Third Meeting of the
Secretary's Advisory Committee on Xenotransplantation

Transcript

Breakout Session: Working Group on the
State of the Science in Xenotransplantation

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******* PLEASE NOTE THAT THIS DOCUMENT HAS NOT BEEN EDITED FOR CONTENT *******

Agenda Item: Concurrent Working Group Breakout Session, State of the Science in Xenotransplantation

DR. SYKES: What we need to try to do this afternoon is to follow on what we discussed at our conference call and really fill in some of the details in the areas that we've defined and add any other areas that we may have missed out on in our first discussion.

So does everyone have the summary that Mary provided us with? It's in Section 6 of your materials and it's entitled "Notes from 11-9 teleconference." So if we could -- maybe what we should do is use the outline that we've drawn up as a starting point. It is the last two pages of that document. And look it over and first open the floor to discussion of any aspects of Xenotransplantation that are not covered in the format that we and also discuss whether or not the format could be streamlined or made clearer in any way. I would like to actually start by bringing up, again, the fact that we have been focused only on pigs thus far.

And now that, well, it isn't the first time, but the alternative as an islet cell donor, the Tilapia fish seems to have generated a fair amount of interest, I think we should be sure that we consider that donor as well in our report, and I wonder if people would like to suggest where that could fit in, how we can structure that into the report.

DR. GROESCH: Megan, only the members have the outline, so maybe you just want to briefly go through it so people know where we are in the overall scheme.

DR. SYKES: Well, the outline is divided into five major areas. Well, the working group in our discussion on the phone we identified five major areas that we want to cover in our report. One is the potential impact on health of xenotransplantation. That includes how large is the population that could benefit from xenotransplantation. What are the economic implications of being able to do xenotransplants.

The second area is the science, including the current state of the science, where we see it going in the future, what are the things that are in the pipeline, what are the major gaps in our knowledge, and incorporating into this the basics, how do we reconcile issues of basic science approaches, including physiology, with industry's imminent need to enter into clinical trials. And I do think that the economic issues do need to be worked into this report in a fairly prominent way because it's something that keeps coming up in the hurdles that we identify.

The third is the infectious disease risks, which we've heard quite a bit about. Fourth is regulations, what's in place, what's in the pipeline. And are they adequate to cover all important areas. And finally future prospects. Identify all obstacles, challenges to moving the field forward over the next several years. And here is where we thought funding issues, resource sharing and what is needed to meet these challenges.

So we then tried to come up with a structure for this report that would cover these areas and that was divided into five fairly similar divisions. So one, potential impact on health; two, the science. And we divided that into five areas again. So actually two major areas, the first one being different types, the different types of xenotransplants including solid organs, cellular transplants, extracorporeal technologies and then transgenic and gene knockout donor animals and finally systems physiology in order to make sure we cover areas that apply to all types of xenotransplants but may not fit into individual
categories easily.

And then the second major aspect of the science was immune rejection and tolerance, divided into hyperacute rejection, delayed genograft rejection, cellular rejection, and finally some discussion of the role of immunosuppresive drugs in xenotransplantation. Then separated out from the science was the infectious disease risks and that was divided into three areas, species-specific risks, exposure to animal-derived feeder layers as a second area, and we felt it was going to be important to say something about ESLs in this context, and third the surveillance issues. And then area four, again, was regulations and policies, and five was future prospects.

Would anybody like to start by commenting on that overall structure and making any suggestions for its refinement?

DR. ALLAN: It's sort of a tremendous undertaking to think about all these areas that we need to tackle.

And I think that the way it's set up is fairly good because it looks as though what we are asking is to have more input from different investigators that have been targeted for each one of these areas. But we don't really have -- I mean, we have already had a lot of discussion and presentations on the infectious disease risk. The only thing I might want to change is under the subheading for infectious disease risk, maybe in B it should be more procedural. In other words, infectious disease risk based on whether it's a bridging, whether it's a fetal air system, so more broad rather than a specific, in that sense, and I think we could probably then categorize them as trying to come up with some idea of infectious disease risk based on the type of procedure and how long the organ or the cells are in contact with human cells, so that's the only thing that I would see that would be -- I'd want to modify.

DR. COOPER: I'm not sure it's the role of this committee to review everything that's ever gone in xenotransplantation. That's been done by lots of groups. It's a huge undertaking but it's also been done. I would have thought this committee is more geared to saying what they want to see completed before they would agree that xenotransplantation should go ahead clinically, which is a much more subtle thing to do is what people are going to come to the table with and say, look, we've got all this in animals and we think we are ready to go to clinical trial.

This committee has got to decide what it is they need to have presented to them before they reasonably are going to think they could go ahead. And that's obviously the science and the infectious disease side of it. So I don't know whether you need to do another complete review of everything that's going on but just take specific sort of areas and say what would we need if someone said they've got islets that they think were going to survive, what would we need to say, okay, you're now ready to go ahead, some sort of guidelines for people to know they have got to meet these criteria before they leap ahead.

DR. MENDEZ: I agree with David, and I really think as a practical matter we have to focus on the science of it and see how we can drive this forward a little bit more rapidly. To spend much time on -- infectious diseases are obviously highly important, as are the regulations and policies, but if we can't do the procedure, if we can't even get it off the ground, I don't think we have to be too concerned about these other aspects. Once we have an airplane that can go coast to coast, then we can start thinking about what are the problems with regards to terrorists or regulations or other things, but we have to develop the science far enough, find out, pinpoint where are the blockages now and see how we can go ahead. And along that line, as Megan said, not limit it perhaps just to the pig. There may be other models that we might look at.

And, again, in focusing on that which is most probably successful looking perhaps at cellular more so than solid organ and certainly perhaps not to lung, which we can't even do allograft-wise and to spend much money and time and effort on that, I think we should probably start with something first, nothing against the heart and lung people, but I would put my money where the bang was.

DR. SYKES: Just before Bill gets a chance to speak, I just want to respond to that. I think that in drawing this plan up we weren't trying to cover the whole history of xenotransplantation. I think we were trying to do exactly what you are saying, which is to pinpoint where the gaps are, what is needed to move the field forward. But in order to do that, we need to say something about what's being done and what the problems are with what's being done and what we've learned from what's being done, so it was more in that spirit that we included all of these things and through that process we'll be able to say, well, the most immediate xenotransplant that is likely to succeed is islets or extracorporeal perfusion or cells. But, that doesn't mean that we shouldn't point out that organ transplantation has enormous potential but there are much larger gaps that need to be met and we need to point out what those are as well.

DR. COOPER: Can I just go back on that. But this outline is going into coagulation problems, so on, it's going through the whole thing, and I'm not sure that even that is necessary because you would need to say to people you need to come to us with ten baboons with pig hearts in or pig islets who have survive this long and have not developed these problems and have been monitored for infections so on. That would seem to be more where you should be spending your time, not saying what delayed rejection is, because we don't even know what

delayed rejection is to some extent. And that's going to be overcome. It doesn't really matter how it's overcome, but if people can provide you good evidence that it's been overcome, then you can look and say have they covered all the other bases that we need.

DR. SYKES: Sorry, Bill, but I just have to say, David, our charge is not to be primarily a regulatory body. Our charge is to give, provide a synopsis of the state of the art and upon that come up with recommendations based upon that information. So I think what you are describing is more appropriate for a regulatory body than really what we see ourselves as.

DR. SALOMON: I think you've got to remember the fact that we are the secretary's advisory committee and therefore what we ought to be thinking about, I think, is what's the work product from that. And to me the work product would be an executive summary to the secretary. It doesn't have to be a 400-page review because nobody, A, wants that from us and, B, the secretary isn't going to read it.

So what we do owe, I think, the secretary for the investment in this committee is an executive summary of where the state of the field is according to this group, not according to the International Xenotransplantation Society or any other group at which have weighed in with their own spin on where xeno is. And then from there say this is what we advise you to do in A, B, C, or D area.

DR. SCHECKLER: Yes, I'm polite, I'm from the Midwest, I'm used to putting up my hand and being recognized.

I might suggest to Megan and John that that might be a useful way to move along. My suggestion based on most of the comments that have been made is that the outline look at each of the five headings and perhaps some of the subheadings in the following way. Cliff notes version of the current knowledge, if you will, a one-pager, a summary with some references, because I agree I've got two feet wide worth of stuff from this committee so forth. There's a lot of stuff out there. The second part would be gaps in knowledge. What don't we know that we really should know, where are the gaps. And the third and probably most useful thing would be a priority of new studies to make progress, which I think is what I heard Dr. Cooper talking about.

