Somebody made the conjecture, and somebody who probably knows about blood deferrals a lot more than I do, that once you defer a population it's hard to go back in the other direction. So, if that's the case then I guess to make a very conservative approach based on a few hundred, once we're at a few tens of thousands it might not be, at least one has to look ahead to that situation.

DR. AUCHINCLOSS: Dr. Coffin?

DR. COFFIN: A few tens of thousands is still a very small fraction of the total population. One percent of the population is several million people, and it's going to be a long, long time before one approaches that. Sometimes this conversation sounds to me like we're treating blood donation as though it was a constitutionally guaranteed right and something the patient is --

DR. AUCHINCLOSS: In my view, using

blood transfusion as a way of defining did the patient have a xenotransplant or not, and can you dispense with is the level of risk so low that you can dispense with the whole gamut of precautions that we're talking about for xenotransplants.

DR. COFFIN: I'm not comfortable saying that yet, I think.

DR. AUCHINCLOSS: That's what I'm pushing you on, and I think that blood donation is as clear an example of where you would consider the risk to present that that's why I'm pushing the blood donation.

DR. COFFIN: Again, I think the net benefit is so small, at least looking forward, that I would certainly think the case is quite strong for recommending deferral and revisiting the issue if it becomes important at a later date.

DR. AUCHINCLOSS: Can I ask you or the three of you and anybody else who claims any expertise, can you imagine a contact with

a nonhuman cell line *ex vivo* which was so safe that you really would dispense with this conversation, the Drosophilia cell line.

DR. COFFIN: I think with insect cell lines I would certainly imagine that we could have a conversation that would turn out differently.

DR. AUCHINCLOSS: Nonmammalian cell lines in general?

DR. COFFIN: No, not nonmammalian, no.

DR. AUCHINCLOSS: Can you tell them some things?

DR. COFFIN: Vertebrates. I would draw the line between vertebrates and invertebrates.

DR. AUCHINCLOSS: So, invertebrate cell lines, they're going to be characterized and tested?

DR. COFFIN: Probably not. I mean, look, this is off the top of my head, but probably not the way I would think about it

right now. John?

DR. ALLAN: Can I just caution a little bit differently, and this may just be a particular case, and it's something I'm not suggesting that anyone do or change or whatever, but part of the interest here is using a mouse feeder layer essentially to grow these human cells, and that's a xeno.

If you say, well, it's not that dangerous and we can allow blood transfusions or whatever, then you're basically saying that mouse cells are okay. Because the other question is could you use human cells because of the mouse cells as a feeder layer. In other words, do you have to have a xeno?

I'm not saying they change at this point, but in terms of you might want to consider that because if you say that this okay then they don't have to use human cells, they can continue to use mouse or monkey or whatever cell type there is.

DR. AUCHINCLOSS: Well, I think for

sure for the point of view of the conversation we ought to assume that the mouse cells are necessary. It may well be that they're not. I mean, there are people who go -- but that's not useful. What we want to do is push this case, that you only get this product with those cells there. Okay? That's the assumption you should work with.

David, what would be the characteristics of exposure *ex vivo* that you would consider to be so safe you'll dispense with precaution?

DR. ONIONS: That's difficult to do in a kind of theoretical vacuum, really. I suppose insects cells still need testing, but insects cells don't actually release retroviruses, as well. Yes, I think probably if you could demonstrate, and I think Dan's point is a very important one, that is that there is no evidence that whatever stringent criteria we want to put in that there are

viable xenotransplantation cells left in and that cell line has been characterized or whatever the monoclonal acceptable criteria are. Yes then in general as a general principle I will go along with that as being a non-xenograft, if you like. It's been exposed to materials, but it doesn't require all these precautionary steps that we've been discussing.

DR. SALOMON: I actually want to amplify that in the sense that what I'm hearing at this point is that the committee has gone too far in the direction of the precautionary principle in the sense that what you said, John, is absolutely correct of course, we'll never know for sure. We've got to stay somewhat based on the facts here.

Otherwise what we're setting here as Steve points out bars that are just impossible. So my feeling is that with respect to the Epicel as the model here, I'm pretty sure you could get around most of the

objections that we've brought up and come back here with some decent testing, and I probably would be ready to actually then say that this is not a xenotransplant product and that it could be safe and these people could be blood donors.

DR. KASLOW: It seems to me that the most important advice we can give to them because I think they've probably heard all of the discussions so far, is maybe to take a position that we very strongly believe that deferral should be reversible, that we should be able to make a decision now that can be changed later and let it be cast in capital letters that that's the strongest advice we can give them in whatever decision we make.

DR. AUCHINCLOSS: Now what I want to do is try to summarize where we are on that and then try to wrap up what I think will be -- well, we'll see. Never mind. Don't prejudge it. So, in response to 1- E, what I think I've heard is that the best

experts think that the likelihood under the best testing conditions that you can develop for Epicel of there being a danger of viral transfer to the product is really tiny and remote, but nonetheless prudence on the part of our experts leads them to suggest that you should still recommend deferral for the recipients of that product is what I think I heard. You're laughing.

DR. SIEGEL: The best experts recommend that, meaning the other experts who recommended something different weren't the best ones.

DR. AUCHINCLOSS: Okay. Sorry.

DR. SIEGEL: Sorry. I couldn't resist that.

DR. AUCHINCLOSS: It was not meant in that manner.

DR. SIEGEL: I don't anyone to go away offended.

DR. AUCHINCLOSS: What I think I was saying is that I don't claim any

expertise. Those guys can claim expertise. So, the experts say that the risk is very small but they still feel it's prudent to defer recipients of this product.

DR. SIEGEL: I guess the reason I asked that though is I guess, did not some of the experts say they wouldn't recommend blood deferral at this point in time?

DR. VANDERPOOL: Didn't we hear David change his point of view and say, look, when the testing is clear and negative then deferral is no longer --

DR. AUCHINCLOSS: Let's actually give me a show of hands on this one, and we don't characterize who's an expert and or not an expert. I categorize myself as a nonexpert. The statement is that the risk is considered extremely low with your best characterized 3T3 cell line. Given that it's very low, would this committee recommend that these recipients of Epicel be deferred as blood donors?

DR. HOLLINGER: With the caveat that these other things be looked at that were mentioned today such as the bovine serum and the cells and --

DR. AUCHINCLOSS: Yes. We're going to have testing to best available testing with modern technology.

DR. ONIONS: Can I also ask implications for withdrawal, because that's what influenced my change of opinion.

DR. AUCHINCLOSS: Yes. We are not talking about patients who have already --

MR. HOLLINGER: You're saying we can't?

DR. ONIONS: We can't say that.

DR. DAYTON: It's very hard to isolate withdrawal. I know there was a preference for that this morning, but it creates problems for us.

DR. HOLLINGER: You're talking just about withdrawal of the product that's available not in a pool. You're talking

about unpooled?

DR. DAYTON: I'll have to think about that, but yes, for certainly for pooled material there's a tremendous problem if you disassociate --

DR. HOLLINGER: Yes. I understand that.

DR. DAYTON: I think it puts it in sticky position if you're saying, well, from a medical- legal standpoint we recommend that this category of donor be deferred, but then we don't do the withdrawal. So, it's not an easy thing for us to do.

DR. AUCHINCLOSS: But nonetheless, I don't think we're here to make your life easy. I think we're here to give you our sense of the degree of risk and what you can do about it.

DR. SIEGEL: It should be noted that in the proposed document, which I think went through Jay and others, we did draw a distinction for example between recipients of

nonhuman primates where we deferred but didn't withdraw. So, there must be thinking that that's doable.

DR. DAYTON: Actually, I think the way we originally proposed it we would have withdrawn for nonhuman primates.

DR. SIEGEL: Right. But for other than nonhuman primates we said deferred, but we wouldn't withdraw.

DR. DAYTON: For product withdrawal for pooled material for other than nonhuman primates.

DR. SIEGEL: Right. That's what I was trying to say.

DR. DAYTON: We were not withdrawing.

DR. AUCHINCLOSS: Show of hands. Who thinks that these recipients of this product in the future best testing should be deferred as blood donors? Who on the committee? Hands up high. Best testing.

DR. VANDERPOOL: Best testing which

is negative?

DR. AUCHINCLOSS: Absolutely.

