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P R O C E E D I N G S 8:40 A.M.

Agenda Item: Opening Remarks

DR. VANDERPOOL: Let us take our seats and prepare for the presentations and discussion that follow. Terry, if you will make a sweep outside?

These opening remarks should be entitled opening perspectives because ever since these meetings began, I have been striving for perspective on what we need to be doing in preparation for our being able to offer, in keeping with our charter, meaningful advice to the Secretary of the Department of Health and Human Services and the government agencies that serve the purposes of the DHHS.

Yesterday our learning curve was steep. It consisted of all-too-brief summaries of bodies of information about the history of xenotransplantation, its scientific difficulties which at points seem to, only at points are resolved. Its infectious disease risk, which, according to yesterday's presentations, can be variously construed as remote, real, worrisome, threatening and so on, the bodies of complex federal policies that are either in place or in the process of becoming adopted or to use a term in religious history becoming canonical.

Now, the word "canonical" brings to mind a comment that I whispered to Robyn Shapiro toward the end of the excellent summary by Eda Bloom, regarding the FDA regulations. This is a slightly better version of the comment I made. "Robyn, we are like the leaders of Jews, Christians and Muslims. To be a leader this Committee has to work with and master a virtual Bible or Koran filled with authoritative documents, all of which confine and direct what we will be doing. We have to know our canon, and our canon was presented only in brief summary for to us yesterday in the form of legislation that has either passed or is in the process of being passed. So, for us to gain perspective we must be well informed about the legislation that pertains to our work, be informed about the daunting science and real but unknown risk, keep ever in mind why xenotransplantation is being advanced, the millions of persons with serious illnesses that can be affected by cellular xenotransplantation, the thousands of patients who are pining away on waiting lists. We must realize that xenotransplantation is already approved and in experimental stage, and we must place all of this perspective in the setting of ethics, law, concerns over and regard for animals, economic issues and so on."

As Dan Salomon just observed to me this is not only an FDA committee. It is a committee that has a broader purview. Our purview as I talked to Hugh Auchincloss at the end of one of the sessions yesterday is a national and indeed at some points international, and we have to attend to those issues and to even the funding that is not yet there for much of this work. We are not yet ready to offer advice. So, we must ask what will it take; what will we need to examine, study and discussion in order to become a source of wisdom and advice. While our learning curve is steep and much of that curve is still ahead of us, having known a number of you for some lengthy period of time and others of you just in your brief remarks of perhaps an occasional visit or two, I have no doubt that this is the group that will be able to gain this knowledge and perspective, to offer wise and expert advice in the future.

We have a way to go to get there, but I do not doubt that we will get there. This will surely be an exciting day, perhaps one of the most intellectually stimulating days that many of us have had in a long time. We already know that there are differences among us, and we already know that there are important areas to consider, and we will only be able to identify issues rather than work through those issues. Let the excitement begin.

DR. GROESCH: This morning we have two more presentations of ongoing clinical trials in xenotransplantation and our first presentation is by Dr. Jon Richards, a hematology oncology specialist from Park Ridge, Illinois. His presentation addresses Part B of the definition of xenotransplantation that we heard a number of times yesterday from FDA, and that has to do with human body fluids, cells, tissues or organs that have had ex vivo contact with live non-human animal cells, tissues or organs. So, it is perhaps not the traditional study that you might think of, but I think it underscores that there is quite a range of studies that fit within this definition. Dr. Richards will be talking to us about ex vivo stimulation of cytotoxic T cells.

Welcome.

Agenda Item: Presentations on Xenotransplantation Clinical Trials. Part II.

DR. RICHARDS: Thank you, Dr. Groesch, Dr. Vanderpool, distinguished members and guests. Thank you for allowing me to come here to present some information touching on a topic that has some new tack on xenotransplantation which is touching on human cells. Although there are two clinical protocols that I am involved with that do this, I am going to be discussing the one which has recently been completed so that I can give you some better perspective on it, and I will be happy to address any issues of what has changed in our second trial. The basis for this, I hope my venue is going to address more of the needs. I have attempted to take out some of the technical pieces, leaving some and present some cartoon formats that will help us understand what this is about.

The principle behind this is to stimulate immune cells, known as cytotoxic T lymphocytes, which are essentially the hunters and killers in the immune system. They search through the body for infected cells, and kill them with remarkable selectivity and sensitivity under ideal conditions. They can often deal with tumor escape mutants by targeting multiple targets on tumor cells and of course we recognize that when not programmed correctly can cause other diseases.

In this cartoon just showing you a normal cell with multiple epitopes on the surface and a cytotoxic T lymphocyte which would normally try to recognize epitopes up here but in a normal cell and under ideal conditions no recognition occurs. In the classic system, a virally infected cell presents portions of the virus on its surface in a specific context, which is then able to be recognized by an appropriately stimulated cytotoxic T lymphocyte, which then recognizes that cell and takes this cell out of the system.

The principle that we are trying to use is to use naive or resting T cells over here and convert them into activated CTL or cytotoxic T lymphocytes which can specifically recognize a tumor cell and specific antigens. The process here is to use a stimulator cell, and this is what we are using the xenotransplantation for, a stimulator cell which has multiple epitopes shown up front, and I will go into more detail later. This cell is able to activate an immune cell here by having an appropriate array of stimulants on its surface, then in the presence of other cytokines can be moved into proliferation, creating a large number of these antigen-specific T lymphocytes which can then subsequently recognize specific markers on cancer cells if we have selected the appropriate markers.

This is the array that we have used to start this treatment here, and I have inverted it, and I apologize. I wanted to keep everything on the same side, but here the T cell is over here. This would be our *Drosophila* cell or fruit fly cell which has been transfected with human genes for these markers here, two of which help stimulate an immune response in a T cell and are non-specific. The transplantation antigen HLA A2.1 is here and presents antigens out here, two additional post-stimulatory molecules and in addition what is not shown on here are the melanoma antigens which we use in our treatment trial. These

are all put into this fruit fly cell for presentation to a human immune cell.

Again, in cartoon format the T cell here with these common markers, and the melanoma specific antigen expressed right here on the surface in this transfected *Drosophila* cell with these markers enabling a stimulation of the T cell, an abnormal presentation out here can desensitize T cells to this antigen or may not stimulate at all, and so being able to engineer the surface of this cell to specifically stimulate a human T cell in this context is particularly important for producing high activity T lymphocytes.

Why would we use a xenotransplantation model? Well, a lack of an immune system in insect cells creates a nice white board for putting in anything we would like or we call it an empty surface, and we can put in human Class 1 molecules for stimulating immune cells. We can then load them with whichever epitopes are appropriate in a given system and engineer stimulatory molecules which I have displayed on the previous cartoons, and we can create these to be specific for individual patients given that we know many of the HLA antigens at this point.

In the laboratory the results can be quite impressive. These curves that I am sure most people aren't used to seeing are remarkably impressive over a period of 4 hours. Essentially this is the percentage of killing of a tumor cell in a laboratory system. This is unstimulated lymphocytes from a mouse. These are stimulated using a slightly modified system showing how much we can get stimulation of these cells using a xenotransplantation stimulation model.

Why would this be ideal? Well, it is selective against the tumor ideally. If these are truly tumor-specific antigens that we are using we should get no other type of killing, and therefore it would be non-toxic. It can deal with both cancer in its original primary site or at metastatic sites and if we use multiple antigens ideally could eliminate our problem with resistance which has plagued us in other vaccine models.

This is the practice of what we are in fact doing. We take a patient who has melanoma. We take out a small portion of their immune cells from their peripheral blood in this isolation procedure. We then use the stimulation procedure which I have shown you before. These stimulated cells, stimulated with the transfected *Drosophila* cells, are then expanded in the laboratory using cytokines such as interleukin 2 and then these are re-purified and infused back into the patient approximately 3 to 4 weeks later, and this is changed between protocols.

Initially we take these cells of which there are many varieties in the peripheral blood. The ones that we are particularly interested in are shown here. They are the cytotoxic T lymphocytes. We isolate them from the peripheral blood using an antibody that is specific for these with a small magnet at the bottom and then we put a magnet underneath it. It pulls all these cells to the bottom. We pour away the rest of these, and then we add a peptide which releases these cells from our dishes leaving us with these naive T cells which we can use for production of cytotoxic T lymphocytes.

Melanoma is certainly an area where we wanted to move, and there are several reasons. There are many tumor-associated antigens which have been identified and well characterized. There are clinical trials which demonstrate that immune modulators can produce regression of this diseases and in some cases long-term remissions suggesting that immune responses are a critical feature for long-term remission from melanoma, and with melanoma we often have lesions on the skin which would allow us to monitor how patients are responding and what the immune system is doing in these sites.

This is the original program by which we did this. We would originally harvest cells back here. In the laboratory we would stimulate with *Drosophila* cells here and here, and then at this point stimulate with

cytokines for a period of 2 to 3 weeks and then re-infuse into the patient just their own T lymphocytes having been previously stimulated. Before we release these cells we are assaying their T cells or immune cells for ability to kill if available their own tumor cells or HLA matched tumor cells of melanoma. We check to make sure they have not altered their HLA genotype. They are tested for sterility within 48 hours of release. We screen them for any contaminants with mycoplasma or Drosophila DNA and then of course endotoxin viability of the cells, any residual cytokines from our stimulation, and then we again look at them under the microscope to make sure they haven't been altered in a way that is obvious to us.

This is done between two sites. We are here in Chicago. Our laboratory is out here in San Diego. We ship the patient's cells by courier overnight, sometimes the same day, and then when these are harvested they are sent back the same day for reinfusion into the patient. Viabilities at the receiving ends have always been in excess of 90 percent. When we do this we isolate initially sometimes close to 1 billion cells at our initial pheresis when we take these cells out after stimulation with four peptides which are specific for melanoma is done in the first week and then they are re-expanded to the point that we usually get a four-fold expansion roughly of the number of cells that we have harvested. These are then shipped back and reinfused basically at day 22 or 36 of our original protocol.

I will skip that.

Concurrent with this treatment we have four melanoma peptides we are stimulating the patient cells with. We try to achieve greater than a billion cells that will re-infuse. We always attempted to use two reinfusions and concurrently we were given low doses of interferon with this treatment in order to up regulate the markers on the surface of the patient's tumor in order to paint the target so to speak.

I will skip that in the interest of time.

This is looking at the total number of patients we treated in our original protocol looking at responses shown in red versus the number of cells that were reinfused in a reinfusion dose. More important than the number of cells as you can see spread all over this slide was in fact apparently the rapidity with which we returned the cells to the patient, and there was a correlation we have recently found with how quickly we got these cells from the laboratory into the patient in terms of responses.

We additionally found that interferon did play a, as we had hoped it might, a key role in painting the target so to speak. This was a patient. This is looking, the dark areas or brown stain would indicate the presence of HLA or various melanoma-specific markers on this melanoma tissue here, and this is before treatment with interferon. This was after our initial treatment with interferon, and you can see the marked increase in the amount of brown dye so that the tumor cells would increase the amount of these markers they expressed. This was maintained throughout treatment as we biopsied patients toward the end of treatment as well.

With these markers now expressed on the patient's tumors the question is whether this treatment actually works, and I am just going to show you a few examples with a small number of patients in a pilot study. Statistics are really unrevealing, and I apologize for changing these from overheads to slides. My colors didn't translate perfectly well, but this is showing the bulk of tumor in three different patient at specific sites where we measured them carefully, the first bar being before treatment and then after two treatments, and then after two treatments and finally this patient was a complete responder in her lung, this patient a progressive partial responder over two treatments and another patient with slight increase and then response in the liver.

For those of you who are more comfortable looking at imaging studies, this is a CT scan looking at the chest with the lung here, right lung, left lung and the heart in the middle. This is the front of the chest here, and the back, and this is a nodule in the lung prior to therapy. This was in June, and then 2 months later, after his first cycle of therapy, this is the size of the lesion. This was a complete remission after his treatment.

In a patient with an axillary mass during treatment, shrinkage progressively over the time, also, in his mediastinum shrinkage to complete disappearance are shown here, and I will try to show you some visual. Here is a periaortic lymph node mass seen in this patient, and following his two treatment cycles, is essentially normal. Looking at various points during the treatment you can see a progressive decline in this, a progressive decline in a large mass in his axilla which eventually went away, and again this mass here which continued to decline and eventually resolved.

Another patient shown here, a small nodule in the lung, and after her two treatments essentially undetectable, and showing also here peritracheal or in the chest lymph node shown here with progressive decline during her treatment course.

One of the issues that we are attempting to identify during treatment, but have not been able to, is the amount of infiltration into tumor cells from our stimulated cells. Since they are not transfected, they look just like the normal cells in the patient. We can identify that, during treatment, the patients actually have increased expression of their melanoma antigens as well as their Class 1 or transplantation antigens. Down here we see lymphocyte infiltration of various subtypes. We cannot guarantee that these are the cells we reinfused or if these are a component of the patient's original immune system.

Just as a summary, since I am sure I always get this question at the end, how are patients doing. Unfortunately, of the 14 patients who were ultimately treated, only two are still alive. That is 2-1/2 years later. Median survival in this disease is 3 to 6 months. This is the overall survival in the treatment program that we have been using. This was a pilot study, and we are trying to make some slight modifications to improve the efficacy of this treatment.

Dr. Groesch, I hope that met with the needs of your Committee. Thank you.

(Applause.)

DR. GROESCH: Thank you very much. Any comments or questions from our members?

DR. SYKES: I am just wondering, had your patients already failed the trial of interferon alpha before undergoing this therapy?

DR. RICHARDS: I took that slide out, but in fact, all but one of them had actually previously received interferon as part of their initial therapies, and most of them had received interferon as part of an adjuvant therapy before they ever received this therapy.

DR. SYKES: Could you tell us a bit more about the Drosophila cells, how long they have been carried as a line and what sort of screening was done of those cells originally?

DR. RICHARDS: The culture, the master cell bank that is being used here is now I think about 8 years old and the working cell bank has changed over I think every 3 months, but I would have to refer to the technical people who do it. But it has been around a long time multiply tested, and I think Dr. Groesch

has all the data for the master cell bank, as well as the working cell bank that has been used here. Does that answer partially your question?

DR. SYKES: Yes, partially.

DR. KASLOW: Can you give us an idea, I am not sure if you had on your slide the protocol for the time of contact between the *Drosophila* cells and the medium that is used?

DR. RICHARDS: The medium is an RPMI 1640 base which is supplemented, and it is supplemented with the patient's own serum. We collect 300 milliliters of the patient's own plasma at the time of leukopheresis which we use to supplement the cultures.

The contact for the first week is absolute, and then they are re-stimulated for a 2-day period in the second week. So, I think we would say that there was direct contact between the xenotransplant and the human cells for probably a total of 9 days. In all of the release testing, we have never detected any *Drosophila* DNA in any of the released cells so far, but we keep watching.

DR. MENDEZ: How do you take into consideration the tumor load?

DR. RICHARDS: The tumor load is not a criteria that is stratified for in our analysis, nor is it used to figure how we can do this, at least at the present time. In general, tumor load is considered a prognostic factor in terms of response and survival, but it is probably way too early for us to know how to use that to manipulate the system in terms of treatment.

DR. GROESCH: Any other questions or comments? Thank you very much. That was a wonderful presentation.

DR. RICHARDS: Thank you.

DR. GROESCH: Our next speaker is Michael Egan. He is the Chief Operating Officer of Diacrin, based in Charlestown, Massachusetts. Michael will be talking to us about XenoCell transplantation in human clinical trials.

Agenda Item: Presentations on Xenotransplantation Clinical Trials. Part II. XenoCell Transplantation in Human Clinical Trials.

MR. EGAN: Thank you and good morning. We appreciate the opportunity to address the group.

My objective today is to take you certainly through some of our work in terms of the clinical trials, but I am going to spend a lot of time focusing on issues such as surveillance and quality control and things like that that have developed over a number of years. Unfortunately, I have been instructed by the attorneys not only to put this up but, also, to say that all of the presentation today is going to be material that has already been presented publicly. I am sure the Committee is aware that there is a lawsuit involving the Freedom of Information Act, and as a result we have this.

To give you an overview of the company as a starting point, we are a biotechnology company in Charlestown, as was mentioned. Our focus as a company is working primarily in the preclinical and early clinical stage. In a word, we get things from the laboratory and move them into the clinic. Our focus is cell transplantation, and that covers certainly xenotransplantation, and we have had a lot of background

in that but, also, allotransplantation as well as autologous.

We have a number of things in clinical trials. What we are going to focus on today is the work in Parkinson's disease. That is the most advanced. It is in a Phase II-III now and heading towards a Phase III. The Huntington's disease, Phase I is now completed. We are looking toward Phase II on that, and the others are all in early stages, and as you can see there are various cell types that are used.

In the area of Parkinson's and Huntington's disease we have been collaborating with Genzyme. Genzyme is obviously a much larger, better known corporation, and their focus is really the second half of that slide. As I indicated we are primarily moving things from the laboratory into the clinic, but once you get past those certain initial clinical stages, it takes a lot more expertise and infrastructure than we have. So, we are working with them in both the Huntington's and Parkinson's disease. As a group, as I said, it is the Parkinson's and Huntington's focus. In this area is porcine fetal neural cells, and I will get into this in a little bit more detail, and the idea here is to replace lost function, and that is pretty much the case with all cell therapy, and therefore you can hopefully ameliorate the symptoms of the diseases.

Parkinson's disease you are probably aware of, and I know there will be a presentation on the details of it later, but to give you a summary, it is a progressive neurodegenerative disease. What its key is is this loss of dopamine production and the objective through all of cell therapy is to replace that dopamine production capability. Quite a number of people are affected, and although the drug therapy is very effective in the early stages, as the disease progresses the drug therapy is less and less effective.

The product that we are pursuing, as I said earlier, is porcine fetal neural cells. They are isolated in a very specific time frame in fetal development. It is from an area of the brain called the ventral mesencephalon. It is harvested in clean room conditions, and we will go through that, and then it has a 72-hour shelf life prior to transplantation into a patient.

We have jokingly called it the GMP pig, but it is actually a pretty good marker. The idea here is that the physiology of the cells that we are transplanting is very similar to the human cell function and yes, we have heard all the jokes you can imagine, but strict quality control is certainly the most important part of it.

You have to be aware that cell therapy, especially in Parkinson's disease, probably goes back about 10 or 15 years using human fetal tissue. Those were the studies that gave people the indication that this was worth pursuing, but you cannot use human fetal tissue on a regular basis, especially with any type of quality control. This gives you that opportunity to do that, and do it on a regular basis.

The transplantation that is used to implant the cells is standard stereotactic surgery. There is a burr hole in the brain done under CT and MRI control. It is a fairly lengthy surgical procedure, mostly having to do with the targeting, and yes, immunosuppression is required at this stage.

I want to give you a little history now in terms of how this has developed and where it has been. I am going to take it in two pieces. One is more the regulatory history and then the clinical history associated with this particular program. This was initiated back in 1994. Our first patient was treated in 1995. You probably heard presentations yesterday on the porcine endogenous retrovirus. In October 1997, we were put on hold because they wanted assays developed to look at this virus. We had actually gotten them already in development and were able to come back off hold in December 1997. We received an 11(?) designation in late 1996.

I will talk a little bit later about the NXD. This is the national xenotransplantation database that we are a part of. We initiated that with a number of other people with pilot submissions back in 1998, and then received a fast-track designation in 1999 from the FDA. Make no mistake, there is an awful lot of regulation in place covering all the things that we do. These are the sorts of things that are in place for anyone that is doing this type of work, but in addition there are, also, specific regulatory guidances in our particular area, the most recent of which is the draft guidelines which were just recently made official.

The time line for the clinical development is that as I indicated earlier in 1995, we initiated the Phase II-III that actually will be unblinding probably in the next month or so. So, that will be the conclusion of that Phase II-III trial then leading to a subsequent Phase III. Based on that we would look forward to a BLA approval in 2004. The oversight aspects of those clinical trials, as I am sure you are well aware, has been obviously the FDA, the Biological Response Modifiers Committee, which we will present it at as well as their xeno subcommittee. The Data Safety Monitoring Board will usually get in place once you get past Phase I, but recently was started to put in place at Phase I trials as well as Phase II-III.

In addition, I am sure you are aware of this, but the process at the particular institutions is, also, quite extensive. There are IRB presentations, IRB's and now, also, biosafety committees. Quite a number of them have xeno subgroups within the biosafety committee, and then the radiation safety committee, and unfortunately a lot of these are done linearly. In other words, the IRB will get it, but then they will want another group to review it before they will take the next step. So, it can be quite lengthy, and then obviously this committee.

To give you a little flavor on the international front, I am not going to spend a lot of time on this, but the MCA has classified it as a medicinal product which is the initial stages in the UK for how your drug is going to be classified and subsequently the approval process. In addition they have instituted a xenotransplantation interim regulatory authority, and they are charged with reviewing all the background and data associated with these types of trials. We have, also, been in contact more than a few times with the Canadian HPB and mostly through forums such as this with background presentations.

Now, in the clinical program to give you some detail, the Phase I trial that I mentioned started in 1995. It is an open label trial as are all Phase I's. It was 12 patients with a 3-year follow-up. It was 12 million cells transplanted unilaterally. Now, obviously Parkinson's disease is a bilateral disease, but in the initial Phase I's we just stuck unilateral transplantation, and we published the 36-month data in April of last year.

We did have one patient that passed away, and we published on that data and we were able to see the cells and that was 7, 8 months post-transplantation. There have been really no unanticipated safety issues and very importantly there has no positive PERV and that goes out to 5 years for people from this trial as well as our others. The patient that passed away, this is a photomicrograph and what you are looking at actually is a brain section. The purple staining is a pig-specific stain that we have access to. On the left it is a high mag, and on the right, I am sorry on the left it is a low magnification and on the right a high magnification. On the right-hand side you can actually see the individual cell bodies that are staining. This is another, also, pig-specific stain but what it shows is that the cells are sending out their processes. I should mention that when we isolate the cells and the reason we use fetal tissue, you cannot use adult tissue is that you have to isolate the cells prior to them sending out their connections. Once they send out their connections if you try to isolate them and you break that connection the cell dies. So, that is why you have to transplant it in its fetal state.

So, the objective is that what you want to have happen is on transplantation the graft takes, and they begin to set up connections. This is not cell division. This is cells sending out their processes. Overall we

are very, very pleased, and we never expect to get significant clinical data from a Phase I in terms of efficacy. It is primarily safety, but we are very pleased in terms of the efficacy we were able to see, and it gave us a lot of the impetus to move forward as quickly as we could. In the group we saw a 20 percent change in the group that pretty much was maintained; it has sloped off a bit out to 36 months in a disease where the progression is consistent. You don't really see reversal of symptoms in Parkinson's disease, and I know that there will be a presentation later that can explain it much better than I.

The Phase II-III which I already indicated is heading towards unblinding, that was a double blind randomized pivotal trial. It was a treatment versus a surgical control, 18 patients and approximately nine treated. We are not aware of the blocking. So, we are assuming it is approximately 50/50. Here we went to 48 million cells, and we transplanted bilaterally. So, that was 24 million cells per side. There is a data safety monitoring board that is very much involved in the day-to-day review of the trial and as I indicated we are headed towards unblinding. The planned Phase III will, also, be open and randomized but confirmatory, and we are looking at approximately 36 patients. This will, also, be the same number of cells and the same transplantation procedure, and we will initiate that once we have the data from the Phase II-III.

I want to spend a lot of time now on the surveillance, and to us this is a very broad concept because the surveillance as we look at it starts right with the animals and moves all the way through the product, and we look at it as a continuum, and that includes the patient surveillance. We start with the animal screening, and I will go through that. That is screening of the source animals and then the screening of the actual animals that are going to be used and then the processing and the quality control that goes along with that, the patient education and patient surveillance and follow-up.

The screening procedure is similar to what you would use in any manufacturing process looking for a critical raw material and that is you audit your vendors. There is a very limited number of suppliers as you can imagine because the criteria are extremely high, but it is done through an audit system, handles serology, repeat serologies on a regular basis. Then a group of animals is selected. They are brought into a facility, and then that screening system is repeated. The testing is one that focuses on parasites, bacteria, mycoplasma with a certain criteria, and that criteria is that anything that could be considered zoonotic, neurotropic, obviously in the case of neural cells will cross the placental barrier being fetal tissue and present in the US.

This is the current list of tests that are done on a per-animal basis. We have additional screens that are done to qualify the herd in the first place, but the point here is not what the list is but the fact that it is fluid. As new things are looked at, and new things need to be looked at they get put on the list. Things that are no longer needed to be looked at can get taken off. Actually I don't think we have taken anything off, but in theory that would be possible.

