cells, if they are expressing a lot of virus, it can be worse. The way I see it is if you are using a whole organ, you have a whole diversity of cell types which each could express a different type of virus. They have a different potential for long-term implantation, for migrating to other sites.

So I think there really is a difference and it may come to whole organs, whether they are ex vivo perfusions versus implantations. So, in some sense, it is like a seat factor. When I was here last year, and we were just talking about Parkinson's patients and putting cells into the brain, I am on the back of my seat.

When we start talking about ex vivo perfusion, I am starting to get to the front of my seat. And then when we start talking about transplantation of whole organs into patients, I am really at the edge of my seat. That is how I look at risk in this particular case.

But you are right. It is really difficult to sort that out.

DR. SIEGEL: Dr. Auchincloss, you put the question about nonmammalian or nonvertebrates to the committee. Several times you talked about, Dr. Allan, the level of risk. But part of the issue here is the type of risk. Some of the procedures that are recommended in this guideline are recommended for particular risks because of particular

risks.

So the notion, for example, of lifelong surveillance of a patient or of notifying sexual contacts or blood deferral may come from specific risks. Lifelong surveillance, for example, arose in significant part because of concern about retroviral and herpes viral chronic risks. Or the notion of understanding what several generations of the feed history of the donor animal arose from concerns about TSE-type risks.

So the question, to kind of rephrase your question, one might ask, if one used a nonmammalian source, do we know enough about, say, insect cell lines that we are not concerned about latent infections, that we don't need to do lifelong monitoring of somebody, or we don't need to do maybe blood-deferral monitoring of somebody who had an ex vivo exposure to insect lines.

I am not answering that question. I am just kind of reposing your question because, frankly, I don't even know what the answer is.

DR. AUCHINCLOSS: The more specific you are, the more chance I have of getting some responses from the committee. I haven't heard very many.

DR. ONIONS: Could I comment? I think this is a very real issue. I will modify my position to say nonvertebrates because, clearly, thinking about it,

obviously chickens carry a particular subgroup of retrovirus, an exogenous one, that can infect mammalian cells, for instance. They carry other viruses that affect mammalian cells. So do fish, for that matter.

So if we go to nonvertebrate cells, then I assume that everyone there will be using cell lines. Is that the case?

DR. SIEGEL: So far, I don't know of anyone using fresh insect organs.

DR. ONIONS: In my view, that comes back to the fact that you can characterize the cell lines so I would have a great deal of comfort about that in comparison to other aspects of xenotransplantation.

So it seems to me that if you have got a cell line of insect origin, then clearly, to me, lifelong monitoring and all these other issues are not real, provided the appropriate monitoring to exclude all the alpha virus and flavivirus and so on that can replicate in insect cells have been excluded.

But that is a standard kind of job that CBER would do and do very thoroughly. So I don't see there is a necessity there to go into this prolonged patient monitoring and advice to contacts and all the rest of it. That is more like a traditional biological product, in my mind.

DR. AUCHINCLOSS: So a specific recommendation

might be drop nonvertebrate cell lines from your screen.

DR. ONIONS: Yes.

DR. AUCHINCLOSS: I tried to state it again rather than look for reactions around the table.

DR. MICHAELS: As long as they are well characterized.

DR. SIEGEL: Again, the testing of the line, itself, is one type of control. We have many controls. Are we going to bank serum on the nurses who take care of the patients who receive lymphocytes that were exposed to drosophila cell lines ex vivo?

DR. COFFIN: I should point out that many of us have, or virtually all of us have, been exposed to certain kinds of co-culture and xenotransplantation with invertebrates with some frequency, actually.

DR. SIEGEL: Insects bite.

DR. COFFIN: Insects do bite and they take in and extrude blood.

DR. HIRSCH: I was just thinking, do therapeutic maggots for wounds and leeches fall into the category of xenotransplant?

DR. VANDERPOOL: It seems to me that one of the problems is you are asking us to opt for categories. For every category like cells, there is someone here who can think of 40 reasons why they are especially dangerous. But

I take Jonathan Allen's comments very seriously and that is if you get a whole organ, it is going to be more dangerous than the liver perfusion experiments we have had presented to us today.

So why couldn't you, instead of looking for categories, think of a wonderful English word like "ordinarily," and put that in your guidelines. "Ordinarily, people will be followed for life, be autopsied at death," or whatever which gives you the possibility of making--I mean, the FDA is not known to be the liberal Marxist organization in the United States.

We know you are conservative in terms of protection. So it seems to me that you could use some kind of language that allows you to have discretion over the things you deem to be safe and do not have to be followed as thoroughly as others.

DR. SIEGEL: We have that language. It is inherent in the word "guideline." These are guidelines. They are not rules. They are not regulations. And they are not laws. What we are seeking here and what we are receiving here is the guidance we need to determine--what we must do when we have a guideline is, nonetheless, look at individual applications and see, either they did everything according to the guideline or they didn't but they may or may not still be acceptable from a safety perspective

balanced against benefit and so forth, based on the fact that they have alternative approaches that are equally good.

And that is always possible with a guideline. But, in order to do that well on a case-by-case basis, we need--the feeling is that the fact that it is fewer cells or ex vivo or a cell line or an insect, how do those weigh into that? I think we are getting some useful guidance in that. Obviously, each case has to be looked at on its own merit.

DR. AUCHINCLOSS: As I went through your list here. Immunosuppression; no, it is not a factor. Time of exposure; no. Barrier encapsulation; no. Dose of implant; no. Cell line and maybe species source and behavioral factors as we talked about. Those are the only places that I could find any reason to think that you could categorize risk sufficiently differently to warrant changes in public policy.

