29TH MEETING

OF THE

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: I would like to call today's meeting to order. I want to once again apologize to the commissioners for being unable to be here yesterday. I had a long time conflict and just was unable to make other arrangements but in any case I want to continue our discussion and try as best I can to pick it up from where we left off yesterday, where you left off yesterday.

I was briefed this morning regarding just what issues have been covered and regarding the capacity regarding the HBM report you went through chapters 1 through 3 and had rather lengthy discussions on recommendations 1 and 2, 2 especially, ending up with at least a thought that perhaps on recommendation 2 we might actually break that up into two recommendations since there was some considerable concern over just the whole issue of what kind of independent stripping of identifiers and so on meant. Who made them unlinked and how that was done and so on was a subject of some discussion and we can certainly come back to that later today.

I do not want to start with that. However, I

would like to come back to that later as something which stills need to be resolved and I do not want to leave any indication to you that I think that is a resolved issue but I do want to come back to it later.

What I would propose this morning is that we go on to recommendation 3 and begin working our way through recommendations that follow both 3 and those that follow and see how the commissioners feel about it.

I understand that, Alta, as you go through in a serial way and we leave some things unresolved that that may create difficulties later on and we will just deal with those as we come to them.

So we will turn in a moment to continue our march so to speak through these recommendations. Recommendation 3 is on page 114 of the draft that is before us.

Looking at our broader agenda for day we have about two hours left to spend so we really do want to go as quickly as we can through these and see how far we get so we know really what the possibilities are for completing this report and setting our calendar for its completion.

I certainly do not want to see this report go past the middle of this year without being completed. At some stage we just have to say we cannot reach agreement on something and deal with it in that way.

But in any case we have two hours this morning. We will then have some time for an update on the International Project, in particular Dr. Marshall will be with us to discuss her work, and then we will have a public comment session, which begins at 10:45. We will break incidently before turning our attention to Dr. Marshall. Then after that we will have a public comment, which is currently scheduled between 10:45 and 11:15. And after that we will go immediately to the stem cell set of issues and spend the rest of the morning, it is going to be a relatively brief time before lunch, and then the rest of the afternoon on the stem cell issues, of which there are many as you all know.

So if that seems agreeable to you, we can go directly to recommendation 3 but before we do that are there any comments or questions you want to raise at this time?

I have been informed that unlike most of the

rest of you my microphone is on all the time so I may interrupt you either inadvertently or advertently as time goes on. If I do so inappropriately please forgive me.

DISCUSSION OF DRAFT REPORT CONTINUES

Let's go to recommendation 3 again on page 114 and ask if there are comments or reactions or concerns about recommendation 3. It is short enough so I will just read it out.

"Research conducted on human biological materials that are linked to information that could identify the individuals from whom they were obtained, even through a code, is subject to the process of review and approval specified by the Common Rule," et cetera.

Okay. Let's go on to recommendation 4. Excuse me. If you have an objection I will take it later. Let's go on to recommendation 4.

Trish, have you got the recommendations in front of you? Page 115 now.

Yes?

PROFESSOR CAPRON: Having participated very extensively in the process of writing and rewriting these

I apologize for only noticing this moment something that we have talked about from time-to-time and that is the way in which we have attempted usually to have a recommendation in a recommendation.

I wonder collectively whether it is our view that this recommendation is one which now reads like a conclusion and not a recommendation, which requires any action by anyone? Is this something in which the recommendation is that investigators and IRB's should, therefore, follow this? I mean, which is the implicit here. I do not gather -- I gather that we are not saying that OPRR has to change any aspect of the regulation. And I just want to suggest to us that we might want to add a sentence as a way of making explicit what is implicit here.

DR. SHAPIRO: I think that is right. I think I have that same interpretation and we can certainly consider that. All right.

Let's look at recommendation 4. Again I think you had some discussion yesterday regarding the word "identifiable." It will come up everywhere here so let's not focus on that. As you know, identifiable sometimes is

still in this draft, at least the draft I am working from, and that just means coded and/or identified samples but let's not stop on that wording. That will all be changed as we go along. We decided that a meeting or two ago.

So let's look at recommendation 4, which talks to what a repository should require. Are there comments or questions regarding recommendation 4?

Okay. Let's look at recommendation 5 which talks about "When reviewing and approving a protocol for research on human biological materials, Institutional Review Boards should require the investigator to set forth..." and it is a), b), c), d).

Alta?

PROFESSOR CHARO: Just a very small change under 5.b). I would suggest deleting the words at the end of the phrase "from repositories" since sometimes the samples will be obtained from something other than a repository.

DR. SHAPIRO: That sounds -- now thinking through it that sounds right although it does no harm. It is the do no harm principle as I look at this in any case.

Any other comments or questions?

Yes, Bette?

MS. KRAMER: I have a question just as to the placement of this recommendation prior to any discussion or any recommendation about minimal risk or some of the other material that comes later. I do not remember the rationale for the placement of it here.

DR. SHAPIRO: I have not got a good response for its placement. I have not thought through its placement itself.

Kathi?

DR. HANNA: I would be happy to move it but please tell me where you would like me to move it.

MS. KRAMER: That is why I should not have spoken up.

(Laughter.)

DR. SHAPIRO: I like this discipline. We will get somewhere here.

Alta?