Once the animals are screened they are moved into a GMP animal facility. Now, the objective here is that you have got screened animals that are in good health. They don't have any infections that you looked for. Now, the objective is to keep them that way, and the way that is done is in this facility which is controlled access, extensive quality control as you can imagine and an awful lot of individual training. We put a lot of emphasis on this both at the animal facility as well as in the GMP cell facility. You need people who really know what they are doing, and you need to have the training records and the background to put that in place, and then the same type of audit systems that you would expect in any GMP facility.

There is a master file associated with this facility, and this, also, has its own set of oversights through the

IACUC and AALAC systems. The actual cell processing begins at the biomedical animal facility because remember this is the uterus. So, we can take it out intact. So, that provides yet another level of containment and safety. The uterus is not opened until it is transported actually to the GMP facility, but as part of the process we have an animal necropsy that is conducted by veterinarians and fairly extensive archiving both of tissue as well as fluid from the animals.

In the clean room facility it is very much like any other GMP cell processing facility. Here is where a lot of the regulations that have been built up over the years as far as clean room capability come into play. It is a Class 10,000 core with a Class 100 production area, validated processes, a lot of EM. Again personal training is really emphasized. As far as the release criteria, these are the release criteria that are used on a batch basis, nothing you wouldn't expect from any cellular product, and as far as results to date, this is the 42 clinical samples, 42 transplants that we have done. This not only includes Parkinson's and Huntington's but Diacrin zone programs in epilepsy and stroke, but it is more to give you a sense as to the data that have been generated to date. The reason that in endotoxin, by the way, and bioburden you have so many more samples tested than the actual N's is because those are all in process tests that are done as part of the release.

Now, as far as the surveillance, again, this whole sort of continuum concept of surveillance beginning with the animals and extending all the way through, obviously the big part of this is the patients, and we break it into sort of three groups, and a lot of this is, also, spoken to in the guidelines as they have been developed, the patients themselves, their sexual contacts and then their close contacts. They are all different. They are all to be handled different. There are different issues.

The main vehicle though in terms of the patient especially is the informed consent. Here is the opportunity to sit with the patient prior to the procedure where you have all the explanations in terms of the science and the background but then, also, the restrictions. There are restrictions on blood donation. They consent to long-term follow-up because as I mentioned earlier, and we will talk about it a bit in a little while there is the national xenotransplantation database. That is a lifetime registry. So, we are asking these people to be available, come back every 5 years essentially for a lifetime. So, it is a long-term commitment. There is a recommendation of condom use and the obligation to notify other close contacts.

The archiving of blood and tissue samples is extensive, and we will go into that in a bit. We, also, although we cannot require, we ask that they consent to autopsy, and then as I mentioned earlier there is the reporting in the database. The PERV testing is, also, something that is done as part of this database. The sexual contacts, right now the risks are unknown. As was indicated it could be ranging from we don't know; it is possible to unlikely, but from the surveillance and from a precautionary standpoint we have implemented restrictions, again, as part of the whole guideline recommendation. There is a restriction especially on blood and blood donation by sexual contacts and again condom use is recommended. Close contacts are something that has been debated, and I know that some of the new documentation speaks to it a little more specifically.

This is more as to how we have operated to date, and the close contact is defined as a person who lives in the same household as the recipient, and the main point here for them is to avoid direct contact with patient's blood. There have been no restrictions on casual contact to date. I said this a minute ago, and we have to emphasize over again education is the key. The patient information on xenotransplantation using things like the protocol of informed consent, they have to understand all the issues that are associated and the IRB input, but education really comes home when they see the long-term follow-up assessments that are going to be required.

This is the type of chart that you will have at the back of a protocol. This is not the detailed testing but the general testing and the time frames that are associated with follow-up to a clinical trial. All the way on the right you will see every 5 years that is the xenotransplantation database that kicks in at that point.

We have developed a PERV monitoring algorithm because clearly this is key and part of this whole follow-up, and this was developed using DNA PCR, RNA PCR, vial co-cultivation assays and an antibody assay that is in development. When we say an algorithm, that is something that you really are forced to develop, and that is your what if. I don't expect people to read this, but basically what it says is if everything looks fine then you keep going; if not, then here are the various steps or options that one can go through based on the data.

This is the time frame not only for the PERV testing, so again you get a sense of the commitment and the amount of testing that is required but very importantly is the archive. Much like I mentioned earlier with the animals the patient archive is extensive. The objective here is that scientifically you want to be able to go back at any point in time and check things or recheck things if something new shows up, and you have the opportunity to do that, and this is, also, one of those things that says, "Easy on paperwork," but if you look at what you are asking these people to agree to in terms of blood draw it moves it from the paperwork to the reality pretty quickly.

There is no way that we obviously could have done this on our own. Now, as part of the guidelines but something that I think a lot of people in this field felt they needed and that was outside help. We have put together a xeno team. As I said, this is now part of the guidelines that each effort has to have a team of advisers. These are the people that we have put together, not only from the transplantation but very important in terms of the veterinary background. It is something that a lot of people in the medical community obviously don't think about and we need to think about a lot, epidemiology and then ID, not only in terms of the retrovirus but, also, porcine specific. Those are the sort of advisers on the broad brush things, but on the safety that is, also, monitored by independent groups. We have a DSMB in place. They review all SAEs within 15 days.

So, now, again, this is a Phase II-III Parkinson's disease trial I was talking about earlier. We are blinded as is Genzyme. So, we don't know who is getting what, but in the background there is a DSMB which is independent academic physicians who are reviewing this data on a regular basis independent of us. There is a pharmacovigilance group, by the way, that handles the data management and things like that, and they communicate directly with the DSMB. There is obviously Medwatch reporting and the SAE reporting to the FDA and then the database that we are finally getting to.

The whole point here, and this was something that was initiated at FDA a while back and makes all the sense in the world, especially as you are starting early on in something like this, and that is to institute a database not only from the standpoint of information but part and parcel of this was the concept of sample archives so that pretty much from the beginning of a new field we would have information as well as samples that one could have access to over a long term. Now, the logistics of this clearly is something that as companies we have just had to contend with but clearly the objectives are important.

We decided it was worth getting in fairly early, and so we have been testing a couple of the databases giving feedback to the people who write the programs but, also, submitting data to exercise those databases, and I should mention that the database runs right from the animal all the way through the patient. So, the objective here is that if something comes up you can trace it right back to the individual animal that led to those cells and then go to the freezer and get blood samples from that particular animal. So, it is completely traceable.

So, to try to wrestle this all to the ground and give you a sense of it, the surveillance, especially as far as the patient is concerned starts with the pretransplantation, and we talked about education. We have to understand through the informed consent which is extensive. Our patient consent forms tend to run about 40 pages, and they have to be gone through very, very painfully in terms of understanding the detail. They have to understand the restrictions. They have to understand the obligations going forward, but there is, also, outside help from xeno teams, but the investigators, the clinicians are key. Obviously they are the ones who have to sit with the patients and take them through that and realize that this is a bond between that patient and this physician for a long period of time.

Post-transplantation, the restrictions that we have already talked about not only to the patient but, also, their sexual contacts and close contacts, and again, this is conveyed through the investigators and clinicians. The actual scientific surveillance is the PERV testing, AE, all of the archiving we have talked about and the data being reported to a number of sources. The idea, again to emphasize, is an integrated approach starting with the animals and working right straight through in terms of the GMP processing both of the animal and the cells, the education and surveillance.

As far as conclusions, clearly a lot of effort has gone into this, and my objective today was to just basically try to take you through what has gone on. From that perspective we feel that the surveillance programs are robust and appropriate. They have certainly been vetted in just about every scientific forum appropriate. We would very much like to continue that as well as far as the scientific review assuming that legal matters sort of get resolved in relatively short term.

One of the things though that has changed, and that in some of the FDA filings of late it is difficult from a sponsorship standpoint to understand, you know, what exactly is driving some of those or what the issues are behind them, but we have worked through them before; I am sure we will work through them again.

We have gotten a fair amount of collaborative effort, and this is not just FDA but, also, people from CDC and NIH who are involved in a lot of the infectious disease issues. There has been a lot of public debate through their own advisory committees. As far as this group it is certainly appropriate to have a debate as far as the social issues. I mean obviously though what we would want is that there be a collaborative basis as far as NIH and FDA and not a redundant one.

Again, to sort of close it because we haven't given a lot of clinical detail, we are involved in a lot of different things but the most important through all of this is the patient and what we are trying to do here for these patients, and I want to try to leave you with some sense of that, and I am not sure I am going to be able to do this. Somehow I knew the technology was going to fail me at one point, but anyway, we will have some films later of another patient where you will see the type of response that patients have to the therapy, and it is this type of thing that has kept us going in terms of trying to move to the next stage.

Sue is going to try to run it while maybe I can answer questions.

(Applause.)

DR. MICHAELS: That was a wonderful presentation and certainly hit on most of the issues or all of the issues that I was going to bring up in discussion for public health, but I wanted to ask you a couple of questions since you do have some vast experience here. I wanted to find out have had any problems with your 30 or so patients coming for follow-up so far?

MR. EGAN: No, actually. You have to understand that Parkinson's disease is a disease where the

relationship between the patient and the doctor tends to be very long term anyway and similarly with some of the other neurological diseases. Their neurologist is very much a part of their life. So, a lot of the patients that we transplanted the physicians picked them because they had known them for quite a number of years prior to even considering being involved in trial. So, in that regard the follow-up has been very good.

Can I do this quick, while it looks like it is going to work?

DR. MICHAELS: Have you had a chance when you have gone back to some of the PERVs when new assays have come in have you gone back to PERVs or say, hepatitis B and did you find any where you had already looked?

MR. EGAN: No, we haven't seen that, and I think that is part and parcel of the overall screening program, but can I speak to this, and then I will get back to it.

(Film clip begins)

This is actually the first patient that was treated. He was treated at Leahy(?) Clinic in Boston. This is a patient that at the time was in his mid-to-late fifties. He was an early onset Parkinson's disease patient. He had the disease for over 20 years, classic symptoms. This particular patient was very sensitive to L-dopa, the different levels of sensitivity to the drug and he is someone where the protocol, let me back up just a second, sorry, the protocol states that in order to test them during this stand, walk, sit test that they have to have been off medication for 12 hours. In other words they don't take their medicine in the morning. They come in, do this stand, walk, sit test, take their medicine and then get measured a second time.

This particular patient couldn't not take his medicine in the morning because then he just literally could not move. So, he has only been off medication about 4 hours, but you can see where given his sensitivity level that is quite difficult for him. As will be explained later the issues are initiating movement. It is very difficult to start the movement process, but then, also, you have things like instability. This is about 21 months later. He has been off medication for over 12 hours. We have seen this in a number of patients. Needless to say you can sort of get a sense as to why we do this.

(Film clip ends)

PARTICIPANT: Is that unilateral?

MR. EGAN: That is unilateral 12 million cells.

PARTICIPANT: Can you comment on the immunosuppression regimen?

MR. EGAN: Yes, we didn't get into that here because that is another whole discussion, but in the Phase I we had two systems. One is basically cyclosporine, and the other one is the technology actually that Diacrin as a biotech company was founded on, and that is an MHC Class 1 masking technology. So, in the Phase I trial we did six and six. In the Phase II-III actually all the patients were treated with cyclosporine, and the reason for that is that we felt that and Genzyme felt through experience that it is best to tackle one issue at a time in trying to get cell approval and not trying to get cell approval as well as approval for a new technology at the same time, but the follow-up to this we will be using a masking technology because if it proves equivalent then we would not have the issue of cyclosporine.

Could I get back to the one question though in terms of the hepatitis? Yes, new things have come up. Hepatitis is one. Circovirus is another. There have been others, and we go back and screen the couple of herds that we use as sources, and we haven't found to date anything that showed up later as something you should look for that wasn't in the archive, but one of the things that has come through in that is that we found that there are very few herds that would qualify to begin with, and when they qualify to begin with they tend to be in great shape across the board. You tend not to have something where it qualifies for you list today and not tomorrow because the criteria are sort of high enough that if they are going to qualify, they qualify across the board. At least that is our experience to date.

DR. SPIRA: You mentioned the extensive education program and the informed consent process with a 40-page consent form which is very long to say the least. Have you had any experience in terms of assessing the comprehensibility of that process with the patients?

MR. EGAN: Right. There is a grade limit on the language that can be used. In addition, we have had it reviewed by clinical psychologists as part of both the Parkinson's and Huntington's program, and there is a neuropsych workup as part of the entry criteria for the trials. So, basically what we have tried to do is put as many things in place to speak to that issue as possible.

DR. SPIRA: That tries to address it before you actually do the consent process, but after the process do you go back to the patients either immediately or after a period of time and ask them key issues that you discussed that you think are important and find out whether they actually have understood those?

MR. EGAN: Yes, because as part of the follow-up there is a neuropsych evaluation, and that is done on a regular basis post-transplantation as well, and oftentimes they will ask, and annually the investigators tend to take them through all the reminder points, especially things like condom use and the like. So, to that extent we try to follow up as much as we can to ensure continued understanding.

MS. SHAPIRO: I am sorry if I was out of the room and somebody else asked this question, but somebody did say, "How compliant have the patients been?" and your response was, "Very." Do you have a plan about what if in the future they are not, they don't come in for their follow-up surveillance?

MR. EGAN: It is a question that has been raised a couple of times, and you have to walk the line between doing everything that you can do to try to follow-up and forcing people because that steps over to the other side. You cannot force people to do anything they don't want to do. So, the way we have done it is really again working with the physicians and trying to ensure that the physicians are well aware which they are, and they see these patients anyway on a regular basis outside of our protocol because even if our protocol says, "Only come in, let us say for your 5-year follow-up visit," they are still being seen every 3, 6, 9 months by that same physician anyway. So, we try to use that mechanism.

DR. SWINDLE: I was just curious. You probably did some efficacy trials before this, animal studies, pig cells into primates?

MR. EGAN: No, it was in rats.

DR. SWINDLE: All right, when you did the animal efficacy studies was that useful in picking up any contaminants that you had to screen for or was there no problem from the start?

MR. EGAN: We didn't use the rat studies to determine that. We did it more from the perspective of looking through all of the possible diseases that are endemic to pigs or pigs have been known to be

diagnosed with and go through them and say, "Okay, what fits the criteria of being potentially zoonotic, neurotropic and the like?" The rat studies per se we didn't use from an ID perspective. That was mostly for efficacy and dosing.

MS. ENGSTROM: As part of the patient education process you mentioned several times the behavior modification with respect to use of condoms. Should I assume that the patients that are in the Phase II so far are all male or you simply meant that generically in terms that the male partners of those patients who are females were recommended to use condoms?

I would like to know one, the gender split in the group of patients that are going to trial and secondly, what about the age range, and we still don't have outcome yet? I wanted to know whether there was any correlation between age and outcome, but you don't have that yet?

MR. EGAN: The split at least in the Phase I is pretty much even in terms of gender. In Phase II I am not aware of it, but the restrictions apply to either the recipient or the partner. As far as age bracket it has been in the mid-late forties all the way through to mid-late sixties, and I think the cutoff was 65, but don't quote me on that.

MS. ENGSTROM: And are they at different stages of the disease in terms of your criteria for selecting patients? Do you actually focus on specific states where you think this would be helpful, and if so could you elaborate on that a little bit?

MR. EGAN: The focus is on later stage patients, and there are a number of measures for that. One of them is the Hoehn and Yahr scale and we are talking Hoehn and Yahr scale patients four and five, which is the patients where the medication is no longer working quite well. We, also, have something known as a unified Parkinson's disease rating scale. It is a rating scale based on quite a number of questions, and there are cutoff scores for that as well. The objective here is to treat later-stage patients because quite frankly earlier and mid-stage patients their medicines work just fine, and there is no reason to go into this.

DR. GROESCH: Drs. Kiely, Allan, and Sykes?

DR. ALLAN: A couple of questions. First is the herd that you used. You say that you get them from different sources and in that particular case do the animals, do the tissues get processed at the animal donor site or do they transport the animals to you and then you take the tissues there?

The second question which is unrelated to the first question is I noticed there is a couple of patients who developed a stroke during the study. Can you address that?

MR. EGAN: We are treating stroke patients. We didn't have any patients that developed strokes.

DR. ALLAN: I scanned the Web site, and there was something on the Web site that said that there were some adverse effects.

MR. EGAN: Right, in the stroke trial there was an adverse effect related to surgery having to do with seizures postsurgically.

DR. ALLAN: So, it wasn't --

MR. EGAN: No, those are stroke patients that we are treating. I am sure if we caused strokes you would probably hear about it.

The first issue is a very good question. We have source herds, and I think actively we only use two right now, and then when the animals are selected that particular group is then moved to a facility where the biomedical animal facility is. That is under our control. We have two of them to be redundant, and they are both in Massachusetts in different locations, but that is under our control, and then the serology is repeated once they are in the biomedical animal facility.

DR. GROESCH: Dr. Sykes and Dr. Kaslow and Dr. Crone.

DR. SYKES: You showed this what I took to be an average improvement score in your Phase II trial. The patient that you showed us on the film, can you tell us what his percent improvement was and how that compared to the average of about 20 percent that then leveled off at 10 percent?

MR. EGAN: That is a good question. That improvement and to give you the idea of the UPDRS score is kind of a blunt instrument because that improvement is about a 30 percent improvement. So, the reason it is hard is because a lot of these tools that were developed weren't developed for this type of purpose. They were more developed to track disease progression, and so they are not very good at tracking disease regression.

DR. SYKES: Have you identified any factors that appear to correlate with good outcome after this treatment?

MR. EGAN: In the Phase I it is hard as you can imagine. In the Phase II, hopefully, we will be able to because we have what we believe will be full dosing. I don't, again, know the splay in terms of the age range, but obviously the disease range. So, hopefully we will be able to narrow that down.

DR. SYKES: And that is the dosing that you have used thus far compared to the planned dosing in your upcoming trial?

MR. EGAN: The anticipated dosing in the Phase III will be the same as the II-III because the Phase III will be a confirmatory. So, we believe we are at the right dose at this point to be proven by the clinical data, but that is 48 million bilateral.

DR. SYKES: Am I correct in thinking that in the Phase II-III that you have done the control group underwent a sham operation and is that going to be continued in the confirmatory trial?

MR. EGAN: Yes and no. Yes, the Phase II-III it was done in such a way that the control patients were brought into the OR. They had their skin opened, and they had essentially a divot in the skull. Obviously we didn't go through the skull. That wouldn't be appropriate, and then were sewn back up, but they had the full time in the OR as the treated patients and the OR was sealed off except to the neurosurgeon and his nurse.

The objective here was that you are asking for people to have a pretty extensive procedure, and you have to be very, very sure through a controlled trial that the data is good. It was a very hard thing to implement, no question. It was hard for the patients. It was hard for us.

DR. SYKES: That won't get done in the confirmatory trial?

MR. EGAN: No, the Phase III it is not.

DR. CRONE: I just wanted to make a quick comment in regard to the questions about informed consent and just to remind that the comment about following up people with neuropsychiatric testing has nothing to do with really, that doesn't really get a sense of whether or not someone is understanding and continues to understand the informed consent. That just says something about their ongoing cognitive ability, and there are obviously lots of other factors including emotional loading of what they are going through that influences really informed consent.

DR. KASLOW: The surveillance system you described is obviously extraordinarily comprehensive and each component has a sizeable cost associated with it, I suppose. It would be helpful, perhaps not now but at some point in the future if you could account for those costs for us to give us some idea of what it really costs you to carry out that system.

DR. GROESCH: Okay, one last question, Dr. Michaels?

DR. MICHAELS: I just wanted to ask again about the PERV surveillance that you did. At this point in time that has been on the blood samples, is that correct, and if you have tissues available just perhaps remind us, did you look at PERV for that as well? So, what compartments were sampled?

MR. EGAN: Yes, there are two parts to the PERV system. One is to qualify the tissue for use in the first place. For instance, we take the fetal neural tissue and do PERV expression in co-cult systems with all the various readouts and all those things. That is to qualify it to even get into the clinic so that you can show that the tissue you are using does not inherently express it, and then there is the follow-up in the patient and that has been blood to date.

DR. SALOMON: May I just follow up on that quickly? So, Michael there was no PERV expression in any of your in vitro studies using these pig -- these are fetal mesencephalon cells?

MR. EGAN: That is right.

DR. SALOMON: And did that include doing RT PCR and there is no message for viral PERV in these cells?

MR. EGAN: The details I don't have, but I know that they did everything six ways to Sunday.

DR. SALOMON: And they are all negative?

MR. EGAN: Right, and we have seen that in other neural tissue as well. We have seen that in the LGE systems as well with fetal neural tissue.

DR. VANDERPOOL: We are going to need to move on. Michael Egan has presented us a most valuable window into xenotransplantation, and the questions show how important your coverage has been for all of us.

I just have one word about our mikes. You noticed we had a problem a while ago. Our electronics expert tells me that if more than three of us punch our on buttons we will have a recurrence of that problem. So, let us be careful about that.

So, thanks so very much for your presentation.

(Applause.)

DR. GROESCH: I would like to echo that and thank all of our speakers. We have had three excellent presentations about ongoing clinical research, and it is very important for the Committee to hear about this.

Agenda Item: Public Comment

DR. GROESCH: Next on the agenda is a public comment session. We did have a request yesterday that we, also, make some time available after the issue identification session, but are there any comments that people would like to make at this point?

Okay, we will make some time available afterwards. I think that, Dr. Vanderpool, we can either start the issue identification section or do you want to take a little break now? It is your prerogative.

DR. VANDERPOOL: I think we should take a very brief break and come back within -- we are going to start within about 12 to 13 minutes, at 10 minutes after so that we will have an uninterrupted time with our first set of issues.

(Brief recess.)

Agenda Item: Identification of Xenotransplantation Issues That Need to be Addressed

DR. VANDERPOOL: We will now move to the sessions in which various members of the Committee will make brief 5-to-10-minute max presentations of what they view as the issues that this Committee may well need to discuss and deliberate over.

We are not going to review the information we have been given but rather target the issues we see embedded within that information. Our format will consist of presenters making these brief points, and during that time I am going to give a try to stepping back and making substantive points on the flip chart and then pasting these flip charts around the room as we go. So, I won't be mumbling or talking as I do this. Hopefully I will come to this mike if I need, if I feel I have something to say or add, but we are going to identify the issues, and if the flip chart works, then I may ask you at some point if the chart is worth the trouble and get your read on that.

After these brief presentations we will spend about 10 minutes or so discussing these issues as a Committee of the whole, and I must say that those who are presenting are simply those whom I identified and called to make these presentations. Every single person I called enthusiastically said, "Yes," to the invitation.

I realize that meant I had to, given the number of issues overlook a number of Committee members who would be equally able to handle this. So, if I didn't call you, it has nothing to do with your not having the expertise and excellence of doing just as well as everyone else. So, those who speak and present have a choice of either going to the podium as I see Dan Salomon going or if you want to, speaking from your seats with your mike.

So, now, we have first of all scientific medical issues with initial remarks by Dan Salomon followed by a

discussion, and I will ask Dr. Mary Groesch, our Executive Director to help monitor the time frame that we have in mind. We will both try to keep up with that so we don't go over time and therefore so we can cover this whole range of issues that we should. As we identify the issues we, also, want over the course of some time to begin to prioritize which ones are most important for us to consider as we think about future meetings.

Now, all the ex officio members are official in this conversation. You have expertise and experience well beyond that of many, if not all of us, and so, you join in about the issues that need to be talked about, about those that need to be aired, about issues that may well call for advice in the future. Your input is as critical as anyone else's. So, without further ado, Dan Salomon.

Agenda Item: Identification of Science/Medical Issues

DR. SALOMON: Thanks, Harold. The only introduction I would have to this is I have not tried to vet or manipulate these questions to what I think the purview of this Committee is, and as I sort of discussed with Harold, I think one of the really big challenges he has with Mary in sharing this is to decide what are the things that are going to be important to us and where we are going to go and what is going to distinguish this Committee from other committees that have looked at xeno, but I have made no attempt to do that in these questions.

So, I have three pieces of paper just so you can keep track. I will eventually sit down, and I will go through this quickly. You could do an hour's talk on this outline, and I obviously will try to do this in 5 minutes.

So, I think one critical point to me in thinking about xenotransplantation is that we maintain an awareness of a dynamic between cellular transplantation and vascularized organs, and this is not so straightforward because it can be isolated cells such as neural stem cells, but it can, also, be for example, pancreatic islet cells which actually in their true functional state are tissues and are vascularized and then we talk about kidney transplants though these are often referred to jargon as cell transplants, and then we talk about vascularized whole organ transplants, kidney and liver and lung, etc., and even though these have many commonalities we are continually going to have to look, also, for their unique features.