And I think that if we look at each of those things, for example, potential impact on health, if you are talking about solid organs, you have one set of numbers. If you are talking about cell, like Parkinson's disease or something, it's a very different order of magnitude in terms of numbers of cases that might benefit. But you have to make that distinction and there are tremendous gaps in knowledge and priorities and new studies. Once that's done it seems to me that we can then get to the issue of resources and what the -- what my good buddy Tommy would like to hear from us is, you know, where should if we have some extra resources, where should they be placed for the biggest bang. It's as simple as that.

DR. ALLAN: I want to come back to what I mentioned in our telephone conversation, which is the way I look at xenotransplantation since I'm not in the field and the only reason I got in the field is because of infectious disease risk, so I haven't gone to a lot of xenotransplant meetings, so I don't have the kind of information that say, Megan does or David does or Dan has or Bob has or many of the others. And so for me, what I think the advisory committee charge is, is first of all objectively looking at the field and to see where it's headed or if it is headed somewhere, rather than the perspective of how do we find the resources to promote this or do this or do that. The first place I want to sit at is, is the field going anywhere, is it really viable, is it going to take us anywhere. I mean, that's where I come from because I'm not in the field.

Whereas maybe others have a lot more insights and expertise and so they feel much more confident that this is going to happen and we just need more resources, for me, since I'm not in the field I tend to look at it and go, you know, is this viable. So that's where I would like to, I guess that's where my role may be is to sort of keep pointing that out as we go along. So for me in terms of what we've listed is a way to get information to the whole committee, especially some of the members in the ethical aspects that may have absolutely no knowledge of where the field is.

And so I would -- I think we are okay with this in terms of getting information out and then as it evolves, it may evolve into where are the resources going to come from and how are we going to get there. But I think it's an advisory committee, not a promotional committee in that sense.

DR. KASLOW: I think part of the problem may be that Dr. Cooper didn't have the benefit of being on the telephone call with us. What we were really intending with the outline is not a literature review and an exhaustive summary, but to identify areas where the committee felt -- we really didn't even have -- we haven't even heard enough to make intelligent comments about it, so these were to be brief reviews. And I think as a perfect example you so eloquently described the issues related to hyperacute rejection that I would argue we can probably cross that one off our list right now in terms of having to hear a lot more about it before we can say something about it. So I think that's what the outline was meant for, not to be an outline of a major review.

DR. SYKES: All right. Well, then why don't we try to move on. I think, you know, Bill, I like Bill's suggestion for a format but maybe what we could do is work with the format that we have right now in front of us just in order to flesh out the actual issues and figure out where we need more information and what areas we have enough information on. And then at a later time we can consider reformatting it in a way that you suggested.

Okay. So potential impact on health is the first item. Is that something that we have heard enough about? How do people feel about that?

DR. MENDEZ: I think we have heard quite a bit about it. I think even the laity know the tremendous potential if we had organs available, cells available for regenerative abilities of organs, terminal organs, and those who have terminated. We have the 77,000 patients waiting on our unit's list. We have -- we know how many diabetics, 50,000 each year are new. We have 2 million of them. I think there's little question as to if we have the capability of replacement of organs, what the impact would be. It would be enormous impact. It would be one of the major areas of medicine.

DR. ALLAN: So maybe we should use that as an introductory to our report, then, rather than a major area.

DR. SYKES: We know about it, but we need to educate the secretary about it.

DR. ALLAN: So how do we do that?

DR. KASLOW: I hate to get back where I was this morning, being misunderstood, but I wonder if we also heard, and I'm really just asking a question now. Have we heard enough about what, if any, potential negative impact there is besides infectious disease? And by that I'm thinking also of perhaps broadening the outline term there to talk about health and health care. Do we know enough about what the impact of major gearing up for xenotransplantation would be on the health care system? Have we heard from whomever we need to about that, both positive and negative?

DR. MENDEZ: I hate to talk so much, but just with regard to that aspect, we did have a committee meeting on the organ procurement agencies with regard to xenograft and what would happen to organ donation in America if indeed xenografts became available. And the general consensus was that it would not have that much of an impact. It would be an additional type of thing, it would not necessarily do away with human altruistic giving. That may be just our naive view, but --

DR. ALLAN: So what about the -- are you also focusing on economic impact in terms of, well, can we afford it? Is that going to fall under this?

DR. KASLOW: I don't have any preconceived ideas here, I just think that the issues ought to be out on the table to produce a balanced view of what, if we are going to talk about impact, I think we need to talk about impact in its full range and not just that which is positive.

DR. SYKES: I thought Ellen Berger did cover that a little bit in the first session and maybe we ought to revisit those notes and see what if there are other areas that --

DR. KASLOW: If there's another perspective on that.

DR. SALOMON: I wanted to start by apologizing to my distinguished representative from the great proud and rural state of Wisconsin. I just thought we were in Washington and could act like Congressmen. The comment I wanted to make was one of the things that Allen talked about.

DR. KASLOW: Which means you can strike that from the record.

DR. SALOMON: No, no, that's how they talk. But what Allen was telling me, just to add a little from his context, is he wanted to hear a little more about a alternatives because he felt that if we were putting xenotransplantation -- again, I can't get beyond the idea of Tommy Thompson sitting right there and we are talking to him. I can't get my head around anything but that, that we're advising him. And I think one of the things he'll want to know in addition to the impact point that Richard brings up so well is what are the alternatives. Where do put xenotransplantation in the context of gene therapy, of cell transplants from stem cells, et cetera. I don't think we should pretend like we could solve it, but I feel we should have a spin on that as well in some sense.

DR. PIERSON: The NHLBI working group addressed some of those things for hearts and lungs so referring to those documents will be useful. In addition, the Council of Europe has put together a set of proposals and guidelines in draft form and within the next several months will be available to you for reference.

DR. CHAPMAN: My thought and reaction to the question about economic analysis, it seems to me that it's not very feasible to be able to do an assessment of economic impact of xenotransplantation procedures if they worked because so much of it would have to be speculative. You wouldn't know what the pharmacologic burden would be, what the associated adverse events and so on would be. That may be a limit of my vision, but what would seem to me to be feasible and probably reasonably available in the literature is to do a reasonable economic assessment of the cost to society at present, both in terms of health care dollars and years of productive life lost of the primary medical conditions for which xenotransplantation protocols are proposed such as diabetes, such as liver failure, that sort of thing.

So it seems to me there should be a basis now for a pretty reasonable assessment of that. Here's the existing cost to society. And then you could go on to do something that would be more limited and more speculative about how, if people were to succeed in porcine pancreatic islet transplants and functionally cure juvenile diabetes, what would the impact be, but that's going to be much more hypothetical.

DR. LUBINIECKI: Along those lines, is there, if there's no good health economic information or speculation regarding xeno, is there enough information around allotransplantations that would allow at least some general conclusions to be drawn and applied to the larger problem?

MR. PRASAD: In some organ systems there is data, for example, in kidney allotransplantation. Paul Edgars, who is now NIDDK, had done some reports on the benefits to the health care system of allotransplantations compared to dialysis and there are a couple of things that are involved, not just the cost of transplantation compared to dialysis but also the effect on lost workdays to society as a whole, so in terms of allotransplantation in the kidney there is data and I guess we could debate on how different the estimates might be between xeno and allotransplantations.

DR. LUBINIECKI: The only caution I would add here is that we are going to consider having any health economic evaluations done or attempt it, it's extremely important to remember that the outcome frequently depends on the assumptions that you use, and even worse there's always a value that's hopefully created and different parties in the patient-payer-doer triangle will see the value differently. So we just need to be, I think we should err on the side of being complete about what our assumptions are and who is getting the value if we are going to do these kinds of things, because depending on your assumptions, you can just get different outcomes.

DR. GROESCH: I'm aware of one study that's several years old now. The Salomon brothers did an economic analysis, I believe, of the xenotransplantation. It's actually in that two-foot stack of background materials that I gave you prior to the first meeting, so you might want to take a look at that at some point.

DR. PIERSON: The ISHTLT did a very comprehensive review to which they appended various summaries which were more detailed, so the documents can be relatively short but use appendices to structure, fill in.

DR. COOPER: I was going to say that the ISHTLT tried to do everything you just mentioned, alternatives, cost, so on, in relation to heart and lung transplants, and that report came out last December. And then this report by the Salomon brothers, which is really way out of date because they anticipated by this stage we would be doing 10,000 xenografts a year, but at least the problem and the costs involved would be very helpful. And I actually reviewed that in that short book I put out last year and also reviewed the need -- I got a lot of figures on the need for xenotransplantation. So that might be helpful.