PROFESSOR CHARO: I actually had a similar concern because it talks about investigators providing documentation from an IRB before we get to the point where we are talking about IRB reviews. I am sure Bette and I

could find a place that follows all the IRB details and suggest a place near the end.

DR. SHAPIRO: It is certainly not critical at this point so there is no problem, I think, in finding a more appropriate place. Thank you for pointing it out and if you and Alta and Kathi will work on that I do not think that will be any problem.

Okay. The next session of this chapter deals with issues on informed consent and we have recommendation 6 which is on page 118. Comments? Questions?

Okay. That is followed on page 119 with recommendation 7.

DR. MIIKE: One thing on 6.

DR. SHAPIRO: Yes. I am sorry, Larry.

DR. MIIKE: I guess it would be imprecise -- excuse me -- the phrase "obtained prior to the release of this report" sets a fairly nebulous date it seems to me and maybe we should be referring more to prior to the implementation of the recommendations of this report.

DR. SHAPIRO: I think that is a very good point. I think that is a very good point. Any objection to that?

PROFESSOR CAPRON: No. We may also wish grammatically, Kathi, to make the “when” clause and the clause that follows fit together. The “when” clause assumes that there is a person or persons taking some action and then the subsequent clause says, "Must not be presumed," and the thought is clear but grammatically it does not make any sense. Do you see what I am saying? When a person conducts such research that person or committee reviewing it should not presume.

DR. SHAPIRO: That is right.

PROFESSOR CAPRON: Yes.

DR. HANNA: Is that -- I mean --

PROFESSOR CAPRON: It is an active passive --

DR. HANNA: No, I understand that.

PROFESSOR CAPRON: -- combination.

DR. HANNA: You want it to be the investigator that we are talking about here?

PROFESSOR CAPRON: And the IRB.

DR. HANNA: And the IRB.

PROFESSOR CAPRON: Right.

DR. SHAPIRO: Any other comments on recommendation 6 before we go on to 7? Okay.

We have now recommendation 7 on page 119.

I know, Bernie, you had a -- do you want to speak to this? You had something which I am seeing for the first time but go ahead and you might want to talk to this recommendation.

DR. LO: I have a suggested minor addition, I hope minor addition to the recommendation and some accompanying text. This comes out of my sense that I would like to see a little more here on the general issues of these tiered consent forms so the explanation is really to encourage people to continue to work on developing these kinds of tiered consents but also recognizing that there is a trade off between being comprehensive and we obviously cannot predict everything that is going to be a future research project and making it practical for both these potential subjects and the people administering the -- or running the collection of samples.

I also thought there is an option missing that I would like to insert, which is really consent to use the biological material for future studies relating to the condition for which the sample was originally collected. It seems to me that falls intermediate between d) and the

current e), which is to do everything. That is actually one of the options that is listed in the -- I think both the NIH and the National Action Plan for Breast Cancer forums. I think there are conceivably some people that would choose that as the preferred option among the list here.

DR. SHAPIRO: Bernie, I just want to -- since I missed yesterday's discussion I just want to make sure -- I understand the 7.e) you have, which is add an option. Is it to substitute for the existing e) or you just want to --

DR. LO: No, I am sorry. I would move existing e) down to f).

DR. SHAPIRO: Okay. I just wanted to clarify my --

DR. LO: Right.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I have a question about e).

DR. SHAPIRO: New or old?

MR. HOLTZMAN: No, I am sorry. New f).

DR. SHAPIRO: All right. Let's deal with Bernie's e) and see if people --

MR. HOLTZMAN: Oh, I am sorry.

DR. SHAPIRO: -- and if there is no objection or people have no objection we could just add that in and make the current e) f) or something like that. But is there any -- first of all, I want to just see if anyone has any concerns or questions regarding Bernie's suggestion?

PROFESSOR CAPRON: Bernie, would it possible to have the wording brought into line with the language of d) and new f)? That is to say the phrase -- oh, I see it is in line with d) and it is f) that is not consistent.

DR. SHAPIRO: Yes.

DR. LO: The f) should be something about to permit as opposed to provide.

DR. SHAPIRO: Let me read it. I have got it. I am sorry. I will pass this along. I thought other people had it.

The new e) is "To permit coded or identified use of their biological material for studies relating to the condition for which the sample was originally collected."

It is simply another specific option to add

which Bernie feels is helpful and I agree with that that it really would be helpful to note this. I have a copy here also.

But then if people are satisfied we will include that as e) and then we will go to f) and see where we are on f).

PROFESSOR CAPRON: Again just for clarification, the existing d) says, "...for one particular study only..." Would it be helpful just to underline here that what you are saying is for all studies or any studies relating to --

DR. LO: That is --

(Simultaneous discussion.)

PROFESSOR CAPRON: The emphasis.

DR. SHAPIRO: Would you like "any?" By the way it says the same thing. We should not talk about that one.

PROFESSOR CAPRON: So it is going to be "any study?"

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: Or "any study."

DR. SHAPIRO: Right. I will leave this with

you. Okay.

Thank you, Bernie. That is very helpful.

Let's go on to what is now f). Quite aside from the grammar here that is to put -- or the vocabulary -- excuse me, “to permit” I guess is a good way to put it here. This is an issue we discussed last time and there was some discussion but clearly the overwhelming majority of the commission wanted f) to -- what is now f) to read exactly as it reads right now but is there any further conversation about this?

Yes, Bette?