MS. DAPOLITO: Four yes.

DR. AUCHINCLOSS: The show of hands is good here. Now the other way. They do not need to be deferred.

MS. DAPOLITO: Did I miss somebody?

DR. AUCHINCLOSS: Future. Best testing, future.

MS. DAPOLITO: I get 10 not deferred.

DR. SIEGEL: Let me clarify. When you say in the future, you say specifically we're not talking about withdrawals? I'm not sure that there's been a vote that we not notify people who've already received this product, that if we were to defer people who receive it in the future, this vote wasn't saying we shouldn't notify people who've already received it that they're not deferred, it's only future people who are deferred. Right?

DR. AUCHINCLOSS: I think it should be possible from here to go back to --

DR. BLOOM: Hugh, I have one more question. I'm sorry. I have one more question for clarification on that vote. When you talk about best testing for the future does that mean patients that are getting it right now prior to the best test, they should be deferred, and then as Dr. Kaslow says since it's possible then to not defer?

DR. AUCHINCLOSS: I think it's an FDA detail.

DR. HOLLINGER: Just one other question just for clarity, if I could. As you know there are perhaps three kinds of deferral one of which we usually don't use, but a temporary deferral which really means soon you'll be able to donate. Then there's indefinitely deferred which I've always interpreted meaning it's indefinite, but you could in the future be allowed to donate.

But as the blood bankers will tell you, it is hard to get those people back into the pool again. Then there's permanently deferred which is just what it means, permanent. So, we were talking here indefinitely, but deferred.

DR. AUCHINCLOSS: In my view, this is a constantly evolving field where information is getting better and better and we're learning things and I could imagine that deferral now could stop being deferral in 5 years, but practicality-wise it may turn out that way. So, do any of the people who said that the individual recipient should be deferred feel that that should not extend to their intimate contacts? It should not?

This would be just the recipient who would be deferred? So, contact-wise, don't worry about them. Because, again, it's all relative risk. Right? The relative risk is just so low that you've gotten to the point where the vanishing returns.

DR. NELSON: I had possibly an irrelevant question, but when you showed all the slides about the procedures for people receiving these transplants, you talked about that they should have protected sex. Does that mean they're now not told they can't have children after they have this 3T3? If so, what's the basis for that? You're assuming it's sexually transmitted or there's something there?

DR. BLOOM: We're assuming that it could be possibly, it being whatever may be there could be sexually transmitted on the basis of previous --

DR. NELSON: I can't see any basis for that. It's kind of crazy because here we have hepatitis C which we know there's some evidence of sexual transmission even though not common, and we're not recommending that these people who are carriers of hepatitis C have protected sex. But here we've got somebody that we don't know that they're

infected with anything. It's not only the protected sex issue. It's the not having children that I think could affect some -- and I don't see any basis for that.

DR. AUCHINCLOSS: I think we're back to question 1-C.

DR. BLOOM: Right.

DR. AUCHINCLOSS: So, how do you educate the recipients of Epicel in the future with best testing in place? Do you tell them that they had a xenotransplant with the implications as outlined by Eda Bloom earlier for what that means which includes some of the things you were just talking about?

DR. SALOMON: Hugh, remember, one of the things that came out here is the possibility of exempting this as a xeno-product if the best testing is completely negative. I believe that that's an option here.

DR. SIEGEL: Well, we can exempt

any of the requirements we want to. There's a written definition of a xeno-product. You can't change that definition for each product based on its testing.

DR. SALOMON: What do you mean then that the FDA on a case-by-case basis can exempt a product? That's what that meant.

DR. SIEGEL: It means exempt it from any of the guidelines that suggested somebody needs lifelong follow-up, that they need animal testing.

DR. SALOMON: Jay, that's all I'm saying, you could do that with this case.

DR. SIEGEL: I was just objecting to the notion that we'll say this isn't a xenotransplantation product.

DR. SALOMON: No. I'm sorry.

DR. SIEGEL: Okay. Right. Right.

DR. AUCHINCLOSS: This is a xenotransplantation product that does not require blood donation deferral.

DR. SALOMON: But it's exempted

from the thing.

DR. AUCHINCLOSS: Does it require patient education. That's where we're at right now.

DR. SALOMON: I don't think it does.

DR. CHAPMAN: Could just clarify something with regard to your question? I'm counting on the FDA and Steve to correct me if I'm misstating this. But what the PHS guideline, both the draft guideline, and I don't believe this has changed in the revised one, say about the issue you brought up.

It doesn't say xenograft recipients should be told that they should never have children. What it says, the language that is used in talking about the informed-consent process is that they should be counseled about the uncertainty that exists; that they by getting this product are accepting some risk of infection that cannot be eliminated and they should be aware, and they are

responsible to educate their sexual contacts that there may be some risk that extends to sexual contacts, and they should be aware if they're considering future child bearing that there may be some risk with a great deal of uncertainty about whether it exists no ability to quantify it to future offspring and that may be a transmissible activity.

They're not told not to do it. They're advised to be aware that safety can't be entirely guaranteed and there be some risk to them and their partner and their offspring.

DR. NELSON: I didn't hear any data presented that there is a risk.

DR. CHAPMAN: There is no data.

DR. SIEGEL: This has been discussed at several other meetings. I would just suffice to summarize that there are unknown risks and that we've been advised by many individuals that some of the unknown risks of greatest concern are those that can

cause latent infection that may not be picked up in the immediate post-transplantation period such as say herpes viruses or retroviruses and that those are often sexually transmitted or blood transmitted, and that underlies some of these concerns. But I guess there we're talking theoretical risks. We're not talking about documented risks at this point in time.

DR. AUCHINCLOSS: Let's take a show of hands on it. Does the committee believe that the recipient of the product made with best-tested Epicel, should that recipient be told that they had a xenotransplant in just the way that Louisa characterized for us, the kinds of education that Louisa characterized for us? Yes, or no. Those who feel yes, show your hands.

MS. DAPOLITO: I have six.

DR. AUCHINCLOSS: Those who feel it's not necessary to go ahead with education as if they had had a xenotransplant.

MS. DAPOLITO: So, that's six.

DR. MICKELSON: I want to abstain too.

MS. DAPOLITO: So, that was --

DR. AUCHINCLOSS: So, it's something like --

MR. LAWRENCE: Hugh, we're trying to have it both ways here, and it's very difficult. You can't on the one hand have a risk that's so low that it's negligible and on the other hand be warning patients that they have this risk that they need to be aware of. So, these votes are muddied to me.

DR. AUCHINCLOSS: These are muddy hearings. Let's talk about the database. They want to know about the database.

DR. SIEGEL: I think we have extensive frequency of follow-up. I guess part of that also is extent and frequency of follow-up. So, the guidelines for example talk about lifelong follow-up on recipients including reporting of infections to the

sponsors of the trial or of the xeno-product and so forth.

I think that's an interesting area that there ought to be some specific comment on. You want to product more clarification as to what the guidance has said for example in that area?

DR. BLOOM: The original PHS guideline said something like I think it was a couple of samples prior to transplantation which clearly is not going to be possible I suspect here. At the time of transplantation, 1 month after, 2 months after, 6 months after, and then annually. So there are very specific recommendations.

DR. SIEGEL: You're talking about archiving samples. I guess I'm also talking about giving instructions to the patient regarding medical follow-up.

DR. BLOOM: Right. But those conceivably would be done with follow-up.

DR. ONIONS: Could I just make a

comment? Because I'm very much of the camp with the exception that I expressed an opinion before that I thought deferral would be a good idea on any new Epicel patients.

I'm very marginal on this but just purely because as John Coffin said, there's no benefit to society of a few additional blood donations, or marginal benefit, where there is an unknown risk, so why take the unknown risk when there is marginal benefit to society. That's the reason I was on the side of deferral purely.

But I do appreciate Mr. Lawrence's point that this does lead to inconsistency because actually on all the other issues, as Dan said, I almost don't regard this as a xenotransplantation. It really is in a different category of risk.

So, I don't think all these other issues of archiving and counseling the recipients are necessary at all. It just strikes me that this just one simple issue,

why take any risk at all when there is absolutely marginal benefit to society of a blood donation.

You probably can't do this, but I'd almost have done it as a counseling thing, well, we suggest you don't give a blood donation because this procedure has involved using mouse cells and we don't think it's a good idea, period.