DR. SALOMON: There also is a whole economic analysis that's available on the web of extracorporeal circulation on the liver, so there are a couple of other sources and I think we could even perhaps get access to some abridged version of what Novartis and Nextran did in terms of their business plans.

DR. SYKES: I think we've just heard about a lot of resources that are available to do this and it sounds like we might not need to bring in a speaker on this area if we can make use of these resources in preparing our report. I guess at this point it might be a good idea to try to assign areas to various members of the working group to take on in the preparation of this report.

DR. MICHAELS: Before we assign areas, maybe we could go through some of this since a lot of this has been covered and just be able to say, okay, this we've heard enough about that, we would be able to summarize and make a report and that way then come back to sort of say what do we need to figure out in the science scenarios.

DR. SYKES: Well, then I guess we can move on to the science and just sticking with our formulation here, we start with solid organs. And it was felt during the conference call that we probably hadn't yet heard enough about endothelial cell host interactions and this was an area that we would like to bring in a speaker or two. Does anybody -- a couple of names that came up were John Logan and Jeff Platt, both of whom would be excellent speakers in this area. Does anyone have anything to add to that, other suggestions?

DR. ALLAN: I was just thinking in terms of you've got -- in terms of the physiologic function, I'm jumping ahead, sorry, I mean, I keep hearing physiological differences and yet I don't really -- I haven't, since I don't go to these meetings I haven't really heard much in the way of what the physiologic hurdles are. I have seen a couple of papers that have been out, but these are the kinds -- to me it's obscure and I wonder --

DR. SYKES: The reason is because there's so little known and because there's being such short survivals in xenografts that it really hasn't been possible to assess subtleties like with liver transplantation there are myriads of metabolic imbalances that might occur. But there haven't been liver xenografts surviving long enough to tell us whether any of those are going to be significant.

But I think this also gets to another issue, which is something that I brought up in our working group meeting at the Heart Lung Institute, which is we are all focused on the immediate problems at hand. And we are not thinking ahead to these potential physiologic incompatibilities that are completely irrelevant right now because we can't get the organs to be accepted that long, and to start thinking about those things we really are going to need to bring in people in other fields. But the way that occurs at the moment is -- the way things have occurred is always that a problem arises empirically and that starts to get people interested. But until we can get longer graft survival, I think we are going to have very few people looking at some of these issues.

There are some data with the graft survivals that are out there. And we have heard those data. When David White presented he talked about some of the issues with epoetin function, but I think there is a need for more in-depth studies of amino angiotensin types of physiology, there's all kinds of physiology that haven't been looked at even in the time that those grafts have been accepted. So there's just not a lot out there.

DR. ALLAN: So how do we attack that? Do we just leave it alone and say it's a black box and right now it's an area that needs attention but we don't have the information?

DR. PIERSON: I think there are a number of examples that Megan has already alluded to. In addition, one of the papers highlighted at the recent xeno meeting talked about metabolism of ATP, that several of the enzymes in that cycle are different in the pig than in the human and the consequences of those differences in that pathway lead to the buildup of vasoconstrictive cyclic nucleotides and the depletion of the ones that vasodilatory insider protective. These are procoagulant phenotype and a constrictive low flow phenotype. That's a fascinating basic physiologic incompatibility and I think if you just highlight those in your report and say that this is the kind of problem that we are going to encounter that we are going then to need to address structurally as we design a pig that's going to be suitable. That's the perspective I would suggest the group bring to the report, with a few examples, rather than try to assay comprehensively, the -- the phosphate depletion that Robert John and David White have reported, that's in the kidneys, that's another excellent example.

To respectfully disagree with Dr. Mendez, the lung, I think, gives us lots of examples where the physiology is all fouled up and thereby helps us to see, gives us a window on perhaps a magnified view of the difficulties that we are going to encounter in other organ systems that are not as physical perhaps but may give us clues about the pathways that need to be better understood to get us there.

DR. SYKES: All right. Well, if there are no further comments on that, the next major area that we had on our list was transgenic and gene knockout animals, with the first subdivision being issues related to ES cells, ES cell lines, cloning, fusion, so anyone want to speak to that?

DR. ALLAN: I think we just essentially didn't have that much information and we thought we would just bring some speakers in to give us the information, so that's where we are headed with that particular area, and I think that would be helpful.

DR. MICHAELS: I just want to ask a point of clarification. So from our conversation that we had when the working group had the phone conference and from today, we are trying to identify what we need to know to be able to advise the secretary of health and that we would plan on having these speakers come in March; is that what Mary was suggesting? Okay. We could get rid of some of -- if we go out of order, we could get rid of some of the areas easily and make it look less daunting. And I certainly agree with David that we don't want to get completely bogged down in minutia, that we must have some of these areas covered to am degree that we can be up to speed to give advice, but I would say from the infectious disease area arena, I think that between today and the previous conferences, that we probably have had enough focus and can probably take those off for having new speakers. Is everyone in agreement with that?

DR. ALLAN: Yes.

DR. SYKES: And then the other area was transgenic engineering, including multitransgenics and cloning, and again we thought we needed to hear more. Allen Coleman was suggested as a speaker in that area and the ES area. Do any of the infectious disease people here who aren't on the committee want to make any further comments about that or other suggestions for speakers?

DR. WILSON: I would like to make just one comment, which is that perhaps folded into this issue of transgenic strategies, that a consideration be made about whether or not transgenic alterations may affect transmission of certain infectious agents.

DR. MICHAELS: I agree that's important and it's going to be critical in our summary as well. Don't you think, though, some of those issues were brought up or no? You think we just need to make sure they are reemphasized?

DR. WILSON: Yes, because I think there hasn't been good systematic data. I mean, everybody is aware of the issues but very few people have actually done the experiments to assess it.

DR. COOPER: Just comment, you mentioned Allen Coleman, who is excellent, but there are a host of people in this country who could speak equally on that, like David Ayers or the people from Infragen (phonetic) or the people associated with Nextran. I don't think you have to go all the way to Scotland to bring somebody who could tell you what's going on in that field. The other area is do you need to consider, is this committee supposed to consider the ethics of manipulating animals, how far can you manipulate these animals, is that to be considered?

Or is the other section going to consider that?

DR. MICHAELS: That's the other section. Did you want to give some names -- or you gave some names, I guess.

DR. SYKES: Just one other issue related to transgenics, sort of conditional knockouts and recombination techniques to be used with transgenic donors. Are there some special issues there that we need to hear more about? Technologies and things like that being used in porcine donors, so allowing these kinds of genetic recombinations to occur in vivo, does that increase your risk of recombinant retroviruses?

DR. SALOMON: I don't know about recombinant retroviruses, I think that's probably going a little far, but I think what we do all agree on is we need somebody, maybe more than one, to really get into what is the potential using cloning and knockout and knock-in technologies in a couple of areas. I don't think that's minor. And I think it would be worth bringing in Tony d'Apici from Australia and Coleman from Scotland because I think this is such a critical area for -- and it is one of the areas that distinguishes in a very unique way xenotransplantation, the fact that we can do genetic engineering. And at that point, there are many issues, for example we could clone out the active PERV species. One of the big issues of doing the pig genome is to identify and map all the different retroviral elements and then potentially knock those out that are transcriptionally active. So it goes everywhere from the immunobiology to the infectious disease.

So what these guys really think they can do, how quickly they can do it, what the impact on the health and viability of the animal is, how that may impact on things like for example putting growth factors in, you know the next thing that's coming along is going to be people putting transgenic growth factors. Those are going to have interesting issues on infectious disease as well as induction of malignancies and immune response, so I think that we really -- that's one area that we really need to do because that's unique to xenotransplantation. I don't think it's been done in any venue very well, to be honest with you.

DR. ALLAN: I think it's something we really need to focus on too. Because I was at a meeting, one of those Boston meetings a couple of years ago and they were talking about alpha Gal knockouts in mice and they said all the mice are blind. So I don't know if you would be dealing with blind pigs or what else might arise, so I think it's important to really look into those areas.

DR. COOPER: They are not all blind, but Tony d'Apici said, he could tell you whether it was a knockout mouse, because he put his hand in the cage and if they ran into it, they were knockout mice, but it was something to do with the technique rather than --

DR. CHAPMAN: I follow up the discussion about there being good people in this country by suggesting for the reasons Dan stated, it's an area worth exploring, but at the same time it's an area where you are really at the very edge of a new field and any one speaker is going to have a vision that's going to be partially based on what they've accomplished, some of which is in the public arena, some of which is going to be proprietary and partly based on their degree of optimism and their own personal vision, which we all know we are not usually always realistic about, so it may be an area in which it's worth inviting multiple

speakers, not just these two who are very big names internationally, but also domestic ones, perhaps in separate sessions, to hear where their understanding of the field coincides and where it diverges, where they disagree with each other.