MS. KRAMER: I think I was actually one of the people who proposed that but I have been thinking reading this text that Bernie provided with the new 7.e), I would like to ask a question of those who do research, and that is that -- is that providing too much leeway for researchers? Should a person actually give that broad an authorization?

DR. SHAPIRO: Well, this is exactly the issue we discussed in which there was some disagreement, including my own disagreement, but I was in a very small minority at least in our last discussion on this and so

this was not a matter of a huge --

MS. BACKLAR: No.

DR. SHAPIRO: -- it was not a huge issue for me so it goes here but if there is any further discussion we could deal with that. That was exactly the issue we discussed.

Steve?

MR. HOLTZMAN: It may be useful just to see where people are at.

DR. SHAPIRO: Yes.

MR. HOLTZMAN: My personal -- I am comfortable with prospective authorization for coded uses. I am uncomfortable with prospective authorization for identified uses of a blanket form.

DR. SHAPIRO: Well, I certainly agree with you. Unidentified, as you know I addressed myself on this last time, I do not want to make -- Alta sent me an e-mail to explain myself and I was really too busy to explain myself so I said I am usually wrong.

PROFESSOR CHARO: I just want to understand when people talk about why they do not like that option whether they are saying they do not like it and would not

choose it for themselves or they think it is so dangerous that nobody should be given the opportunity to choose it for themselves.

PROFESSOR CAPRON: The latter.

DR. SHAPIRO: That is right. It is unpredictable and, therefore, risky.

PROFESSOR CAPRON: And, therefore, not an instance of anything that would amount to informed voluntary consent is my view about it. The risk may be small but you do not really know enough about it. You cannot begin to predict what it would be and that is not a circumstance it seems to me in which an investigator should place or a clinician gathering material and asking these -- offering these alternatives should place a person.

DR. SHAPIRO: Larry?

DR. MIIKE: As I said before, I think that if you look at the rest of our recommendations in this report, which tightens up the whole system, that an IRB -- if you are going to be looking at studies where a past consent was given then that consent -- the adequacy of the consent has to be looked at so it seems to me there are

safeguards enough that I can feel comfortable with this recommendation.

DR. SHAPIRO: All right. Let's just see. I think this is an issue we discussed and I do not want to -- I am sorry, Bernie. I certainly do not want --

DR. LO: One other point. I think there is a big difference between coded and identifiable and I am uncomfortable at least --

DR. SHAPIRO: Coded and identified, right.

DR. LO: Coded and identified, I am sorry. And to lump them together and consent to both makes them sound -- they are sort of close to each other and if we are going to permit people to consent or provide authorization for all future identified uses it seems to me that should be a separate check off signature than the coded ones just to call attention to the fact that one is more riskier than the other.

DR. SHAPIRO: Well, let's -- since there seems to be some -- at least reconsideration here, let me just ask the question separately just to see how people feel and just let's take a straw vote on this and use the distinction that Steve used just a moment ago.

If we thought of f) as reading “to permit prospective authorization for all future coded uses of their biological material”, which is I think, Steve, the one you are comfortable with, how many of you would be comfortable with that? That is coded. We will come to identified in a minute.

(A show of hands.)

DR. SHAPIRO: And how many not?

(A show of hands.)

DR. SHAPIRO: Okay. It is still the overwhelming sentiment of the commission that they feel comfortable with "coded."

How about identified? The same issue. To permit prospective authorization for all future identified use of their raw material. How many are comfortable with that?

(A show of hands.)

DR. SHAPIRO: Just press your mike on, Trish.

MS. BACKLAR: I think -- was it Bernie who made the suggestion of separating it. Whoever made the suggestion I thought that was a very good suggestion. So I would be comfortable with this if it was a separate

option.

DR. SHAPIRO: How many would be uncomfortable with this?

(A show of hands.)

DR. SHAPIRO: I think that -- let's now -- let me make a suggestion here that we will -- to permit prospective authorization for all future coded use of their biological material is something that an overwhelming majority of the commission feels comfortable with. However, there is not a majority in favor of identified -- the same thing, only identified.

Bernie?

DR. LO: Should we then have material in the accompanying text to explain that?

DR. SHAPIRO: Yes, absolutely. Absolutely. And I think -- just speaking for myself, it is very much along the lines that Alex expressed just a moment ago. That is how I felt, in fact, about the coded and identified but I think that my reasoning in any case is very similar to what Alex articulated a moment ago.

PROFESSOR CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: Again just asking if there is anything significant about the change in the wording here. This speaks of all future use. The other language of the other recommendations usually speaks of research or study and I am not sure what uses there would be other than research or study. I mean, there is obviously the development of a partial product but that might be included in the research anyway. And I do not think we want to create a confusion that somehow that is a yet broader category and certainly my objection to it is not based upon that extra breadth or lack of refinement so I would suggest that we add that.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Alex, I wonder if the following language would help because it parallels the others: To permit coded use of their material for any kind of future study.

DR. SHAPIRO: Yes. I think the -- I mean, that sounds -- I have not thought about it carefully but that sounds fine, Alta. I think there was no intention to expand the category of issues which we were considering here. I think that is just the language that got used.

So let me just summarize where we are on recommendation 7. We have adopted a new subpart e) that was Bernie's recommendation and f) now refers to coded using language somewhat similar to what Alta suggested just a moment ago.

Any other comments, questions, reactions, et cetera, to recommendation 7?

Yes, Bette?