That kind of covers, also, my comments on thinking about tissue engineering, but we need to, also, realize that the broad potential applications of xenotransplantation go into skin. They go to bone and joints, etc. It is not just that they are going to do kidney and heart and islet or nervous system cells.

Gene therapy, you know, this is a very natural nexus for gene therapy. Many strategies that will come along in the near future will not just be transgenic engineering of the target organs but, also, gene therapy delivery of molecules perhaps in the local site or post-transplantation to modify the engraftment process or to modify the immune process.

We are going to talk later. Other colleagues are going to talk about infectious disease risk, but let us talk about medical risk. Going forward into clinical trials I think one of the ongoing challenges of any group thinking about doing xenotransplantation clinical trials is what is the medical risk versus the benefit.

The medical risk versus the benefit will be a function of the disease. If you are talking about end-stage organ failure you can talk about a kidney transplantation who basically has got end-stage kidney disease but has dialysis as an option. So, this is not a life-or-death situation. There are some very strong pros for doing clinical research when there is not life and death involved and sometimes that is a con. It just

depends on the strategy.

In contrast a heart or liver transplant patient with end-stage failure, you are talking about dying. That definitely changes the discussion and the balance. Diabetes, you have got insulin therapy, but insulin therapy is far from ideal, again an issue of risk and benefit. CNS disease, HIV, you know, normally I wouldn't have brought HIV up, but remember we were reminded yesterday of the Jeff Getty case where he got baboon bone marrow as a strategy for treating HIV, something that is not so very well known, but the two Pittsburgh liver transplant patients, also, had HIV and hepatitis C.

A function of strategy, let us not just talk about disease. Let us realize that an extracorporeal circulation strategy such as we heard yesterday for liver failure is very different, let us say than a bridge to transplantation strategy or "I am going to transplant, and this is going to work forever" strategy.

Okay, point two, why do organs fail? I think Dr. Auchincloss made a very, very important point yesterday and because he did such a good job I do have to do very little here, except to point out again that we need to understand the immunobiology of xenotransplantation and when we look at new trials, and we look at the rationale for doing this or that strategy those are the things that we are going to have to think about.

We know about hyperacute rejection, and there is a whole number of strategies and significant success recently in reducing the risk of hyperacute rejection, but the ideas that there are other mechanisms such as acute humoral acute antibody-mediated rejection, acute cellular rejection that may even be involved in novel cell types than we have seen in human-to-human organ transplantation and then let us not forget that in the end our pact with the patient is that you are going to get long-term benefit. If I saved your life that it is for 3 months, that is not acceptable. If I save your life, and it is for a year, that may or may not be acceptable. To most of my patients I have to say that that wouldn't be acceptable either.

Point three, animal models. Dr. Auchincloss and I went back and forth on that, and that needs to be highlighted here. Animal models as predictors for a clinical trial, I have already said that I think we set unreasonable limits, an unreasonably high bar in a previous committee, and I don't agree with the bars that were set in that meeting.

There are rodent trials, and there are non-human primate trials. There has been a tendency for us to move toward non-human primate trials because of a concern that we need the best representation of the human clinical trial. These are more expensive. These are more involved. They have a higher ethical barrier.

Yet, I just point out that Mike Lee did this beautiful work today with very dramatic preliminary results and it was interesting what preclinical trial he did; he did it in rodents. So, we really don't necessarily have to do non-human primate trials for everyone, but if we are going to do non-human primate trials or you are going to do rodent trials my only point is that you need to validate these, and you cannot take naive views that a non-human primate trial is just some generic thing because the immune responses and metabolism and biology of the cyno and the rhesus and the baboon and the different non-human primate species is not identical.

Okay, point four, immunosuppression, when is it too much? In the history of human-to-human transplantation increasingly powerful immunosuppressive drugs have traced the increasing success. Unfortunately that has, also, become a trap for many transplanters. So, the idea when we began xenotransplantation, the idea when we began trying to get successful human islet transplantation is well, if it is not working it must be a failure of the immunosuppression, and if it is a failure in the

immunosuppression we have got to have more, and what I often point out to people is that as doctors we have got to remind ourselves that we don't work for the Defense Department. We are doctors, and so immunosuppressing someone to death is not exactly and objective.

Moreover, do we really need more potent drugs? Well, I can kill anyone with all the drugs we have now. So, do I need a more potent drug? No. I need a more effective drug, and we need to go back into xenotransplantation and get rid of the idea that just stringing a whole bunch of different drugs together, not knowing the immunobiology, not knowing the mechanisms, not using a validated model makes no sense to me as a clinical validation for a trial that I am proposing to do in human patients.

Consistent with that the corollary question is what is right for xenotransplantation, and we have to realize that even though much of what we have learned about human-human organ transplantation can be relevant controlling immunity in xenotransplantation there is, also, a whole set of potential reagents that are novel to xenotransplantation, and that is perfectly fine and not unexpected.

So, we have complement inhibitors, natural antibody absorption columns and other technologies, clotting cascade inhibition, monocyte inhibitors because the monocyte may be playing a more dramatic role in some of the early vascular and subacute vascular changes that occurs in human-to-human transplantation, cytokine inhibitors. There may be differences in cytokine release and other modulators in xeno.

So, this is just to give you the idea that even under immunosuppression what is true for allo needs to be validated for xeno. I think that some comments here from Megan who I look to as one of the world's experts in tolerance induction just to put it in balance, it is reasonable to argue that immunosuppression isn't the way to go with xenotransplantation, and that success will only come from successful tolerance induction, and I think you could make a very good argument for that.

With that said, we have to realize that tolerance is not a single concept. There are probably going to be multiple ways to induce tolerance. Operational tolerance may be different from true immunologic tolerance, and as far as the patient is concerned operational tolerance works just fine.

You know, when I wake up in the morning if I don't have to take any immunosuppressive drugs, I am perfectly happy. I don't care if I have true tolerance or just functional tolerance. Cellular immunity, acute versus chronic, I just want to point out that one of the things we are going to have to be careful about is to be a little conservative here. Tolerance induction, we had a great animal model where we had tolerance induction. In fact, there were five different ways to get tolerance induction in rats 20 years ago when I was a fellow, and we were just so proud of the fact that it was great.

You could give cyclosporine for 7 days and stop it, and you had tolerance. Now, the fact is we conveniently ignored the fact that about 9 to 12 months later all the organs were dropping dead because we were so excited we had tolerance. We didn't really want to break that little love fest we were having about it, but now a couple of years after we realized that chronic rejection was a bigger problem than acute rejection everyone went back to these model, and now, they are the model for chronic rejection, but I think we just need to realize that if we are going to go forward with these strategies, just look at them in a practical way trying to learn from what we have gotten out of history.

Tolerance for natural antibodies is going to be very different than tolerance for cellular and humoral immune responses. So, that is a really interesting question. There has been some really nice data. Actually Megan has some data actually with a tolerance induction strategy that reduced natural antibody formation, and maybe she will talk about that at some point.

Okay, the last point on this, the cell biology of xenotransplantation. I think this is an area that has gotten very little attention frankly from the transplant field, and it is an area that we are very interested in in my own laboratory. What we are talking about here are two things, dynamics between survival of the patient, i.e., the function of the organ and survival of the transplant.

So, from the point of view of survival of the patient, we talked about yesterday the fact that it turned out pig kidneys didn't make an erythropoietin, an important hormone in blood formation, at least that it worked in the primates but there are ways to deal with that, but this is an example which potentially has to be thought of in every situation, but a transplanted tissue or a transplanted organ won't make a hormone whose structure will be recognized by our receptors, and that is a serious issue.

You can get around it, but it is a serious issue. In contrast we have the good news that pig insulin works fine in humans. So, it is a dynamic that can work either way.

Now, we have to realize that health is actually the result of a very incredibly complex dynamic between tissues and the whole body, that no tissue stands alone to paraphrase an old line from a novel, and what we need to realize is that when you put a pig organ or another animal's organ in a human being it isn't going to stand alone. Its survival as a functional organ, as a functional tissue requires that it be engrafted and that it constantly participates in this remarkably detailed dynamic between its host, the rest of the body with circulation of growth factors and circulation of matrix proteins and circulation of cells, etc., and if we ignore that we are missing a whole piece of what is going to happen in xenotransplantation because it is not at all trivial.

In addition to just survival we need to think about the dynamics of injury and repair. So, if you do human-to-human transplantation except in the rare and fortunate situation of an identical twin, you always have rejection.

Sometimes it is a lot of rejection, and sometimes it is a little rejection. Sometimes it is one big rejection episode and sometimes it is just a bunch of T cells infiltrating the graft at some point post-transplant, but you always have rejection, and when you have rejection you have some tissue injury.

The question I am asking here is we need to be sure that a xeno organ can repair tissue injury because repair of tissue injury will require, again, an engagement of this dynamic; extracellular matrix proteins and growth factors and infiltration matrix-producing cells will be contributed to this process of injury and repair from both the host, the human patient and the organ itself, and lastly, no one who works in a lab doing genetic engineering, sticking gene after gene into different cells can ignore the fact that just sticking a gene into a cell is not a neutral thing.

I mean yes, it is great I stuck this gene in, and I got this human protein on the surface, and it is going to prevent rejection. That is good. That is a good start, but that doesn't mean that overexpressing the gene isn't going to affect 10 other downstream single mechanisms or other functions in the cell, and that may not be that relevant for the first 5 minutes but I would like to know what it means at 3 months and at 6 months and at 12 months post-transplant.

So, the impact of genetic engineering is not trivial. Now, I have one last slide which is going to show you the cross here as we go from transplantation to infectious disease risk.

Now, Marian, I think you are going to talk about this, but I will go through this really quickly, but I just want to show you sort of where the cross goes here which is another major interest of mine. So, I call this

the nexus of transplantation and porcine endogenous retrovirus as an example. You could fill in other retroviruses or other infectious agents.

So, what does a transplant do for viral transcription? I am not talking yet now about what is the risk. We will get to that. I am talking about what does the transplant do to proviral transcription. Surgical injury, tissue ischemia and stress, local cytokine release, we already have published data demonstrating that this significantly increases the transcription of proviral RNA.

So, even if, let us say we talk about the fact that all the neural stem cells that were looked at in vitro were PERV messenger RNA negative which is a really good start, we need to realize that it is possible under certain circumstances of ischemia, stress and cytokine release that PERV proviral RNA might be activated and transcription and formation of infectious viruses.

What are the PERV receptors? It turns out that there are probably at least two, one for PERV-A and one for PERV-B, but there could be more because we know from HIV, for example, that there are receptors and co-receptors. So, the story can get much more complicated.

We don't know the PERV receptors. So, we don't know their distribution, and without knowing their distribution we don't know what cells are targets; therefore that has a lot to do with risk. If I transplant something here is there a risk there? We don't know what the receptor expression is going to be. After transplantation receptor expression could increase dramatically.

On the other hand, is it possible that immunosuppression might actually reduce receptor expression and in that case immunosuppression ironically might not be bad for one aspect of PERV infection which I realize is a bit counter intuitive to some.

Then lastly, the effect of genetic engineering of the transplant to get something accomplished for the rejection process or the engraftment process can certainly affect PERV.

Now, Marian, are you going to talk about this? You are, okay. So, Jon Coffin yesterday did a beautiful job of explaining this. So, really in two or three sentences the expression of the gal residues on the pig cell surfaces when the PERV virus buds it carries with it these gal residues on the viral surface which then are the targets for these natural antibodies.

So, these very powerful natural antibodies that we all have that are beautifully adept at killing our xenotransplants if we don't engineer around them are, also, good at preventing the endogenous retrovirus particle from surviving, but you guys obviously realize where I am going.

All this engineering that we are doing to get around gal including making gal-negative pigs is basically also going to do a damn good job of allowing the PERV to have full access to you. So, that is just an example. If we go with tolerance, I already talked about what a great idea that was, but depending on the tolerance-inducing strategy if we are reducing tolerance with tissues that are expressing PERV antigens and you have to know that many pig tissues express PERV antigens, then we might, also, induce tolerance to PERV.

So, we just need to think about whether there are strategies to split tolerance or whether our tolerance might work against us in essence, and then the last thing I would like to point out to you is can PERV cause rejection. If you have a cell that is not normally expressing PERV antigens and you do this beautiful job of tolerance induction, and then through let us say a viral infection that releases some local

cytokines you get a trigger and now you express PERV antigens on the surface of cells, so for example, endothelial cells in the organ you have now escaped your initial tolerance induction strategy, and you have PERV antigens being either presented indirectly or directly and that could instigate an immune response and cause some form of rejection, acute or chronic, so, again, PERV at the nexus of transplantation risk.

So, I am done.

DR. VANDERPOOL: Okay, let us have a few minutes of discussion. We are almost pressing 20 minutes at this point, but let us have several minutes of discussion regarding these scientific issues, and if we see some as more important than others in terms of pressing discussion needs, feel free to make suggestions to that effect.

DR. SYKES: Dan, that was a quite thorough summary in a very short period of time, and I thank you for bringing up the issue of tolerance because as you know I am of the persuasion that tolerance is not essential for the success of xenotransplantation in part because of the enormous barriers that will make the amount of immunosuppression needed, given as a pharmacologic expression and I certainly welcome an opportunity to talk at more length some other time about some of these strategies for tolerizing T cells and natural antibody-producing B cells.

I would, also, like to extend that consideration to other cell types of the immune system about which we know less and particularly cells involved in innate immunity such as macrophages, natural killer cells; even neutrophils and eosinophils likely have mechanisms for recognizing foreign antigens on pathogens, many of which may be shared by pig, and we need to find out more about what the role of these cells is and whether they can be tolerized by any means that we know.

The other thing I would like to extend about what you said about knowing more about the function, the physiologic function of proteins produced by xenogeneic organs and the function of that organ in a human recipient. Beyond that I think we have to think about the immune response to critical proteins produced by those xenogeneic organs, and I see that as another reason why tolerance is likely to be necessary because the liver, for example, many of its functions include the production of complement, proteins of the coagulation cascade, a whole variety of secreted proteins that if we respond immunologically to those our liver transplant is going to end up being quite useless. So, we need to think of the immune response not just in terms of organ rejection but in terms of responses to products of the xenograft.

Thirdly, I think in considering scientific issues of xenotransplantation and particularly if this group is going to ultimately end up reviewing protocols I think we need to be fully aware of what the alternatives to xenotransplantation are for every type of transplant and as artificial organs, such as artificial hearts and closed-loop insulin pump systems are being developed I think this group really ought to be kept abreast of what those developments are and what the expected timing of success of those kinds of strategies would be.

DR. SALOMON: And that is what I was trying to get at when I was talking about medical benefit versus risk, exactly.

DR. VANDERPOOL: I just want to second what Megan has just said about our need to know where we are in terms of artificial organs. We really need to keep that in mind, and we may need to have a rather thorough overview of that as we proceed. That may be a priority issue.

Now, Dan, not to put you on the spot, but you enjoy being put on the spot anyway, which of these issues do you think are most important and pressing to deal with in the near future?

DR. SALOMON: I think probably the medical benefit versus risk since any protocol will because of the fact that that is so determined by the strategy. I think the animal validation issues, because if someone, any trial is going to come forward, and the first question we are going to be asked is is there reasonable likelihood of benefit, and that is going to be then given to us on the basis of an animal model, and I think we have to be very clear and intelligent and objective about looking at these animal models, and again, as I expressed yesterday I just want to highlight the problem I have is that if we insist on a given barrier, and you have to reach that barrier to allow a clinical trial you are actually holding the whole field up to that barrier, and I think it is irresponsible to do that unless you are damn sure that that is a validated model.

There are lots of models where we know what is going on in human patients. So, it is not that hard. You can go, "Hey, this is what autoimmune disease looks like in my patient, and this is what it looks like in my model, XYZ, and we can talk about validation, but I am just not sure how we are validating what happens when you put in a pig heart into a human patient." I think we just have to take it down a notch and be a little conservative about it.

So, I think those are the big issues. There will have to be immunosuppression. I hope that we don't succumb to the more is better Defense Department strategy and do more of the, well, more recent Defense Department strategy of using smart bombs. I think that is the direction we will have to demand from people when they are presenting strategies.

DR. ALLAN: Dan, nice presentation, by the way. When I came to this Committee I wasn't aware except from your personal views about the question about primate models in terms of validation, and so I would think in listening to David White and others that that probably has a relatively high priority.

My experience in HIV and AIDS and animal model systems is that, I mean, and this is something we will get into which is if you don't, if you use an animal model system, and you don't get the results that you want, then there is a tendency to say that the animal model is no good, and we still need to go into humans, and that is a real problem, and what I have seen in the AIDS field is that in many cases there are some very good studies that have been done in vaccine work and in pathogenesis with SIV in animal model systems and yet a lot of the HIV researchers don't even read the papers, and say, "Well, that is irrelevant because that is SIV," and then they make a SHIV and they say, "That is irrelevant because it is still not HIV," and so these are really important issues I think that can be addressed because to me it is a similar thing with the transplant situation.

DR. SALOMON: Right. Just for equal air time let me for a second not be Dan Salomon but maybe be Hugh Auchincloss. He is not here today. So, I have to sort of try to be him, and we have made the joke before that we are the evil twins. So, I will be the twin now, the good twin by being him for a minute, and what he would say is the immunobiology in a primate is still predictive based on other models where validation has occurred, and so part of his response to me would be, you know, it is okay to insist that you get 3 months without basically totally destroying the lumen of every blood vessel and I would say that that is important for balance here.

Okay, I am looking for validation, and I have made my case, but I, also, want to make sure that I acknowledge the fact that colleagues that I respect have a very solid case on the other side, as well. So, it is a dynamic we have to think about.

DR. VANDERPOOL: But as Jonathan Allan has said I think that issue did come up yesterday. How much do primate models tell us about the problem of human response, and that is a very important issue to air in the future. We cannot give a full layout of these issues but certainly identify them.

Brad, did you have a point?

DR. COLLINS: Thanks, Mr. Chairman. Dan, you made an excellent overview there. I wanted to focus on a couple of points. One, I think when the trials are embarked upon we have to decide whether it is a life-saving transplant as you mentioned, a heart or liver transplant or whether it is something that is easily reversed like a kidney transplant which can be removed, and the patient does okay.

I think it is, also, important, hyperacute rejection, I think that can be taken care of as was discussed yesterday, but I think a big hurdle is still that vascular rejection which comes several weeks later. So, that, also, has to be thought about, and then the third and final point that I wanted to make, there aren't a lot of functional studies out there for the large organs, the vascularized grafts such as the liver and the heart, especially for, well, Dr. Bailey has concordant work but for discordant work. So, I think those are studies which would be good to see, something we need to think about.

Thanks.

DR. SALOMON: Yes, Brad highlights a really excellent point here that I didn't highlight enough and that is the physiology of these organs, of course, is exquisitely adapted to working well in a pig. That means a pig heart, a pig liver and a pig kidney.

Now, pigs don't eat the same things we do. They don't have the same upright posture. I think my point is obvious without going into any more details, but it is really true that there are set points for electrolytes, uric acid, sodium, glucose, etc., not all identical to what is going on in humans, their response to hormones. If you take a female pig and you put it into a male is it going to miss all the estrogens? These are not trivial issues.

DR. VANDERPOOL: Okay, we are going to need to move on unless there is another pressing, oh, Dan?

DR. ROTROSEN: Yes, I thought that was a terrific list of scientific and biomedical problems you brought to our attention. I am interested in your thoughts on the cadre of scientists we have out there to answer those questions, and is it adequate and what needs to be done to really get research in this area moving at a pace that is appropriate to move to clinical trials in a broader sense, and also your thoughts and others on the appropriate locus for that research. We are very tipped right now towards an industry locus as opposed to federal funding.

DR. SALOMON: Yes, thanks, Dan. Okay, everyone should get over accusing me of the, "Oh, here is an NIH official giving me the chance to say that we need more NIH grant funding." Okay, so, let us get through that. This is obviously self-serving as an NIH investigator, but now, with that behind us to really seriously respond, I think that No. 1 we need to get out of this industry focus for a lot of reasons.

No. 1, if we want to move the field forward, that shouldn't be moved forward purely on whether or not it is going to make money. I mean there are lots of issues in science and medicine that just aren't going to make money for a long time, but it doesn't mean there aren't compelling human reasons for doing these kinds of transplantations and moving this field forward.

We have already seen so much retrenchment and reorganization, I mean companies that we were looking to for leadership in xenotransplantation just got closed down, and money got contracted. Investors decided that they don't want to invest in this kind of thing anymore, and I think it is irresponsible if that is the only way that we are moving research forward.

One of the comments I made to Harold, Lily made a nice comment to me yesterday when I talked about rogue xenotransplantation programs. My comment that I didn't make was you know, what did we do with rogue nations for antiballistic missiles. We were willing to spend a trillion dollars for defense, and what do we do for rogue nations for bioengineering? We got DARPA with hundreds of millions of dollars, and my only comment is triple their grant funding because it is really scary when you go there and talk to them as I did last spring.

So, then the question is what do we have for xenotransplantation, and I am not talking about just infectious risk but just to move the whole field forward. So, I really think that we do need to have something like the immune tolerance network for xenotransplantation try to provide some sort of a cadre of investigators that have the money to attract them to doing this kind of work.

DR. VANDERPOOL: Okay, Megan?

DR. SYKES: I would just like to add to that to reinforce what Dan said. One other critical reason why we have to go beyond industry to move this research forward is that industry by definition has to have short-term goals in order to succeed, and I see this problem as a very complex one as you have outlined, and it is going to need a lot of research, long-term research, forward thinking research, and it is not something that is going to be accomplished in 2 years. So, we cannot count on industry to do the basic research that takes a lot of time, that is really going to get us there.

Secondly, you asked about whether there is a cadre of scientists to do this. I think we have a problem in that regard, and I think that we need in some way to encourage scientists, physiologists of various organs to start to move into this field, and there needs to be some sort of initiative to get more research going that will help us to understand the biology of porcine organ function and how it might differ from human, and one could even think of a porcine genome project. That could do enormous things to move this whole field forward.

DR. VANDERPOOL: Okay, we are going to have to move on. These are excellent points, and I have starred some of the ones that you have starred. Some of these issues are economic issues. I am so pleased that Dan and Megan did not let this discussion of scientific issues escape without funding long term and of course, short term, also, but certainly long term for the initiative.

Now, we move to safety, public health issues with initial remarks from Marian Michaels and William Scheckler. Let us keep these remarks as short as possible so we can have discussion, but nevertheless this is an important set of issues, and we are fortunate to have these two persons as initial presenters.

Agenda Item: Identification of Safety/Public Health Issues

DR. MICHAELS: Thanks. I think I will just sit here so that we keep it in discussion format, and I will try to really just do this in very general overall viewpoint to let it open for discussion and not get bogged down in specific viruses or organisms.

Obviously infection is the major public health risk. It is unlikely that we will ever attain a zero risk. So,

really from the way I would look at this is that we need to consider how do we minimize these risks so that they are acceptable from a public health perspective, and the questions I would pose, therefore, are, one, can the animal microbes from the source animal be transmitted to a human; can it thrive and replicate in the human; does it actually cause disease or is it going to be a complete innocent bystander that doesn't do anything even if it is there, and then finally, from a public health standpoint is it going to be transmitted beyond the recipient onto other people?

So, if there is no disease that is created by an infection even if it is transmitted, then from a public health standpoint it really may be of limited consequence. If disease is limited to the recipient while obviously quite important for that person, and I would say quite important for xenotransplantation as a field, from the public health perspective I am not sure, again that is really of major consequence because it becomes a dead end for that microbial organism.

So, let us assume that transmission can occur from the public health standpoint. Then the issues are really what can we do to either prevent it or to minimize it. So, the first part when we look at protocols is going to be what did they do; what did we do or what can we do to try to prevent it being in the source animal in the first place, the animal husbandry that was talked about yesterday and again today. We really have to question that what is left in the animal, what is left in the tissue, what is left in the cell that might become a problem.

Alternatively something which I think was just touched upon yesterday briefly by Jon Coffin is there another strategy; if there is PERV left in the tissue that is going to be put in is there a way to develop a vaccine that could be used for prospective recipients; is there prophylactic strategy or treatment strategies that can be given to the patient?

The next issue is really what are the surveillance procedures that are in place to look for evidence of infection either ones that are known or ones that aren't know; how does the protocol look for it; at what time points; how long afterwards; who is going to pay for it which gets into a different subject altogether; and what compartments are being examined; and what compartments is it fair to say that we need to examine?