DR. KASLOW: Again, I'm not sure I argue in favor of it because of this but following up people is one of the ways we find out where the risk exists and, in this case, given the low thresholds and the uncertainty, it may be the only way we'll ever find out. So, again, I'm not arguing for it but we at least ought to make the decision knowing that.

DR. SIEGEL: Right. I would knowing, to help and firm this discussion that we've had prior discussion I know in developing this guidance and I think with

committee that this may not be as simple as it sounds cause when you ask an investigator or a sponsor or a manufacturer, if it's an improved product, to take responsibility for life long follow up of all recipients of the product given the way the patients move around, given the way doctors move around and investigators move around, this, this is not a simple thing to do.

So, it's one thing to say yes it would be nice to follow up the patients. It would be another thing to suggest that the treating physician or the company should implement some procedure that would ensure, to the extent possible, life long surveillance of these patients if that's what we're saying we want.

DR. SOLOMON: I was going to follow up and say that having been in many times the, just desperate to get one year follow up on kidney transplant patients or heart transplant patients on a clinical trial,

thinking about not glibly recommending that we should be following these patients for years and years and years, archiving everything and keeping track of it.

I think we have to be resource sensible here. I don't think this is trivial. Moreover, what concerns me is if you spend your resources and energy on something with this low a risk profile, you're not necessarily going to have the resources left over to do the stuff that's a lot more significant.

Lastly there's a statistical problem here and if you have a real, real, real low chance, and you do a hundred different tests, what are you going to do with a couple positives? I mean, that's Bay's Theorem of Uncertainty. So, I think that it really would almost be argued even on statistical grounds that it's not worth doing.

DR. ALLAN: It's the same situation

too where if we're not going to defer blood donations, then it just seems to me that that's the best way to prevent an epidemic and to then just do follow ups and allow blood transfusions to happen.

It just goes against the best way to prevent an infection. So, if you're not going to do blood deferrals then I'm not certain that all this follow up is going to be necessary. Because if you believe, as many people have because they voted not to defer blood that the risk is so small that we don't have to worry about the blood supply, so then why put all the, all this effort into follow up. I'm sort of like a devil's advocate kind of thing.

DR. AUCHINCLOSS: I understand but I agree with you. I thought the green theory is an expression that blood donation was okay. That everything else would fall by the wayside. If you're not going to do that why, then you surely don't really have much

indication to do anything else. I guess I would say you'd want a data base of who got the pot in the first place so you could go back and try and capture information.

DR. NELSON: I'm not really arguing for an intensive follow up but there's nothing like data and I'm very glad that people in the U.K. decided to setup a new variance or a CJD Disease Registry in 1992 or whenever it was. We got a lot of data from that. I mean, I'm not saying intensive follow up but it is given that this area is really new, I think that there should be some data collection. I don't want to specify what it is.

DR. AUCHINCLOSS: Let me ask the committee that question because, in fact, I agree. I think as Dr. McCauley said, you could in fact find many of the patients, the 552 patients. I really believe you could.

If you wanted data, that would be

the group of patients to go to in just the way that Novartis is coming to us later on today to say hey, we went out and tracked down a whole lot of people who were exposed to Pinktus (?). You could, in fact, find people who had deceived Epicel in significant numbers and look at them. I'm not sure that you'd know what you'd look for but you could do it.

DR. CHAPMAN: I'm noticing that the people arguing for data and follow up are the epidemiologists. Being one myself, what has occurred to me is as a question is I'm wondering if we're all to give out the same thing in terms of follow up because I'm interpreting these questions in terms of the very specific follow up that's recommended in the Pages Guidelines for xenotransplantation which is quite extensive. Are you all familiar with that?

DR. KASLOW: That's a good point. I think the distinction between simply having

a registry and being able to track them, if necessary, is very different than saying we're going to have active follow up on the schedule that was described. Yes, I am familiar with it and it is quite burdensome.

DR. CHAPMAN: So would it be worth having you expand on what you think would be appropriate in terms of follow up because as an epidemiologist I really respect your, the value placed on that.

DR. KASLOW: Well, I think the compromise position. That there is some recording and some way to get back to it if necessary but not necessarily a fully prospective approach with all of the intense, intermediate specimen collection and so forth.

DR. VANDERPOOL: I'm in agreement with that, except for one proviso. It strikes me that this is a judgment call. If it looks like the, the risk are "very low or negligible," of course you wouldn't as a

judgement put them in them in lockstep follow up frequency scheduled that's been outlined in the guidelines.

At the same time it would make sense to say well we think that on a periodic basis or six month basis first, maybe a two year basis after that, we'd like to see one, a follow up study. That's where you add to the data base. But the lockstep, no. But some follow up beyond registry I would say would be, would be in order on a judgement call.

DR. MCCAULEY: I think as a routine if you take care of these patients, particularly those that have at least 60 percent total body surface area burned and have received Epicel, you can follow these patients routinely at least one a month probably for the first six months. Then you follow them about every three months probably up to about two years.

So the opportunity for data

collection is present. These patients will always come back for problems related to open wounds, problems related to rehabilitation, problems related to reconstruction, and you can follow them, I think it's very easy to follow them at least five years out.

DR. NOGUCHI: Are you volunteering? No, that sounds a little specious but it's not. I think that it's good to talk about data and it always is better to make policy decisions based on data but we have to have commitment to have the, the data being generated.

DR. MCCAULEY: I'm just saying this is what was routinely done at my own institution. This is without any additional requirements. I mean, this is what we routinely do.

DR. KAGAN: Yes. I would echo what Bob says. Both of our Shriner's Hospital which is run very differently then theirs.

We would have a certain set of

rules for follow up and actually variables to capture the majority of these patients, particularly the ones with more extensive injuries because they need us during that time. The same also holds true for the adult population which you would imagine to be more difficult to follow because those first three to six months, not only are they in pressure garments to reduce scar and they need to follow up but they need pain medication, they need antipyretics, they need us for insurance papers, they need us for return to work, they need us for disability, they're in touch with us because they need us. So I don't think follow up is as difficult as it had been portrayed.

DR. AUCHINCLOSS: So you have 100 patients in front of you who have had Epicel. What tests do you want to do on them?

DR. ONIONS: I don't particularly want to. I already said I don't think it's necessary. So, and you were just looking at

me. That's why I answered.

DR. AUCHINCLOSS: Yes. No, but I was looking at you. John, is there a test that we can do to find out whether a horrible thing happened?

DR. COFFIN: I just want to find out if a normal thing has happened. But I don't think, no. I wouldn't recommend any tests.

DR. AUCHINCLOSS: So the fact that we know that they're being followed these patients.

DR. COFFIN: Yes. I mean, I'm not, I'm not. I haven't even decided on this issue at all whether I'd be in favor of it or not.

DR. NELSON: I think you would collect major morbidity. I mean, they didn't decide to collect data on introsusception after the rotavirus vaccine. But that's what turned out. They found it, right?

I mean you don't know what you're

going to find. You'll look for whatever's there and if nothing happens and it's just an antibody, well, find. I mean, you're not going to screen but if, I mean, surveillance is, we're looking for morbidity, mortality, problems.

DR. ONIONS: I don't wish to get into and drag something else into the debate but that probably highlights precisely the problem with this rather kind of ad hoc surveillance because there's great debate about the significance of those introsusception data particularly from the company concerned about what's the reference control here and clearly I don't want to get into that debate because that's something that doesn't need looking at. But I think it's --

DR. NELSON: Nevertheless it's data.

DR. ONIONS: Yes, but bad data is sometimes worse than no data.

DR. AUCHINCLOSS: All right. We need to take a break but we haven't really addressed Question Number Two where we tried to generalize. But have we addressed Question Number One adequately, I mean, from your point of view.

DR. BLOOM: I think just for the sake of completeness if you could look at the next couple of slides because I think some of the recommendations that we made for the next slide for example is very close to what you guys have been saying.

DR. AUCHINCLOSS: What number?

DR. BLOOM: That one you just previous, previous.

DR. AUCHINCLOSS: 1D?

DR. BLOOM: Previous. That one.

DR. AUCHINCLOSS: 1C.