MS. KRAMER: Harold, I am sorry, I missed this. Back on 6, this is just a textual question, on page 118, line 25, I was confused when I read it. What does "among and among individuals" refer to?

DR. SHAPIRO: This is on the last line, "...in different settings and among different individuals."

MS. KRAMER: Right.

DR. SHAPIRO: I will have to read the sentence carefully. Let's come back. I would have to read the paragraph. Just reading the sentence leaves me a little stymied on it so we can come back to that. It is in the text.

Alex?

PROFESSOR CAPRON: Is it your understanding

that as revised -- under f) we are now only going to say coded.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: -- that we will have at that point a footnote rather than leaving this to some appendix.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: Which will state that commissioner so and so and so and so believe that this -- that the option should extend to identified samples and commissioner so and so and so and so believe that the option should not even extend to coded samples?

DR. MIIKE: From my point of view it is not necessary if the group wants to limit it the way it is I will go along with it.

PROFESSOR CAPRON: Okay. Because there were three or four of you who were voting for identified samples.

DR. SHAPIRO: I would think -- let's see what -- when we get to the final report, how strongly people feel about it. I think we can do it a number of different ways. We could either identify a disagreement without

naming commissioners. We could name the commissioners. Let's just see when we get to the final stage.

PROFESSOR CAPRON: Okay.

DR. SHAPIRO: We will keep a note of that.

PROFESSOR CAPRON: Well, I would hope that since we have made that change that somewhere in the commentary we draw attention to the fact that recommendation f) only goes as far as coded samples because of the view that the risk with identified samples is just too great.

DR. SHAPIRO: Yes. No, I agree with that because that is something we have been back and forth on and I will take this issue to be settled and I do not want to bring it back. I may even declare any other discussion out of order on this issue. But in any case I agree with that comment. It is a very helpful suggestion.

Okay. We now move along in this report. There is a section on obtaining consent in the clinical setting and then there is recommendation 8, which is on page 121, which is short enough so I will just read it just to -- as you are thinking about it. "When informed consent to the research use of human biological materials

is required, it should be obtained separately from informed consent to the clinical procedures."

Comments, questions?

Okay. Let's go on to recommendation 9, which is also meets my criteria of being short.

Excuse me.

PROFESSOR CAPRON: Wouldn't it make sense to switch 8 and 7 if we say it should be obtained separately and then here we are specifying what kinds of options should be included in a consent form that looks forward to that research use?

DR. SHAPIRO: I think that may be right. The only reason I am hesitating is as this chapter reads now there is sort of text and there is recommendation, text and recommendations, and we would probably have to move more than just these recommendations but I think that is an interesting suggestion and we should really consider it. I think that may very well work that way and we just have to make the appropriate movement in the text.

PROFESSOR CAPRON: I see that obviously 8 and 9 are linked together so it would be a matter of moving 8 and 9 before 7.

DR. SHAPIRO: Right. We have to move them together, right. Okay.

Recommendation 9 meets my criteria for brevity where I can read it out so I will do so. "When seeking informed consent in the clinical setting, it should be made clear to subjects that refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care."

Bernie?

DR. LO: This is a minor grammar correction that needs to be made in terms of when seeking that we sort of specify who is seeking rather than "it" to make it undangle.

DR. SHAPIRO: Kathi, you have a question?

DR. HANNA: I just -- whenever somebody wants an action --

DR. LO: Why don't we say "clinicians and researchers should make clear."?

DR. HANNA: Right. I just need to know who you want added in there. Thank you.

PROFESSOR CAPRON: How about not a dependent clause at all and just say "persons seeking informed

consent in the clinical setting should make clear..." et cetera, et cetera "...to potential subjects that their --"

DR. SHAPIRO: That is right. It is just to identify the persons.

Other comments or questions regarding recommendation 9?

Okay. We then have a number of other sections which follow on this. The criteria for waiver of consent, minimal risk, and so on, and that takes us all the way over to page 125 where we have recommendation 10, which goes from the bottom of 125 off on to 126. And that recommendation concerns institution -- it starts as follows: "Institutional Review Boards should, in general, operate on the presumption that research on existing coded samples is of minimal risk to the human subjects if..." and then there is a series of clauses which I will not read out loud.

Are there any comments or questions, et cetera, regarding recommendation 10?

Thank you.

Then the chapter -- this is chapter 5 again -- goes on and talks about rights and welfare, and then over

on pages 128 and 129 there are two recommendations but on 128 is a recommendation 11 and it deals with the rights and welfare and begins as follows: "In considering waiver of consent, the term..." in quotation marks now "...adversely affects the rights and welfare of human subjects should be interpreted to mean that the waiver does not violate any state or federal statute or customary practice regarding entitlement to privacy. Considerations of rights and welfare should also include an assessment of the potential effects of a study that examines traits commonly considered to have political, cultural or economic significance to the community to which the sample source belongs." That is recommendation 11.

Comments, questions, issues?

Yes, Bette, I am sorry.

PROFESSOR CAPRON: I have on comment.

DR. SHAPIRO: I am sorry.

PROFESSOR CAPRON: I think we mean "on the community." We do not usually say "effects to the community," do we? Should we specify adverse effects, potential adverse effects of the study or is it -- is the -- or is it significance to? Is that where the "to"

belongs?