So, are we taking blood from the patient, storing plasma, storing cells? Are we looking at saliva? Are we looking at semen if we think that there might be transmissibility through sexual contact?

So, those are some of the issues that I think we have to, also, evaluated and in fact, with that does the protocol have in place a procedure that modifies it if disease is present?

So, if we have a patient who has received a xenograft that now comes in with an upper respiratory infection, well, it may turn out to be influenza season or RSV but what is being done to look for that and to increase the archiving of samples at that time?

The other major issue I really want to mention is really determining how the organisms could be transmissible from the recipient to others, and without asking that question I think you really cannot develop strategies to try to minimize that transmission. So, is it in the blood? Is it in secretions? What bodily secretions could be infectious? Is it aerosolized which obviously would be a problem for public health casual contact? Can it survive on surfaces which is another method of transmission that would be important for more casual contact, and then with that in mind what kinds of things can we do? Obviously enforcing universal precautions or standard precautions in the health care setting so needless systems whenever possible being used, having glove and gown use when contamination is likely with dealing

with bodily secretions.

I think counseling and education of the patient cannot be stressed enough and, also, to include the contacts, the close contacts or sexual contacts, and that may entail having to do counseling after the procedure if there are new people that come into the life of that individual.

So, things like not sharing razor blades, not sharing toothbrushes, using barrier methods with sexual contact and finally, sort of incorporated into that is there a point where we might be able to say, "Okay, this method of transmission hasn't been proven. I think we can back off from that," or is that not something that we can ever back off from?

So, I sort of wanted to just put everything into a few minutes. I know that we are limited in time, but I wanted to bring up some of those issues to help further discussion.

DR. VANDERPOOL: Okay, comments, questions? Jon and then Bob?

DR. ALLAN: Marian, that was great, and you covered a lot in that short period. One of the ways I look at it, also, is to step back and not assume that we are going to be transmitting a virus to the patient and the virus is going to replicate. That is an assumption I think Jon sort of made that assumption using the Jonathan Stoy model for that, and you could argue that that is still controversial.

I mean obviously you are going to have PERV in cells. Whether they actually express themselves in human cells is another question, whether they can infect human cells is another question. We still don't know the answer to that. So, there is a lot we don't know.

So, what I would do is rephrase the question and go back and say, "Is it acceptable to have a virus transmitted through a recipient? Is that even acceptable?" and so from my perspective that would be the starting point. Is it acceptable to transmit a virus and then all of the other things that you have mentioned.

The second thing that came to mind for me is do we want to get involved in an exclusionary list of viruses that need to be screened for. It is something that is a very difficult process but it is one that has come up before and then what would you do if let us say there is a new pig virus, and the FDA obviously is going to deal with this issue, but I mean the case in point is sercovirus(?) and some of the others.

Do you allow these things to go forward and say, "We will develop screening assays and just keep going," or do you say, "Well, you know, how do you determine whether a virus is important enough to stop a clinical trial and say that we need an assay system to evaluate this or not?" and that is something we might want to discuss.

Then the third thing that came to mind for me which is something that I really don't want to discuss, personally I really don't want to discuss it but the issue of whether you want to use primate tissues or not in humans and the only reason I bring that up is I don't even want to bring it up; I don't even want to go near that, but the reason I bring it up is because the FDA's guidance to industry has suggested that this Committee address the issue, and that is the only reason I am bringing it up.

DR. VANDERPOOL: Okay, Bob?

DR. MENDEZ: I thought that was just a beautiful summary of all the problems that we have and we face and how we can perhaps look at it and perhaps I would submit one of the ways we can look at it is to

look at the past experience in the human allografts and see we have passed on diseases. We have passed on diseases that are lethal. We have passed on diseases that are viruses or fungi that are passengers, passed on organisms that are replicable and that will be sent on to future generations, EBV, CNV, hepatitis C. Some of them are acceptable. Some of them are not.

I think your question is well taken, Jonathan. Is any virus important or is any particular organism important, and I think we have to look at the, perhaps we can go back retrospectively and look and see what the effects in the human passage of these types of organisms in terms of their benignness, morbidity, mortality and their effects and how we might use that as a substrate or a methodology by which we can look at the future.

DR. VANDERPOOL: One of the questions I have is from the FDA, namely given this array of issues that we have, thanks to Marian and others, have these been sufficiently accounted for even in the form of legislation at the present time or do we need to revisit; this is my question for this Committee. Do we need to revisit these issues and relook at the federal guidelines we do have and make some changes, and so it seems to me that is the critical issue as to the degree to which this Committee ought or ought not to really focus on this near term.

Now, we have Jay and then Megan.

DR. SEIGEL: I would like to respond to that and to a couple of other comments. First of all, just for clarity there is relatively little legislation regarding this field. There are lots of terms out there that it is easy to get confused about. There are regulations, and you are hearing about rules and proposed rules.

When proposed rules become real rules that is the same thing as a regulation, and a rule and a regulation is something that sponsors are obligated to follow as they reflect an interpretation of the law and are based in the law.

The law might be very general in the PHS active law. There is authority for biologics approval, for IND and also, ample authority for, broad authority I should say for protection against infectious disease risks and communicable disease risks.

So, we have rules and regulations. Then we have guidance documents, we call them in the FDA. Guidelines are the same thing, and those are interpreted as ways we think are appropriate ways to meet the rules and regulations, but they do allow exceptions. They are guidance. They don't have the standing and authority of regulations.

I think many of these issues we have discussed, Dr. Vanderpool do in fact, need to be revisited not so much because they were done wrong or they are a problem but just because these are all evolving fields. That is one of the main reasons we are dealing with guidelines, and I would talk specifically about a couple.

First, I do want to talk about the issue of primates because of Jonathan Allan's comments. I don't think you meant exactly what you said, but perhaps I am wrong. I think our document does suggest that the science is not there to make use of primates, non-human primates, we have yet to see the science to demonstrate adequate safety and at such time when a company or sponsor thought they had adequate data to demonstrate such safety and submitted it to us, we, also, laid out that we felt that an important part of the process for determining its adequacy would be to take it to a national advisory committee, and we were certainly envisioning the future existence of this Committee as a potential venue.

I would think that this Committee would, in fact, want to see those data and evaluate them. I assume the alternative you are talking about is that there is no amount of data that could ever make it adequately safe. If a Committee such as this were to say that, that would be one thing, but I would, also, remind you, and this gets to one of the points Dan was making, that we are not just talking about using a baboon heart. We may be talking about using an extremely well-characterized primate cell line that has been in labs for decades, that has been studied, that has had a DNA sequence that we know exactly what is and isn't in it, and that might be an important source of a cure for a disease, and the risk/benefit may be very different from transplanting a heart from a great ape or a vascularized organ.

I don't want to take up too much time, but I think the question of validation of animal models to put that in the framework of the issue as we have discussed it and debated it in other committees is everybody thinks animal models should be validated, but the real way you validate an animal model is by going into humans, and the critical question before the Committee in the past and one that I think in response to your question does need to be updated as we get more information and as we rethink these issues is before you start that process of going into humans how much money, time and effort do you put into trying to improve things in the animal model; is it a waste of time because the animal model can take you so far or is it unsafe to barrel ahead in humans because there are more questions that could be answered more safely in animals? Those are very complex. Those are the issues that Dan and Hugh and others did not come to complete consensus on. Well, there was a consensus, but it was somewhat different from Dan's opinion on a specific issue, but those are issues that will need to be revisited because the science changes, and the data changes, and you need to re-answer that question as you move along, and I will leave it at that.

DR. VANDERPOOL: Okay, thanks. I should have had Bill Scheckler comment right after Marian. So, Megan, we will hold your remarks just a minute. Bill?

DR. SCHECKLER: As not one of the xenologists on this august group what I thought might be useful for you is to put things in a context where I live, both as a clinician and hospital epidemiologist, sort of well outside of your field but still well within the public context.

Let me just comment first reading this morning's paper I note that, or the paper yesterday that tetanus toxoid for adults is going to be in short supply or disappear because the company making it cannot make much money on it. They made a business decision not to make it.

Not so many months ago we ran out of aqueous penicillin G IV because of an action in terms of how well the company was following protocols in making that. So, one of the contexts that you have to realize here is that there are, also, larger health care issues and industry issues that are very important. So, the comment made earlier about putting everything in the hands of companies that need to make a profit is very valid when you start looking at basic things that we use and need every day.

I want to touch on three things briefly, the Institute of Medicine report, *To Err Is Human: Building a Safer Health System*, the Accomplishments of Hospital and Health Care Epidemiology and finally a conundrum that I think this Committee has to deal with. The IOM report and I have no slides or overheads was published in December 1999. How many of you are familiar with it or have heard something about it?

All right. It was released at a Presidential Press Conference with great fanfare. It is old data, interestingly from the eighties and early nineties, but it was extrapolated in a way that would make an epidemiologist blush or actually make them angry. It is an action plan that was suggested that is very top down, federal

agencies, federal reporting which is typical I think of the way sometimes we think about things, but it was a national media event because of one simple reason. There was an extrapolation from that old data of deaths due to errors and language is very important, and all you will probably have remembered is that in our hospitals in the United States every year 98,000 patients are supposedly dying due to medical errors, error meaning blunder, something that should never have happened.

If you actually read the full IOM report there is a lot of good in it, but one of its strategies, one of its reasons for existence was to bring to the public's attention the issue of patient safety, and they did it with language, and they did it with negative outcomes.

Now, Troy Brennan who was the first author of the two studies from the New York hospital study and the study out West in Colorado and Utah that wrote the two articles that led to this extrapolation of data wrote an editorial in the New England Journal saying that it was simply wrong to use that type of terminology. However, I must point out in his study he used the term "negligence" throughout the study.

So, this is a major issue. It is out there. The politicians love it. The public is wanting something to be done, and the issue of errors and negligence comes up because if we make any kind of mistake in any kind of protocol that is being done here we are going to be pretty much in hot water.

Now, the models that were used were aviation models, OSHA models. They talked about successes in anesthesiology machines. They talked about a lot of issues with medication errors but totally ignored 3 decades worth of work in my area of hospital epidemiology and hospital infection control where patient safety has been uppermost in our minds for a long time and where a lot of progress and processes have been made, and then they, also, at the end of the IOM report talked about reporting things confidentially, but then they, also, talked about blame. So, there was a favor of trial lawyers throughout that.

DR. VANDERPOOL: Bill, could I ask you to clarify which IOM report you have in mind? I know the IOM Report on Xenotransplantation appeared in the summer of 1966.

DR. SCHECKLER: No, this is the To Err Is Human: Building a Safer Health System.

DR. VANDERPOOL: Nineteen ninety-six, I am sorry.

DR. SCHECKLER: Nineteen ninety-nine. What I am trying to do is not tell you anything about xenotransplantation which I am incapable of, but I am trying to put this in the context of what is going on in society and medical care around you, and I picked this up in our Medical Staff Office the other day, Medical Errors Recording and Prevention: Weathering the Storm Ahead.

So, this is now on the radar screen for everybody for the Agency for Health Care Research and Quality has a big initiative. The AMA has a big initiative. Hospital groups have a big initiative, but let me again show you the language because this is one of the barriers that we get in, and this is in this article. "Medical errors and the advance that they can cause have been health care's dirty little secret for years. Studies have shown that medical errors, botched surgery, misdiagnoses, medication errors and others kill tens of thousands of patients each year. In addition errors and adverse events result in untold medical complications and extended hospital stays."

This is the language that we are dealing with. This is the language the public deals with. This is the language legislative policy makers use. That is the context that I wanted to put it in. All right, now, what is some of the answer to this? The accomplishments of hospital epidemiology are extensive. Ever since

Semmelweis proved that washing your hands can prevent people from dying after delivering babies and Lister showed that antisepsis was a good idea in the operating room and the Staph aureus outbreaks of surgical wound infections in the 1950 and 1960s got everyone's attention.

So, the CDC began a hospital infections unit back in 1966. I joined that program in 1968, and in 1970, the CDC set up a national nosocomial infection surveillance study which is really a paradigm for a safety program and a paradigm for a surveillance program, and the elements of that probably should inform us in terms of the elements of the kinds of things that are important in any kind of surveillance that we even think about.

Voluntary participation and confidentiality, that runs into some barriers right away in terms of freedom of information. Standard definitions and protocols, that is pretty straightforward. Target high-risk populations to look at. They are obvious in this case. Cite specific risk adjusted infection rates comparable across institutions and comparable across studies. That is a real challenge in this. Adequate numbers of trained infection control professionals or people that can do it, that was just touched on in terms of the researchers, but you need the clinicians as well. Data dissemination to health care providers, in other words making known what is found and links between monitored rates and prevention efforts.

Now, all of this has led to a very substantial improvement in reduction in the hospitals in infection rates, in bacteremias, in pneumonias and so forth and the analysis and feedback loops have been very important. I have been tracking bacteremias in my own hospital for 25 years. There has been a striking decrease in mortality in our sickest patients, those with rapidly fatal underlying illnesses. In the 1970s 75 percent of them died. In the 1980s 42 percent of them died, and in 1998, the last time I looked at it only 20 percent died. That is a huge improvement in outcome in those patients. There, also, at the same time between the eighties and the nineties was a 50 percent in all kinds of nosocomial bacteremias or those occurring in patients in the hospital.

So, that field has moved ahead and epidemiology in the hospital and the health care setting has developed strategies and methods that are sort of the quintessential ones to protect patient safety, but the issues for xenotransplantation are trickier, and they come back to the final point that I want to make, the conundrum that we have. All the risks and the ones that Marian talked about are pretty much speculative risks.

A lot of the things that I see in the regulations now are based more on speculation or hypotheses and a concern about the fear as expressed by the policy makers and the public than they are based on science. The public wants a no-risk solution to everything. In science and biology we have a relative risk issue that we always deal with and some risks are unknown, and some risks are unknowable, and I would like to think that in putting cells in people like the pig cells in somebody like Jim that after a period of time you are going to find that there are no curves in those cells. Stop worrying about it and stop thinking that you have one size fits all regulations that require you to follow everybody forever and sort of put a condom over our thinking. Take the condom off of our thinking and let us be a little more free range. I have got to be careful where I go with that analogy.

(Laughter.)

DR. SCHECKLER: And I think that part of what I will try to do in these discussions is try to put it in the context of where I am as a health care epidemiologist and as a clinician, and I will try on occasion to say if it seems to me the emperor has no clothes, "The emperor has no clothes," and my final comment then is is there an essential difference in infection risk between injecting cells into someone versus putting a whole organ. It seems to me there are huge differences in those two things and that we might

simplify some of the issues that we are dealing with when we are dealing with cells versus dealing with whole organs and make things much more straightforward.

DR. VANDERPOOL: Thank you, Bill. We are already out of time on this, but, Megan, we are committed to your comment. So, please?

DR. SYKES: This is a very quick point, just something that hasn't come up yet in our discussion that I think should be on the table as a possible strategy for avoiding PERV infections and that is that there is a line of MGH miniature swine that evidence so far indicates is different from other pigs, in that it cannot transmit PERV to human cells in in vitro studies, and this is work that is being carried out at Biotransplant, and I think this group ought to have a chance to hear about that at some future meeting.

DR. SALOMON: Harold, may I make one other real quick comment?

DR. VANDERPOOL: Sure.

DR. SALOMON: We will get into this later.

DR. VANDERPOOL: I cannot quite talk yet anyway, Dan. I am going to put this up there, and then we will proceed.

DR. SALOMON: I think a very important issue that has come up before in the FDA's advisory committee is this issue of cellular versus a large whole organ in terms of risk, and I just want to go on record as saying that I totally disagree that there is any difference to be honest with you, because I think we are assuming that there is some sort of direct logarithmic relationship between the number of cells being transplanted and the exposure of the individual that is directly related to risk. That precludes the possibility that you prick your finger with a needle from someone with HCV, hepatitis C virus or HIV and you get HIV or hepatitis C. You don't need to get gallons of blood exposed, and there is no difference in the risk between the needle stick and a gallon of blood if you get the disease and the virus replicates. I just think we have to be, I think that there actually is an argument against that. That was actually a question from Marian. So, she can answer that.

DR. ALLAN: Harold, could I just say one more thing?

DR. VANDERPOOL: Sure, Jon.

DR. ALLAN: To the issue of PERV I want to be very clear that PERV is a marker for infectious disease. It is not the whole infectious disease. It is not as if we get overly ratcheted down in terms of looking at one particular virus. It is really a marker for unknown viruses, for viruses that are already present. So, it is just one virus, but it is an excellent marker but we shouldn't think that because this is PERV free therefore it is safe.

Agenda Item: Identification of Ethical Issues

DR. VANDERPOOL: Okay, before I break we are going to cover two more issues. The next one in line is ethical issues. I will make a few comments about those and then let us have some discussion of them.

You are now receiving a sheet of paper. I limited it to one sheet of the different types of bullet issues I

see here, and I will make brief comments about these. The ethical issues inherent to the transplantation of animal cells, tissues and organs involves the notion that the word "inherent" means that these ethical issues are inseparable or intrinsic to all aspects of xenotransplantation. We have been talking ethics essentially all morning, and you will see as I just review some of these issues how infectious disease issues, for example, are ipso facto an ethical issue regarding harms to other persons.

So, the risk of infectious disease involves an accurate and ongoing assessment of risk and how to minimize and control for these risks by measures deemed to be sufficient and that is the ethical judgment. The ethical judgment is do we think it is sufficient or not, and in ethical thinking one often if not very rarely comes to an ironclad no questions left decision, but one makes a judgment call is this sufficient to move ahead given the other issues, and I view risk of infectious disease really as a precondition for many of these issues that follow.

Second, foreseeable balance of benefits and risks to the subject participants, again, this has already been discussed, but it has to do with the ethics of benefitting and/or harming others, if we use the principle of beneficence and non-maleficence, benefit rather than harm. Now, what are some of the aspects of this harm risk/benefit determination? Evidence that rejection is sufficiently controllable, evidence of immunosuppressive tolerance and identification of populations of patients who stand to benefit from xenotransplants with respect to length of survival and quality of life.

Now, that is a critical issue. What thresholds do we have in mind? We have had 50 percent and 60 percent and other things suggested, but who are the populations of patients who stand to benefit with respect to both length of life and quality of life?

Four, an understanding of the probable emotional responses of humans who receive animal transplants. So, I think that Catherine Crone's area of psychiatry and counseling that Karen brings to us are ipso facto part of harm/benefit equations and five, for the sake of not undermining the future of xenotransplantation, and this is what we call a consequentialist argument, it may appear that we should move ahead on intrinsic for intrinsic reasons, but it may be that in terms of the consequentialist decision what is best for the future is important.

So, for the sake of not undermining the future of xenotransplantation an approval of clinical trials that are likely to secure the public's approval which requires judgments about social responses to xenotransplantation; so, I view this as an important ethical issue. We are going to have to make judgments about what is the public's probable response. We have evidence about that. If we move forward with this what are the possible responses? Might we secure a negative response that would set the science and experimentation back for maybe a significant period of time?

Informed consent, and by the way another issue ought to be added to the benefits and harms and that is knowledge of the physiological functions of organs in humans must be far better understood and that is just of course speaking about organs and not cells. Informed consent, a range of knotty issues. I think we heard some of the complexity of this by hearing that there is a 40-page consent form. Gosh, I wish it could be shortened. I think it ought to be, but clarification and honoring of fully informed and voluntary consent for prospective research subjects, that is a daunting challenge in itself, given the desperation, as well as deliberation and decision making with respect to informed consent for third parties, that is family members and possibly health care workers and possibly respective communities if the risks are significant enough, and informed consent ought to, also, you can add another factor to that and that is the complexities of informed consent for xenotransplantation go beyond those of usual medical research because we are talking about life-long consent and signing a form that okay, I will go back to the doctor.

I will be surveyed again, and you can even take an autopsy of me and see how my tissues are. So, informed consent is indeed complex.

Responsible oversight of clinical trials, the sufficiency of regulatory rules and of expert national and/or local approval and oversight. We need to probably think about that conundrum that the Institute of Medicine Xenotransplant report presented to us, namely, what balance between national and local oversight. If local oversight is the thing chosen, what should be the criteria of the rewards and the FDA has given a significant amount of thought to that.

Issues of justice. Justifications of xenotransplants with respect to one, justifiable allocation of health care funds and that is an issue in itself and fairness which includes notions of equality, need and merit with respect to the availability of transplantable human and animal organs for US citizens. Are we talking about just those who can pay well for these or are there plans in place for the disadvantaged to receive them, also, and if so, should they have equal or less than equal choice given payment and merit and other considerations?

Issues of justice are not easy. Now, ethical philosophical issues, I say that because sometimes ethical issues are a little more straightforward, but there are certain philosophically complex issues including concern over the violations of natural law or the laws of nature. This is surely a public response, and we have seen this in a couple of articles, several articles already, but isn't it kind of strange? Hasn't nature told us, hasn't God through nature told us that these are animal barriers and you scientists are working so hard to overcome the natural barriers that are inherent within nature; I mean isn't that in some way wrong? And so how is that going to be, quote, answered, not only intellectually but psychologically?

And second, the respective moral status of animals vis-a-vis human beings; Lily will speak about this very soon, but that is a complex area of investigation.

Subheading one, that is over violations of natural law include social fears and possible disgust over human-animal unions and transformation. We saw the question of when is a pig a pig. Well, when is a human only a human, and one can answer natural law arguments rationally, but I suspect the rubber hits the road psychologically, that the rational reasons won't do for the psychological response the public may have. Psychologic response is likely and truly informed by science fiction and traditions of writings such as the Island of Dr. Moreau.

Also, the subheading of violation of natural law includes germ cell alterations or engineering of animal species.

The next issue, moral consequences over how enthusiasm regarding xenotransplantation may impact human organ donation; there is too much hype here which we are not getting a whole lot of right now. Might that have a negative effect on organ donation, and finally, but certainly finally is just the last point I am making but not the end of the issues that we could identify is the responsibility and accountability to the public nationally and internationally, and I think we have already, Dan Salomon and others have talked about you know if we are going to do it right in the US and let whatever take place abroad take place abroad, then have we really met our responsibility as a Committee, and this Committee does bear in my judgment a significant load of responsibility regarding national and international involvement and recommendations insofar as we can effect such changes.

Okay, discussion, and, Robyn why don't you oversee the discussion. Since I am on the hot seat here or should be it is hardly fair for me to say, "I am glad you asked that question, and I have a ready answer for

it," because you are going to identify issues and whether I have had a complete or an incomplete list or a problematic list is up for all of you to discuss now.

MS. SHAPIRO: I would love to, and I would like to start with a comment which is I think it is an excellent listing of some of the major ethical issues, each of which I am sure you will agree with me could be broken out into many more and two that I would just like to hear your comments are relate to the tension between autonomy and doing good for the community vis-a-vis public health concerns when we think about, and I have raised this a couple of times already here, we think about the non-compliant recipient or the non-compliant close contact who doesn't want to do the monitoring. How do we work that line between respecting autonomy and individual rights and protecting the community, and the second one has to do with some justice questions and again the question about how much money we want to spend on this is one aspect of that that you have identified but the other has to do with allocation of organs in a different way, and if we had a xenotransplant recipient and that transplant fails and that person therefore jumps the list what does that do to allocation of cadaver organs and how can we be sure that we have justice?

DR. VANDERPOOL: Those are absolutely excellent questions and need to be both added to the list. I think we could get in a long discussion. We could go into the evening I suppose on this one as to whether individuals who are, quote, thought to be likely to be non-compliant which is a judgment whether they have equal rights to xenotransplant organs or should they have all other criteria involving sickness and desperation and so on as those who are likely to be compliant, and my take on that given the importance of merit and responsibility is no they don't have equal rights, but now, to put that into effect is another thing, but I think that we can argue either way on that, but I think is incredibly important because when you move to the question of who is going to be acceptably included you know you have people often with some compromised rationality and certainly a compromised sense of how long they are going to live, and they could, you know, like the classic case of Dr. Frankenstein going in visiting the monster, and he says, "Now, look, when I go in here don't open the door," and of course, the monster starts growling, and he comes back, and knocks, and says, "Open the door." He made the wrong decision, and he wants to backtrack out of it, and I do think that some commissions and others will make the right decision about who gets a xenotransplant and may want to back out of it in terms of non-compliant patients. What would that do? Would quarantine be called for or what? So, yes, very critical issues.

MS. SHAPIRO: Other questions?