DR. BLOOM: Yes. The first. Since no known agents have been identified we would request no passive monitoring and I think that's what we've kind of been hearing but

I'm not sure. We request, for example, that if there is an incident of unknown infectious, or of infectious disease of unknown origin that then there would be passive monitoring.

But you didn't quite address that pre se. I was hearing, well, we don't need to look at these people actively. What do we do when we follow up? Do we take samples? I don't know.

DR. SIEGEL: Either way. It might be useful and take not to much time to read both for 1C and 1D. What we've put down as a strawman for what we would do and just get a sense as to whether that's on, as a, on the whole is on the right track for them.

DR. BLOOM: Right. Since no known agents have been identified in the murine cell line, FDA requests no passive monitoring but rather achieve being baseline patient samples and samples as indicated, only for a suspicious event infectious episodes. It is

acknowledged that long term recipient cooperation would be integral in compliance with this request.

DR. AUCHINCLOSS: I think that sounds pretty reasonable. Who thinks that sounds reasonable?

DR. BLOOM: That's what I thought they were saying.

DR. HOLLINGER: It depends on what you can do.

DR. BLOOM: Yes.

DR. HOLLINGER: It depends on what you call an infectious episode. I mean, if you believe, as some people do that coronary artery disease may be, may be caused by a virus or diabetes. I think this is part of the issue and I would agree with what Ken said that just looking primarily at either hospitalizations or major life threatening events, or something like this; death, things like this are what's really critical.

Who cares if you get diarrhea or

respiratory infections or things like this. That's not really so criterial. But something that causes chronic disease, is more critical and that's all one would really have to look at.

DR. AUCHINCLOSS: Steve?

DR. ROSE: Hugh, I'm sorry. Dr. Nelson, I'm confused. This says passive monitoring. You were just talking about collecting data when patients come in. Would you please tell me what you meant if that's not passive monitoring?

DR. NELSON: The borderline between passive and active surveillance or monitoring is sometimes, sometimes vague. But I think we could passively, possibly collect major life events or major morbidity or mortality and if we saw some clustering that looked significant or looked suspicious then more active surveillance would be set up.

DR. ROSE: But this says no passive monitoring. Not no active monitoring. It

says no passive monitoring.

DR. NELSON: Just for clarification really.

DR. ROSE: No. I would argue for passive monitoring.

DR. NELSON: Yes.

DR. SIEGEL: I just voted yes on it.

DR. NELSON: I didn't vote on anything.

DR. SIEGEL: No.

DR. NELSON: We are discussing what level of excuses we disagree on.

DR. SIEGEL: Yes. Let us make clear what was read there is relevant to archiving of patient samples not the discussion about medical histories. More relevant to that, and quite to the point of looking at high risks is what's at the bottom of the next slide that we recommend that the data base that currently exists be expanded to "document clinical episodes potentially

related to murine-derived infectious agents (e.g., fever of unknown etiology, neoplastic conditions, neurologic disorders)."

Those things that we, those are e.g.s I'm saying that's the list but the idea would be not, not to capture every episode of the flu but to capture those things that might raise concerns about some of the types of pathogens we might be concerned about.

DR. AUCHINCLOSS: Louisa?

DR. CHAPMAN: Can I try restating the epidemiologic terms. What I think you meant and they meant. I think that, for people who are not epidemiologists, passive monitoring and active, passive surveillance and active surveillance, are technical terms and active surveillance means you put human effort into intentional and going out and acquiring data and passive surveillance means you accept the data when it comes in.

So you capture more complete data when you do active surveillance. You risk

capturing less complete data or only really major episodes with passive surveillance. I think what was intended here by the FDA and what, if I'm hearing people correctly, would be in line with what epidemiologists hear are talking about is the intent was to say no, the risk is low here.

It's necessarily to do active surveillance monitoring. Rather you can capture information on major like events onset of chronic diseases needing medical condition, hospitalizations and their causes and causes of death by doing passive monitoring and collecting the data when these things bring people to medical attention. Is that what you all meant?

DR. NELSON: Perhaps an analogy that's relevant to what the FDA does is after a drug is licensed and somebody has some sort of thing, event that might be related, it may be reported as an adverse event in a licensed, tour licensed drug. But it doesn't

mean that each patient who's on that drug gets a phone call every week to say, what's happened to you last week.

That's the difference. I'm saying that we should collect passive data for all of these xenotransplants or maybe this is a non-xenotransplant. It's a transplant delay. It's not the whatever.

But we still, there maybe risks there that are undefined. I think we all agree with that even though we can't grow an agent or we can't find reverse transcriptase. That doesn't mean that there is no risk. Nobody's talked about prions and all these other things that you can't measure and that are resistant to radiation.

Who knows? But, the fact is that I, I don't think we want to close our eyes in that there should be some system of passive collection of data on cohorts or sets of people who have had a xenotransplant or exposed to animal tissues.

DR. AUCHINCLOSS: Unfortunately, I apologize to my subcommittee members. I actually have to go at this point. I think you're very nearly done Question One. John Coffin has agreed to take over as chair and I guess I'll leave it in your hands whether you have a break before you go to Question Two or how you want to handle that and I apologize for leaving you early. Thank you.

DR. COFFIN: So where are we with Question One finishing up? Are we, as he suggested, about done here?

DR. SIEGEL: We're comfortable. If there are members of the committee who would like to make further comments, that's fine.

DR. MICKELSON: I think all we're really talking about is taking the no out of there for the passive. Isn't that what the committee is recommending? Is it something akin? 1C. On 1C aren't we just saying take out the no for passive monitoring? Not no passive monitoring.

DR. KASLOW: No. I think we're still making distinctions between getting samples from people versus getting reports of events, clinical events.

DR. MICKELSON: Passive monitoring. That not passive monitoring.

DR. KASLOW: Certainly taking samples isn't. But, but what we're really saying, I think is that you have a list of people who received whatever we're going to call this. A transplant. You say tell us about what happens.

DR. MICKELSON: When they come in. That's not passive monitoring.

DR. KASLOW: That's passive monitoring as opposed to we're going to call you on a regular basis and find out whether you're seeing anything.

DR. MICKELSON: But, don't we want passive monitoring?

DR. KASLOW: Yes.

DR. MICKELSON: Isn't that what the

committee --

DR. KASLOW: Yes, yes.

DR. MICKELSON: All I'm saying is that the wording in 1C says that the FDA requires no passive monitoring.

DR. KASLOW: But that refers to patient samples there.

DR. SIEGEL: But I think it was meant to say active and they didn't get it right.

DR. MICKELSON: So it was meant to say active?

DR. BLOOM: Yes, it was meant to say active.

DR. COFFIN: Given that change, are we happy with this statement since we already voted we were happy with the statement even without the change. I assume we're even happier with a statement with a change. Is there, is there anything else on Question One?

DR. SIEGEL: So that means the

sense of the committee is, just so we understand, that if somebody comes in with a certain, with a suspicious type of infection, there should be both a data base recording but that also may well. It's the standard for archiving specimens as well but otherwise there shouldn't be efforts to reach out and find them.

DR. HOLLINGER: No. No. From my standpoint, I'm sorry, I would feel that something a little bit more aggressive than that and I guess this would go under active.

That would be that on a very minimal basis, whether you look at death certificates, I mean, those are easy to look at. Whether you look at it at one year and five years. But at some point, I do think that somebody ought to find out if there's a major problem that has occurred in an individual whether it's neurological, chronic or otherwise. I don't think that's, that's a very difficult situation to do. I mean,

that's my own personal feeling with this.

MR. COFFIN: It may be useful to see how many people share that particular sub-feeling of this. Just a quick straw, show of hands. It looks like a sizeable majority of the committee although not quite unanimous.

MS. DAPOLITO: That was fifteen.

MR. VANDERPOOL: John? So there seems to be saying substitute, the FDA requests no active monitoring rather archivial base lines and then we're making another sentence there, "periodic reviews of the, of the data from, of the passive monitoring of data, of patient data should be done."

DR. COFFIN: Would be advisable. We're not writing regulations here.

DR. VANDERPOOL: Would be advisable, would be advisable.

DR. COFFIN: Yes. I think that's probably enough guidance on this particular

point unless somebody has something new to raise. One deal, what are we done here? Are we okay for Question One?

DR. SIEGEL: I think we are.

DR. COFFIN: Why don't we take a short break, reconvene at 3:30. Can we get settled again, please.