DR. SHAPIRO: It is significance. It is the issue that goes with both political and cultural as I understood this. Something could be --

PROFESSOR CAPRON: Then "to" is correct but we do not specify who the adverse effects would be on and who would be adversely affected.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Actually, although I have no commitment to this particular wording, I think that by simply saying that we are asking -- essentially the implicit thing is that the IRB is supposed to assess the effects. I think we can leave it up to their common sense that if the effects are benign that they are not going to get worried and if the effects seem to be adverse they will so we do not really need to be spelling it all out.

PROFESSOR CAPRON: Fine. But are we saying effects on anybody in the world? Is that what we are saying?

DR. MIIKE: No, Alex. Just the last part of that sentence says that a community to which the sample source belongs. It is a phrase in which -- maybe it is an

imperfect phrase but that is what we are trying to capture.

PROFESSOR CHARO: I agree that the rephrasing is less than felicitous. A sample source belonging to a community is a little odd. We are using sample source to mean an actual person. It does not read that way so it sounds like a piece of tissue floating out there that belongs to a community. But if we agree on the meaning maybe we can scribble and try to come up with the precise wording later this morning or by e-mail.

DR. SHAPIRO: I think the wording does need some work here because I, myself, do not like this second sentence. I understand the point. I have no objection to the point at all. We have discussed that many times but I think this does need to be reworded.

Alta, do you want to work on that?

PROFESSOR CHARO: Sure.

DR. SHAPIRO: And you and Kathi provide something.

DR. MIIKE: Harold, I think in our past discussions we used words like "kinship" and, you know, social group or something along those lines.

DR. SHAPIRO: Yes.

DR. MIIKE: There is something in the text.

DR. SHAPIRO: There is something -- a number of points. You are right about that, Larry.

Bernie, I am sorry. Did you want to say something?

DR. LO: I think we also need to make a grammatical correction to the first sentence. "In considering waiver of consent, the IRB should interpret the term." The phrase otherwise dangles.

DR. SHAPIRO: Thank you. Other comments, questions on this particular recommendation?

Let's go on then to recommendation 12, which again appears on the bottom of -- principally on the bottom of page 129 with the clause going over on to page 130. It reads as follows: "If research using..." and again we will not use identifiable here but let's not stop there but "...using really coded and identified but existing human biological materials is determined to present minimal risk, Institutional Review Boards may presume..." and so on. That is the one. I am not going to read this all out at this time but let's see if there

are comments or questions on this recommendation.

Steve?

MR. HOLTZMAN: So my question was do we feel this way about both coded and identified at least with those two cases?

DR. SHAPIRO: Yes, that is what identifiable is. That is right. And you want -- and your feeling is?

MR. HOLTZMAN: I am just doing a listening check.

DR. SHAPIRO: I see. It is a listening check.

As written it includes both coded and identified. That is how this was written, which was use of the old word "identifiable."

Yes, Alex?

PROFESSOR CAPRON: Well, our long discussion of this has said that for purposes of consent coded samples are identifiable the same way as identified samples are. Although we are getting rid of the word we have not changed that concept. Since informed consent is required, the question is can it be waived. And what we are saying is that the presumption that it is impractical to obtain consent can exist before the rules pursuant to

our report come out. Thereafter the usual rule that you have to show impracticability ought to apply. And it seems to me it makes equally good sense with coded because they fit within the need for consent in the first place.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I was actually coming at it from the opposite way. Should this presumption apply to identified samples? That is my question. I am asking do we feel that we should have this presumption even in the case of identified effectively because we are saying the rights and welfare and other carry the weight?

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Well, Steve, I will start by saying that as I had mentioned at the last meeting I was in the minority in thinking that we might want to have IRB's still have to pay some attention to this requirement but the majority here, I think for good sensible reasons, would like to make it easier to use existing collections.

Now I am not sure that identified, which we commonly imagine to be name and address, is any more practical to track down than coded where it could be a one step process to get the name and address. The difficulty

that is typically encountered is not in identifying whose sample it is but where that person is now located and how to reach them.

So I would advocate if we are going to go this way to just leave it be.

DR. SHAPIRO: I feel the same way and I think this -- well, I would just be repeating the recommendation so I will save time. So I think it should stay in. My own view is it is quite satisfactory as it stands.

Okay. Let's go on then to the next recommendation which appears on page 13 and it is as follows: "The Office for Protection from Research Risks should make clear to investigators and Institutional Review Boards that the fourth criterion for waiver, that 'whenever appropriate, the subjects will be provided with additional pertinent information after participation,' usually does not apply to research using human biological materials."

Comments or questions with respect to this?

Okay. We now go on. There are some materials. The "Opt Out, Rendering Existing Identifiable Samples Unidentifiable," and so on, and let's not worry

again about the identifiable language which is throughout here and you need to have a spell check or word check every time you come across this.

But we get then on page 134 to recommendation 14, which goes as follows: "When samples are to be drawn from..." and of course this deals with coded and identified specimens "...investigators who choose to have identifiers stripped from the samples should explain to the Institutional Review Board the decision not to work with the samples on a coded or identified basis."

That is recommendation 14. Yes, Jim?

DR. CHILDRESS: A question. Is this a case where given our earlier difficulties with identifiable we just mean identified?

DR. SHAPIRO: This is the issue coming up again and that is whether we want to distinguish here between coded and identified is the question that Jim is raising.

DR. CHILDRESS: Because we are referring to them as specimens.