MS. KING: I would like to just make a comment on the adherence or compliance issue. Again, my background is the renal field, and specifically in looking at whom we decide to transplant within the dialysis population we typically have based issues on adherence or compliance as a criteria if they are adherent. The only thing I am familiar with is one study that did look at whether fluid adherence which is a major issue with renal dialysis patients affected or related to transplant compliance, and indeed there was no correlation which would make sense because we don't have the fluid research in but to my knowledge, and I have inquired at numerous meetings and of other researchers there is no study that has actually correlated whether non-adherent dialysis patients for example with medication regimen or dietary regimen actually translates to non-adherence with kidney transplant patients, but again, we practice as if that is actually a correlation which has been proven, and I don't know of any study that has proven that, not to say that non-adherence is not an issue because it is, and we can reject organs for that reason but how we can actually predict that to my knowledge has not been scientifically really proven.

DR. VANDERPOOL: Excellent point

DR. MENDEZ: Every single one of these issues is an all-day issue. I mean they are all so very important. There are just three points that I would focus on with regard to that.

There have been small studies that show, again, that non-compliance on dialysis is not correlative to compliance after transplantation because of the severe psychological aspects of being tied to a machine that is freed afterwards. So, there is a tremendous psychological variance here between an individual who is on a machine and one who isn't.

The same issue has been taken, of course, with who is a candidate and who isn't in a life-saving organ transplant like a liver transplant. Should you accept alcoholics or non-alcoholics, and do they become compliant after they have been given a chance or not, and these are very significant issues that unfortunately will take a lot of time to dissect out.

DR. VANDERPOOL: I want to just add a point about this that Dan made about science, and that is in the IOM report published in 1996, lip service was paid to the importance of giving attention to ethical issues, but not much attention has been given outside of two or three persons who have really taken it on as an important topic for publication and discussion, and so, I think we need to think about some funding for good studies related to this.

I mean what are public attitudes towards xenotransplantation? There are just not very many studies about that, and as Karen pointed out, what are the good studies and do we need others about non-compliance and compliance? I mean we are just going to be guessing without a particular amount of evidence unless we call for better studies.

So, it seems to me that that is a possibility for this Committee to do. Lilly, do you have comments about these ethical issues? I know this your area of expertise, also?

DR. RUSSOW: As already said each one of them could be a day-long topic of discussion, but I think that you have done a very good job of hitting the main issues in a general sort of way in just getting them out on the table.

DR. VANDERPOOL: Other comments?

DR. MENDEZ: One very quick comment on the moral consequences and how it impacts on human organ donation. We had done a white paper study in 1991-92 with regard to, say, payment for organ donation and find a tremendous negative effect if that were to be allowed in the United States. The fact that other sources of organs might be available, I think would have to be studied. My gut feeling is it would have a tremendous negative effect on general organ donation which has been improving incidentally dramatically in the last 18 months.

DR. VANDERPOOL: I want to make a final comment about this, and I think some of these issues really do deserve deliberation and some decision making. I think we need to look over questions of informed consent and get out a list of things we think are important that could become guidelines for either national committees or IRBs.

I mean is the 40-page consent form, to what degree does it cover all the issues; does it cover some issues in too great detail? All of us who work on IRBs know that one of the things we do is protect patients. The other thing we do is protect the institution. So, how much are the 40 pages protective of the institution and so, I think several of these issues need to be discussed in length because as we move to clinical trials

there are going to be there for us.

MS. ENGSTROM: Harold, at the risk of prolonging the discussion I have got a couple of comments and questions to ask. First of all, when you came up with this list which is a very impressive list of the myriad issues that need to be addressed in terms of ethical concerns, the way you actually listed them did that imply in any way the importance of the issues? For example, I do agree risk of infectious disease, risk versus benefits, informed consent are probably among the most important. I just wondered whether or not the way you listed them indicated at least from your perspective you thought the ones that were most important were appearing first?

DR. VANDERPOOL: That is an excellent point. They do not, except for risk of infectious disease. I do think that that is at the top of the list because others flow but other than that the reason why I used bullets is they are wide open.

Someone here might take the second philosophical issue, the respective status of animals which we are going to move to as the most important one of all, and so, which ethical issues are most important is an ethical judgment. So, thanks for asking the question.

MS. ENGSTROM: As I was looking at this it seemed to me that when you are talking about benefit/risk ratio and you are talking about informed consent, part of informed consent process as we know is for the patient to weigh the risk against the benefit. So, one is almost substituting for the other, and at the same time you could tease apart those two issues into multiple subissues as well, and the fourth bullet on responsible oversight of clinical trials there are really two major categories of concern because there is the regulatory oversight for which FDA has responsibility; there is actually the social public policy oversight for which this Committee will provide advice to the Secretary on, and then there is the ethical oversight. I assume that since this is part of your list of ethical issues you are addressing only the third or did you, also, mean to bring in the other two as well?

DR. VANDERPOOL: Good question. The reason why I listed responsible oversight of clinical trials in that list is because A, they have to be responsible, but B, if you move toward federal oversight is that going to discourage local initiative? I don't think it needs to, but I think there are some consequences, concerns about how far the research will be aided or perhaps discouraged in terms of the degree of intensity and location of the oversight.

MS. ENGSTROM: My last comment on this issue would be that since this is such a broad and lengthy list of concerns, obviously as a group we would all want to address them but obviously the order and the sequence with which we address them is really important, and inasmuch as I don't see xenotransplantation being an allocable health care service anytime in the near future, I wonder if the issue of justice probably might be more of a secondary issue than a first, and I want to pose that to the Committee as a whole. That is just reflecting my personal point of view. I mean we are so far away from that day at this point.

DR. VANDERPOOL: Excellent questions. Okay, one final comment here.

DR. RUSSOW: Loath as I am to cut into my own time, I did want to make one additional point about what you referred to correctly as a consequentialist approach. Consequential approaches require not only that the ratio of benefits to risk be sufficient but rather the question is of all the available alternatives which one has the best ratio of benefit to risk. So, you have to consider alternatives.

DR. VANDERPOOL: And consequentialism is a way to argue for what is right or wrong in terms of what the consequences are likely to be, and of course, the assurance or lack of assurance about these being the actual consequences is part of that. So, we are restrained from using the 25-cent philosophical words here, and we need not do that to do ethics. Thanks very much.

Let us move to the next topic, animal welfare and Lilly Russow will make presenting remarks.

DR. GROESCH: I recommend that we go with this discussion until twelve-fifteen and then take an hour for lunch, and that will keep us on our schedule. We did well yesterday with just the hour for lunch. So, let us try that again.

Agenda Item: Identification of Animal Welfare Issues

DR. RUSSOW: The role of animal welfare has by and large taken the role of second fiddle, and that may be as it should be, but I think ethical theory has some interesting broad points to make, and it is worth exploring them in some depth, and then I will talk about the practical implications as time permits.

The theoretical point is that the wording of the Animal Welfare Act as revised in 1985, and the new NIH policies that came about at roughly the same time actually imply a radical paradigm shift, a radical change in the way we think about animals, and I think we need to be aware of that. To use the philosophical terminology which I will explain as we go along, the shift is from treating animals as if they only had indirect moral standing to the view that they do, in fact, have direct moral standing.

What does that mean? Indirect moral standing is defined solely in terms of human interest. So, the moral question of how we treat animals is to be determined solely by the interest that human beings have in seeing the animals treated a certain way.

That sort of involves viewing animals as merely resources or tools. That is their status. Direct moral standing on the other hand says that the animal's welfare must be considered on its own terms, that what makes an action morally correct or incorrect is not determined solely by human interests, but by the animal's interests as well, and what happened in the Animal Welfare Act is that it recognized animals as having direct moral standing by demanding that we consider the welfare of animals as it were from the animal's perspective as well as from a human perspective, and that as I said is a tremendous paradigm shift.

So, direct moral standing implies, for example, that pain and distress in animals is real and must be taken into account in moral evaluation of how we treat animals. Just to avoid misunderstanding about direct moral standing by saying that animals have direct moral standing that does not imply that animals and humans have equal moral standing. So, one can easily talk about human values, in some cases trumping the animal's direct moral value or that human moral standing is much higher and broader than the direct moral standing of animals. So, I am not advocating a pig is a boy is a rat.

Okay, I think that that is relevant to xenotransplantation because xenotransplantation sort of invites going back to indirect moral standing and considering animals simply as resources, donors and tools and I think that would clash with the general public opinion, the legislation and policies where direct moral standing is almost taken as a given.

Okay, that is all there is for the theoretical at least for now. I want to talk a little bit about the practical implications of treating animals as having direct moral standing. Where does this come out? First of all,

IACUCs, that is Institutional Animal Care and Use Committees are charged with primarily considering the animal's welfare from the animal's point of view, if you will, and IACUCs have to be properly equipped to consider a number of specific considerations dealing with animal welfare, and as new technologies develop it may be that IACUCs don't have the proper training, include the appropriate expertise to deal with that new technology such as xenotransplantation.

So, I think we need to think about how to better equip them to have that expertise, but one of the first things that an IACUC does is to make sure that animals aren't unnecessarily wasted. IACUCs are directed to look for protocols that have the appropriate number of animals used and the appropriate species. So, all of the debates on both sides as to non-human primates as valid models for human reaction would fall under the is that an appropriate species question. Appropriate numbers is always an issue with transgenic protocols because at least what I believe it was Dr. Cooper referred to as the traditional old-fashioned method of transgenic research is really very much a hit and miss kind of proposal, and you know you are going to use up a tremendous amount of animals to get a few that have the results you are looking for and so the question about numbers might be as was discussed more efficient ways of producing transgenic animals using fewer animals, and so that is a question that is obviously directly relevant to xenotransplantation.

What should be the end point of the procedure? Now, a lot of people have talked about these animals eventually die. Normally unless you can argue for an exception based on what is necessary for the protocol, death is not an acceptable end point for an IACUC. As soon as the animal shows, for example, a high level of untreatable pain and distress it ought to be euthanized then and there, so taking a level of pain and distress that cannot be alleviated rather than death is the preferred method, and as I said a lot of people are using in their xenotransplant protocols death as an end point. So, that is going to be coming open to question by an IACUC.

Approved method of euthanasia, there are approved methods for different species, different sizes within a species and so on, and again, unless you can argue for an exception based on what is necessary you have to use an approved method of euthanasia.

You have to have a plan for treatment for pain and distress. So, just as one example, if you have a recovery surgery, the IACUC is going to demand very careful monitoring of that animal as it recovers from surgery and, also, routinely use analgesics for postsurgical pain. That is sort of the standard, and that is an issue that obviously affects any kind of transgenic research or xenotransplant that requires a survival surgery.

Other concerns are housing, and then other specific details that apply not to every protocol but may be raised for your particular protocol. So what effect does early weaning have on the pigs, and, also, if you are using non-human primates how do you ensure physiological enrichment that is required under NIH and USDA policies? The side effects of genetic engineering both in some cases anticipated and in some cases unanticipated; do you have a plan to treat pain and distress caused by the side effects that occur all too often in transgenic animals?

So, those are some specific details that apply. As far as general issues that need further exploration I think that one is on what basis do we make exceptions; how many exceptions do we accept as justifiable and why? By exception I mean not having to comply with standard concerns like these based on needs of the research. How much is too much, and secondly, another issue that needs exploration is the make-up of IACUCs and that gets back to my first point that they need to have expertise in new technologies, including xenotransplantation, and now that is often not the case.

So, what sort of additional training, additional guidelines are appropriate; do we have to rethink some of those guidelines or do we even have to require that in any institution that is doing transgenic or xenotransplantation research that one of the committee members is an expert on those particular technologies? Right now that is not the case. IACUCs are required to have a veterinarian. They are required to have a general public member not affiliated with the institution at all and an ethicist, and some of those roles could be combined, but those are current guidelines for the requirements for the make-up of an IACUC and maybe we ought to think about adding another requirement, at least in institutions where that is relevant.

Okay.

DR. VANDERPOOL: Thank you. Do you have comments about these points, Sharon?

DR. KIELY: Thank you, Lilly. You have instructed me in an area that I had absolutely no background, and so forgive this question if it seems clear, but you made a comment that xenotransplantation invites a shift back to the indirect moral standing of the animals, and I was wondering if you could maybe point out some specifics in what ways that actually occurs and then if you could maybe even point out some ways that that could be alleviated. Thank you.

DR. RUSSOW: A specific instance of inviting a move back to indirect moral standing is when we think of animals strictly in terms of, the care of animals strictly in terms of ensuring that they are good donors.

So, getting back to the housing issue, the donors are typically raised in, I will call them clean facilities, gnotobiotic facilities or specific pathogen-free facilities. That really puts them in a special category because all of those facilities are in some way or another more restrictive than an open facility in terms of everything has to be sterilizable and sometimes restriction in terms of how many animals you house. I know in our gnotobiotic facilities they only have at most two littermates in one room. Early weaning was already mentioned. Those are some of the specifics, and how we can ameliorate that is first of all getting away from treating animals as mere resources, and that has to be a shift in the way we talk about it, because a shift in the way we talk about these issues often carries with it a shift in the way we think about these issues.

The other point is that indirect moral standing and direct moral standing can be combined, that is something can have direct moral standing, speaking to things like pain and distress, and, also, in addition indirect moral standing that has to do with the humans, and as long as we keep a good balance between those two, we avoid the slippery slope back to mere indirect moral standing.

DR. VANDERPOOL: Okay, Mike Swindle?

DR. SWINDLE: I just wanted to clarify something on the IACUC make-up. There isn't any legal requirement to have an ethicist.

DR. RUSSOW: But NIH guidelines require that.

DR. SWINDLE: The term "ethicist" doesn't appear in the regulations, and the other thing to be considered is that every institution is not going to have somebody who is an expert in xenotransplantation just as they don't have in many fields, and they are free to use consultants, and I have consulted for many other institutions just by e-mail on particular protocols. So, those things are already in there.

DR. RUSSOW: Yes, but IACUCs vary widely in how much consulting, outside consulting they do, and that is another way of sort of changing the charge to IACUCs to ensure that consultation is done in any protocol that doesn't fall within the expertise of the committee.

DR. VANDERPOOL: Jon Nelson?

MR. NELSON: Thank you, Lilly for the clarity. Could you describe how or whether your theoretical model distinguishes between species? Are the same rules applicable in the various animal models that have been described previously?

DR. RUSSOW: No, it is not one size fits all. So, as I mentioned direct moral consideration of non-human primates or the direct moral standing of non-human primates may cover a wider range of considerations than the direct moral standing of a mouse, and that is recognized in requirements for psychological enrichment. You don't have to provide mice with a psychologically enriched environment.

DR. VANDERPOOL: Okay, Alan Berger?

MR. BERGER: Besides the legal requirements of the AWA the Committee should be aware that there are changing perceptions in terms of how the public views animals. For most data you could probably see that about two-thirds of the public is very nervous and is not accepting of animals feeling pain and suffering.

Going to this chart where you watch or you have an experiment that goes to death, it really does run counter to what the public perceives that animals should in fact feel and even on to of that there is approximately 30 percent of the public that is not even in favor of using animals for medical treatment and medical research.

DR. RUSSOW: That is they put direct moral standing alone not combined with indirect moral standing. I challenge the idea that the general public is nervous about direct moral standing. They may be nervous about how we measure pain and distress and that might make them nervous, but do they feel pain and distress and if so is that a bad thing just in terms of the animals' moral standing then I think you get a much higher percentage of people who would agree to that.

In fact, there was a survey done about 15 years ago which found that 85 percent of the general public would agree with the statement, "Animals have some rights." So, you know, there may be a shift back, and again it is sort of the carrot of we can do better medicine that makes it more likely that people have changed in their opinions, but I think basically when put in terms of what sorts of rights do they have people generally agree that they have some rights, not equal rights and I think people assume that when you talk about animal rights one of the things that makes them nervous is that they think having rights is equivalent to having equal rights with human beings, and that is as you said, 30 percent of the population might think that way. I wonder if it is that high, but put in terms of yes, they have moral standing but not moral standing as broad and as deep as human moral standing that is one way of alleviating the popular tendency to associate granting moral standing as equivalent to granting equal moral standing.

DR. VANDERPOOL: One other comment and then we will break for lunch. Yes, Jon?

DR. ALLAN: I have a real basic question and maybe Michael might address this question which is if you are going to use pigs for organ donors is there anything different between in the Animal Welfare Act, I mean would you consider pigs like a production species so that it is treated differently than say a

research animal? I mean is there something about domesticated species?

DR. SWINDLE: Farm animals are exempted if they are used for, quote, agricultural research, food and fiber and things like that, but this is not production. This is biomedical. They wouldn't be exempted in any way.

DR. RUSSOW: And again, that is another area of wide variation among IACUCs. Some of them take all research involving domestic animals including production research as subject to an IACUC review and IACUC standards. Some follow the letter of the law which makes the distinction between production research and biomedical research.

DR. VANDERPOOL: Thanks so very much. You have made some very clear and important distinctions for us, and I am sure there are controversies that can continue to come from this, but a very helpful overview for all of us. Now, let us take our lunch break and be back here in 1 hour. Let us be back here by twelve-twenty-five, a little over one hour.

(Thereupon, at 12:20 p.m., a recess was taken until 1:30 p.m., the same day.)

AFTERNOON SESSION 1:30 PM

DR. VANDERPOOL: We are faced with a very important set of time deadlines from here on, and I have posted behind me what schedule we are going to have to stay with, with 20 minutes for socioeconomic, 20 minutes for legal issues, 20 for psychological, 30 for patient perspective, 45 for SACX ex officio members and then some room for public comments.

Now, if ex officio members need some more time just let us know as you start and we will make every effort to accommodate that somewhat, but we need to be finished by four-fifteen and my closing comments to these 2 days of meetings can be given now, but I probably will say it then. It has been great. I wish you well. We will stay in contact. So, that is going to take about 4.5 seconds. so, we can finesse that. We are not going to take a formal break and so you are responsible for your own quick breaks. As you leave this door and close it you are going to have to walk all the way back here and so at one I left this door open and thought I will sneak in and I had some responsible party close it on me and you saw me wade through everyone back here.

So, let us begin. We are going to be very tight about these time constraints and begin with social economic issues with identification of the issues by Alan Berger and then discussion. I think the presenters from here on out need to highlight the issues and not discussions of the different ramifications of the issues, primarily highlight the issues so we will have time for some discussion of those issues and move on to the next topic. So, economic social issues?

Agenda Item: Identification of Socioeconomic Issues

DR. BERGER: It makes it easier to do this standing rather than sitting. I will try to go through three or four basic issues. I am going to make a few comments, and, Harold I will try to keep this as short as I can. It was noted today that social and ethical debates are still needed on this subject, and I tend to agree strongly with that statement.

It seems to me that the train has left the station on xenotransplantation, but we still don't have a firm base in terms of social and economic issues. Economics, the first point is really just basic economics 101,

supply and demand. It seems to me that this Committee could make a recommendation today and economics 101 is very simple, supply/demand. We do need to do something to increase the supply of human organs, and this really should be the first responsibility of this Committee to make a recommendation to the Department of Health and Human Services, and it fits into two real areas.

No. 1, there have been some very good changes that have occurred in terms of increasing the number of human organ donors, but we can still do more with that in terms of changing the criteria, in terms of marketing, training, education, but the second point that we should be really looking at is the legal aspect.

Personally, I really prefer mandated choice laws which are more state oriented, but I certainly recommend that we should recommend something like a presumed consent law which should increase the number of human organ donors, consent laws which are common throughout Europe and presumed consent laws that do not allow family members of patients to change a decision that has already been made.

The second part of this is the supply, increase the supply. It was noted yesterday that that is the reason xenotransplantation came into play, to solve this problem but we need to do something more long term to decrease the need or we still have a major problem before us, and the major thing I think we need to look at is preventive medicine, things that we already know, and we can make recommendations here as a Committee to reallocate research dollars to go more for preventing illness rather than curing disease, and you can have marketing programs. You could have incentives. You can have legal and regulatory restrictions that really go towards improving and changing our life styles, plant-based diets, regular exercise, forms of weight control, stress reduction, things that we know really have an effect and will decrease the need for expensive medical care.

My second social point is really the utilization of resources, and I have done some economics on this. Right now we spend about \$4 billion a year in terms of organ transplants. The Institute of Medicine in their 1996 report claimed that if xenotransplantation were successful and took place that would jump to about \$20 billion per year. I have done some estimates using the Solomon Brothers report from 1996, which is in that three-volume 200-pound set of information that Mary and her staff put together for us, and I got approximately \$34.8 billion a year.

It is an amazing amount of money, and the amount of money that goes in that will have a real effect on both public funding for health care, for instance Medicare and Medicaid and could have a real effect on private insurance, higher premiums, more limited coverages and possibly higher levels of uninsured people in this country which brings me to my third point.

Xenotransplantation does not exist in a vacuum. It is part of a national health care policy, and it needs to be directed as to how xenotransplantation fits into that. What is it we are trying to do? Are we trying to extend life, improve quality of life, cure disease, prevent illness or provide basic health care for all Americans?

According to World Health Organization the US spend more money, more of our gross national product on health care but in most health categories rates 37th out of 191 countries which is showing us that maybe the way we are allocating those finite health care dollars may not be the way that they should be allocated, and that may be the first thing that we end up looking at.

It does appear to me that if you are white, you have middle or upper income, college educated, live in an affluent suburb or in housing in urban areas that are higher income level and you have easy access to

health care services and of course have insurance you probably have the best health care in the world. If you don't fit into that you probably don't have that at all.

As a matter of fact we see areas where the life expectancy for certain groups can be 15 years less because of where they end up living and they are at a poverty level.

The uninsured, part of this problem 42.6 million Americans are uninsured. One out of every five Americans under the age of 65 does not have health insurance. Even more than that, an even bigger social issue is that 50 million adults have difficulties getting adequate needed medical care, and about 70 percent of those or 35 million it is a serious problem.

The Federal Government funds about 3000 clinics to serve this, but it is only \$1 billion a year spent on that. A reallocation of funds to be able to provide clinical support for uninsured people would make a lot of sense. It is a priority. Where does xenotransplantation fit into that model?

Let me leave you with just one last thought, and I can cite a number of other things, but I just want to leave one thought, and I will put back on my animal welfare cap for a second. This is a quote from one of our noted modern authors, Alice Walker. "The animals of the world exist for their own reasons. They were not made for humans anymore than black people were made for whites or women created for men." Thank you.

DR. VANDERPOOL: Comments on the economic issues?

DR. COLLINS: I have one. Mr. Berger, I enjoyed your presentation. You brought up some excellent points. I do agree with you that we should push for more human donation, and that is going to be limited certainly, but we could do better, and I think it is important that we talk about that. We have noticed for instance at Duke Medical Center that since we have offered the laparoscopic or the small incisions for taking out donor kidneys the number of living donors has increased and that trend has been seen at other medical centers, also, but I think we could do a lot more with human donations, and that will take us to a certain point, and that is why I think xenotransplantation may have a place, but you bring up some excellent points.

DR. VANDERPOOL: Other remarks? Of course, a number of these issues are macro economic issues and therefore political issues, and the influence of this Committee on those issues is in question, but you bring up pivotal questions. Some rather extensive discussion of these economic issues as you know, Alan is found in the 1996 report of the IOM committee.

Okay, let us move on. I think that your mentioning presumed consent as a possibility might well be something of importance to our next presenter, Robyn Shapiro concerning legal issues. Robyn?

Agenda Item: Identification of Legal Issues

MS. SHAPIRO: It is but not on my list for some reason. I am just going to mention in no particular order of priority to me five or six legal issues that hopefully we will be able to struggle with. The first is liability. What is going to happen when lawsuits are brought against institutions or providers or a company with regard to recipients who are probably at least in the short term going to be facing terminal illnesses? In fact, the February 2001 FDA guidance says that only those with life-threatening illnesses for whom safe and effective alternative therapies are not available should be candidates, so that death or other complications probably would not result in a successful lawsuit for very much damages anyway.

It may be very different with respect to close contacts or family members who may become infected. An analogous situation includes the French Government's \$2.2 billion fund to compensate those who got AIDS-contaminated transfusions in 1980 to 1985, the Vietnam vets who were exposed to Agent Orange, the Gulf War vets who have experienced unexplained illnesses filing compensation and our courts dealing with these things in a very ad hoc manner.

Now, I realize I am making some assumptions which may or may not be true, but if that should happen, the questions of liability would be big, and I think that we should think about that now and maybe in thinking about that the court of federal claims offers a model for us to consider. That court which mostly hears non-tort money claims against the government administers a pretty costly and pretty extensive system of compensation under the National Childhood Vaccine Injury Compensation Act of 1986, who those who have suffered injuries associated with childhood vaccinations. It is basically a no-fault system by which people who are alleging injuries associated with standard childhood vaccines could be compensated without having to sue the vaccine provider, the vaccine administrator, the vaccine manufacturer and there are special masters who rule on claims, and there is a presumption in favor of the petitioner when certain conditions are met. The discovery procedures are fairly relaxed and specific payment schedules and caps on pain and suffering awards.