(Recess)

DR. COFFIN: We have a number of questions. It's actually one question but its got an awful lot of parts that the FDA still wants advice on and then we have a presentation following that so we're going to have to move right along. Edie, do you want to introduce Question Two?

MR. LAWRENCE: Can I make a motion first?

DR. COFFIN: Yes.

MR. LAWRENCE: Right after lunch we had a presentation opposed to the xenotransplantation and Dr. Vanderpool mentioned that he had written a response to

it and so forth. None of our colleagues here have seen that. I would like to move that those two documents be made a part of the record here and distributed to the committee.

DR. COFFIN: Without objection, so ordered. Now if we could move on to Question Two.

DR. BLOOM: The FDA is now seeking advice regarding other xenotransplantation products. Recognizing the inability to bring for expert discussion each application to study xenotransplantation, we seek additional guidance as to how various characteristics of the products may impact selection of appropriate approaches to address infectious risks.

We ask the committee to consider and discuss the following characteristics of xenotransplantation products and the impact these characteristics or risks on the optimal procedures for controlling risk. In several cases we provided again another straw person

and requested the committee discuss whether or not it agrees with these proposals. Next slide, please.

So here we have at the beginning of Question A which is regarding the species of source animal. Clearly a different source species pose different risks. FDA believes that the types of controls which are appropriate for different species may vary based upon these risks.

Several of the controls recommended in the draft, PHS Guidance, are targeted at specific risks such as transmissible spongiform encephalopathies, latent viruses and so forth; blood born diseases and so forth. We ask that you discuss the following approaches.

We've actually already issued our non-human primate document that this committee discussed six months ago and we said that we publically stated this but we have yet to see sufficient safety data to

warrant the use of nonhuman primates as source animals.

The use of nonhuman primates raises specific concerns because of their proximity to the feral state. Currently possible levels of animal husbandry and isolation and the history of transmission of initially inapparent infectious disease to humans. We have already based guidance based on. We already based guidance on these concerns.

However, in regard to nonhuman primate, excuse me. Non-primate mammals, it is possible that certain species or strains do not express, for example, infectious endogenous retrovirus. FDA suggests that the use of species retrains lacking infectious endogenous retrovirus may lower concerns about latent infection but not to the extent that changes in life long follow up or deferral of close contacts from blood donation would be prudent at this time.

DR. COFFIN: Why don't we stop here

and discuss these two points.

I think regarding the primates, we've been in general agreement on this for quite some time. Does anybody want to change our opinion on that? Okay.

So the issue with non-primate manuals, it's on the slide in front of you. While there may be the point here is while it may be lower concerns, the, they are not really adequate especially given what we've heard from people who are concerned about exogenous agent introduction. They're not adequate to really change our minds about how we treat one animal or one cell type or one strain versus another. Is that a fair statement as far as the committee is concerned?

Good. We're moving right along.

DR. SIEGEL: While we're waiting for Edie to come back, just point out that we don't anybody to be unduly bias by the fact that on some of these questions we put down

positions. We put them there just to be used as you did to help facilitate either discussion or consensus and, but we feel quite open and encouraged any disagreement that people might want to express.

DR. COFFIN: Fair enough. Yes?

DR. KAGAN: A point of clarification there. Have we changed the word close to intimate in all of these documents or are we going back and forth?

DR. BLOOM: The slides still say close. For the purposes of discussion, if you wish to change it back to close please feel free to. However, I think what we're going to discuss is what you meant by intimidate.

DR. SIEGEL: Let's not discuss which word we mean because, in fact, and I understand that in some blood regulatory documents there, they are sometimes used interchangeably and we don't have precise definitions for either. Let's simply say

that to the extent that the deferral, we understand the sense of the committee to be that any deferrals that are made should be only for the more intimate contacts. That's what we're talking about. Whatever you want to call them. Okay?

DR. COFFIN: Okay with me. So the next regards non-manuals. One of us can read it.

DR. BLOOM: Yes. For non-mammalian cells including invertebrates, as noted previously by this advisory committee, that would be last June, data regarding ability of each species to harbor human pathogens should be carefully reviewed and controlled procedures designed accordingly. Some of the controls designed with manuals in mind, may not be routinely necessary for protocols using invertebrate cells such as the Drosophila.

FDA suggests that for use of non-mammalian sources including invertebrates

in particular, source animal, colony surveillance and animal testing and procurement requirements may be quite limited and blood donor referral of fill in the blank contacts and health care workers, may be unnecessary.

DR. COFFIN: Is there any discussion on this, on the issue of invertebrates? David?

DR. ONIONS: Just two very brief comments. I think, there's always a little bit of a danger if you assume something's safer, by some arbitrary criteria, let's lower down the phylum genetic scale. That would be my first comment.

My second comment is, yes, in general agreement but certainly the testing or approaches might have to be different. But I would just flag two points.

One is that, and I'm no expert in this area so, but there are certain transposable elements that have been taken

from insect cells that have been used successfully in cells of mammalian origin, Not very efficiently but they have been used. So there are, there are other dangers that one might have to consider that are not normally ones we consider with mammalian cells.

On this there are still surprises. For instance it is now clear that the tag retroposed on TB cells is actually a true retrovirus. It's actually a infected retro verse and it's not an impact to other insect cells, it can affect viruses so you can get integration in tubercular virus.

So often the amount of work that is being done has not been as extensive on mammalian cells so I think we need to just be a little bit cautious about assuming you don't have to do as much is really what I'm saying.

DR. COFFIN: Anything else? That was a point well taken. Then otherwise I

think, I think that probably would. Well, does that reflect everybody's position, that comment? More or less? So we'll move on.

DR. BLOOM: Extensive testing and characterization of cryopreserved cell lines may often provide an adequate or superior substitute for other recommended controls. We've already discussed the case of Epicel.

For extensive characterization and testing. For some cell lines, information about the source animal is quite limited. In such cases and in general, FDA proposes that extensive testing and experience with long-term cell line may obviate most or all need for animal procurement sources and source facility controls.

Additionally, definitive exclusion of various pathogens such a herpesviruses and retroviruses could lead to less intensive long-term monitoring and sample archiving and could obviate the need to inform contacts or defer them from blood donations. So this is,

basically, we think that this earlier discussion may be more generalizable.

DR. COFFIN: Go ahead.

DR. VANDERPOOL: It strikes me that this paragraph fairly effectively summarizes all two and a half hours of turgid and complex discussion. That's what we came to agree to with and here we have it in print.

DR. COFFIN: I have the same sense. Is that also the sense of the committee?

DR. SIEGEL: This reminds me. Thank you. I was thinking the same thing as well. It does remind me though, we talked about informing contacts. I don't know if we discussed that vis-a-vis Epicel. We had some discussion and maybe some difference of option about donor deferral but it's another interesting question, would you tell all these burn patients that they should tell all their intimate contacts in for the remainder of their life that they're potentially exposing them to risk of an infection from a

mouse.

DR. NELSON: If they had a baby it would look a little bit with long ears, is that what you're saying?

DR. SIEGEL: Well, just a, I'm sorry. I guess everyone wants to go home now. But these are pragmatic questions we will be facing in these and I wonder is there a general sentiment?

I guess a lot of people felt that many of the, the precautions were not necessary. Is it safe to presume that that would be one that there's some consensus would not be necessary for a product given that the well-characterized cell line and given some agreement with this paragraph?

DR. COFFIN: Is there any disagreement on this point that extensive discussions of this sort in this particular kind of a case where all? We're happy with all of the safety tests that have been done as the hypothetical we discussed with Epicel.

Is there any feeling that there should be extensive requirement or at least urging for extensive discussions of these issues with contacts?

DR. VANDERPOOL: To urge extensive discussions with intimate others and on grounds of virtually no evidence, would be, to put it somewhat stickly, making a mountain out of a mouse hill.

DR. COFFIN: Particularly, even the scientist at this table would have a lot of trouble trying to make, have this kind of discussion. I think it would be extremely difficult during practice to actually see how you even approach such a thing. It's probably reasonable. Well, I'll stop there. I guess we can move on.

DR. BLOOM: Thank you. Regarding the products, cell line versus fresh tissue question. Homogeneity of cell type in particular.