DR. ALLAN: Are there any other comments on the transgenics for the knockout issue?

DR. SCHECKLER: Just, John, in view of what you said earlier, are we also going to invite skeptics? Most of the people so far are people who have been working in the area who are committed to the area, have a belief system about the area, most of the people on this committee have a belief system about the value of xenotransplantation. And I think to be fair in terms of developing these things we ought to, I mean sort of my take on this is we are trying to develop the perfect pig and that will help answer the question about solid organ transplants, and maybe the Tilapia, I'm not sure about that, for diabetes, but there's huge barriers to overcome and I'm sort of back to the economic issue. I was struck this morning when the comment was made that since 1964-'65 we poured federal money into an artificial heart and what do we have to show for it, how much has it cost, how many years of quality life have been extended based on that rather large investment. And that's the kind of question that I know the policymakers and the Congress will ask compared to other uses of money. We don't have everyone in the country with health insurance right now. And that's a competing issue. So I think we ought to be realistic about this.

DR. ALLAN: So are there any skeptics that you know of in the transgenics or knockout area that we could have come talk rather than just companies or, do you know, Dan?

DR. SALOMON: No, I don't skeptics because they are not in the field. But I think to put this into context, I think we have to be a little bit careful. I absolutely agree with everything you said but the point here now is to what extent is that part of this working group in the science of xenotransplantation. So I think that by articulating where the science is and I mean being critical about the science is what we are supposed to do right now. And then I think the whole committee should sit down and start talking about, okay, but if you put X number of dollars in to screening for hypertension it would be much better for preventing heart disease. I'm not afraid of those discussions. I think they're very reasonable points.

DR. COOPER: It might be a good idea to have an expert on genetic engineering and cloning who is not involved in xenotransplantation to tell you whether these other guys are going way beyond their imagination and whether it's really realistic to expect what they think they are going to do. So that may be a tempering thing.

DR. ALLAN: And I think that's what Bill was looking for, this is not for a skeptic but just for someone who has knowledge, because sometimes you get really kind of a jaded view of what's really happening unless you can find somebody outside.

DR. COOPER: Skeptics can have a jaded view. Jonathan.

DR. ALLAN: What did they say about, is it a skeptic is an informed optimist, is that what it is?

DR. KASLOW: But a skeptic transgenic is oxymoron.

DR. ALLAN: Let's move on to the next point, which is cellular transplants. And we just stuck Dan's name down there because I think he knows more than most of us about cellular transplants since he works in that area. Is there something you want to add in terms of what we need to learn and what, where we are going? Can you provide that information if we get you to give us a talk?

DR. SALOMON: I mean, of course it depends on the scope of what we are talking about, but if we are talking about just reviewing what's been done in cellular transplantation and setting a stage for, let's say, the next three or four likely types of cell transplantation, which would be neural stem cells, islet cells and possibly myoblasts in a cardiac setting, I think we can do that. I don't think that I need -- in other words, if you are trying - I'm not trying to tell you that I'm the world's end-all expert on cellular transplantation, but if we are talking about an executive summary of where the field is, if people are comfortable with it. I don't think there's a whole lot of new stuff we need to hear about yet.

DR. SYKES: Dan, I hate to keep coming back to the Tilapia, but would it be worth our while hearing from this guy Wright, I think is his name. It seems to me there are different infectious disease areas as well that we ought to hear about.

DR. SALOMON: Yeah, it's an interesting point. Why stop at Tilapia. The Tilapia thing has been going on for a couple of years, and I think it's very interesting. I'm not aware that they've done any clinical trials with it. The problems have been particularly that it's got -- the Tilapia islet, if I understand it right, it's got a reverse structure of the human islet, so its beta cells are on the outside and there's a central core of alpha and delta cells. So it's not really clear whether you restore glucose homeostasis with it. But I'm sure these are all things that you could figure out. But there are other alternative donors, right? You could use the sheep, you could use bovine insulin. So we probably should acknowledge the fact that the pig right now is safe, tremendous amount of livestock, husbandry information is available and it's been logical to use, but it's just a start.

Do we need to educate ourselves to have this guy to come down? I'd enjoy it. It would be a good experience for me. I don't know if we need to do that, though.

DR. ALLAN: I guess it would depend on how many speakers we end up bringing in. That person is probably someone who would be optional based on priority, I would think, but I agree, I think you could probably cover all of the cellular areas in an overview sort of fashion. And that would be probably sufficient.

DR. CHAPMAN: If we are going to talk about alternate donors to pigs for diabetes, you are talking about insulin production, you are talking about pancreatic islets, the one thing you didn't name that to me is the most crucial thing is that we have many years of experience of managing human diabetes with porcine insulin and my understanding is it's been sequenced and there's like one amino acid difference from humans. The most basic question when you look at any other donor including these fish is has their insulin been sequenced, how does it differ from human insulin and is there any evidence that it will be effective in, say, a diabetic pig if you don't want to begin by experimenting on humans, so it seems to me there are some very basic questions like that you could simply ask these people. If that information isn't available, then I would say probably that's all the information you need to be able to put in this report to say this is the state of the art in this area and you don't really need to bring the guy in to tell you about the anatomic structure of the pancreatic islets.

DR. SALOMON: Fish insulin has been sequenced, it works, and sheep insulin has been sequenced and bovine insulin has been sequenced and mouse and rat and human and they are very little differences. In fact it's remarkable how conserve the insulin receptors are.

DR. CHAPMAN: What about the normal glucose range in those different species, how much does that differ from humans' because that's the thing the islet's going to respond to?

DR. SALOMON: That I already mentioned that there is an issue with islet structure in the Tilapia. That would be an interesting question. I could call the guy too and talk to him.

DR. SYKES: They did actually have a paper. They did sequence the Tilapia insulin and they found some pretty substantial differences from human and so they actually engineered the fish to express human insulin under the insulin promoter and they did some studies in rats where they showed that it was -- no, actually they showed that in those fish there was normal glycemia and normal regulation and production of human insulin. That's one of the advantages of the fish, that you can easily manipulate it genetically.

DR. ALLAN: Okay. Let's move to the next, number 4, extracorporeal technologies, and what we have listed here is liver perfusion. I don't know if there's any other technologies that we want to cover that are sort of extracorporeal. And do you think we need to bring in a couple of investigators to give us some information in regard to where we are at with liver perfusion either through like devices or even through transgenics. Would this be -- yeah, I think we could probably -- what do you think?

DR. FISHMAN: Just a comment, I don't want to speak to the charge of the committee, but one of the issues that has come up in the biosafety committees at Harvard recently related to extracorporeal infusions is the question of what types of subjects it will be used for. In general one of the groups that have been targeted are individuals who are not eligible for whole organ transplants, drug addiction, alcoholism, noncompliance issues, psychiatric issues, people who would not in general be eligible or for some reason cannot currently receive a whole organ transplant.

The issue that we have grappled with and we have not resolved obviously which is if you do essentially a xeno experiment, although a different one, on these individuals, what do you do about lifelong monitoring or if you want 50 years? What do you do in terms of the biologic experiment not just is it efficacious but the infectious disease issues related to extracorporeal perfusion in terms of asking the question can an IRB reasonably say not only is this informed consent, but that these people are going to come back and be compliant with subsequent need for testing?

Our conclusion was, it may be wrong, but our conclusion was that this was impossible, that if you use subjects that are otherwise not acceptable for whole organ transplant, that the likelihood of these people coming back for subsequent follow-up is zero, very low. Obviously that's an exaggeration, but it's a central concern given the fact that these are the people who are often being proposed for studies of extracorporeal devices, and they're exactly the people you don't want to involve in a clinical trial for that reason if you want lifelong follow-up. So these are issues that have spun out of the extracorporeal perfusion that I wasn't familiar with before.

DR. MICHAELS: Jay, I think those are critically important issues which have come up from time to time at other meetings as well. I hope that this is one of the important issues that they are discussing next door, not only that but on the whole concept of how do you get informed consent from someone in a hepatic coma, but I believe that's going to be sort of their jurisdiction to then bring to us as a whole group.

DR. SALOMON: Just trying to stay on track with the charge of the committee, I don't think that there's enough new in the technology of hepatocyte, extracorporeal hepatocyte perfusion that would require us bringing a speaker in. I think all this has been published. There's a paper recently also even on the infectious disease issues with extracorporeal circulation that suggested that the PERV did not effectively cross the membrane that they were using at least in one of the devices. So I think we've got enough for that.