DR. SHAPIRO: Well, how do people feel about that? Whether this recommendation should deal separately

or perhaps only, depending on one's views with identified as opposed to coded and identified?

PROFESSOR CAPRON: Excuse me. I do not think that that is actually Jim's point. Jim's point was that we define -- and I have to find it. Is it in this chapter again? Yes. On page 109.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: That we have two categories of collections.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: Unidentified and identified specimens.

DR. SHAPIRO: Oh, I see. Specimens. Excuse me.

PROFESSOR CAPRON: And so instead of saying identifiable specimens we should simply say identified specimens.

DR. SHAPIRO: Excuse me. I misunderstood your point. I am sorry, Jim.

Steve?

MR. HOLTZMAN: And I think to make it clear if we use identified specimens, investigators who choose to

have the identifiers stripped, and then use our term, that is to use them as unlinked samples? That is what we mean, right?

DR. SHAPIRO: Right.

MR. HOLTZMAN: So then I just have a technical question, which people like Alta and Alex will know the answer. Is the IRB currently ever in play when you have got the unlinked samples. So the investigator now unlinks it, it is now exempt. Does this get into where we are implicitly recommending here the role of the IRB, which it does not currently have?

PROFESSOR CHARO: It is a good catch. It is a good catch. If this were a relationship simply between, for example, a repository and an investigator and the repository did the stripping there would be no IRB at the investigator's end. There might be an IRB at the repository end which is a separate issue. But you are quite right.

PROFESSOR CAPRON: Is this something we could deal with in our re-examination of recommendation 2 because it really is saying -- if we ended up with a 2.a) or a 2.b) or --

DR. SHAPIRO: That is right. It would change this.

PROFESSOR CAPRON: -- and had a process, it would fit nicely into that process.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: Just the flip side of it.

DR. SHAPIRO: That is right. It is the other side of what you discussed yesterday. Right.

Okay. So let's table this issue for the moment and come back to that when we get back to dealing with former recommendation 2. Thank you very much. That is really a very helpful set of observations.

We then come to a section on reporting research results to subjects and then come to what is now recommendation 15, which is on the bottom of page 135 and then goes over on to the top of the next page, followed immediately by recommendation 16, 17 and 18.

Recommendation 15 itself goes as follows: "Institutional Review Boards should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general,

these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following obtain," and then there is a), b) and c). "a) the validity and clinical significance is high; b) the threat to the subject's health, as indicated by the research finding, is significant; and c) there is readily available a course of action to prevent, avoid, ameliorate, or treat the threat to the subject's health."

Alex?

PROFESSOR CAPRON: What is the meaning under a) of clinical significance? Do we mean -- as opposed to what is discussed in b). Do we mean the validity of the research findings, the reliability of the research findings? I mean, what are the technical terms, those of you from scientific background, that differentiate different points here? It seems to me that clinical significance is covered in b).

DR. SHAPIRO: Bernie?

DR. LO: I think there are a couple of issues that a) and b) are trying to sort out. Clinical

significance is usually used as distinct to statistical significance so that things could be statistically significant but not clinical by meaningful because the absolute difference is still small. They just had such a huge number that statistically you know there is a difference.

You could have a meaning of clinically significant difference but it is on a trivial health problem so that you could say whatever. You -- I am just trying to -- for some reason I am blanking on it.

DR. SHAPIRO: I think you are --

DR. LO: Your serum sodium is higher but it means nothing for your health.

PROFESSOR CAPRON: And isn't that what b) goes to? That it is only findings that are significant as to a threat to the subject's health, not --

DR. LO: Yes. I mean, you could --

PROFESSOR CAPRON: I am sorry. As I understand it, you are saying that a) says that the clinical significance of the finding has to be high and b) then says "and that highly significant finding must relate to a significant health effect."

DR. LO: Right. Right. But you could have a health effect that is very ominous but the significance of the finding does not -- is not solid enough that you would want to go out warning people.

PROFESSOR CAPRON: Could we find another word for "significant" in b) then?

DR. CASSELL: Important.

PROFESSOR CAPRON: Important or something else.

DR. SHAPIRO: Yes.

DR. LO: No, that is not quite right.

DR. BRITO: If you change that then -- no, because then "the threat to the subject's health is significant." It sounds to me like what we need to change -- let's go back to the a) and change "clinical" to "statistically significant" and then discuss b) in terms of clinical relevance to the patient or to the subject.

PROFESSOR CAPRON: What if we said --

DR. BRITO: Okay.

PROFESSOR CAPRON: -- "clinical relevance" under a). Would that --

DR. LO: But maybe we should probably fix this

at a break or something.

PROFESSOR CAPRON: Right.

DR. SHAPIRO: I think as I understand the discussion here, I just want to make sure I understand, Bernie, we could deal with a) with -- a) could be focused on the significance of the result, not having to do with the clinical significance but its scientific significance; b) with the issue of how it impacts the particular patient's health and whether that is significant or not; and so on. Maybe it would be helpful just to straighten those things out. I think that is a useful idea.

And the word -- and we might also want to think -- Bernie, maybe you could work on this during the break. Significance is -- it is an easy word to use but sometimes it is a confusing word to use because it means different things to people. People who are statisticians think of it one way. Others another way. We might be stuck with the word but if there is another one it might be helpful.

Okay. We will -- yes, Arturo?

DR. BRITO: Pending the wording but I am still confused. Why would a research subject need to -- why

would an investigator be required to inform a research subject of something that is statistically significant and valid that is not clinically relevant to that subject?

