR. MICHAELS: I think somewhere in here it got lost, some of the definitions of exogenous and endogenous, and then the way of attacking the exogenous viruses that we know about, or the exogenous microbes, the parasites, the bacteria, and the viruses, to do the good husbandry and screening and the various ways to attack the endogenous retroviruses in what are known and what are unknown. And then the need for on-going screening in terms of the microbes that may be there. I had a question which I can come back to because it's off this subject and one that I wanted to ask the group about. So I'll wait for a moment and see if there's things on this particular item first.

DR. SALOMON: I think what I'm hearing is just bothering me a little bit at the end here. I don't think we should be saying we should change that because it's so scary. In the other words, again, this document isn't going to be to pave the way.

DR. SYKES: I said unduly scary. What I meant by that was I'm not trying to make this a propaganda document. I'm saying that you're scaring people unnecessarily about things that are not dangers.

DR. SALOMON: I think that the point I'm making is fine. We don't want to unduly scare someone, but at the same time to make the point that there really are some scary issues here and, that you can't just go out to the farm yard and take healthy animals that would otherwise be a part of our food chain. And I think if you don't get that point across to lay people, then we are not doing our job.

This is a scary proposition. Yes, Megan, sure we can do this and that to mitigate it, but there are a lot of people that don't even get the way in, that if you don't even put a couple million dollars into a specific pathogen free herd, these wonderful healthy pigs that I'm eating tomorrow -- so I don't think it's wrong completely to be a little scary.

DR. ALLAN: So let me put it a different way. When xenotransplantation first came out there was an education follow through on infectious disease risks. And it took a really long time to sort of get it nailed down that there are really true risks. We don't want to be complacent and say, well, everyone knows there are risks so we don't really need to be talking about it too. We still need to make the point. But I think you're right.

In the context here you can talk about the agents. You're not trying to scare anybody. But what you're saying is that you need to push that control right into the middle so that you've got virus, you've got diagnostics, you've got husbandry, and the other types of control issues that you can all bring in together. And I don't have any problem with that. I think that will all probably work really well. So I think your points are good.

I don't think the document will be such that we'll try to unduly scare somebody. But we still want to get the point across that there's still infectious disease risks.

DR. CHAPMAN: I have a couple of comments on a series of things that I think have come up before. On this -- I think you summarized what I was thinking Jon, which is, it sounded to me what Megan was asking for was not the things that might be concerning be removed, but that the length that is currently implicit between the section that talks about porcine infections as potential pathogens for humans and the

following sections about control of infectious disease risks and husbandry source animals just be made explicit and not implicit. So that connection would be lost to the reader. I had a couple notes in here about things that you may want to consider a little more than is addressed here. And I believe they've already been raised, but let me just mention them.

I had a note that maybe you wanted to have a little more discussion about the issues of investigational assays and the uncertainty about the specificity and sensitivity and serology and sort of elude to that here, but it's not quite as explicitly. And Jon, I think you eluded that you wanted to put more in here. There's also a question raised in one of Carolyn Wilson's papers about whether PBMC's are the most appropriate tissue to look at in humans when you're trying to assess whether people exposed in the past have been affected with PERV. And that's not explicit here now. That may be superseded by the fact that people are applying serology as well, which is a pretty global test.

DR. ALLAN: What page would you suggest the insertion of the PBMC? In that same section?

DR. CHAPMAN: I was inspired to put both these notes on page 20 in the section, Studies To Address PERV Risk in Humans, after the third paragraph in that section. That's when I got triggered to write it down. On the earlier discussion about the comments on regulatory guidance and the issue of whether you should go so far as to say that this committee should periodically review and upgrade those guidances, I'll just tell you that CDC a few years back -- CDC produces a lot of guidelines on usually medical practice issues and preventive health issues which are based on, you know, practice of medicine and science, both of which are continually moving edges. And a few years back CDC decided to produce a guideline on how to produce guidelines, which I can provide to you if you want. But one of the points in that guideline -- which I confess we didn't enact in the PHS guideline -- but in the CDC guideline on guidelines, it actually says that every guideline should explicitly state when and how it would be reviewed and revised, out of an acknowledgement that if you're providing guidance on science and medicine you're providing guidance to something that's always going to be a moving target.

And if you don't review it, against the current state of medicine, the current state of science, your guidance is going to become rapidly out of date. I don't know if you want to be as explicit as you are here, but it is this committee that should revise it. But the suggestion that one thing the committee might want to comment on is that these guidances will need periodic review to assure -- and perhaps revision and perhaps not -- but periodic review to ensure that they're still appropriate in light of current state of science and medicine, it's not a radical concept as far as CDC's guidelines on guidelines goes.

DR. ALLAN: Good point.