DR. ALLAN: So we are really talking about in terms of the extracorporeal area, really the infectious disease risk, which would be under the heading of science of surveillance rather than the actual procedure. That's what it sounds like and that's what I'm hearing. David.

DR. COOPER: Well, I don't know because if you are going to advise the secretary, you have to advise him is this worth doing. And we just had a paper sent to "Xenotransplantation" by a guy from Germany who has reviewed all the work on extracorporeal perfusion of livers, et cetera, and his conclusion is on the data available it doesn't add anything to medical therapy.

Now, that surprised me, but I think that's quite important for you to know, to say at the moment, if that's correct there is no information to suggest that this is actually beneficial to the patient and therefore at the moment we wouldn't recommend pushing ahead with it.

The other thing is, too, that it is something that's being done now, it is xenotransplantation in a form that's being done now, so I think you really should be pretty well up on that one and to know whether it's any good or not and what the problems are.

DR. SYKES: Right. David, that paper, in fact, was presented at the recent IXA conference. And I think beyond that, it's not really a static field, I mean, what's being done so far is perfusion through livers of pigs and there's a lot of things in the pipeline in the way of bio artificial devices being developed that we haven't heard about.

DR. SALOMON: Well, there is data out there, Megan, on perfusion on hepatocytes and a couple of different strategies on beads through porous membranes, there's the Nextran device, there was the device that Gary

Levy reported from Toronto. There is data out there. And I also agree that everything that I have read, including some consultations that were confidential with companies that were looking at this, I agree, it really didn't look like a very promising direction right now. But I think that, I would just say now to me there's kind of a line that we are getting close to crossing. If the idea was to give an executive summary of sort of where the state of the art was, then I stand by my comment that there's enough literature out there to talk about it. If, however, we really wanted to go to the next step, and I'm not objecting to it, but if we really wanted to go to the next step and say this is not a good direction right now, then I think we should bring in some people representing a couple sides of that argument, because I don't think we should make a statement like that as part of an executive summary without due -- there's a word I want to use, but anyway, due service.

DR. SCHECKLER: Without hearing the pitch.

DR. SYKES: But still I do think that as a committee, the committee as a whole is not aware of what's in the literature and so having somebody come in and educate the committee who is putting this report together, I think is worthwhile.

DR. SALOMON: I'm agreeing with that. If we want to go to the point of making a comment of whether it's good or not, then we definitely should bring people in.

DR. COOPER: Again, you would need to know what all the alternatives are. There are artificial devices out there that use human cells, not pig cells.

DR. SALOMON: There's even a dialyzer from Germany.

DR. ALLAN: How do we find somebody to give us that kind of an overview that has the information on all these different types of procedures that could give us that kind of thing, do you know of anyone?

DR. SALOMON: One source in the States would be Circe.

DR. ALLAN: But they are going to be covering their particular device. I'm wondering if we could find somebody who would give us an overview of all of the different procedures and alternatives, because I would like to get a summary rather than get each one come in.

DR. MICHAELS: Someone should be able to do a summary. The problem is anyone we get is going to have a bias towards theirs, but I think we should be able to get someone to try and summarize everything.

DR. ALLAN: But that's easier said than done. That's the problem.

DR. SYKES: Do you think Peter's friend would be able to do that?

DR. COOPER: I don't know if Peter's friend is up enough on the devices. I presume you could get up on it, but it's quite a bit of work to do that, you know. And you are quite right that nearly everybody in the field, of course, is biased in some way or other and would not give you an unprejudiced report.

DR. SALOMON: I think a good person might be Russ Weisner at the Mayo, who is a nationally, internationally respected hepatologist, who has been involved in this area for a long time. He was involved in one symposium that tried to come up with outcome variables for these extracorporeal hepatic devices, which is a damn hard thing to do actually.

DR. COOPER: I'll tell you who else did a review at MGH, the nephrologist that works with Nina.

DR. SYKES: Manuel?

DR. COOPER: No, the other one. He did a review on these because they were going to use these devices in patients with hepatic failure. He looked into it in some considerable detail. In fact, he gave me a very good review on his paper that reviewed everything else. I forgot his name, but I'll get it to you.

DR. SYKES: Right. He was on our list originally, our original list. He's at the University of Nebraska. Did he cover everything at our meeting?

SPEAKER FROM THE AUDIENCE: I'm not sure what the breadth of his knowledge is.

DR. MICHAELS: When we get these speakers, we just have to remind them that a number of people that are going to be in the group obviously listening and needing to learn about this aren't going to be scientists themselves.

DR. COOPER: I think Ira Fox is probably the best person that you could think of. I think it's an excellent idea.

DR. SYKES: Now, we move on to the systems. We haven't really heard anything specific about complement systems. And we had a discussion in our conference call about whether this should cover what's known about complement in relation to xenotransplantation or whether we should have a more global overview of complement. And we had differing viewpoints on that and hence, we came up with four different names, some of whom are more xenotransplant oriented than others, Jeff Platt and Augustin Dalmasso being more who would speak specifically about complement as it relates to xeno, and I think Tony Yugli (phonetic) was one of the more basic people suggested by Dan. And Doug Feron (phonetic) is another. So maybe we should just re-open this issue for discussion. My own feeling was that the -- we need to be as focused as possible in our efforts to educate the entire committee and that, therefore, given that complement is a fairly dry and complicated area, it might be most efficient just to bring in the people who know most about it in the context of pig-to-human xenotransplantation. Any other views on that that anyone would like to?

DR. SCHECKLER: As I'm looking at this again, I'm not quite clear why it isn't part of solid organs where you have species differences and physiologic function and how much there's known that's really specific to the pig or to specific to the various even cells potentially that -- I mean, isn't there a subheading of that or does it stand by itself and complement would be boring as hell to listen to.

DR. SYKES: I think it does have to stand by itself because there's been a lot of work on what antibody does to islet transplantation, for example. So I think we have to think about it in the context of cellular transplants as well as solid organs. So it would make sense to leave it here.

DR. COOPER: I think it will only confuse the committee totally. As well as bore them.

DR. KASLOW: Well, does that say more about its relevance to xeno than it does about complement, because if it's important, then we need to hear about it, however boring or confusing it might be.

DR. COOPER: I don't think it's as relevant as we first thought it was, but on the other hand, I think what you need to know about it from a functional point of view is much less than these guys will tell you.

DR. SYKES: Can you make a suggestion?

DR. COOPER: I just wouldn't have a talk, I would ask somebody with the transgenic technology to talk about complement in relation to complement regulatory proteins.

DR. SALOMON: Just to defend this a little bit, David, I don't know the scientific basis of the comment that it's less important than we thought it was. Maybe based on the idea that we are going to get rid of Gal and that's going to save the day, I'm not convinced of that yet. What's happening in the complement field has been continued advances in the biochemistry of complement, including the development of a whole new set of pathways that link mannose and mannolectin (phonetic) binding pathways which are just brand new

in a nonclassical complement activation pathways, bradykinin system has been linked to complement activation.

So there's a lot of new stuff in complement biology that most of us have turned off because it is so damn complicated and boring when you hear it. I'm not certain, though, with that said, that you -- again, here is this line, when are we educating ourselves and when are we engaged in a productive dialogue that is going to help us advise Tommy Thompson, and I think the complement thing is probably on the other side of that line, so after my defense of complement as an interesting area, I don't think it's necessary to go into it either.

DR. ALLAN: So do you want to take the whole systems physiology and stuff it under solid organ?

DR. COOPER: Just stuff it.

DR. ALLAN: Because we have got 5C, which is whole organ physiology, which would certainly fall under suggested here, species differences and physiologic function, it's basically repetitive. So the question, if we put that one under there, basically we're left with complement systems and coagulation systems, and do we want to talk on coagulation? That sounds to me as boring as complement, so.

DR. SYKES: John, as boring as they are, they are really important and they are not limited to solid organ transplantation. In our own model we are finding coagulopathies in animals getting large numbers of porcine cells and so I don't think you can confine either of those topics to solid organs, and I just don't see how we can have, say our committee is educated on xenotransplantation without thinking about these areas, unfortunately.

DR. SALOMON: Well, again, just so I'm clear, I think it's a really interesting area if it can be presented well. There is new things. Really where complement field is today is not where it was even five years ago. The other area, and we have talked a little bit about at lunch. So if Marian and Megan will forgive me. Another area that I think is really important to bring in here is this exploding area of sialic acid residues, the siglecs (phonetic), the sialic binding, immunoglobulin liglectons (phonetic), there are eight new human genes discovered in the last five years for these siglecs including the innate immunities killer inhibitory receptors. And there are at least 28 different fucosylation (phonetic) and specific sulfation enzyme genes that have been cloned and a whole project going on to map the genome on that.