Related to this question of liability vis-a-vis the contacts, the family members are questions surrounding the legal obligation to inform these individuals of updated information as soon as possible about newly discovered risk/benefits, needs for additional treatment and so forth. Whose obligation is this, and how is it going to be discharged, and who is going to pay for that?

The second category of legal questions has to do with privacy, and we have heard about our national registry which will track patients and their families and their contacts and health care workers and archive information about and samples from these individuals in an attempt to obviously mitigate risks that may be latent, may present later, to let the health care professionals address problems quickly but it does all raise Fourth and Fifth Amendment questions.

The right to privacy and to be free from government intrusion could be encroached if this isn't done right, and especially I think the concerns are especially heightened with respect to the context. They are going to have to consent apparently to postoperative monitoring, and I haven't seen addressed at all any talk about the future usage of these archive samples. Obviously we could, and some may want to do a lot of things with that stuff that may not be directly related to this procedure, and I think that that has to be addressed, and protections have to be put in place.

Third area of legal issues has to do with the whole notion of regulation versus legislation versus guidance, and we heard some talk about that today. Guidelines, and we heard about this from Jay, I believe are non-binding on the industry although it certainly does provide some evidence of standards that FDA is going to expect to see, and there is reason for guidance, and that is that it is more easily adaptable as technology progresses because regulations involves comment period and so forth, but is that good enough in terms of protection?

Some say that the FDA shouldn't be involved in this at all because we are talking about procedures, by the way, but it is, and coordination of the FDA's regulatory regimes is, also, something that we need to be aware of and be careful about because relatively small substantive variations could involve different regulatory authorities depending on whether we are dealing with a drug, a biologic or a device, and that we have heard some about already today, too, and yesterday.

The third legal area is informed consent, and we have been talking about that throughout. The guideline talks about certain major areas of information that need to be disclosed to the potential recipients as well as certain obligations where you need to get out of them on the consent side of informed consent.

There are huge questions. I was talking with Dr. Rose about this previously about what informed consent is and how doable it is, and that applies not only to this but to virtually all procedures that are performed on patients, especially when we are dealing with vulnerable recipient populations. That is a big concern I think. We should spend some time thinking about how to do that as well as we can.

The indeterminate nature of the potential risks, also, are huge challenges in informed consent vis-a-vis what we are talking about here. There is another aspect of this that really is a problem, and that is that implicit in this informed consent process is the requirement for life-long, I mean I have heard it said long term, but then very shortly thereafter it is always life long, so, life-long surveillance.

So, that really twists the nature of informed consent in clinical trials as we have known it which always includes the right to withdraw without penalty. Really it seems to me at least in what has been talked about so far not allowing for that option, so it is really not informed consent; it is really a binding contract, and that changes the nature of what we think we do in research and what we think we have in the doctor-patient relationship. I think we need to think about that particularly in light of the fact that this change, this twist from consent to binding contract is being fueled by third-party interests. So, that makes it a very interesting little change.

Public health laws are the next category of legal issues we need to talk about, and as I mentioned before I believe that in most states the public health laws could be used to quarantine or detain individuals if we did know that there was a serious risk posed by an infected patient, but we don't have, I don't believe a current law that allows for compelled continued surveillance, and do we want that? Do we need that? What would we do in the absence of that? I don't think we have answered that.

Another category of legal issues has to do with patents, and I haven't heard that talked about much so far. There are key United States Supreme Court decisions as well as Patent Office actions lately having to do with what can or cannot be patented, and some discrepancies between all of this. This all raises the interesting legal issue about the propriety of ownership over forms of life and whether through licensing of artificially engineered and created species certain corporations may develop monopolies over the building blocks of life. I am exaggerating some on purpose, but that is the issue.

If we assume the eventual success of xenotransplantation companies that hold certain patents will likely face the same kind of cost and access controversies that we see that companies have faced with regard to their expensive life-saving products in the drug industry. So, all that I think, also, is on the horizon literally speaking.

Another second class category of legal issues that we are bound to see has to do with employment law. Will health care workers and their organizational union representatives agree to extensive worker surveillance including extensive post-exposure examinations and so forth? Not everybody is unionized, but some are, and what is employment law going to have to say about that, and finally there are international regulatory concerns, and we have touched on that as well.

Xenotransplantation may start quickest in environments where regulation is lax and facilities are inadequate, and we have examples, and it has been said here that viruses are not confined by geographical boundaries. What are we going to do about that

Those are some of the legal issues as I see them.

DR. VANDERPOOL: Well done. Questions and comments?

DR. SCHECKLER: I have a question regarding the issue of informed consent versus contract. I think a number of people have raised the issue about the 50 years and the family and so forth and so on all the way to autopsy. What do you think the resolution of that is likely to be? Is there any other case law that is comparable that would inform us about what we have talked about with xenotransplantation and that distinction between informed consent and contract?

MS. SHAPIRO: I think that there are really two aspects of an answer to your question. One is contract law would say that as long as up front you know what you are getting into, and you agree to that that is consent. It is not binding contract, but the question, the really interesting question I think comes when the person who has agreed to that up front nonetheless isn't living up to that agreement, and I talked to industry representatives about what they thought they might do about this. They are not coming in for their surveillance and their tests. What are we going to do or what should we do, and then you really have autonomy and freedom of the individual pitted against possible public health concerns, and I don't know of any paradigm that I can use to answer.

DR. SALOMON: I have a question about one of the laws that we follow is that you cannot test for HIV, a retrovirus without the patient's permission. I am not familiar with the details of how that law is actually written, but does that by its very nature mean that we cannot test for porcine endogenous retrovirus or another sort of retrovirus and then can you carry that a little further, because again porcine endogenous retrovirus is not the only viral risk here? So, does it mean any virus like for example, a herpesvirus, like CMV? I mean how far can you go? What can a patient and a doctor do in terms of diagnosis?

MS. SHAPIRO: The very protective HIV test laws are state specific, and many or most states have them for a lot of reasons that had to do with great fears of discrimination against that information being too widely available so that in Wisconsin, for example, we have a very explicit and very protective HIV testing statute that requires specific consent.

For the most part though, if you are going to draw blood, and the patient knows that you are going to use that blood to test for a variety of things you don't have to get disease-specific consent out of that patient, and I would hate to see that happen with respect to PERV or other relevant pieces of information that we would want to know. I wouldn't be afraid about that.

DR. VANDERPOOL: Other questions or comments?

DR. SWINDLE: You opened up a lot of things that I never even thought about which I guess is why I am a veterinarian and not a lawyer, but I was just sitting here thinking when you were talking about this what seems to me to be impossible follow-up of family an all that, would there be a liability issue at the transplant center level if a pandemic did arise or some zoonotic disease did come out of one of these things and it spread to Europe or something like that. I mean is there a real liability issue here in terms of that happening?

MS. SHAPIRO: That is why I ask the guy what kind of insurance he has. You know, you can sue for anything, and would I be surprised to see a lawsuit about that or a million lawsuits about that? No. I really wouldn't which I guess is why we are taking such care here to think about how this should best proceed.

DR. VANDERPOOL: Robyn, you have been incredibly informative. I can just imagine a situation where there is a contest over informed consent for patients because of an adverse event and not only would we have to prove that you gave certain bodies of information, but you would have to deal with the questions of the understanding of that information as well as the competence of the person to be able to understand and receive the information and make a choice, and so all those three elements of consent stressed in the Belmont report are on line when it comes to a legal case, I guess contesting consent.

Louisa?

DR. CHAPMAN: That was a very informative discussion, but I just want to correct one small misstatement which is that the national xenotransplantation database at least in the US is not and never has been proposed to track information on contacts of recipients, only information on recipients.

MS. SHAPIRO: But is the recipient supposed to urge that the contact, either him or herself talk about what is happening with any of the contacts or urge the contacts to be involved?

DR. CHAPMAN: I would suggest that everyone here should read the guideline, but the guideline talks in the informed consent section on the responsibility of health care providers to educate and get informed consent from the patient and to educate the patients about their responsibilities towards contacts including educating the contacts and to be available if requested by the recipient and the contacts to provide information and counseling.

DR. VANDERPOOL: That is exactly right. The question is are the patients physically and psychologically and mentally capable of doing all the things they are supposed to do under those regulations, but that certainly shifts the burden to the patient. Other comments?

DR. SALOMON: Following up on travel if we establish as other committees have already that there is a xenogeneic infection risk albeit we have choked on quantifying it, but we all agree unanimously that there is a risk at some level, and let us say a transplant program then opened up, and I already mentioned that there are two just below my city in San Diego across in Tijuana, and we saw one in Switzerland and one in Germany and we, also, know it is going on in Russia. So, we know they are there. So, now we have what we call publicly risky processes going on where American patients are being encouraged to go there and then return to the United States. That is happening now. How is the law going to deal with that?

MS. SHAPIRO: We cannot shut down Mexico's program, and I think I would defer to some of the public health people, but I would think that if you as a physician of somebody who came back and you knew that they were infected and that they caused a public health risk that going to the public health authorities would probably be the right thing to do.

DR. SALOMON: So, it is okay to enter the United States?

MS. SHAPIRO: You mean do we have physicals at the border?

DR. SALOMON: No, it is just it is okay for them. They are going to enter the United States, and then they get sick. Do physicians have to take care of them if they have got some potentially unknown virus? I mean this was an issue in the early days of HIV, and I am purposefully being a bit dense, but the question then is do I as a physician have to take care of this patient who I know got a chimpanzee heart in Tijuana last week? I am just making that up totally. They are not doing chimpanzee hearts in Tijuana.

MS. SHAPIRO: If you are not discriminating against patients on suspect categories you don't have to take care of anybody unless you are an ER doc, and they come in and need stabilization, and so the answer to that is no.

DR. SALOMON: But I come in the ER, and I am called to the ER even though I think they should be in BSL4 and no one has made any accommodations for BSL4. I still have to take care of them?

MS. SHAPIRO: I realize as a nephrologist I might be called to dialyze them or my colleagues might be called on to operate on the heart.

DR. VANDERPOOL: Okay, a few more comments. I am so glad we have Robyn on this Committee. She may complicate what we do but we sure as heck need her on here. Megan and then Marian.

DR. SYKES: I am just wondering is there any legal precedent for an individual say with HIV knowingly having a sexual contact not informing that contact and then being sued by that contact who contracts HIV?

MS. SHAPIRO: Oh, yes, not only sued but criminally charged as well for attempted murder and things like that.

DR. SYKES: I understand that proving informed consent to be really understood is a limitation, but couldn't one use that model to consider a patient liable rather than thinking about legal, other kinds of recourse, couldn't a patient be held liable in a lawsuit kind of situation if he didn't comply with the follow-up requirements, contributory negligence, that kind of thing?

DR. SYKES: Yes, I mean all that. You know, lawsuits are a mess but that would be the counterclaim, contributory negligence.

DR. MICHAELS: Actually on that same line of thinking though I think we are beginning to get things a little bit confused, and I am so glad that you are here and did give that talk because it is absolutely wonderful, but you are making the assumption or I think that at times we are making the assumption there is a proven infection.

Certainly all the rules with HIV there is not a question about the infectivity, the risk of infectivity whereas if we are talking about individual who has received a xenotransplant we are hypothesizing the infection. Once an infection is recognized and recognized as being transmissible then I think we go over to a different model.

MS. SHAPIRO: Right, and the analogy, I suppose is to the blood banks when before they were able to test for HIV were not successfully sued but after the test was available, and they chose not to implement it they were successfully sued. That is probably the analogy.

DR. SYKES: But in a sense the patient has agreed to do this follow-up with the understanding that there are unknown risks to his or her contacts.

MS. SHAPIRO: And so, a contributory negligence claim could still live no matter when this happened. You are right.

DR. SALOMON: Of course, they could agree in the United States to do the study if the study was done in the United States, but with my new company which I set up just across the border I can do whatever I want, and you cannot stop my patients from returning to the United States.

DR. VANDERPOOL: Okay, final question, Bob?

DR. MENDEZ: Just a comment. This will never be completely stopped at the border no matter what country you are talking about. We have been working with Conacho(?) which is the Mexican group of UNOS(?) equivalent of UNOS, and I have been trying to establish guidelines for their organ procurement and having the same quality control type of issues that we have in the United States, but nonetheless there will be people flying in there, 15,000 illegals flying in from the Asian areas into LA every year just to give birth on soil in the United States. So, these things will be particularly difficult.

In caring for people whom you know are infected or who have had, as we have had to do not legally but morally people transplanted in foreign countries with organs that were paid for, and who had no screening whatsoever, over 30 percent of them have been having infectious diseases. It is causing significant problems, morally, ethically and legally.

DR. VANDERPOOL: Thank you, and thank you, Robyn for this excellent set of points and the discussion that followed from it. Okay, now, psychological issues, Catherine Crone.

Agenda Item: Identification of Psychological Issues

DR. CRONE: Hopefully I will bring up some stuff that is a little bit less controversial, but, Robyn, that was a really great presentation. I certainly don't mean what I am going to present is going to be comprehensive and it is really with the idea of just getting the talk started, and I think there are certainly issues that even take greater precedence at this point in time, such as the risk of infections, and how are we going to deal with issues of vascular rejection. Nonetheless, I broke it down into three categories, and one is patient attitudes and issues, family attitudes and issues and staff attitudes and issues.

Under patient attitudes and issues one of the issues is informed consent, no surprise about that, and I guess my comment is they were saying earlier about a 40-page document that you are going to have to do a signed consent, and I would ask everybody here to think of if you were given a 40-page document that you had to review and sign before going through a procedure I would tend to think it would be one thing if you could take it home with you, mull it over and return it in a week after you have mulled it over, let alone and not be in a situation where it is life or death.

If you were put in a situation where it was life or death, if you turned this opportunity down you were going to be gone in a year and you have to read this 40-page document within half an hour and make a decision, tell me what that would be like and after you sign it or don't sign it could you really truly feel like you were adequately informed and could really understand all of the risks? Being someone in medicine I understand most of the terminology and even then I don't think I really could or I couldn't guarantee it. So, I am thinking of what it is like to be a patient put in those shoes and what informed consent will really mean, and that is why I made the comment earlier that neuropsychiatric testing or neuropsychological testing alone will not capture that aspect of the emotions involved.

I think once we get onto actually doing xenotransplantation there is the question of how this will affect someone's personal identity, and I think this has been brought up before in writings of xenotransplantation, the incorporation of this foreign body. Early on when allotransplantation came up

there were writings about people who were having difficulties accepting the organ because they felt like they would take on new characteristics, new personalities. Occasionally you will see things in the magazines that are in the grocery sort, but those sort of concerns have tended to die away over time as allotransplantation has become much more commonplace. I hear it very little now, but it still does come up. You are talking about this time around, this is new technology all over again, how will people accept that; what will it mean; when is a pig a pig; when is a human a human; and when does it become a little bit muddled?

Survivor guilt. Patients already deal with cadaveric transplantation. Even though they know that the person who donated was going to die anyway, nonetheless that doesn't necessarily spare these patients of survivor guilt. When you talk about an animal that is bred specifically to be sacrificed for this transplant how will patients feel? Will there be problems with survivor guilt.

Questionable future. The fact that we aren't going to know for those people if we ever get to do this long term what are they going to be living with, the anxiety of how long are they going to live; what sort of quality of life are they going to be faced with, and the quality of life overall is sort of questionable when you think of financial concerns down the road, relationships, if they are going to have to have protected sex and yet they are developing new relationships with people or if you are dating how are you going to bring this up if it brings new concerns that you have new risks, and I think quality of life to me, also, I am looking at long term. So, those people who need to be on immunosuppressants on a long-term basis there are long-term side effects of immunosuppressant medications such as renal failure, such as lymphoma. There is a risk of that, hypertension, other complications that can certainly affect quality of life and the effects of publicity.

Those people who are going to be the pioneers, what is it going to be like for them to be recognized out in the public, and I guess I have to defer that to James Finn in some ways, but how are others going to interact with them? How are they going to treat them? How are strangers going to interact with these people, coworkers and, also, I think there is a caution about making somebody into a professional patient. That is different from having a person who wants to seek out and educate others. I think some patients become so consumed by the experience of transplant that that is all their life, and they never do resume a more normal life style, and really that is what I think transplant is all about.

Family attitudes and issues. I think there is one question of altered perceptions. Now, your loved one has gone through one of these transplants. Will you think of them in different terms, and it follows along with the idea of incorporation of the foreign body. Who is this person? Will that change at all, and also, the uncertainty of the future. Can they really breathe easier now that their loved one has a transplant? Are they going to be more protective of them? Are they going to let them resume a normal life? Are they going to resume normal relations with them, and I think, also, the risk posed to family members and friends, those that we have talked about such as zoonosis.

Staff attitudes and issues, I am talking about hospital staff, the acceptance of technology, new technologies and the risk posed to hospital staff. I would not underestimate the power that hospital staff on interactions with patients even the fact that allotransplantation has been around now quite a long time. I still I hear some striking comments sometimes from nursing staff and others that still show a lot of misunderstanding, and I think sometimes they convey that to patients and family members and that unto itself is very difficult, and it is, also, stressful for the staff members because they aren't really sure, and I think education is going to be very important.

The last two points are the neuropsychiatric effects of infectious disease and antivirals, and I am just

going to consider the effects of things like herpesvirus or cytomegalovirus, things that can cause delirium, depression, anxiety, other problems, some of these antivirals such as gancyclovir, such as interferon can, also, cause considerable neuropsychiatric complications, and lastly neuropsychiatric effects of higher dose immunosuppressant therapy with the idea that some of these patients who get xenotransplantation might require higher doses of immunosuppressants and even if not just that there are a lot of neuropsychiatric effects of these immunosuppressants, such as when we use tacrolimus(?) and cyclosporine. It is not unusual. Again, we revisit things like delirium, anxiety, depression. There can be irritability. There can be a lot of complications involved with that as well.

DR. VANDERPOOL: An excellent survey and identification of issues. Comments and questions from the Committee?

DR. MICHAELS: I just have one comment. I think it was a wonderful talk. Your comments about educating the staff, I really have to agree with that. I was actually quite surprised at how many questions, particularly from the nursing staff about taking care of a patient that was to receive baboon bone marrow and without them having that opportunity to discuss those issues before the procedure occurred, I think we would have had more trouble, and I think that that was really important.

DR. VANDERPOOL: Karren?

MS. KING: Several of the issues that you raised especially relating to patients and family issues are not unique to xenotransplantation, I think you would agree. So, I do think there is a body of literature out there that deals with transplantation in general that we can really learn from and kind of help us along in xenotransplantation issues in this regard.

Just to refer to it as well, there are several studies that have looked at informed consent forms in general, not obviously the 40-page type of form but just general hospital consent forms, and I think research would bear out our concerns that oftentimes patients just in general do not understand informed consent forms and what they agreed to, let alone something as cumbersome and lengthy as a 40-page document that is really unfamiliar to them, and then lastly looking at staff attitudes and the importance of staff education and not estimating staff and their impact studies in long-term care, such as again dialysis where you have ongoing relationships with staff very much like we are going to have with xeno with ongoing monitoring have found that staff attitudes often have a greater impact on patient behavior than family attitudes. So, I think all of these are going to emerge again.

DR. VANDERPOOL: As we seek to empathize into the world of patients we are fortunate to have Jim with us who will speak very shortly, but we may wish to call in a number of patients and let them tell some things about their stories, what it is like to be on a waiting list, what effect their receiving allotransplant has had on their relationships. There are so many things. We need as Catherine has told us more understanding of whatever the effects might be for receiving an animal organ and living with it.

I have a couple of stories about that, but I will resist because I said we should stick to our time frame. Other comments or questions? Alan?

MR. BERGER: Catherine, how do you anticipate the reaction to a choice of whether I get an animal organ or whether I get a human organ and will somebody feel if they are only offered an animal organ that there is a problem?

DR. CRONE: That is difficult. I was thinking about that actually yesterday during all these discussions.

I have no idea. I would really question about sort of how someone would react if they felt like they were going to be, does that mean you are a second-class citizen; is that a judgment, and we already have, you know, there are already concerns within allotransplantation about the availability you know, if you are white middle class versus someone whose socioeconomic and from a different ethnic background. So, I think that is another thing that we are going to have to really think about.

DR. VANDERPOOL: One of the suggestions made in the FDA subcommittee on xenotransplantation at several points is that the initial patients should probably be those who are ineligible for allotransplants, but that is an issue that this Committee will need to do some deliberating on. Dan?

DR. SALOMON: I think there is an important reality to bring up about transplantation, particularly of livers and hearts right now, not really for kidneys as much. What really happens now is if you tell the patients that they are going to be candidates for a liver transplant or a heart transplant you basically are telling them that they have to stay alive until they get so sick that they have to be hospitalized, not just in a regular hospital room but actually in an intensive care unit, and right about that time when they are running down to their last days, and to me I think you just don't think about the immensity of that facing our patients.

We talk about oh, there are these long waiting lists, and we talk about oh, there are about 6 or 7 thousand patients dying every year on this list, but that doesn't get us in touch with the suffering that these people are going through. So, a counterpoint, if xenotransplantation should ever be successful what I am trying to point out at least is that all of a sudden you could technically be doing informed consent on patients who weren't lying in a bed with 1 week left to live who essentially might agree to getting a liver from a pig or a kidney or a heart because they could do it before they got so sick before they lost all their vascular access before their heart had turned them into concentration camp survivor prototypes.

So, I think that is something to really remember. I don't think we stress that enough.

DR. VANDERPOOL: It seems to me that these psychological issues are of such importance that we need to think about real research and attention to these issues as clinical trials get under way, that to have organ failure is not simply to have a major medical problem that happens to have certain psychological sequelae. It is to have a physiological and an emotional response all tied together, and so, it seems to me that these need to be interconnected as clinical trials are initiated.

Other comments?

DR. COLLINS: I was going to make one comment to echo what Dan said. That is an excellent point. We will never do a liver transplant on someone who comes in from home. You are absolutely right. Every one that we have done this year the patient has been in the ICU. Otherwise we don't get the organs, and that is the way it is all over the country. Your points are well taken.

DR. VANDERPOOL: Okay, let us move to patient responses, and we are fortunate to have James Finn with us who is going to present a brief video and then make some remarks, and as soon as Jim finishes I will ask Karren King to, also, make some comments about health perspectives and this should be a most important contribution to us for this meeting. Jim?

Agenda Item: Patient Responses

MR. FINN: Hi, everyone. I am a xenotransplant patient. I was done in 1996, in September. I was

implanted with 12 million cells from pigs into my brain. At that point I was at my 16th year with Parkinson's disease, and I was entering what they call the end stage.

In the end stage of Parkinson's medications no longer work and/or produce horrible side effects. I can give you an example. I used to go like this about 4 hours a day. Luckily there was success. Xenotransplantation works. It is a viable alternative to human cells and eventually perhaps organs, also. It is somewhat less politically sensitive as you all know.

I have had virtually no side effects from this procedure except for one, and I will get to that in a moment. I am definitely not cured, but I want you to take a look at this tape.

(A videotape was shown.)

MR. FINN: It shows me, I think, just before the surgery in the off condition where I had no medication. I have 50 percent improvement in standardized motor skill testing and a 50 percent cutback in medications resulting in fewer drug-induced side effects.

Let us not forget PD is a progressive disease. S symptoms have actually been reversed in my case. I have a vastly improved quality of life. I have been monitored every 90 days for the past 4 years. No problems have been detected whatsoever with my blood or curve(?) or anything else.

This story and my small role in it has received an enormous amount of publicity. I have been interviewed by PBS, Popular Science, the BBC, Sixty Minutes. The 27th of March Frontline is going to do an interview that they conducted with me about a year ago.

Oh, that one side effect I mentioned, I don't wallow in mud, but I like to search for truffles.

(Laughter.)

MR. FINN: Thank you very much.

(Applause.)

DR. VANDERPOOL: Karren, why don't you present your comments, and then let us talk to Jim and Karren about these issues.

MS. KING: As you all know, I am a clinical social worker, and I cannot presume to speak for transplantation. What I can do though is speak on their behalf by sharing with you the results of a survey that was conducted by the National Kidney Foundation of individuals who are transplant recipients primarily.