While most fresh tissues are

particularly, excuse me. While most fresh tissues, in particular, vascularized organs, should be assumed to have an adversity of cell types, a cell line, or in some cases, a highly purified cell population, may lack or have the ability to transfer certain types of pathogens. FDA proposes that the caution should be tailored to that type of pathogens of concern.

DR. COFFIN: I think, and it's my opinion in circumstances like this, yes, having cell lines can, can simply the testing procedure for known pathogens but I don't see how it helps us very much with unknown potential pathogens. But the other people may feel differently about that.

Apparently not. See what a break does for people. Getting a little sugar back in and allaying the hypoglycemia.

DR. BLOOM: Examples of approaches which may quantitatively now reduce risks, include the use of barriers or encapsulation,

transient or short-term exposure, low dose exposures. For example, a few cells versus vascularized organs.

These practices have a potential to reduce but not eliminate risk. Barriers impermeable to infectious organisms may provide protection but may also have a failure rate. Shorter term and lower dose exposure may be less risky but are exposures nonetheless.

In general, we feel that these factors should per se have at most a modest impact on safety precautions. If you agree with that, however taken in combination with each other and/or other factors that may provide significant protection, obviating the need for certain precautions.

For example, if a patient's blood is circulated over an animal's secretory cell line using a low molecular weight barrier which has been extensively validated to prevent transmission of infectious organisms

under conditions of the study, not to break, risks may be substantially reduced.

Does the committee agree that such consideration should be taken into account in determining additional protection such as frequency of long-term monitoring and archiving of specimens, notification and deferral of intimate contacts?

DR. COFFIN: What's the committee's pleasure? Does anybody? We had some discussion I think about this the last time. Does anybody? Derrick?

DR. ONIONS: Yes. It strikes me that just the way that this phrased it's slightly inconsistent with an earlier comment that suggested that, one of the ones we discussed way back but, it seems to me that I agree with the first statement.

That is there's clearly going to be a failure rate. It strikes me that the two main procedures that are being looked at are encapsulating cells and putting those back

into the, say, the abdominal cavity. Those definitely are going to have a failure rate. I mean, there's no doubt about that. The slightly safer procedures it seems to me are the ones that are *ex vivo* and involve the semi-preamble membranes for instance the liver cells that we've seen discussed here before.

But it seems to me that both of these procedures are still new and at the moment would not alter my view about long-term telemetry. But, again, that's something that I think in the light of experience you might wish to change but at the moment my view would be that you would still want to adopt the same kinds of monitoring procedure until there's some established record with those procedures.

I'd have to say that with the kinds of approaches within encapsulation, I would find it hard at the moment to see that you would ever change that view because there's

going to be a definite pronounced failure rate.

DR. COFFIN: Other comments to this? Let me. Go ahead, Prem.

DR. PAUL: I don't feel quite comfortable with this especially some of the agents which, viruses which, are very, very small and I have not followed extensively what type of physical barriers that are available but it would be difficult for me to imagine that, like circovirus is probably very, very small that they could, that they would be stopped.

Again, what happens in case there is the filter or the membrane is broken? So what's the quality control? So what happens to the monitoring and does that changes the picture? It would for me. So there are a lot of questions.

Again, I think about getting some experience and the records and eventually you can have a little more faith. But at this

point I don't feel very comfortable.

DR. SIEGEL: As to the types of barriers here, there's a, there's a broad spectrum. Some do get down to the hundred kilo-dolten or so range that have been used to allow passage of certain low molecular weight secretory proteins. I think that the comments about failure are points very well taken. I gather, Dr. Onions, that you are suggesting that there's a general presumption with any encapsulation of anything going *en vivo* we should work on the general presumption that there will be failure. That you'd be more open and in certain *in vitro* cases possibly to validating ability to avoid failure.

DR. ONIONS: Yes. I prepare to be stand corrected but at the moment without evidence in front of me I would assume that there would be a definable breakdown rate of encapsulation procedures that I've heard about that are being used at the moment. I

think the *ex vivo* systems that use semi-permeable membranes are inherently a lot safer.

I think they are much safer systems. But because those, nevertheless because these are still new systems, I would want, at least for the next few years certainly for that, for monitoring to proceed. So we build up a data base that gives us comfort and I'll be then happy to change in the light of experience.

DR. COFFIN: Yes. I think, the general problem I have with these things is that as you subdivide the risk it's still a very small hypothetical risk and it goes to a very small hypothetical risk. So until one knows the starting point, one doesn't know where one's gotten to and I don't see how we can deal around that.

DR. VANDERPOOL: It strikes me that the paragraph, that the summary question to the committee doesn't particularly follow

what the paragraph is saying. It seems to me the question should be does the committee agree that such considerations should be taken into account in determining either fewer or additional detections should be required.

Then I don't know what to do with the phrase such as a frequency but we're being asked, whether fewer requirements should, should be in place at times but then there's also the question of additional protections at other times and basically I as a committee member would agree, yes.

You have, we would charge you with the ability to alter 19-6 regulations to be the stiffer or less, or slightly altered with fewer regulation requirements.

We've been doing that and we will do that here. I want to make one more point and that is, I generally agree with the wording of this paragraph but I think we ought to maintain what we've been maintaining

through much of our discussions. That the burden of proof for ever-moderating safety precautions should be on the IND Sponsors and in consultation with the FDA.

This committee will help maybe alleviate some of those burdens of proof. But the burden of proof is to prove exactly what we are about. It should not require safety precautions XYZ. But I think those safety precautions, we should assume that they stay in place unless certain conditions would allow for some of them to be modified.

DR. COFFIN: Good point. One thing that strikes me here is that with some of these device, I don't know enough about these devices to be sure but some of these devices there may be some good way of monitoring whether barrier failure has occurred or not. Then that might be, it may be possible to take that into consideration regarding some of these issues.

DR. SIEGEL: Can I make a point? I

recognize your concern Dr. Coffin but when you're going from an unquantitative risk to a lower unquantitative risk, you still have an unquantitative risk and you don't know where you are.

On the other hand, everything we're dealing with is a spectrum of risks. Some have noted even to lots of things like that we're not dealing with like eating for example or handling animals and there's a natural, these quantitative issues naturally come up. There was earlier discussion this morning about what if you knew that a small number of 3T3 cells were carried over with the Epicel product. Would that matter and for example Dr. Auchincloss said, that wouldn't bother him.

I'm not sure what he would answer but I think some people might have, who think that wouldn't bother them if you had a protocol where you were injecting several million 3T3 cells into the abdomen or into

the skin or into the blood. What might be, you might have a different level of concern then some possibility that there is some small number of cells carried over. So you know what I'm saying?

DR. COFFIN: But one has to be very careful on a case-by-case base because it's possible that some large numbers of some purified cell type like allod cells may, in fact, just because of what they are may be, might be expressing some endogenous viruses at a level that we don't know about.

You can in some cases say clearly where there's a barrier, you can say clearly there is a reduced risk in general of things being transmitted. But in other cases it's not, it's not so clear that you can always make the argument that the risk is reduced.

You had your lights on. Are you? Does anybody have anything else to add to this? Then we'll move on.

DR. BLOOM: Immunosuppression of

recipients is often cited as a reason for concern about risks of xenotransplantation. Please discuss whether the extent of immunosuppression of the recipient should be a factor in determining the types of protections involved. At the current time, FDA proposes not modifying any recommendations for non-immunosuppressed recipients.

DR. COFFIN: I think the issue is similar in a sense we don't know. We can imagine that immunosuppression could make a big difference but we don't really know that for sure and until we do, is that? Committee in general on agreement on that?

DR. ONIONS: Just for clarification, really, John on what the actual stemming is. What do you mean by protection here? I'm not quite sure what's intended?

DR. SIEGEL: I'm sorry?

DR. ONIONS: Sorry. I don't quite

understand the question Phil, and it's late in the afternoon.

DR. SIEGEL: Let me say for example that Dr. Auchincloss, again, I hesitate but won't restrain from citing him in his absence but he said this morning that actually part of his reason for not being so concerned about Epicel was not simply that it was a well-characterized cell line but he said even if cells were carried over he wasn't so concerned because these individuals receiving it were immunocompetent than somebody who's being suppressed to tolerate a, a harder kidney graft.

So what we're trying to, having talked about a specific, we're sort of trying to tease out so that we can do some generalization, recognizing that we're not going to have definitive answers to every product we might see but ought that just some general advice, what will role ought that play in the equation as we look at it.