So my point being is that I think this is an area of immense potential importance to what's going on, particularly when we know that at two or three months, a lot of these organs are dying for vascular events, so if we are going to do it, Megan, let's have complement and let's also have someone come in and talk about siglecs and fucosalation and sulfation enzyme changes.

DR. SYKES: Have you got any ideas who could cover all that?

DR. SALOMON: Jim Paulson at Scripts just got a 32-million-dollar glue grant from the NIH to put together a national project on siglec (phonetic) biology.

DR. SYKES: And would he be able to try to put that in the context of xenotransplantation?

DR. SALOMON: I can talk to him and if he doesn't feel like he can do it -- he's a Ph.D. He's very well spoken. He could maybe suggest someone else in their consortium, which is, I think, six different institutes.

DR. SYKES: All right. Well, so given that we are going to have these topics covered, does anyone have any other ideas? We had Jeff Platt and Gus Delmossa as xeno oriented complement people. Is there anyone else that anyone would like to suggest who could speak to the committee as a whole? And for coagulation, we came up with Simon Robeson, who is very knowledgeable, but does tend to be detail oriented. So if anybody can think of anyone that presents things in a more simplified way, I think that might be better. Do you have any idea?

DR. COOPER: Well, I think Peter Cowan (phonetic) did a good job, but he's from Australian again. You are going to have a big bill if you bring all these people in.

DR. SYKES: Next area was immune rejection and tolerance and I think I felt that I could cover tolerance and I think most of us felt that we had heard enough already from some of the speakers we've had to be able to come up with something on hyperacute rejection, delayed xenograft rejection and cellular rejection. And David Cooper, we had you down there as well.

DR. COOPER: I think you did a better job on that topic than I would.

DR. SYKES: So I guess we could hear about that at the next meeting.

DR. ALLAN: Can you just give that overview -- you can take care of that, right, so the only other aspect would be the immunosuppression drugs.

DR. SYKES: And we came up with Randy Morris and Robert Zhong as possible speakers in that area. Randy Morris does it all the time, he'd be great if we can get him. So we are set there. Okay. We're making great progress here. Infectious disease risks.

DR. ALLAN: Before we go on, is there any other area or topic related to either the types of xenotransplantation or the science that someone feels that should be included that's not included?

DR. MICHAELS: You guys mentioned, but I think we then forgot to put it in somewhere but did we want to have someone come and talk about alternatives or we decided not to do that?

DR. SYKES: It's under potential impact.

DR. ALLAN: Alternatives to everything or alternatives to whole organ or?

DR. MICHAELS: I guess it was more in the -- where did we think about putting it? I guess we were talking about alternatives to the solid organ, to the whole organ.

DR. SYKES: I think that we thought that we would be able to find material on that in the material we discussed already for potential impact because from what we heard, the alternatives were covered as well in some of those documents. So infectious disease risks.

DR. ALLAN: Okay, infectious disease risks. The last meeting we had we covered a lot in terms of infectious disease risk. When we had our teleconference call we decided that we probably had enough information to write a report on current state of the infectious disease risks. I mean, it's always evolving so we never have exactly up-to-date information on what's going on, and I think that was one of the issues in the last meeting was there were some members who thought that maybe we should put out a document that said that, you know, it's not that dangerous and we've covered a lot of the risks, but obviously since it is evolving, we really need to just stay focused on what the risks and what organisms are present and what do we know about them, and I think that is where we could certainly start to break that down.

So I think this is an easier area in terms of focus at this point because we just need to break it down and how we are going to put it together. Okay? So we could even discuss how we are going to write the document, how we are going to focus it, how we are going to outline it. And I think that might be an interesting thing to break this subcommittee into a sub-subcommittee so that we can -- so that certain individuals who have infectious disease risk perspectives can start to do that, and then we'll bring the document back. And I think we can do the same thing with the science of xeno, that we can break this committee into subsections so the people with the expertise in the science area can put that document together and then it will go back and forth. So we'll get the input from all perspectives regardless.

DR. SYKES: I think we decided that we would try to assign people to areas after we had gone down the list, so maybe if you want to --

DR. ALLAN: The only reason I was saying that was because we are really at a point with the infectious disease risk area that we could start to do that. Carolyn.

DR. WILSON: Not for the purpose of the talks, but for the purpose of the report I noticed you have animal-derived feeder layers down, so do you plan to discuss infectious disease risk in terms of primary cells from animals versus established cell lines or will you not differentiate?

DR. ALLAN: What I suggested when we first looked at this was that that probably wouldn't be a good subtopic, that it was probably infectious disease risk associated with different procedures, whole organs, fetal areas, whatever, break it down that way which is more appropriate.

DR. KASLOW: Specifically on the issue of feeder layers years, though, do we think we have either in the form of some written published document or from some other source enough information or do we need to hear more about that?

DR. ALLAN: I think we are going to hear more about that. Don't we have a speaker tomorrow? I think so. I think we do.

DR. WILSON: Yes, tomorrow one of the FDA speakers will talk about one particular product that's grown on a murine feeder layer. In this case it's an established cell line. What's not clear right now with all the different ES lines, in terms of the human ES story, whether or not it will always be as it will be with the Epicel product where it's an established cell line where you can make a master so they can test it or if there are primary cells that are used as a feeder layer and so that's still getting sorted out, but then if you address the issues in terms of primary cells and cell lines in the generic way, I think you have both sides of that covered.

DR. SYKES: I thought also that one of the issues with the existing cell lines was that it wasn't -- that the cell lines on which they were derived, the feeder lines that were used earlier in their derivation may not be available now for analysis. So in our conference call we sort of discussed the fact that this is a somewhat time-related political issue, the fact that we are confined to using existing ES cells and that we would try to acknowledge the issue but perhaps not go into too much depth on it because it may become moot in the future.

DR. WILSON: And I think that one way of getting around that kind of a problem is that you can test the human ES lines for potential agents that might have been present in a murine cell feeder layer that no longer exists.

DR. ALLAN: So what's the consensus about touching this topic and how we would discuss this particular topic? Dan?

DR. SALOMON: I would love it to go away. But it isn't going to go away. And the minute you think it's going away, then you get some news report last week that they through parthenogenesis and whatever, cloned humans again, so I think what we've got to deal with is -- but I don't think we should put this in the same section as infectious disease. That's the main comment I want to make. I think we should have a separate section and try to put into context this and make sense of it, I mean, be reasonable about it. That this is really not a big deal but you need to hear about it and there is -- we're cognizant of the issue. I think if we fold it into the infectious disease, it will get lost and it will sound like it's more legitimate than it is.

DR. LUBINIECKI: If I could suggest perhaps a slightly alternative way of organizing it. We might want to considering separating it into risks that arise from source material, risks that arise during processing and risks that arise in the patient after the procedure because the reason for doing it that way is the means of controlling the risk or abetting the risk or dealing with it, mitigating it, will vary depending on what it is and where it's coming from. It's sometimes easier to then deal with the risks you've identified if it's organized that way.

DR. SCHECKLER: I agree with that and my structure for this would be there are infectious disease risks that are every bit like allograft infectious disease risks because of the immune suppression and the chemotherapy and so forth, and that's probably a fairly brief section that just alludes to that, and there are those that are unique to xenografts and then the structure that you just mentioned is fine. And then when we get to the issue of how to follow those, that's the surveillance piece, so it's those that are unique, particularly those that are unique and unknown are the reasons for setting up the surveillance system the way it's set up, however, whatever sort of pig arrays we use to look at cells in a different way or whatever, but I agree with that.

DR. ALLAN: So I don't know that we need to make a decision on how we are going to work with that at this point because it sounds to me like there's three cans, the I don't care, and that's always a major group that's represented, but there's the I don't cares, there's the people who want to break it out, and then there's people who want to fold it in. So I think that we will -- I think it may be that we'll have to work with that a little bit more.

DR. SALOMON: I just want to point out that the danger of folding it in is political. I personally don't want to make any move that could be perceived at any level of the public as this committee saying that issues right now with feeder cell layers on embryonic stem cells is xenotransplantation, just because I think it's politically very charged and scientifically very gray.

DR. ALLAN: So you are saying because the FDA considers it as xenotransplant, they do, it is considered as xenotransplant. So you are stuck, that if we are going to consider feeder layers, then this is going to be part of that process and you can either say it's just another feeder layer issue and the FDA has already dealt with this issue and they already have everything in place or you can break it out and you say this is a special thing. And that's I guess the issue.