DR. SHAPIRO: Well, all of these conditions have to hold as I understand this recommendation. So all of these.

DR. BRITO: Okay.

DR. SHAPIRO: There is the word "all" in the top of the recommendation here.

Bernie?

DR. LO: I want to go back to the text that preceded this on page 134 at the very beginning, line 19. I am still troubled by our using "interim findings from research." And as I read it, what we are really talking about is that the research may not have been confirmed, which to me is different than interim. So I am just wondering if we could strike the interim term both there and at the top of 135, line 1. We seem to be saying interim results, preliminary results, and results that are final enough that you publish them but that have not been confirmed. I think we should stick to the latter category, not interim or preliminary results.

DR. SHAPIRO: Any comments or questions regarding that suggestion? I am only looking -- I have not -- you mentioned a number of places but I am only looking at line 20 right now. It does not seem to -- I have no problem with deleting "interim" from there but there is a number of other places you suggested, I think. Am I right?

DR. LO: Yes. I guess I would sort of be inclined to start by just striking it from all things. If there is a modifier needed I would use "unconfirmed" rather than "interim" or "clinically inconclusive" or something.

DR. SHAPIRO: Okay.

DR. LO: Because you should not be publishing at all if they are clinically inconclusive.

DR. SHAPIRO: Further comments or questions on Bernie's thought?

DR. MIIKE: That is trouble if you strike "interim" on the top of the next page because it is about interim results. So you have to edit that paragraph.

PROFESSOR CAPRON: One thing to do would be just to drop that phrase entirely and say that MacKay

writing about the development of genetic tests contends that preliminary results do not yet constitute information. In other words, not the action but his basic contention.

DR. LO: Right. I mean, isn't he saying "unconfirmed" again rather than "interim or preliminary?"

PROFESSOR CAPRON: Yes. But we will drop the language, that clause --

(Simultaneous discussion.)

DR. LO: Absolutely. That is great.

DR. SHAPIRO: Yes. That would work.

Steve?

MR. HOLTZMAN: I do not think this is angel's on a pin head. Much of the literature and the concern is the distinction between research findings versus, for example, approved clinical tests. So I think the issue is research findings per se. Not whether they are interim, conclusive, been published in Nature. As long as it is still only a research finding, a research test that has not gotten to the level of approved clinical test practice of medicine accepted and whatnot. So at least in my dealings with these things typically that is the -- can we

just distinguish whether it is a research test versus a clinical test?

DR. SHAPIRO: I think there are two -- more than one issue swirling around here. One is interim, which on reflection I do not like that word either because you can have a perfectly complete study which does not -- either successful or unsuccessful but it is not interim. So I think the word "interim" is misleading in this context, in all these contexts, I think.

And the issue -- there is a second issue of under what conditions are we allowing disclosure according to this recommendation. And as I understand it, it requires, without going into a), b) and c), which might need to be somewhat revisited, it requires all these things to be true. That is you have your research results, they are valid, you know something is of clinical significance, you know it impacts this or you think it impacts this patient's health, and you -- there is some kind of clinical procedure to help out. It is trying to be comprehensive here as I understand the recommendation and so I think all these things really are covered.

Alta?

PROFESSOR CHARO: I think in addition one of the reasons why it gets very confusing is that there are two very different reasons why people's instinct is that research material -- research findings are different. One is the almost false assumption of clinical equipoise is that we do not know whether a particular research intervention, this is paradigmatic case here, let's say testing two drugs.

You do not know whether the research intervention is going to be better than standard therapy. And often even at the beginning of the research, and certainly halfway through, you will have a very strong suspicion as to whether or not the research drug is going to be better than standard therapy but you still act as if you genuinely do not know, which is why you could still have a purely randomized placebo control trial, et cetera. So part of it is that we pretend that we do not really know if the research results are any good but sometimes we know that they are.

And the second has to do with the relationship between the investigator and the subject, which is different than the relationship between a doctor and a

patient, and these tests are being done not with the patient's interests in mind but they are being done with the investigator's needs in mind consistent with the protection of the subject's interests.

And the combination of those leads us, I think, to kind of presume that you do not want to be sharing the information becasue it is probably not good information with a little asterisk that that has got a bit of a phony content to it, and it was not developed for this person's particular needs and uses.

But I thought that the three criteria that were spelled out actually seemed to be very sensible ones for determining when those two assumptions did not apply and we really were in the exceptional case.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Two points. One, I think this area is difficult both for the reason that Steve mentioned, which was not included in your listing, and it is actually, I think, more difficult than Alta suggests is true of clinical trials because this -- these could be materials which are being studied without any direct intervention with a patient at all from whom they came.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: And so we are talking not about that delicate situation in which your patient is really a subject and you are using him with the patient's knowledge and so forth but here something that just came out of the blue. So I think that that needs to come out here if there is anything going to be made of the very good points you just made about clinical research.

I am concerned, however, that actually the restrictions that we give are two tight in one regard. Certainly a good deal of what might be found by the kinds of studies we are talking about is genetic information and I think we need to broaden b) and c) to recognize that the threat might not just be to the subject's health but the health of offspring because the one bit of information you might get would be something that would alter your reproductive plans, although it is of no -- there is no intervention for your own health. You have a disease that will be fatal at the age of 45 but if this is an inherited condition, which has now been discovered to have a genetic locus by looking here, it is perhaps equally urgent that that information -- if it is -- if it meets Steve's

objection that a research test does not have the same process of validation that an established test has.