DR. NELSON: Is this discussion, again, related to Epicel? Is that what we're talking about? Or are we talking about --

DR. COFFIN: No. We're generalizing here.

DR. NELSON: We're generalizing. I have problems with generalizing because people could not be generally immunosuppressed but could have a specific immunologic defect and if we don't know what the organism is, we could have a normal person, a seemingly normal person who is at high risk to a specific agent. There are a lot of examples of that.

DR. COFFIN: You could also have a circumstance where somebody becomes a high risk later on and something latent gets in the graft reappears, too.

DR. ALLAN: The other thing about immunosuppression is that, I think it's overblown. Generally it's the introduction of the virus and immunosuppression may or may

not increase the levels of the virus that's present in the body but even without the immunosuppression it's the introduction through the xenotransplant that begins the process so I agree with what the FDA states here.

DR. VANDERPOOL: It is late in the day and some of our neurons are beginning to rest but I think there's a very important question. I don't think we're giving it, right now, with the brevity in which we're reviewing these, the attention it deserves.

Because I think we really need to open this question up about what data is there for far greater or greater or not so great vulnerabilities who a) infection, b) mutations occurring. What data is there?

Does your expert in this area or all the other experts who can bring to us those issues because I think you're right, Jay, in talking about the degree to which Dr. Auchincloss said really doesn't bother me

if someone's not immunosuppressed.

The compliment is very powerful. The human compliment is very powerful but what are the levels of vulnerability under immunosuppression? There would have to be experts here and the experts here are dealing with immunosuppression tolerance who can give us a reading on that so we could give much more considered judgment to what you're asking. It is, to me, it is a very serious question and I certainly don't have, I haven't heard, enough of people talking about it to feel I have any kind of a handle on it.

DR. SIEGEL: I'm not presuming to be an expert authority. I am an immunologist in infectious disease physician and I think the problem with that question is, I think, was highlighted in one of the prior comments that it's hard to even speak about levels of immunosuppression.

There's loss of skin barrier in a burn patient, there's losses or partial

impairments of human immunity or cellular immunity, defenses against different types of pathogens. There was a comment about not even knowing, whether you might have a patient with a deficiency for a specific with a disease that might have a deficiency in their ability to defend against a certain pathogen. So I think your question is an important one but I think what you've heard from some of the committee is it's hard to address in the general. You almost have to, because immunosuppression is so complicated.

Maybe that's why this is not in. I should note that we recognize, we're asking this committee to do the impossible. We often do and you often come through in giving general rules and what we hope to do is and what we have been doing is to have an ongoing back and forth process and when we get more specific questions as we have in the past about certain porcine products or at-risk issues or this morning regarding Epicel,

we'll come back for more specifics but in the, in the interim, we are dealing with the case, with proposals and need some general guidance because, unfortunately, although one can't often know what the right answer is, one does have to give an answer. That's kind of, that's sort of where we are not in trying to get the general guiding principals.

DR. COFFIN: David?

DR. ONIONS: Just to try and answer the specific question, I agree with Jonathan and I think Jonathan is absolutely right that when the key thing, does the virus get into the animal? Can it replicate, I mean, if it infects us can it replicate that? Those are key, perhaps the key elements.

Once the immunosuppression can modify the patten of infection that's seen afterwards. You almost have to go do it on a virus-by-virus basis. But we do have a very clear example and that is the example of anthrotrophic murine leukemia viruses that's

been used in gene therapy systems in primate models where we have the one study from core matter and not so badly immunocompromised animals that didn't do anything. Then we have an example from Donahue's Study where these animals had whole body radiation and were profoundly immunosuppressed and three out of eight of those became virulo-developement infirmed.

So, the answer is, if you have to give a crude answer to this question which I think you have to, then clearly in the suppression in general, however defined, is probably worse than not having an expression.

DR. NOGUCHI: I'd like to follow up specifically on that one because we've also done experiments at FDA in which we tried to do a control injecting this retrovirus into juvenile monkeys.

DR. ONIONS: Yes.

DR. NOGUCHI: Actually they became both acutely and chronically infected and

after follow up for a number of years seemed to be developing a very peculiar kind of disease.

So what you may be seeing, what you're seeing is correct but, if in terms of latency it may well be that a normal physiology might under some conditions lead to a chronic condition which then could lead to some disease.

DR. ONIONS: Understood, yes.

DR. NOGUCHI: So I, every example has, as you see Harold, every example has these nuances which makes it very complex.

DR. SIEGEL: Let me ask another. Oh, go ahead, Louisa.

DR. CHAPMAN: If I could just speak to your question a moment. I think Jon Allan's point is the most salient one because, if I understand what the FDA is asking, they're not saying should we begin with a base of precaution and then impose additional precautions based on specific

kinds and degrees of immunosuppression.

They're saying, we're beginning with the base of precautions that assumes immunosuppression. Should we lighten that based on degrees of absence of immunosuppression and, from clinical infectious disease, the examples that immediately come to my mind where I'm aware of interactions between immunosuppression and infection. There are opportunistic infections in immunosuppressed persons which are things that are latent in the body all the time and are given the opportunity to cause disease by immunosuppression. But they're not new infections.

So there are HIV and Hepatis B and HBV have clearly pursued more aggressive courses in immunosuppressed organ recipients. But remove the immunosuppression, those are still aggressive and destructive viruses. So that does not give me a feeling of greater comfort.

Influenza has been shown in immunocompromised hosts to become a persistent infection with multiple, with evolution of the viruses within that one host that you're isolating. But that host actually by being hospitalized and under isolation precautions actually probably causes less risk to the general population than you or I when we get influenza and shed it prolifically for a few days and get on a plane and infect a plane-full.

So I think if FDA had asked the opposite question which is should we impose greater precautions based on degrees of immunosuppression, it would need a very sense of discussion like your suggesting. But I think Jon Allen hit the key point for the question they actually asked which is, is anyone comfortable at this point saying if you're not immunosuppressed we don't have to worry about these things. Is that it?

DR. SIEGEL: Let me carry some of

those concepts one step further. Something I thought about but I haven't heard much discussion about which is that since most of these guidelines are designed to address the largest concern we have, or the most different or unique type of concern which is not so much that the risk to the patient, although there's a lot there and we have those concerns, but the risk to the general public.

Then in fact the concerns we should be most concerned about, are those infections that are infectious to the non-immunosuppressed that among those infections that occur in an immunosuppressed individual, there's those subsets just discussed that also, that affect immunocompetent but there are also some subsets that you see the patient and you don't worry to much because this is not a disease I'm going to catch because I'm not immunocompromised.

I guess in the logic in saying we should be more worried about immunocompromised individuals would apply only if we postulate that the immunocompromised individual may provide, if you will, the breeding ground for the development of an infection that may then also later be infectious to non-compromised contacts. Which might happen or maybe that is the biggest concern but if the serious concern is about infections that are infectious to non-immunocompromised individuals, then surely the non-immunocompromised recipient is also at risk for those.

DR. COFFIN: Combined with the fact that, I think was a little to early that the immunocompromised person is always often in a situation where they are unlikely to be in, transmitting anywhere as readily. They're not donating blood, may not be having sexual activity and so on and forth.

But I think the issue that we are most concerned with is that of a pathogen undergoing some sort of evolution while it's in the recipient so that what comes out of that recipient is changed from what went in. That, it seems that in all the discussions we've had, that has sort of been the major focus of concern and there you have, do have to worry about it in cases of somebody who is immunosuppressed transiently so they come out of it at a later state and then are able to spread around.

Now what's a now a modified organism, it's had a change to replicate and again we're talking hypotheticals but we can probably think of examples of things that might actually have happened or one can imagine thought experiments with viruses that we know about where such a thing could imagine to happen.

DR. HOLLINGER: I think that for most viruses, not all, and many of them which

we may not know, immunosuppression at least leads to higher virus concentration which often are more likely to be associated with a non-percutaneous transmission through like sexual contact.

So we see it with HIV, we see it with Hepatitis B, we see with Hepatitis C and so on. It's very much, somewhat, not always, but related to viral concentration which seem to be higher in immunosuppressed patients.