A little bit about the survey. It was conducted in 1995, and it is a fairly simplistic non-scientific survey. Basically the survey was distributed to 7500 subscribers of Transplant Chronicles which is the NKF transplant patient newsletter.

Of the responses, the basic response rate was 25.7 percent or 1924 surveys. Of those 1424 were actually transplant recipients, and I will break that out for you. Approximately 60 percent were kidney transplants. I want you to keep that in mind when I talk about some of the results because obviously as we all know those with the kidney transplants, unlike some of the others actually have an alternative to

fall back on should they reject beyond xenotransplantation. Sixteen point two percent were heart. Fourteen point five percent were liver and the remaining going to other categories such as lung or kidney pancreas transplants.

Five hundred of the individuals who responded were non-recipients meaning they were typically family or friends of the transplant recipient or on occasion they are also transplant professionals or may get this more directly to them at their office or home.

Just a little bit of the demographics, 86.5 percent were Caucasian, 6.1 percent African-American, 3.2 percent Hispanic, 2.3 percent Asian and the rest under other categories.

This is a very well-educated group. Ninety-five point nine percent of the individuals had at least a high school education. Looking at religious affiliation and how that might affect their attitudes and perceptions related to xenotransplantation 43.1 percent were Protestant, 30.3 percent Catholic; 11 percent reported no affiliation and 6.3 percent were Jewish.

In looking a little at the results as far as being aware of xenotransplantation in some form 92.8 percent of the non-recipients and 87.9 percent of the recipients said that they had heard at least of xenotransplantation.

In looking at whether or not they approved of the concept, approximately 99 percent of the non-recipients and approximately percent of the recipients said that they approved of the concept of xenotransplantation.

Whether or not xenotransplantation should continue, the research should continue, also, got a fairly high affirmative response. Eight-eight point seven percent of the non-recipients and 90.4 percent of recipients suggest indeed the research should continue.

Then they were asked if they would accept an animal organ if they needed one, and a human organ was not available to them. Approximately 73 percent of the non-recipients and approximately 74 percent of the recipients said, "Yes," they would. However, they did indicate that the type of animal used would affect their decision. They did not get specific, but 13.6 percent of the non-recipients and 15.7 of the recipients said that it would affect them depending on what type of organ was used in the xenotransplantation.

Also, we asked them to rank their potential concerns related to xenotransplantation. The first concern for both groups was the ability of the animal organ to function adequately. The second concern, again, for both groups was the same. They had concerns about cross-species infection. The third and fourth concern for the recipients, the third was opposition to killing of animals, and the fourth was the experimental nature of the procedures, and the non-recipients had the same concerns, but they were in reverse order.

Also, interestingly we talked about, and I cannot remember I think it was Catherine who spoke about the concern in the past with donors of cadaver transplants, for example, being concerned about taking on characteristics. That was listed as the least concern to both the recipients and the non-recipients whether or not they would take on characteristics of a donor animal. So, to this group that was not an issue of concern for them compared to the other issues.

In speaking with Dr. Vanderpool about sharing some of these results we, also, talked about me sharing with you some results of a public consumer survey that the NKF did. In 1997, they decided to take this

first survey at a more sophisticated level in a wider audience. In addition to randomly surveying transplant recipients and physicians, specifically primary care and transplant surgeons and nephrologists they worked with a firm that looked at consumer or public attitudes relating to xenotransplantation, and I would like to share with you some of those issues and results that were raised. I, also, might add that I am not going to go into the details here but there was statistical analysis basically looking at significance done on the data that I am going to report as well.

This is a consumer quantitative survey. Basically 1200 households across the US were randomly selected, and they did this according to time zones to get geographic diversity, and they were telephone surveys, and again, a little bit of the results with this group.

In looking at demographics Caucasians were 79 percent, African-Americans 9 percent and the others broken into other categories. Education. Ninety-four percent had at least a high school or greater education. Sixty-five percent were female. Looking at religious preferences approximately 56 percent were Protestant and 25 percent Catholic and again other, and income level, and again looking at xenotransplantation and how we wonder if the cost factor is going to add into who actually gets such a transplant, 41 percent of these individuals had an income of \$30,000 or less annually. Twenty-eight percent had \$50,000 or greater annually income, and some of their results. Nearly all of the individuals who reported said that they had at least heard of xenotransplantation with only 11 percent saying that they had never heard of it at all.

Interestingly 15 percent say that they had heard a lot about xenotransplantation, and I would wonder how they would define a lot. Nevertheless, that is what they told us.

Sixteen percent said that they were opposed to the continuation of xenotransplantation research. Seventy-one percent would consider xenotransplantation for a loved one if a human donor was not available.

Interestingly this, also, included one-fourth of those who said that they were actually opposed to research continuing, but yet if something became a need for their particular family member they would consider that even though they were opposed to the research which I think shows you the ambiguity and maybe the lack of information that people do have.

In looking at their concerns about xenotransplantation, 27 percent verbalized concerns about organ compatibility. Ten percent were concerned about the transplant success rate. About one in eight or 13 percent had concern about disease transfer, again, making me wonder how educated these individuals really were and 12 percent voiced concern about animal welfare.

Providing information to the public could increase support for xenotransplantation according to the information we obtained in the survey. Seventy percent said that their support would increase if they knew more about the deaths from the lack of organ availability, and also they said that if they knew more about the lack of success increasing the number of human organs that we have had in the US. Fifty-four percent said that that could influence or maybe make their support increase for xenotransplantation research.

Issues that potentially weaken the support included such things as 79 to 81 percent saying that learning a potential disease transfer could impact their support, so learning more about that could negatively impact how they support it depending on what they learned.

There appeared to be more potential negative associated with the use of pigs than with the use of primates. Specifically the greater number were more interested in xenotransplantation research if they heard that baboons or chimps were used as donors rather than pigs, and fewer said that they would be less interested if they learned that primates were the donors. Thus, the use of pigs had as many positive as negative responses, and the use of primates elicited two times as many positive responses as negative responses with this population.

Looking at options to increase organ donation, and that has been touched on, xenotransplantation and implied consent were basically the same, 43 and 41 percent, basically chose those two as the top options to increase organ donation in this country. So, implied consent was really as supported as xenotransplantation. Very few supported financial incentives for families. Looking at what might, also, influence individuals 53 percent said that they would be inclined to support xenotransplantation if the clergy actually endorsed xenotransplantation.

Twenty-one percent went on to say that it could make them accept xenotransplantation if the clergy said that it was consistent with religious teaching, not just endorsed it but, also, said that it was consistent with what they believed and taught. Interestingly even those who were agnostic and really didn't identify any religious affiliation said that the clergy could, also, influence their decision.

Sixty-two percent want the government to pay for research rather than as we were discussing earlier looking at pharmaceuticals and other companies. However, they did not want the government to actually regulate or oversee the research. They felt this should be done by physicians or by an appointed board to regulate, and overwhelmingly these consumers saw physicians as the most reliable source for answering any questions they may have about xenotransplantation.

That is it.

DR. VANDERPOOL: Thank you. Okay, questions or comments both for Jim and Karren?

DR. SWINDLE: Thank you, James. You put everything into a real perspective I think for everyone in the room, and I think I appreciated your talk more than any other I have heard in the conference because it brings it all home. I wanted to make that comment, and then I want to clarify an issue.

I am not sure I heard this right. Did you say that people, if they heard they were getting an organ from a primate were more in favor of it than if they were getting one from a pig?

MS. KING: Yes.

DR. SWINDLE: And only 12 percent have an animal welfare concern?

MS. KING: I have to look back and see. Yes, and again, this was a quantitative study, and I cannot explain it.

DR. SWINDLE: Twelve hundred households is like a Gallup level survey though, right? Isn't that right?

MS. KING: That I don't know.

DR. SWINDLE: Does anybody know? It is not that much, I mean when Gallup does their national

predictions. It is somewhere in that ballpark. I don't know the exact number.

MS. KING: There definitely were inconsistencies. In looking at this people would obviously, with the agnostics, for example, they would be influenced by the clergy, but yet they were saying that they had no religious preference. So, it is interesting when you look at the variations.

DR. SWINDLE: All right, thank you.

DR. SCHECKLER: I have a question for Jim. We were talking about lunch, Jim, about informed consent, and you told me that your consent form was more than 10 pages. You couldn't remember if it was 40 pages. What is your perspective in terms of what you are willing to consent for given where you were and your advice to us about the complexity with which we make informed consent forms?

MR. FINN: I was at the point in the progression of my disease where they could have handed me anything and I would have signed on the dotted line for it. I was going to die if I didn't have this operation. As far as the forms are concerned, I guess they have to be that long because they have got to cover every legal base that they can think of.

DR. SPIRA: Could I just continue that line of questioning? In terms of the information that was given to you outside of the consent form which is really the main part of the consent process, can you give us some idea of what information you were given, what you recall of that, and if there was a component in that process of actually assessing how well you understood it, regardless of whether you would have been willing to do it, regardless of the information, how would you view that now?

MR. FINN: I am not sure how to answer. I was told everything verbally before I signed the document. I don't know what else I can say actually.

DR. SPIRA: What I am trying to get at is if you were asked to make sure that you understood all the major issues involved in consent for such a procedure and if you failed to answer certain questions whether that would have promoted more of an effort to educate you so that if there was some objective finding of understanding, would that have concerned you at the time, and if you had failed to understand those points and the investigator sort of said that based on lack of that informed consent or understanding of the informed consent that you weren't eligible what would you have thought?

MR. FINN: I am sorry, I am not thinking too clearly right now. You just have to excuse me.

DR. VANDERPOOL: Jim, did you receive porcine cell implants?

MR. FINN: Yes, they were pig fetuses, yes.

DR. VANDERPOOL: Okay, did that make any difference to you had it been human fetuses versus piglets?

MR. FINN: If you are asking if it was from pigs did that bother me? No, it didn't at all. I put my trust in medical science. They told me it would possibly help, and I went for it.

DR. VANDERPOOL: At one conference I had there was a recipient of a heart transplant, and I asked him before the group whether receiving a human heart or a pig heart would make a difference to him, and his response was, "As long as I felt that pig's heart would help me and make a difference I would say,

`Give me the pig's heart, and when I get to feeling better I will take a ham sandwich on the side'."

MR. FINN: I have heard every pig joke you can imagine, and I do have a penchant for ham sandwiches. There is no question about that, and I love bacon and pork chops, too. What you are asking or telling me is that this guy who would take the pig heart is in the same position that I was in and when your back is against the wall, and you want to live, continue living; you want some quality left to your life you will do anything. You will sell your soul to the devil if you have to.

DR. VANDERPOOL: Other comments or questions from the Committee? This is very powerful and I think moving for us and your voice is immensely valuable I think to all of us.

Any questions of Karren? It was excellent survey material and I hope more studies are done. Okay, let us move then to the federal agency perspectives and have the presentations from any of you ex officio members of our group. Believe it or not we are actually 15 minutes ahead of time.

Agenda Item: Federal Agency Perspectives

DR. ZOON: I will volunteer to go first. Thank you very much, and I want to thank all the Committee members for their excellent comments, and I apologize to those this morning that I did not hear, but Dr. Segal and Dr. Bloom briefed me on many of the issues that you raised, and I think they are very important, and I was particularly both moved and listened very carefully to the comments this afternoon based on the patients and the caretakers and I think it is important as we go forward to pay close attention to those issues.

This Committee, as you know, FDA has worked very hard with the other members of the department to complement as well as look at many difficult issues that aren't now directly dealt with by our biological modifiers committee and the xenotransplantation subcommittee.

This Committee has a much broader scope of responsibilities and really looking at our own committee, really dealing more with the specific science issues and really I think progressing in this field and have to make regulatory decisions on either particular issues that that Committee will continue to play a role but certainly the issues that we have discussed today are very important, and FDA has a number of issues that we would like this Committee to consider because of your expertise and hopefully none of these actually will be new to you after 2 days of discussion because many of you either have raised these issues or have heard them from some of our presenters and have questions during the presentations.

My handouts are in your book. They are actually under the last tab. So, you could follow along if you wish and take notes. Is somebody working the slides?

It is okay, I can just start, and if we catch up it is fine. If not, I will just speak from my notes. It is no problem. The first issue is really in looking at transplantation and FDA's role we are the regulatory arm for overseeing the xenotransplantation products and clinical trials, and this is a responsibility like many that the Center for Biologics has of very complex new technologies often with potential safety issues as well as issues that go well beyond the standard science issues that we normally face in many of the products regulated by the FDA, and I think in looking at the future the issues that this Committee we hope will address include such things as preclinical models.

We have heard some of that over the past 2 days and looking at these preclinical models for organ

transplantation and really dealing with the appropriateness of some of the models and their feasibility, their validation I think are issues that we are interested in pursuing.

We are, also, interested in looking at the results from these animal studies and looking at how they support progressing into human trials; what are the types of data we want to see; how that data should be interpreted and the context of designing human clinical trials.

The next issue that I think is one we would like some additional help on is on the spectrum of risk. We heard a lot about today the great span of xenotransplantation, everything from a whole organ through using cells, such as James described, and I think that one of the things that we would like to consider is are the controls equal for all of these or could a well-characterized cell line have less restrictions than a whole xeno organ and to try to triage and look at risk/benefit and the types of data and information one would like to look at, and I think these are important questions, one, because we have everything from co-cultivation with an animal cell line through using cells through using whole organs, and in some cases we may have data that could impact on the ability to look at these in a different way or research can be encouraged in specific areas so that we could get a better understanding.

Again, the issues surrounding ex vivo and in vivo contact are clearly important, the duration of the exposure, the temporary versus permanent dose of exposure, types of barriers that might be considered as well as the species being looked at. All of these things bring to bear questions in terms of risk assessment and how one would view these.

The next question really deals with the patients themselves, and this is again a very difficult area of long-term follow-up. How long should we follow up patients? We have heard a lot about some of the concerns and some of the difficulties, but some of the importance from a public health stand of being able to follow patients and how does one guarantee that? I think that is an issue that we have to discuss, and what types of follow-up tests should be performed is another issue. Do we want to use postcards? Do we want to use physical exams? What kind of specimens should be collected if we wanted to do further analysis along the way if something did arise?

So, I think these are very particular types of issues but ones very important because the presence of an infectious zoonotic agent could have major ramifications and the ability to track these appropriately do become very important.

The other issue is in terms of follow-up could it be modified based on individual and public health risks with a particular type of xenotransplantation product, again, in accordance with potentially lower risk products versus higher risk products.

Another area that we are very interested in pursuing is patient populations. Should certain patients be excluded based on their ability to comply with the necessary follow-up and restrictions or their ability to give informed consent? This is a very difficult issue.

Some of the things that come to mind in this ware would be if you are treating patients with known alcohol or drug abuse problems and how would you manage that, and should they be involved in early trials? How about children or comatose patients? Should they be given this treatment, and how do we handle that, and this is something we very much would like the Committee's feedback on.

Another issue and one that I think is very close to the heart of this Committee is the issue of public disclosure, and I would encourage all of you to read the latest proposed rule that the FDA has published

in the Federal Register, and please give your comments on this?

This may be something that we would like to bring back to the Committee in the future as well for additional comment. Some other issues we would like to see at some point again are potentially the identification of microbial or infectious agents. The fact that some of these, would the different sources be delineated and asked for; should any animal sources be excluded?

As you know currently non-human primates are not viewed as acceptable for xenotransplantation, and then there would be besides sourcing what kind of additional testing would we like, both on the source animals and human recipients, and what would be helpful testing and follow-up in that case for these infectious disease agents, and again, the issues that have been raised over the course of 2 days, we feel it is very important to get community involvement and provide a vehicle for input into these very important new scientific breakthroughs.

I do believe the education and understanding of the risk/benefits in a setting where we can discuss the science but, also, have appropriate involvement of all parties will very much be considered important by the FDA.

Again, issues of the economics as was discussed, animal welfare and other ethical issues are not things that FDA normally is involved in, but we would very much appreciate hearing some of those issues discussed as well. So, thank you very much.

DR. GROESCH: Any specific questions for Dr. Zoon or comments? Thank you.

Okay, who volunteers to be next? Oh, we do have one comment.

DR. VANDERPOOL: Catherine, I am sorry I was toting yet another sheet around. Hopefully I asked several people are these helpful, and particularly the federal persons involved said, "Yes," and hopefully we will get an outline of all of these issues we have identified and raised.

My question is that a lot of the issues you identified are very much scientific judgments of validity of preclinical models and studies, questions involving risk, the species that are being used and so on, and this means that we have some more learning to do and will need to call in real experts to assist us in addition to the experts we have on this Committee to air these in detailed fashion because these scientific issues are inescapable for us and yet many persons on this Committee are not involved at the cutting edges of scientific research, and so we will need real support in hearing these people out, understanding what they are saying so we can make rational and wise recommendations, but thank you, a very challenging set of issues from your standpoint, and I think we take all these charges very seriously.

DR. ROTROSEN: I will go next. I think many of the issues raised in the past couple of days are important to NIH and I think that of those that are of primary importance to us we have alluded to all of them here in the last 2 days.

So, I will be very brief and just highlight some of these that are of critical importance. One is the topic we discussed a little bit this morning in the context of Dan Salomon's presentation, assuring an adequate research base to make informed decisions both at the preclinical and the clinical level.

This is much more complicated than just infusing more research dollars into the equation, and I don't mean to suggest that either Dan or Megan's comments were a simplistic approach to generating more

research. The issue is really one of scientific advances and public acceptance and support for xenotransplantation research, allowing this field to become a viable career path for new investigators and one into which established investigators want to devote more and more of their effort. Without that acceptance and the scientific advances it is a risky business for somebody to devote a lot of effort to xenotransplantation research.

NIH can certainly do a lot to accelerate that, but we have to be mindful of the risks and keep in mind that NIH is roughly two dozen institutes and centers that don't always have the same priorities. Many of those institutes currently fund xenotransplantation and related research, but none of the institutes are currently funding clinical trials in this area.

As we discussed this morning this balance is very heavily tipped towards industry, and that may not be the best long-term approach for the nation. I would imagine that this will change. NIH receives unsolicited applications for clinical trials, and we solicit applications for clinical trials, and we will be speaking to other institutes and within the PHS working group about how NIH can best facilitate and support these types of applications when they come in.

We are, also, going to need to talk about multi-institute partnerships, collaborations between NIH and CDC and the FDA and how we can best work as a team to support this whole area.

One thing that we didn't really talk about in any detail is NIH's role as a research sponsor. The word "sponsor" has been thrown about in the past couple of days and sometimes rather loosely. Sometimes it refers to the drug company sponsor. Sometimes it refers to the academic institution and sometimes maybe in a sense to the principal investigator and sometimes it should refer to NIH as the funding agency of clinical trials when they occur, and the NIH may be in a unique position there as opposed to all these others in terms of our accountability to Congress and to the public, and we need to proceed cautiously and I think the institutes will be looking to the input and guidance from this Committee as we talk about our role as a research sponsor.

I think I will stop there, and I will be happy to answer questions.

DR. GROESCH: Any comments or questions for Dan?

DR. SYKES: I have a question. Could you just clarify your comment about the need to have more NIH funded as opposed to industry funded work? Did you mean that to apply only to clinical trials or were you referring, also, to more basic research?

DR. ROTROSEN: I think my view is that it would apply across the gamut from fundamental research to clinical research. There is no reason to, you know, I don't differ at all from I think the comments Dan made this morning about industry support or perhaps you made as well, industry support not necessarily being the long-term view that is needed to support a field as risky and with as many unknowns as this.

So, NIH support currently is all in the preclinical and fundamental immunology and microbiology areas, but we could use more.

DR. RUSSOW: I was almost ready to make a comment on Harold's summary and your talk sort of prompted me to think that I ought to make it.

There is a tendency to think that scientific issues are separate from value judgments, and that simply isn't

true. When we decide what standards to demand for preclinical trials, when we decide which project to fund, you have scientists making value judgments, and I think that there ought to be recognition of that and a putting to rest of the idea that there are scientific issues and then completely separate value judgments. That is simply not the way science works. We make judgments about what is important, what is more important all the time. I should have said, "You," not "Me," although I have done grant reviewing for both NSF and NIH, and of course, the first question that you are supposed to use in ranking the grant proposals is how important is this project.

So, that was my comment.

DR. ROTROSEN: Let me respond? If I gave you the impression that we could dissociate the scientific and the value and public health policy issues here I don't think we can. It is worth keeping in mind that the peer review of grant applications at NIH and other planning for solicited research goes through many levels of review. The scientific study sections are just one.

After that each of the institutes has a council that reviews funding decisions for not just scientific merit but programmatic interest of the institutes, whether this research fills a gap that is not otherwise being filled, whether there is overlap that is unnecessary and in terms of public health policy.

So, I think there is quite a bit of attention paid to those issues, and it is just as an extensive approach when we do long-range planning and solicit research in any of these areas. That goes through a very extensive review that involves outside experts.

DR. RUSSOW: Thank you.

DR. ALLAN: I just had sort of a clarification. I think what I heard was that xenotransplantation is at a point where it is still a bit risky in terms of whether it is a viable long-term option, and so what I was wondering is it sounds like you are amenable to at some point like stimulating preclinical research through either an RFA process or some other solicited way of generating more input from the scientists in terms of basic research. Is that what I am hearing?

DR. ROTROSEN: I think we should steer away at this stage from talking about specific solicitations, and you know an RFA is not necessarily always the best way to support and facilitate research. Sometimes if the timing isn't right putting additional dollars into the fray does not bring out the best researchers or the best projects.

There are other ways NIH can facilitate research providing core facilities, collaborative groups that work on issues that could be very basic science issues. They could relate to virology and microbiology as much as they do to the clinical end of xenotransplantation.

DR. SALOMON: I think one of the things that really resonated with me in Dan's comments, and we discussed it a little bit at lunch as well is his very insightful view that part of what we need to do is make sure that we are attracting scientists, both junior scientists and mature investigators to xenotransplantation, and for that we need to take a second and look at where xenotransplantation is and I think it is a really interesting challenge Dan puts forth for us.

From my point of view the organ shortage is there, and I don't think there is anything more to add to such an awesome responsibility to medicine, and I think that we get mixed up when we forget and we are reminded by men like Jim that xenotransplantation isn't just for failing kidneys and hearts and livers,

albeit that is a perfectly appropriate target, but central nervous system disease and diabetes and a whole other thing.

On the other hand what is counterpointed here is that we are in a sort of an odd time for xenotransplantation. An early wave of major claims that we would be in clinical trials and curing things left and right that rocketed xenotransplantation forward in the public's mind at least and funded a bunch of biotech endeavors from large pharma have slowed down. They reached a number of rocky spots. We have to remind ourselves that there is probably just a little too much hype in this area and that a lot of what has failed is in the very first prototypes in an area.

Yet at the same time we face xenotransplantation trying to go forward in kind of an awkward area. You know we are talking about animals. We are talking about genetic engineering. We are talking about gene therapy, a bunch of things now that everybody is nervous about, and those are things that actually could be viewed as impediments to attracting talent and resources and dollars, things that I think Dan has done a really good job of articulating for us as challenges for the NIH to help.

I just think there are lots of very important things Dan has made me think about at least and the bottom line here is I think the irony of telling me, "Oh, don't worry about xenotransplantation; really you don't have to worry about it because of stem cell transplantation or stem cell research is right around the corner" is ridiculous, and I hope it provides all kinds of new exciting strategies. Don't get me wrong, but xenotransplantation is a pretty darn good technology to invest some energy in in the next decade.

DR. GROESCH: Dr. Spira, did you want to go next?

DR. SPIRA: Thank you for having us here and discussing this important issue. What I would like to do which the other agencies haven't done, but I thought since I was a non-Washington-based agency I should still do because you may not all be familiar with what CDC does and what its mission is is to first give you just some general background of what our concerns are going to be.

The mission of CDC is to promote health and quality of life by preventing and controlling disease, injury and disability, and as you can see it is a fairly broad mission. We don't have the regulatory powers that FDA has. Many of the things we do we do either on our own or when we are invited in by other agencies to assist.

How do we accomplish these missions? The accomplishment of this mission is predicated on CDC's ability to build on the following agency strengths. One is the prevention strategy is based on scientific knowledge; two, leadership and technologic capabilities of state and local health organizations and integration of those capabilities with private health organizations; the use of trained public health workers and leaders and the ability to serve a diverse population with a diverse work force.

Now, as the nation's prevention agency we accomplish our mission by working with partners throughout the nation and the world. This is to monitor health, detect and investigate health problems, conduct research to enhance prevention, develop and advocate sound public health policies and implement prevention strategies, promote health behaviors, foster safe and healthful environments and provide leadership and training.