DR. VANDERPOOL: Given the lateness of the hour, I hope we can finish the discussion of this section and give some feedback on the xenotourism section for a few minutes and then allow for public comment.

DR. BLOOM: I just wanted to make a comment that FDA also has a guidance on guidances. We say the same thing. Except along with good manufacturing practices and good laboratory practices, and clinical practices, we have good guidance practices. So we deal with ourselves the same way.

DR. SYKES: I have two more comments. On page 20 at the top there's a sentence, "Despite further risks from unknown viral infections, PERV represents an immediate concern and is unlikely to be removed by conventional breeding." I mean that's true but there are those who -- as you've heard today from David Ayares, who think that it can be genetically engineered out. And I wonder if it might be worth mentioning that at this point.

DR. ALLAN: Genetically engineered. That's possible to do. Yes, we should probably address it.

DR. SYKES: Given that there's now a knockout pig knocking out these genes -- they're not all functional genes, and that was his point.

DR. VANDERPOOL: I also put a question by that, unlikely to be removed, statement in the light of what we've heard today and in light of what we've seen earlier.

DR. SYKES: Then my second comment is that I think this section should end with a summary of where we are, you know, what are the remaining -- just a brief paragraph saying that there are all these different types of infections; we can control these with good husbandry and close colonies; and there are still risks from PERV that we can't assess from the other potentially unknown infections.

DR. SWINDLE: I believe that is what we had in mind for an executive summary. Because as a group we were totally in favor of an executive summary of a document and coming up with that as the type of thing that will go in that guideline, given the people that are going to read it. It's no more than a page to read.

DR. SYKES: I just thought it I would be nice for this section.

DR. SWINDLE: We can cut and paste it into the executive summary. But that's what we had in mind for a summary.

DR. CHAPMAN: One last comment on the comments. Megan points out that your statement on Page 20 of PERV represents an immediate concern that, unlikely to be removed by conventional breeding, may not give the reader the full sense of the techniques people are considering bringing to bear here. I'll just comment that you can change or modulate your prediction by bringing in the possibility of transgenic techniques, or you could just get out of the prediction business by changing your statement to say something like PERV represents an immediate concern and has not, today, been removable by either conventional breeding or transgenic techniques.

DR. SYKES: Why say that when nobody has tried?

DR. CHAPMAN: You elude to the possible things that might be applied in the future. You make a statement about the current state of science and you don't get into the business of predicting how easy or uneasy or how likely or unlikely this is going to happen in the future.

DR. SYKES: I don't see a reason to bring up the strategy if it's not being tried, and you don't want to mention that its going to be tried.

DR. ALLAN: We're talking about an immediate concern, and the immediate concern is, it's in a temporal sense. This means within in six months or a year, immediate risk. Knockouts to knockout all PERVs is going to take a few years. So I'm saying if it is doable you won't find that out for --

DR. SYKES: Well, then let's say there's no immediate way of getting rid of them.

DR. SALOMON: I think we should be careful though. The idea that Julia described to us, and that I'm familiar with in my private conversation with Clive, plus what he's reported, you may be able to breed animals that affectively do not have a xenotropic strain of PERV. That doesn't mean that that won't have many of the genes that could assemble, under the other circumstances, a xenotropic version.

But there are a lot of open questions. You want to give them credit for the possibility that it doesn't all

have to be done by knocking out 40 different loci before you substantially reduce the risk.

DR. ALLAN: The only thing I would say is that the data that Clive has is basically an infection. It's not molecularly based, as far as I can tell. So at this point we really don't know whether or not they have eliminated quote, xenotropic viruses through inbreeding. Those still may be present, it's just that they weren't -- we don't have capacity under the techniques that were used to detect those viruses.

DR. SALOMON: Given the lateness of the day, it's probably to scientifically detailed. We'll discuss this later.

DR. SYKES: Marian?

DR. MICHAELS: This portion really dealt just with the infections of swine. And I realize it's late so we can table it until tomorrow, but just something to think about. I noticed when reading the first section about the science and talking about the different source animal, and not only potential source animals, the fact of the feeder lines being mouse line in a murine cell. Do we need to go back and address that in this section, which is not done at all, or at least to try and make this a little more abstract, to have the other potential source animals included.

DR. SYKES: I think you do. And in fact I think we need to tie that in, in a larger sense, to the whole report and the consent document because as we were discussing the informed consent document I was thinking to myself many of these things might not apply in such a stringent way to a cell line that had been exposed to a murine feeder layer. And so I think we need to keep that in mind and find a way to include it in sections and integrate it into the document as a whole.

Dan, you're on for the xenotourism section.

DR. SALOMON: I think it was excellent.

DR. VANDERPOOL: Dan, you asked on the first line, should this section be a separate document? My answer to that was yes. I think it's an incredibly important issue. I think you've certainly alerted not only us, but us the department to the issue. But I guess my question -- I have two questions. One is, why should it be part of the science of xeno statement?