DR. SALOMON: No, I understand. And my conclusion is that the FDA, I know the FDA said it was xenotransplant and it is no special deal. If it comes out that way, I'm all for it. I'm just saying as a political issue it ought to stand as something that we recognize as something that's on the table now, it's in the news as of a couple of days ago. That's all.

DR. CHAPMAN: I was just going to suggest that it's basically already been said but that whether products, human products taken from one human being put back into the same human being but in genes grown on feeder layers in the laboratories is xenotransplantation has already been addressed. So I agree with you, John, that it doesn't seem obligatory for this committee to address the issue of do nonhuman origin feeder layers have application for it, may not be necessary for it to be embryonic stem cells. I do tell you that if you do choose to talk about that, none of your federal employees will be allowed to comment in any way.

DR. ALLAN: I think what we've -- one of the discussions about this working group is that any federal official would be a consultant rather than part of the working group because of these types of issues. So first of all, that -- you know, I think that might result what you just said, but I'm not interested in political issues. I don't really want to go there, I don't think it's necessary. I don't think it's the charge of this committee to do those kinds of things. I just think that we need to deal with the scientific issues and if it requires us at least saying a few words about the fact that this is considered a xenotransplant and therefore these are the kinds of things the FDA has stipulated, I think it's fine.

DR. SCHECKLER: All right. I'm just a small-town doctor from Wisconsin. If there's a feeder layer of an organism other than a human on which human cells grow and that feeder layer could have some type of unrecognized prion or some other type of virus in it that we haven't yet recognized, why is that any different intellectually than all the other type of unknowns that we are dealing with? I've heard you say I don't want to go there, I don't want to deal with this, this has already been dealt with, et cetera, and I've also heard, yeah, but the FDA is considering this xeno so we can't ignore it because we are supposed to advise on this, and it seems to me the only thing we are really talking about is infectious potential problems from this and nothing else, so I can't -- I mean, it seems to me more problematic to set it out somewhere by itself than to fold it in and I kind of like Louisa's comment on there are other examples that we could use, let's use the other examples that we know something about and say whatever we can say,

whether it's a paragraph or two paragraphs, but I agree also with John, it ain't going to go away just by not -- willing it to go away. But am I missing something? Isn't that the fundamental hypothesis?

DR. SYKES: I think the other issue is what I said before, is that people are confined to using existing ES lines which have been around, some of which have been around for a while and were derived on cell lines or at some point were on feeder layers that may no longer exist in the same form, whereas with other types of xenotransplants that are now ongoing, this definition of xenotransplants, the feeder layers are available for analysis. So I think there's a special issue there with the use of existing.

DR. SCHECKLER: I know a lot of nice little Wisconsin mice, too, that were the feeder layers for the stem cells.

DR. SALOMON: I just want to say I agree -- what we want to do is not color xenotransplantation with these, with this politics. So whatever we do that does that successfully is good with me. But it isn't going away. And the problem I have is that by sort of -- it may sound like a clever idea right now to put it into, well, there's the skin layers, the skin product that's going on 3T3, I assume that's what you are going to bring up. I forgot the name of the company right now, but we reviewed that at the BRMAC a couple of months ago, and it's real reasonable and they've done a very good job of characterizing the mouse so it's very reassuring. So that's a good story and we should tell it, as I think Carolyn was implying.

The problem is that I think again, I told you I can't get my head around the idea of Tommy Thompson sitting right there, and I can see us going through this whole big thing, and he goes, yeah, but what about those embryonic stem cells. And he and a lot of other people are going to see that as a major issue right now and he's got to have that in the executive summary as a separate thing. That's -- just trying to explain what I was thinking.

DR. FINK: Donald Fink, with cell and gene therapy at CBER. I'm also kind of in charge of the embryonic stem cell initiative from CBER perspective, and I've been working with the office of science policy on the development of the stem cell report and had contributed to the chapter on assessing safety. Since August 9th I can tell that you the only question that they want an answer to is this particular question of whether or not -- by "they" I mean from the president on down and it's being delivered all the way through the commissioner's office at FDA, whether or not any of the existing NIH registry cell lines -- this is the first question, not whether they are going to be used scientifically, but can these cells ever be used in the clinic, and so the first issue that came up raised through the press was on xenotransplantation. Well, it seems to us since you are growing these cells in feeder layers, those are xenotransplants and you couldn't ever use them, and so we tried to straighten that out and say, no, no, no, that's not true at all and have been quoted as saying in fact we are not concerned by the xenotransplant characterization because we do have a mechanism for dealing with these products.

Just listening to this conversation, I can assure you that if you put, even if you put it cryptically or if you bury it or if you bring it out, that's going to be something that comes out to the secretary because he's going to go through this report and he's going to look for that specifically. And the reason I know this is because the part that I did with the NIH report, which was ancillary, which was FDA, we would like you to have a little part of it, why don't you go ahead and contribute something to it, ends up being the only thing that gets quoted in the paper and the only thing that gets called on and that's assessing stem cell safety.

You can put 150 chapters of state of the science, but if you put one chapter about safety, that's where they are going to go, and so I think it's important that somehow it gets discussed. And I agree with what you are saying, it can get overblown politically at this time, so there's caution there, but it would be best served to at least try to deal with that.

DR. KASLOW: It sounds to me like it's all the more important that we address the scientific issue per se and where we put it is less important.

DR. LUBINIECKI: Politics aside, though, is there anyone who is aware of any scientific difference between the use of feeder layers for the skin product and the potential use of feeder layers for human stem cell work? Is there any reason to think that the science is different?

DR. WILSON: The only issue may be in those cases where primary cells are used as feeders as opposed to an established cell line where you have a master cell bank and you can do really extensive testing.

DR. KASLOW: But that would be true for any cell you were going to use for any ultimate purpose.

DR. WILSON: It's no different than what we deal with the big xenotransplantation. So it's not that we don't have a framework for dealing with primary cells, but then you are going to need more information about the animals and so on.

DR. SALOMON: There is one, from a scientific point of view, the major difference that we are forgetting is that if you put -- if you expose an embryonic stem cell to an infection and it gets incorporated in the embryonic stem cell, then every cell down in perpetuity including the germ line cells of the organism created with that could potentially have the infection. That's a lot different than the skin monolayer being developed for a burn that might have five percent of the cells exposed to an extraneous virus in the feeder cell area. I don't want to be too dramatic, but the idea of using a stem cell and growing up millions of them from the original stem cell does really change the discussion a little bit.

DR. KASLOW: The other possibility is that because by definition it is a stem cell and more primitive, it may be more susceptible to an infection than a more differentiated cell, which is something we talked about this morning out of this context as well. So again, the generic issues, I think, are the big ones, not the specific.

DR. MICHAELS: Carolyn, you may or may not know this and we'll know tomorrow. But do you think these issues of safety are going to come up in tomorrow's talk, do you know, with the FDA?

DR. WILSON: In terms of the talk from FDA about epicell? Yes, he's -- not in great detail but he will cover the safety testing that has been done on the 3T3 feeder layer and he's also going to discuss the advisory committee that was held, I think actually it's now about two years ago, and the discussion of that in terms of surveyance and so on with subjects that are treated with that product.

DR. MICHAELS: And perhaps if we could have the chapter available to the members too on the safety issues, that would be helpful.

DR. ALLAN: So tomorrow we are not going to hear about human embryonic stem cells, we are going to hear about epicell. So from what you've just said, I'm still up in the air about whether we need to bring in an embryonic stem cell guy to tell us what the -- what exactly they do and what cells are put on them. I mean, that's the issue.

If we wanted to tackle it, really tackle the scientific issue, if the secretary wants the facts scientifically, we don't have them, so that's the issue. So do we want to bring in someone who is going to tell us how they grow embryonic stem cells on feeder layers or whatever? Do we want to bring in somebody just to tell us that so we have some idea?

DR. WILSON: That's not going to give you a lot more information than what you have from the epicell because, again, it's going to be one specific example, and our sense is that probably different derivers have used different methods and have different types of feeder layers, and I don't think one speaker telling how they did it is going to cover the whole field and I don't know that any one speaker knows how everybody did it. So I would, again, deal with it in a more generic way and you could address embryonic stem cell issue by discussing things like the epicell that there are precedents for this nature of product and that there is a framework for dealing with these issues rather than -- I don't think it requires a speaker. That's my opinion.

DR. ALLAN: From what -- I haven't read very much about it, but it seemed to me that the human embryonic stem cells are grown on mouse embryonic stem cells, at least some of them. Does anybody know?