There are also very major differences in what happens with immunosupression. You take a patient with Hepatitis B who gets a liver transplant and they often will get to a much more serious disease in a much shorter period of time then an immuno, then an immunocompetent patient. On the other hand, with Hepatis C, it's a little, it's the reverse of that.

In five years they seem to be very similar with very little disease at the time. So I think it's very complex and we don't

know. I think for the immunocompromised, I'd be more concerned about the fact that they're more likely to so some transmission if there was a virus present then those who had a good immune system. But you really don't just know what happens in the immunocompetent patients. They may have more serious disease, they may have less serious.

DR. COFFIN: Jon?

DR. ALLAN: I just want to go back to what Louisa has said which is, regardless of the degrees of immunosuppression, if you're going to do this for the non-immunosuppressed, if you're going to do these types of things for the non-immunosuppressed individual, it's going to take care the immunosuppressed individuals, you're even more concerned about them and so you're going to do all the same things as well.

So, it really doesn't matter in terms of the levels of immunosuppression

because if you're going to do it for the non-immunosuppressed, you're going to cover the immunosuppressed. Does that make sense?

DR. SIEGEL: I think Louisa has got the question right which was, given the guideline which suggests a whole bunch of things and is in part based on the fact that many people would be immunosuppressed, should, for those cases where there might be a recipient who is immunosuppressed, should we take different approaches?

Our proposal here was no, that probably that we don't know enough that that's a factor that should change it and I think we've had some interesting discussion about the implications but I also see a lot of head nodding which I take to be a general agreement that, on the basis of current knowledge, this proposal is what people think is the right approach.

DR. COFFIN: It certainly sounds to me like that's the sense of the committee.

Does anybody object? In that case, we're right on schedule with the agenda.

Unless somebody has something else to add at the moment to these issues. We can move on to Topic III which is a couple of talks updating us on current state of knowledge of porcine endogenous retroviruses. The first talk will be given by Dr. Khazal Paradis from Novartis.

MS. DAPOLITO: When you get a chance will you mention that we'll open it up again at the end.

DR. COFFIN: Yes. We will also at the end, following this we will have a brief reopening of open public discussion for another comment.

DR. PARADIS: I'd like to thank the committee for allowing me to present finally the results. It's quite a relief to come to this committee and to actually be able to present this.

This is a study on the

retrospective multi-center state to detect circulating porcine endogenous retrovirus or antibodies to PERV in subjects who were intimately exposed to living pig tissue. As you can see, there's a lot of names there that, a lot of people participated in this study and I was counting a little earlier and there are about 21 people in the audience who either directly or indirectly contribute to either testing and the design in the writing of the paper or, and as well as in reviewing our data. I want to thank, I want to take the opportunity to thank everyone who participated in this.

Now, when testing for PERV Infective States, if we're looking for active infection, since this is a retrovirus we're testing for RNA. An RT-PCR was carried out and, either on serum for all patients or on saliva in a subset of patients. These tests were carried out by Zephram Long and Ed Otto at Generic Therapy Institute, Inc. which is a

Novartis company as well as under the direction of David Onions at Q-One.

For latent infection we're looking for a DNA of the virus incorporated into human cells like PCR, and this was also carried out at GTI as well as at the Center for Diseases Control under the direction of Waleed Heneine.

Now to look for the recovered or cleared state we're looking for antibodies and this was done by Western Blot on serum by Q-One as well as the CDC under the direction of Paul Sandstrom. Now, since this study was carried out we've also had some serum retested by Professor Yokum Denner of the Paul Ehrlich Institute in Germany.

Now, as mentioned before, when you do an allo-transplant, their leukocytes leave the transplanted organ and will migrate through the patients body in a condition that has been termed microchimerism. Seeing as we had some patients who, especially the splenic

perfusion patients, who had their blood perfused through the pig spleen. We expected that there could be some pig cells that would be present in the patient's body.

Now, as seeing every pig cell would contain PERV DNA, we had to find a way to distinguish between just simply microchimerism and a PERV infection. So, I'm going to talk about the strategy which we used in the paper but I won't go into the actual details of the sensitivities of the tests.

So, if one does a PCR test looking for PERV DNA, there are four potential outcomes. If you imagine you have a sample here where there are only human cells and no infection, your test result would be negative.

If you have a test sample where there are human cells and a pig cell such as you would find in microchimerism, because every pig cell contains PERV DNA, you would

get a positive PCR. If you have a test sample where there are infected human cells but no pig cells, then you would get, because this would be infected, of course, you'd get a positive DNA PCR for the PERV DNA.

Finally, if you have a test sample where you have pig cells present as well as infected human cells, this will also give you a positive test. So you have to have a way in which to distinguish between the positivity because, of course, if you only have microchimerism, that does not mean infection while the other two mean infection.

So the area in which this was carried out was to know whether or not there were pig cells or infection was to look for a pig genomic sequence. So, at GTI, this was done looking for the centromeric DNA sequence for the pig. At the CDC this was done looking for pig mitochondrial DNA.

Again, there are three potential outcomes. If you have simply just

microchimerism because every pig cell would contain a centromeric copy, you would get a positive test. If you have in PERV infection, your PERV DNA was positive but here you have no pig centromeric sequence so this test will be negative. However, if you have microchimerism in the presence of infection of human cells, the pig cell will also give you a positive result for the pig centromeric sequence.

So, once again, we need to have a test to be able to distinguish between simply microchimerism and microchimerism and infection. So the way in which this was done at GTI was to perform these tests as quantitative PCRs. We know that on average a pig cell contains approximately 2,500 copies of pig centromeric sequences. While, on average, a pig cell would contain approximately 50 copies of PERV DNA.

So that if you have a sample that has pig cell in it, you would have a 2,500

to 50 or a ratio of 50. If you continue to add pig cells to your sample, the ratio does not change. On the other hand, if you have a microchimerism and you keep on adding infected human cells, the ratio, because of the number of copies of PERV DNA changes, the ratio will change as well. So this was used to distinguish microchimerism alone from microchimerism and infection.

Now this technique, with this technique, you could detect infection in the presence, if you had 20 pig cells in a sample with 10^7 human cells, and you could detect when greater than part .01 percent of the human cells were infected. So quite a sensitive asset.

Now we were able to recruit 160 patients into this study. There was one patient from Canada who was in liver failure and had her blood perfused through a whole liver failure and survived to a successful human allo-transplant and has been

immunosuppressed ever since. Two patients participated in an experiment in Sweden where there blood was perfused through a pig kidney.

There were 28 patients who were in liver failure and who had their blood profused through the HeptaAssist device. Twenty-six of these patients were subsequently transplanted and immunosuppressed. There were 14 patients who had had pancreatic islet cell transplants. Eight of these were from Sweden and were in association with a human kidney transplant and were immunosuppressed. While six of them came from New Zealand and did not have immunosuppression.

There were fifteen patients from Bochum, Germany who had had pig skin grafts and the most interesting and largest group, of course, were 100 patients from St. Petersburg in Russia who had their blood perfused for approximately an hour through a

pig's spleen for severe burns or cancer with chemotherapy.

Now, although only 36 of these patients are pharmacologically immunosuppressed, as you heard before, a lot of these patients are actually immunosuppressed, the liver failure patients and, and the skin, the burn patients.

So in total you had 83 males and 77 females and the exposure time was from the same day and these were the same patients with splenic perfusion. You had perfused in the morning and blood tested in the afternoon up to twelve years prior to the testing.

There were unusual symptoms that reported in six patients. One patient had bone marrow aplasia and, and it says actually one of the Circe patients and this is a common thing seen with fulminant hepatitis. Then transplantation where bone marrow aplasia occurs. There were four patients who reported skin rashes. Three of these were

liver failure patients and one was a skin graft patient. Again, I think the clinicians in the room will tell you that in liver failure, the number of skin rashes of unknown etiology that occur is quite common. This is a retrospective study so that it was difficult to make any conclusion.

Again, there was one fever of unknown origin in a liver failure patient that lasted for three to four days. So in turn we had 36 patients who had pharmacological immunosuppression continuously since the procedure and one patient who had received intermittent chemotherapy for a gastric leiomyoma.

Now, I'm going to go straight to the results and in order to save time seeing I presented the sensitivities and specificities the last time. So, when we're looking for active infection, that is the presence of RNA particles in the serum, we tested 160 patients and 160 patients were