And the second question would be, it seems to me that what you've laid out here, which is an expansion of what you've given us before, is an agenda for a meeting and for our making a position statement on this very important issue.

We're going to hear tomorrow from Dr. Zucker and see what he has to say. But at this point I'm not sure. I mean, I like what you say about nearly everything. At the same time, I keep saying, okay, should we have representatives of these people from Mexico to come and tell us what they're about? Should we do a more thorough analysis of how much is going on and what the dangers are?

I think it's just an incredibly important issue. I'm not sure, depending on what the time frame for this report is, whether it should be part of this report, both in terms of time frame and in terms of our not being able to give it the attention it deserves. But it needs to be attended soon.

I mean, if Mary calls me up next week and says, look our committee is supposed to cease to exist as of July 4th, with the fireworks we go too; then at that point I'm going to say, put Dan's section in there, we're going to go down with xenotourism. But the other than that, I have a different position. I can be argued off that position, but that's just some thought.

DR. SYKES: Can I ask in what format you think this document should be forwarded to the secretary, because I feel like we've been through this already. The last July, we talked about sending a letter to the secretary. We even wrote one. We even sent it around for comment. And we ended up in a conference call where it got shelved. So I don't want to do that again.

DR. SALOMON: I want to point out, I didn't write this question to put it as a separate document because I agree with Megan, we did discuss the idea of a separate document. I think what Mary was talking about was something that had been suggested by Louisa, if you're going to leave it in here, definitely split it out as a separate section. I think that's well taken. I don't think any of us who were involved in editing this thing thought that it fit into science specifically; right? So this either should be a separate section or, Harold's point, just don't put it in here. It's just too big a thing.

And I can relate to that. I think in that case that I would probably do a "New England Journal" sounding board or something on xenotourism tourism just because I think it's time to do this right now. So I guess it's just kind of a question of how you want to get this point out and where the committee wants to go with it.

DR. ALLAN: I think you should break it out as another section because it would sit very well that way. I had another way of looking at this, another question based on this. And this is obviously not the same degree of infectious disease risk, but what about U.S. citizens who have gotten xeno products in this country, what if they go abroad? Let's say they go to France and they're not compliant and they're not getting tested and they're sitting there in France? So there's the potential of putting French citizens at risk. So I think there's something to think about in terms of state departmental situations where it could go the other way. And I don't know how we would to introduce that, but it's something we need to consider.

DR. MICHAELS: Should we have section that looks at our relationship with the other countries in a more general fashion and then the xenotourism as one concept in it, or is that really going to make it too large?

DR. SALOMON: I'll have to defer to someone else to write that. I don't have any expertise. I found myself going to Eda and Louise at different times, and Mary, to try and find out what it was we could do internationally. And I think that would come back to something Harold said which I have some sympathy with, maybe you have to make it a section where you bring as much of this to bear as you can, or send people to these places. But I mentioned that once to Mary, and she thought that was above and beyond the call of duty of an advisory committee.

DR. GROESCH: Well, the concerns of the committee have been relayed to the department, as I hope we'll hear about from DR. Zucker. And perhaps it will be useful to ask him what he thinks would be useful about this.

DR. VANDERPOOL: That might be a place to end, because ask Zucker, he's at the end of the alphabet. And let's ask DR. Zucker tomorrow about that and see what his suggestions are. And then the committee can take it up as a deliberation within the breakout sessions.

(Proceedings adjourned.)

Agenda Item: Public Comment

Now we have a few minutes for public response if there is such response. Does anyone have any comments or questions vis-a-vis this discussion. Yes, come forward, identify yourself.

AUDIENCE PARTICIPANT: Hi. There is a new emerging technology of the knockdown. Are any experiments going on in the private companies or in the lab to find out the suppression or the messonegy which could be used in some of these studies, such as the endogenous retroviruses. Knockout, you have all discussed this. Knockdown is an emerging technology.

DR. SALOMON: That's a great question. Now, there's a couple of different technologies that are being pioneered in HIV research, for example, the use of intrabodies to block receptor, the use of ribosomes which would basically cut up Messenger RNA before it's processed, and SIRNAs which are the interferring RNAs. So I mean those are really interesting questions.

And I'm pretty sure that I don't know of anyone in our group in PERV research doing that sort of thing. But that's a good question. Yeah, that's definitely an area to go.

DR. VANDERPOOL: Thank you. Any the other comments to the query? Other statements or questions from the public?

We've had a full day. We should be back here tomorrow 8:30. And thank you very much for an excellent day and a pristine group.

(The 5th Meeting of the Secretary's Advisory Committee On Xenotourism included at 6:50.)