SPEAKER FROM AUDIENCE: Fetal fibroblast. Mouse fetal fibroblast generally if they are primary.

DR. ALLAN: In one sense I think we do an injustice to it if we don't have the information. If we try to make some sort of conclusion in our report without adequate information, I think that does a disservice as well. So how do we deal with that?

DR. SCHECKLER: Well, I -- just happens Jim Thompson, another Wisconsin Thompson, the guy that sort of figured out how to grow the stem cells is at the University of Wisconsin Madison. I was actually planning to try to talk to him or somebody from his lab to understand how this works because I surely don't have to deal with that in my day-to-day work.

And one of the things I might be able to do is do that prior to the next meeting and see what Jim Thompson has to suggest in terms of where his head is at with all of this.

And by the way Tommy Thompson has been in Jim Thompson's lab, has met him and knows him reasonably well. And one of the reasons there is any stem cell research that's going on at all is because of that connection. And Tommy's convincing W. that at least we ought to do something.

DR. ALLAN: I think that's a good idea.

SPEAKER FROM THE AUDIENCE: Let me just follow up, first. I would probably point you first to the IH stem cell report, which you can get online. What I'll do is I'll bring the chapter out for each of you tomorrow, Chapter 10, which is the safety. But I'll also bring the web site. It's a 210-page report that covers everything up to June 1st regarding stem cells from adult fetal embryonic sourcing. And there's an appendices in there with nice pictures that shows the derivation process for getting embryonic stem cells from the intercell mass, growing them on the feeder layers. It has nice pictorials and it describes, I think, in sufficient detail that you would be comfortable that you would have enough scientific knowledge about the procedure and the process for doing that. And beyond that, I think it would be a little bit premature to go much beyond just the technical art of doing it. I don't think anyone has been looking at it for anything beyond that, but let me give you that web site and then you can decide for yourselves if you need to go beyond that.

DR. SALOMON: John, I would like to second that. I think some input from John Thompson would be great informally. I think, though, the good news here is we don't know. No one is going to know what the risk of putting mouse retroviruses or other infectious agents into the stem cells are, so I think we could recognize it as a scientific issue and there's plenty out there to do it. Plus the FDA has already dealt with this, the feeder cell layers. That's the whole point. And I think there's no one that's going to come in here and say, at least I don't know. If someone could tell me there was a guy out there actually activating 3T3 cell lines with different types of murine retroviruses and had some data, now that, I would stop right there and say we need to talk to that guy.

DR. KASLOW: That's exactly what I was going to suggest. If there is somebody who can tell us that there is something other than the balance of ignorance about whether stem cells or more or less likely to be infected by viruses because they lack receptors that are specific to host viral interactions and so on, if there was anybody out there who could tell us that, then I think it might be worth hearing from them in some form, whether by telephone or publication or whatever. But if there isn't anybody there, then I think you are right.

DR. SALOMON: I think one of the things that was suggested to me by Clive Patience, I think I heard you, was John Coffin, who is one of the world's renowned experts in murine retroviruses. While we are checking with John Thompson, I can query John Coffin to see what he knows about it.

SPEAKER FROM THE AUDIENCE: The only reason I mentioned John Coffin is because he has data going back 20 years on various mouse strains and mapping of endogenous viruses which are in the germ line so he can essentially give a yea or nay on a lot of mouse lines before you even starts and therefore a lot of advice on which murine feeder lines would be sensible ones to start with and which ones you would want to avoid the ecotropic and xenotropic viruses. With respect to expression of receptors, that's a two-week experiment. The receptors are known if you get the stem cells themselves, it's a RTPCR, it can be done.

DR. KASLOW: The question is has it been done.

DR. SALOMON: Clive, you know that what you just said isn't true, that the receptors are known for a handful of murine retroviruses. But for example, that large group of 25 ecotropic viruses that we're talking about, they don't have the receptors for all of them, do they?

SPEAKER FROM THE AUDIENCE: They're all the same receptor. It's --

DR. COOPER: I think all this needs to be mentioned in your report so you cover xenotransplantation in full. But obviously I think whoever suggested before it should be perhaps put a little bit aside is also important because it's not really what xenotransplantation is all about. And that's probably what you are supposed to be concentrating on, so it is a matter of including it but not having it as a part of the --

DR. ALLAN: We have to move along really quick because we are going to have to get together with the other group at 4:20 and you probably need a few minutes as a break. We've only gotten -- we have just discussed infectious disease. The question I have is, we have some more here too. So the question I have is do we want to meet this evening over dinner to hash through some more of this? I've got one no. Anybody else? No, no dinner.

DR. KASLOW: No meeting.

DR. ALLAN: No meeting. Okay.

DR. MENDEZ: But do we have to outline the specifics of the recommendations.

DR. ALLAN: We would like to do that, too, so there are several things we still need to do. We still have science of surveillance. And the question there is how much more information do we need to know about surveillance? Do we want to write a report? We've had very little on that.

DR. MICHAELS: We did it last time or the time before. We had Louisa.

DR. CHAPMAN: What I talked about was considerations in interpreting testing, which isn't necessarily the same as surveillance depending on what you had in mind by surveillance. Did you want someone to talk about current strategies that have been proposed in general for surveying for adverse events with xenotransplantation, which a lot of you have heard those multiple times, clinical surveillance and specific laboratory testing and so on, or did you want someone to talk in general about approaches to -- what public health people mean when they talk about surveillance and what works and what doesn't work and why conceptually simple things tend to work much better than complex things? I guess I'm not sure what you want here.

DR. ALLAN: Good question. I'm trying to remember why we put this down here. I think we thought that perhaps it was we needed to have something in a report which went to the subject of the end game, which is the surveillance of contacts and society, so basically the public health risks association with surveillance. I think Louisa has already covered a fair amount of this already.

DR. SCHECKLER: Yeah, I think it's already been covered. And it's how to follow the risk of infectious disease. It's as simple as that. And how to follow things we don't know yet exist. And that's really part of the public health service guideline and the connecting the database that they talked about this morning with the, that liquid nitrogen base.

DR. MICHAELS: Archive.

DR. SCHECKLER: Archived serum and tissues and so forth and being able to connect those seems to me to answer that question, but we need to address it. And this is the place to address it.

DR. MICHAELS: But we don't need another speaker on it.

DR. ALLAN: Okay. So what we need to do now, I think, is decide on -- we still have regulations and policies here and future prospects. So we've got two other areas to work with. I don't know if you want to get into them at this point. We are running out of time. I think we can probably shelf that for now. But future rospects obviously is important because it goes to several issues. It also goes to the future in terms of funding, all those issues that Megan was bringing up earlier.

Okay. So in terms of how are we going to break this down to deal with this report, should we just -- we'll go on the basis of expertise and I can tell right now that I'm probably on the infectious risk end. Marian is probably on the infectious risk end, I can see. And you. Where do you fall?

DR. SCHECKLER: Surveillance.

DR. ALLAN: Okay. Surveillance. Now, Dan is a difficult one because --

DR. SYKES: Maybe we should go down the area.

DR. ALLAN: Some people can do both, I think. And that would be helpful, actually.

DR. SYKES: For example, potential impact.

DR. ALLAN: Potential impact on health.

DR. SCHECKLER: I don't want to be the lead person on that, but I would like to be involved in looking at that piece because I think it's a crucial piece even though everybody says, oh, it's already well-known. I will be the skeptic.

DR. ALLAN: Who else do we have?

DR. MENDEZ: I don't think I would like to be the lead person on that, but I will be involved.

DR. MICHAELS: May I just ask is that, the potential impact on health seems as though that would be actually the lead for both sides, for both the ethical side and this side, so perhaps if both of you are interested in helping with that, that we could get some of the people next door to help on it as well.

DR. ALLAN: So they are leading. So if we run down the list here, let's see. I don't really think we have to deal with the science of xenotransplantation in terms of how we are going to write this report because we are not ready to even begin on this.

DR. SYKES: We need to hear --

DR. ALLAN: We need to get all this information. That's what this whole process is going to be about. So the only thing we need to deal with is the infectious disease risk and how we are going to break that down. We could do that by e-mail, at least to start that process through e-mail.

DR. MICHAELS: Are you going to help on that thing too?

DR. SALOMON: Which thing? Yeah, I thought I would be cell transplantation and IV.

DR. ALLAN: Anyone else who would like to participate in that arena, what we'll do is we'll have discussions by e-mail and maybe phone and start to work through that. I think that's probably the best way to approach it. Okay? So let's take a few minutes and then we'll get together with the other guys.

(Whereupon, the breakout session on the State of the Science in Xenotransplantation was concluded at 4:10 p.m.)