DR. SIEGEL: Is that a reasonable sense of other committee members as well?

DR. ONIONS: Yes, except I would, perhaps, just like to--I concur with all of that except that I do feel that there is this possibility with primer cells where they can be characterized before they go in that you might alter the way in which the testing level--whether you go to herd level or the cell level. It doesn't mean that you don't have the same rigor, but you might alter where you do it.

DR. AUCHINCLOSS: Clearly. There are some very practical things that you don't do to a cell line that you do do to a live pig.

DR. CHAPMAN: Two points I would like to put on the table. One is I would like to amend your statement to say, on the basis of current knowledge, because it seems to me there are things you listed as not being reasons for determining a gradation of risk such as barriers which are, in fact, however, very easily readily addressed by preclinical experimentation which may define a body of knowledge which, then, may give us a basis for determining a gradation of risk.

The other point I would like to bring up. Let me begin by acknowledging the tremendous respect I have for the depth and breadth of expertise represented on this committee and in this room. But, these nonvertebrate arthropods that we are discussing as minimal risk are, in fact, such prolific vectors of human disease that there is a whole field of expertise of medical entomology.

Let me say the one course I took in it was one of the more difficult ones I ever took in my life, including organic chemistry and physics. So I would humbly suggest that, the expertise of our attendance not withstanding, it might be wise to consult some medical entomologists on their vision of the risk posed by nonvertebrate cell lines before

taking any action.

DR. AUCHINCLOSS: Both are good points.

DR. GORDON: I would just like to, if I could, throw my hat into the ethics ring and then probably run for cover. But there has been discussion of benefits and risk. I have heard expressed, maybe twice, the notion that the benefits were largely theoretical, speculative and potential.

But, in the case that I am most familiar with, I think it is well beyond that. In the case of islet transplantation, we have known for the last seventy-seven years that the product of pig islets, namely pig insulin, works to control blood sugar in humans and works very well.

Therefore, what we do know is that if we can keep pig islets alive in people, we will have cured diabetes. On the risk side, there was an interesting irony expressed early on that, in order to prove the safety of xenotransplantation, we need a population of PERV-infected animals or people to use as positive controls.

I won't even comment further on that, but, obviously, the fact that we don't have such a population--in fact, we don't even have one single case--I think, in itself, stands as very important evidence.

The final thing is on the notion of justice. I think it is very discriminatory to allow extremely risky

behavior for some people, risky behavior such as providing surgery to AIDS patients or allowing people to travel to countries where the ebola virus is endemic while we may restrict access to others where no in vivo risk has ever once been demonstrated.

So I don't think we can set a higher hurdle for this procedure than is generally accepted in medical procedures in general.

DR. AUCHINCLOSS: Jay, I have been taking, under topic II, the discussion questions for the committee. I have been taking them essentially as one big group, questions 2, 3 and 4. We have been pushing it. At this point, I have gotten what I can get. Have you gotten what you can get? Do you want to push the question in a different way to the committee?

DR. SIEGEL: Well, I think that we have been discussing topics 1 through 5 and I am pleased with the discussion. I would ask my colleagues here if they have other specific issues they think need more comment.

DR. NOGUCHI: No. In spite of the fact we have been going around, this is exactly the kind of advice we need.

DR. WOODLE: Hugh, I just want to get back to the benefit issue. I think several people have come very close to making a point. I think David Sachs came very close. I

am not sure that--I'm sure that you have sat down and thought about what the Brave New World would be when xenotransplants actually work and we are able to do these.

But the potential upside on this is so tremendous and we haven't had anybody actually stand up today and say what it might be like if xenos work. Sure, we are going to have less deaths on the waiting list, but there is going to be a huge number of patients out there in whom, in the course of their disease, they can be transplanted earlier.

They will be in better condition. They won't sit in the hospital for weeks deteriorating, being nutritionally depleted in a serious condition where we know the outcome of an allotransplant is going to be worse than it would if they could have been time electively.

The operations can be done in the morning when the team is rested. No more night-time operations. No more operations under suboptimal conditions. The organ should be in optimal condition, minimal storage times, no more human living donors, decreased risk of transmission of HCV, HBV, Epstein Barr virus. Those are just a few of the things that I think, unless we sit back and think about what this Brave New World is going to be, we don't really know what the potential upside is.

DR. AUCHINCLOSS: That is a perfect transition for me, Steve, because that I think brings us towards tomorrow's

conversation about some potential early trials of xenotransplantation where risk-benefit analysis clearly becomes part of the equation.

Before I close the meeting, let me, because on our agenda we had the open public hearing scheduled for 5:30, did anybody come in who wanted a chance for a formal open public hearing, just so I didn't miss somebody by the change in schedule.

Are there any other comments that anybody on the committee wants to make on these discussions this afternoon or questions from the FDA? Otherwise, I would end today's meeting and reconvene tomorrow morning at 8 o'clock.

DR. PAUL: I think this has been an excellent discussion. I just would like--there is one reason that I am on the advisory subcommittee and that is I bring an expertise in swine virology as a veterinarian. It has been wonderful to get educated on endogenous retroviruses, but I think that we should, at some point, give some time and discussion for exogenous porcine viruses.

DR. AUCHINCLOSS: To the other nonendogenous viruses.

DR. PAUL: Right. I think that is something that would be very beneficial.

DR. AUCHINCLOSS: Barring any other comment, we will go ahead and end this meeting and tomorrow morning

reconvene at 8 o'clock.

[Whereupon, at 5:40 p.m., the meeting was recessed, to be reconvened on Friday, June 4, 1999 at 8 o'clock a.m.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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