These functions are the backbone of CDC's mission, and each of the CDC component organizations undertakes these activities in conducting their specific programs. Xenotransplantation activities are clinically based in the Center for Infectious Diseases, and many of my remarks will relate to those issues.

The mission of CID, Center for Infectious Disease, is to prevent illness and disability and death caused by infectious disease in the United States and, also, worldwide.

How do we accomplish these goals? Through a variety of mechanisms. One is surveillance and response. This is to detect, investigate and develop ways to stop the spread of newly emerging and drug-resistant infectious diseases. We have a research component which conducts and sponsors laboratory and epidemiologic research for prevention of emerging and re-emerging infectious diseases, and there is a prevention and control component providing public health information about emerging infectious diseases and ensuring the implementation of prevention strategies and then, also, building infrastructure, strengthening local, state and federal public health departments to support surveillance and response activities and implement prevention and control programs.

Now, how does this relate to xenotransplantation? I think our main concern in this area is for the potential transmission of a known novel infectious disease agent through xenotransplantation. The specific goals that I see for the agency are No. 1 to participate in surveillance of xenotransplantation to detect the transmission of infectious disease and infection. We have already heard about some of the systems that are being put in place like the xenotransplantation database to address that. I think in terms of questions we have regarding this activity there is how we can best fulfill this function, and this means continuing evaluation of the database and other mechanisms for doing surveillance so that we do not do more surveillance than is necessary because there is a cost to these programs and also do enough to potentially detect problems that can occur.

Second is improving the capability to diagnose novel infectious agents. We are very much concerned with re-emerging diseases and newly emerging infectious diseases. Although in general our concerns are more for human diseases one of our questions would be should more be done to be able to detect infectious diseases in source animals that we are not currently aware of. Should more be done than is currently done to investigate outbreaks in populations of source animals that might detect agents that we are not currently aware of and that we should be aware of in terms of source animals for xenotransplantation?

We, also, want to make sure that recipients are followed up adequately so that we do have the potential to detect an infectious disease problem, and we have already heard many of the issues regarding this, both in terms of education of the recipients to long-term follow-up if that is necessary to detect either immediate or long-term infectious problems, the adequacy of the informed consent process so that the subject is knowledgeable in terms of the risks that he is going to bear because I think that is again one component in the compliance of subjects for potentially long-term follow-up.

CDC has been involved in conjunction with some of the biotech companies in doing retrospective surveillance of our existing transplant recipients. Some of this was related to PERV. Should more of this be done? As new agents are discovered that may infect source animal populations should we go back additional times to patients who have already received material from such source animals to at least get some preliminary information on whether there is a risk for those specific agents?

Unfortunately, these retrospective reviews currently are limited by the small numbers of patients that are available so that we cannot necessarily rule out a risk although we might be able to say something about the level of risk or if there is no evidence for transmission we may say that that to some degree is a less likely possibility.

We are already doing surveillance of emerging pathogens. We have a number of mechanisms in place to

try to detect new agents that may be causing human disease. Some of this is done through looking at unusual cases of disease where the etiologies are not readily apparent to see if they may be due to emerging problems. I think using those types of mechanisms and applying them to xenotransplantation may be useful but I think we may have to adapt the types of surveillance we do for this.

We have a long history of providing emergency response for evaluating transmission of infectious agents, outbreak investigations through the EIS, the Epidemic Intelligence Service. This is always done with the invitation of the local investigators or the local state or local health departments or internationally through intergovernment requests.

We presume that that will continue for any situations that might occur, but this is late along the line. Hopefully we will prevent those situations from occurring through some of our other activities.

Since we were involved in writing the PHS guidelines on infectious diseases in xenotransplantation I think another area where we would like to have input is the continuing evaluation of the adequacy of those guidelines. When they were written which was over 5 years ago we never expected them, I think, to be set in stone, and already in the process of just being published and accepted they have had major changes, but I think this Committee should have input in terms of making future changes or recommending future changes for those guidelines.

I certainly haven't meant to be exhaustive with my comments because many of the issues that I think we will deal with have already been covered by others, but I think we view this as a fluid, ever changing process and as they relate to some of our mission goals I think we would like to have as much input from the Committee as we can.

Thank you.

DR. GROESCH: Thank you, Tom. Any comments or questions?

DR. SCHECKLER: A question. As a big supporter of the CDC I enjoyed your presentation. As far as the guidelines are concerned when the advisory committee that I sit on does guidelines, the Health Care Infection Control Practices Advisory Committee, life is relatively simple because we know what we are looking for. We know how to define it. We know most of the time how to find it in terms of surveillance, and we even have some reasonable science on what to do about it once we find it.

In terms of the Public Health Service guideline on xenotransplantation when I was looking at it it didn't have and cannot right now have the evidence base that the HICPAC(?) guidelines currently have with level one, level two confidence of the information.

Your last comment about the fluidity or plasticity of the current guideline and your concern that it be set in stone, do you have any specifics for us? Should we be reviewing that once a year? Should you all be providing us with evidence for or quite possibly against continuing to do something that is currently in the guideline on a regular basis? It seems to me that might be a useful strategy. Have you discussed that at all?

DR. SPIRA: Obviously the agency will be reviewing the guidelines. The working group dealing with xenotransplantation will, also, be reviewing those issues. It is hard to predict how frequently we as a group or this Committee as a group needs to review that. I think part of that is based on, will be based on how many xenotransplant protocols are actually implemented and how much objective science-based

information will be generated over the next year or 2 years.

If the field moves very rapidly I think we will, also, have to re-evaluate those more rapidly. If the field moves relatively slowly I think you know we will not have adequate information to make well-considered changes that rapidly. So, I am certainly willing to play this by ear and determine when those time points should be based on the level of activity.

DR. ALLAN: I think the CDC has done a great job with the xenotransplantation diagnostics work that was done in working with some of the companies to look at some of the ongoing clinical trials.

The question I have, and maybe you can give me some feedback on it is in terms of the way companies are screening either the source animal and patient, some companies are doing their screening in house. Some are using commercial companies, and some are going through the CDC to provide samples. Is that working well? I mean is it suitable for the CDC? In terms of the clinical trials what percentage of them do you actually get samples from that you can actually screen yourself?

DR. SPIRA: I cannot answer that question directly. I know we have been involved in some of the clinical trials and doing some pre-screening. I am not sure we have necessarily the capability to screen for every agent on the long list that we have seen projected, and the issue of whether that is absolutely necessary for many of those agents I think is open for discussion.

I think in areas where we do have the expertise and the diagnostics available or we will be developing those diagnostics I think there certainly is a willingness to collaborate on those issues, but I am not sure CDC should be the only source or the central source for such testing. I think having that capability in a variety of places as long as it is well controlled adds to the research effort.

DR. GROESCH: Louisa, did you want to make a comment?

DR. CHAPMAN: I was involved with the labs that are doing the screening. Maybe I could just augment Tom's comment a little bit to say specifically early in discussions there were some expressed hopes that CDC would sort of become the surveillance testing center for the nation, and that is not a role that we can really take on.

What our laboratories have to be able to do is respond to an emerging public health interface with development of new diagnostics and shifting to the most pressing public health issues, and what we have done so far in our laboratories, my colleague, our colleague but in my branch, Wally Haynini and his group have taken the lead in developing when it was a question of how you could screen for endogenous retroviruses. Our division director, Dr. Jaffe came back from an FDA subcommittee actually and said, "This is our responsibility," and our laboratories took the lead in defining a way to test in the laboratory for endogenous retrovirus infection, developing assays, getting those into the literature where they were available for other people and it is an approach that has been widely replicated.

Our labs have, also, been involved in, and we have been involved in scientific collaborations to define levels of risk and we are involved in screening some specimens from sponsors who are under clinical trials, but our involvement in that is and always has been defined as a research collaboration and when we have answered the questions that we feel it is our responsibility to answer the understanding has always been that they will then be responsible for finding screening elsewhere.

So, does that address your question? We were involved in defined limited research collaborations to

address specific, ask specific questions of public health significance. We are not involved in providing routine ongoing screening.

DR. GROESCH: Thank you. Megan?

DR. SYKES: A thought that has occurred to me during the last 2 days, and I would like to throw it out right now and get your thoughts and really throw it out to the Committee, and it may be totally unrealistic, but it seems to me that with respect to the exogenous viruses there are some that we know about, and there is concern about others that we may not know about, and the risk from the unknown exogenous viruses could be limited if we had one or maybe two colonies of pigs from which all xenotransplantation trials were conducted so that there would be fewer sources of pigs and therefore less potential to introduce new unknown viruses.

I realize that logistically and from a regulatory standpoint and financially there would be enormous barriers to doing things that way, but I would just like to get your thoughts on whether you think that would help to limit the risk to some extent.

DR. SPIRA: I am not sure that I as a CDC representative can answer that question specifically because I am not sure, you know, in terms of limiting the risk it might be useful, but it might have an effect in terms of limiting the availability of animals for the process. I am not sure who would take on sponsoring that colony. It is not like primate colonies that have some federal funding, and I am not sure if the federal agencies are at this point willing to take on that responsibility.

It is, I think difficult to eliminate the risk completely even by screening for known viruses. In my years at CDC we have had at least a dozen or more new infectious agents that cause disease in man discovered that we were not at all aware of, and I suspect that the same will be true for source animal populations as well although as I say, surveillance there may not be as adequate as for human disease.

DR. GROESCH: One last question. Marian?

DR. MICHAELS: If someone had another question I would give up the floor to that, but I was sort of going to answer Megan's question. In fact, that would make me a little bit concerned if we had only one or two colonies just because of the chance that we might have that in fact that colony be one that has one of those exogenous viruses.

I think a good example of that was the hepatitis E virus that initially I remember a report came out that I think Purcell was on that said that when they went back and screened some of the SPF colonies that they didn't find the hepatitis E virus in them, and I was like, wow, that is wonderful, you know, because they were being screened for other organisms, had a clean colony that was closed and they didn't get hepatitis E virus into it.

So, when I had reason to talk to him more recently, and he had screened more colonies around the country in fact it came out about 50 percent, and it was just a chance that if they did not have hepatitis E virus in the initial starter colony they never got it in because they had good closed colonies. If they had it in there in the initial time because it wasn't one of the viruses being screened for then they continued to multiply in that particular herd. So, perhaps having one herd would actually be a detriment. I am not sure.

DR. GROESCH: Thank you. Our next commenter is Dr. Laura St. Martin from the Health Resources Services Administration.

DR. ST. MARTIN: Mr. Jon Nelson had to leave to attend a meeting with Secretary Thompson, and he asked me to speak on behalf of HRSA. I will be talking briefly about HRSA's interest in xenotransplantation, the need for organs for transplantation and some of our concerns related to xenotransplantation.

The Health Resources and Services Administration's Division of Transplantation in the Office of Special Programs provides federal oversight of the nation's organ procurement and transplantation network, the scientific registry of transplant recipients and the national marrow donor program contracts, coordinates national organ donation activities, funds grants and coordinates special initiatives to learn more about what works to increase donations and provides technical assistance to organ procurement organizations and other transplant-related entities.

The organ procurement and transplantation network is charged with developing bylaws and policies that maximize the utilization of organs donated for transplantation, assuring the quality of care for transplantations and addressing other complex medical issues related to organ transplantation in the United States.

Historically the Division of Transplantation has concentrated its efforts on increasing organ donation. A substantially larger portion of our budget goes towards activities to increase organ donations than the portion that goes towards management of our contracts. Currently there are over 74,000 patients on the national waiting list for organ transplantations.

In 1999, only 21,655 transplants were performed limited by the lack of available donor organs and over 6000 patients on the national list died while awaiting transplantation in 1999. Other patients were removed from the list because they became too ill to tolerate the transplant procedure and were no longer considered suitable candidates. There may be other patients who could possibly benefit from transplantation but are never added to the list because the procedure is reserved for those with greatest need and presumed greatest benefit given the limited resource of donated organs.

The success of transplantation has resulted in a growing demand for the life-saving or life-enhancing procedure and waiting time for organ transplantations are steadily and rapidly increasing. Efforts to increase the supply of donated organs through expanded donor criteria such as using older donors and non-heart-beating donors and intensified efforts to educate the public about the importance of organ donation has had moderate modest but encouraging effects thus far and there are still other avenues to pursue.

The current system of allocation of human organs strives to balance the ethical principles of justice and utility to achieve equitable allocation of the scarce resource. If and when xenotransplantation becomes a clinical reality it will introduce more variables into the justice and utility equation. As has been mentioned or discussed, how will xenografts versus human organs be allocated, who will be appropriate candidates? Will patients and graft survival be comparable? There will be other quality of life issues related to restrictions imposed on xenograft recipients and possibly their close contacts and health care workers who are exposed to minimize infectious disease risks, and some of these restrictions that have been discussed include life-long surveillance, requirement for autopsy upon death, behavior modification and access to medical records by appropriate public health agencies.

There will be a need to put in place safeguards from vulnerable populations such as children, minorities, women and the poor who may not have equitable access to transplantation or may be more willing to accept the increased risks that may be associated with xenotransplantation. Other issues to consider

would be should children or women of child-bearing potential be considered candidates for receipt of xenotransplantation products.

Probably of more immediate concern is the effect of xenotransplantation on the supply of donated human organs and bone marrow which is, also, one of our interests due to restrictions on donation by xenotransplantation product recipients and their close contacts. This will become more of a concern as recipients and patients involved in clinical trials of cellular and tissue-based xenotransplant products increases and if and when there is clinical use of cellular therapy involving xenotransplantation products.

As the development of xenotransplantation as a medical therapy progresses and enters the realm of clinical use, there will be a much greater need for interagency collaboration to address issues that affect human organ transplantation, including organ donations, allocation policies and donor screening and deferral. And I just wanted to mention because I believe it was developed amidst some other discussions that occurred earlier in this session HRSA recently formed a Secretary's Advisory Committee on Organ Transplantation. While the work of that committee will primarily involve making recommendations to the Secretary on organ allocation policy there will be some focus on organ donation.

Secretary Thompson has identified organ donation a one of his top priorities as the new Secretary of Health and Human Services. So, I just wanted to make the point that organ donation, human organ donation is a top priority for HRSA's Division of Transplantation.

DR. VANDERPOOL: Excellent remarks. I think there may be a need for us to meet with members of that organ advisory committee especially hashing out issues, for example, over equitable access. Maybe those in the federal agencies feel you have this under control, and some people on this Committee have worked with some of these issues involving equitable access to transplantation but a lot of us haven't, and that is certainly an issue we could focus on at some length if we needed to.

DR. GROESCH: Lily, did you have a few comments?

MS. ENGSTROM: I have just a few brief comments to make, and I wanted to be the last one on this side of the room. First of all, I want to commend this Committee. You have done a very able job of really identifying a broad range of issues that need to be addressed and in a way that is really, really daunting.

Since the Office of the Secretary doesn't have any regulatory funding or research role per se I don't have a specific agenda to recommend to the Committee. However, I would like to suggest that because the range of issues that needs to be addressed is so broad that the Committee attempt to develop some priorities among these issues so that we would have a long-range action plan of some sort, and my colleagues and I stand ready, willing and able to assist you in any way we can.

Having said that I, also, want us to be mindful of the fact that there will be issues that emerge either within the purview of one or more of the agencies represented on this Committee that may require the immediate attention of the Committee, and of course that would be brought to the Committee's attention and to Mary's attention as soon as possible so that in fact it can be put on the agenda of the Committee when it next meets, but on a long-term basis I would like to see some sort of priority set so that in fact we can go ahead and approach and try to address these issues as they come up, and I think that one of these that you probably should know and Lilly has already alluded to it a moment ago which is in Tommy Thompson's first public address to employees of this Department he mentioned a number of things that were high priority. He mentioned Medicare reform. He mentioned prescription drugs for seniors and then he said the following, and I think I am quoting him somewhat correctly. He said, "In the next 100

days I want an aggressive plan to increase organ donations."

I think that is very precise. He did not couch anything else in those exact terms and that tells me a couple of things. One, he recognizes that transplantation is important, that there is a severe shortage of organs and that he comes from a state which has been quite successful in terms of the number of donations that they are able to get each year and, Bill, you may want to speak to that as you know more about it, but I think that inasmuch as he has actually made that kind of public statement I think that it would not be a leap to believe that he would be very encouraging of the kinds of issues, very supportive kinds of issues that this Committee is addressing because if in fact if one day xenotransplantation is successful, it is going to provide the answer to the question facing all of us which is what do we do with the immense disparity between supply and demand.

So, I think that the Secretary will be looking to this Committee to come up with policies and procedures that while encouraging xenotransplantation is going to safeguard public health and at the same time not discourage the development of a very promising technology.

Thank you.

DR. VANDERPOOL: I want to express my personal appreciation, Lily for your being here every minute of these meetings and participating as you have and thank you for being a conduit, and hopefully you can rein us in on the types of issues we need to discuss and keep our attention riveted on the issues that the Secretary is most interested in dealing with.

Thank you.

DR. GROESCH: I would like to hear from the public now. I know that there are some people that would like to make some comments. If you would please state your name and any organization that you are affiliated with that would be appreciated as well if you could write it down on a piece of paper and provide it to the court reporter at the end of the table. I think that would be very helpful, and could we just see a brief show of hands of how many people would like to make comments?

(There was a show of hands.)

DR. GROESCH: Okay, if you could come up to the microphone, that would be great.

Agenda Item: Public Comments

MS. TALLACCHINI: Thank you very much. My name is Maria Tallacchini from the Kennedy School of Government at Harvard and perhaps I need to say that I am in the US with a grant of the nationalist(?). The nationalist title is reframing rights in a technological change because this can make clear my question.

Actually I have two questions and one problem, and the first question is again about the informed consent and while informed consent was born in a forgiving voice and protection to patients and individual autonomy, but it is clear that in xenotransplantation procedures there is little room for autonomy, and actually the FDA guidelines talk about information and education much more and there is little room for autonomy both because some features are constraints and limits to freedom and others are linked to responsibility and obligation. So, my question is is it still useful to think about the patient involvement formally with the tools and the terminology of informed consent when we are dealing substantially with

something that is quite different and this is not a formal question and Professor Shapiro raised that problem. This little change is something that it is important even from a constitutional point of view because the main task of law is that of being clear and providing clear means of protection and not being misleading, and perhaps in this case to talk about informed consent is in some sense misleading.

My second question is about the public, and the public has been mentioned here in relation of the need to make more studies on social response or in terms of disclosure and education of the public, but a lot of studies, and I am from Europe and while both in the European Commission but closest to the United States is now a proposal by the Canadian Government has been made for concrete participation of the public, that is the public is seen as a source of knowledge and a partner in the decision, and so the problem of the public is that and within that of the democratization of scientific issues when they affect in such a strong way the society.

My problem is how to link these dimensions, the individual one and the public one and how this is made in the FDA guidelines, and perhaps this is not the task of the technical regulation, and so the problem is that regulation versus legislation.

I mean there is this strong tension between the big amount of safety measures that are stated and the individual responsibility. It seems that all these means, the legal means for providing safety are given to the compliance of patients, but legally how can you do that? You can exclude the patient from xenotransplantation if it seems unreliable since the beginning, but if it becomes not compliant what happens? There is no mention and this is a tough problem for compulsory measures.

The other legal tool we should mention is that of liability, but there are two objections to liability. One is that perhaps it is too big a burden for one individual toward these kinds of social change and social distinction and in this respect I think that there are lots of differences with HIV because HIV happened in many ways by chance but this is a society decision, and the other objection to liability is that liability is an ex post measure, that is it takes place only when damage already has occurred.

Thank you very much.

DR. GROESCH: Thank you. We appreciate your comments. Dr. McArdle?

DR. MCARDLE: My name is John McArdle with the Alternatives Research and Development Foundation. A lot of useful and interesting information these last 2 days. What I would like to do is just to identify three very specific suggestions that I would like to offer to the Committee that build mainly on things that were said this afternoon in the areas of economics, animal welfare and alternatives.

In terms of economics a couple of times over the last 2 days suggestions have been made about the possibility of spending more money, putting it perhaps into research or into clinical areas related to xeno.

I think it might be useful for the Committee and certainly I, personally, would find it very interesting if there were some statistics available on how are we currently allocating funds for research on xenotransplantation both basic and applied; how are we allocating money for the alternatives, such as tissue engineering, artificial liver and that sort of thing, both basic and applied, and how much money is being allocated toward improving organ donation?

I heard that it is going to be that there is an increased priority, but how much money are we actually putting into that?, I have never seen that kind of information available. We could actually compare the

three together, and I think it might be useful.

On the issue of animal welfare obviously this is a major perspective that I am coming from. Two concerns that I would like to share. If xenotransplantation becomes a procedure that becomes widespread we are going to create a new class of organisms, animals, if you will that are going to be used as the organ donors, and two areas of concern that I have with those animals, one is we are talking about them being SPF facilities. Those kinds of facilities for those specific animals are going to maximize their behavioral and their environmental deprivation, much more so than animals that are currently being used in research. So, I think one of the things we are going to need to consider, are there going to be special needs that group of animals is going to have that may not in fact be incurred in other animals used in research from the same species that certainly are not covered by current regulation or law.

We have, also, been talking about genetically modifying the donor animals. Now, in Europe over the last couple of years there has been an increasing level of concern on the special needs of transgenic animals, and it is starting here in the United States. Usually that has to do with an animal that has had one gene changed, maybe two. The possibility with these donor animals we are going to see multiple genetic changes done to these animals to make them suitable donors. That may increase the number of problems that they have to deal with as the number of genetic changes are increased.

So, one thing the Committee might consider is making recommendations that there be special care standards set up for these donor animals because of the special circumstances under which they are going to have to live in order to be these donor animals, and lastly the issue of alternatives.

I, personally, was very pleased to hear this morning that the Committee is going to be kept abreast of developments in the biomedical alternatives to xeno, what is happening in that and considering that, but the alternative, also, that is of concern to me is the increase in organ donation. Again, it was just mentioned that efforts are going to be made to find more organ donors.

I think probably the weakest link in the argument supporting xenotransplantation is that you cannot in good conscious go to a patient today or go to the American public and say that as a society we have done everything we possibly could to maximize the number of organ donors. We have not in comparison to societies in other parts of the world.

I think the Committee has the ability to go to the Secretary and say as part of this overall package for the patients that are out there we need to be doing more, and maybe we could consider the following and look at what other countries have been doing to increase their organ donations.

There have been significant improvements in certain areas. As a suggested starting point you might want to look at the General Accounting Office study from 2 years ago that looked at OPO performance here in the United States and found in many cases it was seriously lacking. They, also, came up with their estimate of what is the organ pool out there that we are trying to sample and how good a job are we doing. Whatever assumptions they may have made, whatever criticisms you have of their technique, they came up with a rather large number of potential organs that are not being harvested for the patient population.

So, I think if we are going to be talking about alternatives we have to, the Committee has to also consider the possibility of recommending ways to increase organ donation over and above the ones we have been traditionally using for the last several decades.

Thank you.

DR. GROESCH: Thank you very much. Any other comments?

DR. BAILEY: Len Bailey from Loma Linda. I, too, would like to commend this Committee for your very thoughtful deliberations. I learned a lot sitting through these 2 days. I think your discussions were wise and very appropriate.

I would like to make two appeals. One is that I heard very little about pediatrics and pediatric donors and recipients. My life is revolving around infants and children each day, and I hope that you wouldn't exclude the realm of pediatrics in your deliberations and the uniqueness of childhood and consent by proxy and those sorts of things.

The second appeal is that this Committee and other agencies in the Federal Government keep an open mind about the donor species, particularly for AIDS-related uses. I have been focused for a number of years on newborns and I would submit to you that there are age-related differences in both donors and in recipients in that age group, and I would be happy to share some of that with you, but in reviewing some of Jon Allan's work in the literature already I think you would have to suggest that he had a hard time finding the FOMI(?) virus for instance in baboons under 15 months of age. I am not at all surprised to hear that these fetal pigs did not easily express the viral fragments known as PERV and so there is a whole area of age-adjusted thinking that perhaps this Committee needs to consider as well.

Thanks very much.

DR. GROESCH: Thank you. Any other comments?

Agenda Item: Closing Remarks

DR. VANDERPOOL: Let me just say that we welcome the comments of all of you and take them seriously and that is part of what our task is in keeping with the encouragement of, within the body of the new proposed disclosure regulations that we be open to the public and that we seek in ways possible to educate the public and we welcome suggestions as to how those responsibilities of education can be carried off.

I promised to have as closing remarks the comment that we have had a most productive meeting, and I wish everyone well, God speed, and we shall be meeting again.

Thank you.

(Thereupon, at 3:57 p.m., the meeting was adjourned.)