It would still be of relevance to you so that both under b) and certainly under c) in which there would be no action to prevent, avoid, ameliorate or treat the threat to the subject's health is too narrow.

DR. SHAPIRO: Interesting issue. How do people feel about that? I understand the point.

DR. MIIKE: If we are talking about generational effects I need to ask the scientists over here in considering there is not very clear straight forward direct line evidence about this, what are we really talking about if we are talking about threats to generations after the subject? I mean, it seems to me we get into really uncertain ground there.

PROFESSOR CAPRON: Well, if you are talking about an autosomal dominant disorder like anything that -- and it is an adult onset disorder or even something that is not dominant but you find the person has the allele and could pass it on but certainly with a dominant disorder it is not multi -- that is not multifactorial -- I mean, take the discovery of the Huntington's gene. If you were doing

research on samples that were coded samples and you could find out, the question would it be right not to reveal that information on the ground that there is no treatment for Huntington's disease today, there is no cure, you know, it -- what we are talking about here are not -- we are not saying that when these are met you must reveal it.

What we are saying is until these are met you ought not to reveal it and, you know, the manner of -- in which it is revealed and so forth is still subject to IRB approval and we ask that the investigator anticipates what he or she would do if such results are forthcoming.

DR. SHAPIRO: Steve, do you have a comment about this?

MR. HOLTZMAN: Just for clarification, Alex. You were not raising the issue of disclosure of the results to a third party. You were just raising the issue of what if the result could affect a choice of significance to the person even if it was not a health choice?

PROFESSOR CAPRON: Precisely.

MR. HOLTZMAN: Okay.

DR. SHAPIRO: Trish, and then Bernie.

MS. BACKLAR: Well, it seems to me that if this is going to be a study and some consent is involved that this is part of the consent process. We certainly found out that people were very interested in having results told to them if they were, however you want to read the word, significant and important to their health. And so that you are looking at this out of a context of which surely there is going to be some consent in which somebody says, "Yes, I would like to have results disclosed to me if they are of a certain kind."

PROFESSOR CAPRON: I am not sure that is accurate, though, is it?

DR. SHAPIRO: That is right.

PROFESSOR CAPRON: Isn't -- couldn't -- doesn't this apply even to a study in which there was initially the view that it was impractical to contact people and it is a coded sample and you end up adventitiously, or because that is the point of the study, finding results which are the kinds of things which people ordinarily want to know like you ought to be getting screening for this or that on a regular basis because we found a gene linked to a disease which is preventable or

we found a disease that is lethal, not preventable, but inheritable and you might want to know that because you might decide not to have biological children and adopt or something.

DR. SHAPIRO: I think the point is here, Trish, I agree with this Alex that this covers cases where consent was not necessary and was waived.

Bernie?

DR. LO: I think this is one of those situations where are now getting into issues that we had not really contemplated when we wrote this but I think are important. There are several different situations where this might occur. One is -- I think it goes back to what Steve was saying -- people who knew their materials were being used and actually are eager to find out information even when scientists are saying, "Wait a minute. The information you are seeking is not really validated. It is not clinically meaningful. We think it may be more confusing than helpful and we do not think it is right to do it."

There is a whole other set of circumstances that Alex has referred to where someone had no clue that

their materials were being used, a finding is obtained and now there may be a significant threat to the health of either the subjects or the offspring but there is no treatment.

I think Huntington’s is a very illustrative example because most people who have -- who are in a family where they’re is a family history of Huntington's do not actually come forward and get tested so to actually go out and look them up and say, "Here is some information we have that you did not even know we were in the process of possibly obtaining and we want to give it to you," may be regarded by some as an imposition.

All the literature talks about a right not to know and I think we need to distinguish here between subjects who know their research subjects and have a high need for information and they exceed the willingness of scientists to provide it because of concerns about validity versus sort of seeking out people who are unwitting or unknowing subjects at least because of the exemption requirements and sort of thrusting information on them that many people in that situation who have a choice do not choose to seek out.

And so all that, I think, gets swallowed up in these discussions and maybe we need to start unpacking some of that because I could agree with Steve's situation but I am very reluctant to go seeking out people whose only recourse is a reproductive decision. They may not -- they may well -- I mean, the statistics are many of them do not choose to get that information.

PROFESSOR CAPRON: But I want to emphasize that what we are talking about here are the criteria that have to be met before you could do that. 16, 17 and 18, it seems to me, really speak to what you are talking about because it might very well be that the IRB would say the proper contact would be a contact which would preliminarily simply say we have done a study on your cells.

"The results seem to us significant enough that we have taken a great deal of effort now to contact you to let you know that we have such results. Do you wish us to provide this information to you, to your physician or to no one, you know." And we can have a sort of back and forth dialogue in which you probe the kind of information and decide whether or not you want to know it

or you want to not know it.

In other words, it is not a matter of a call in the middle of the night saying, "Hey, we found out you have the Huntington's gene."

MS. BACKLAR: But this is the whole point of c) that there must be readily something that you can do about it.

PROFESSOR CAPRON: Right. And I was simply asking that we think about language, whether it is to the subject's health or the health of offspring or whatever, potential offspring, or something that takes into account that one of the things that at least some people who have available to them this kind of information do seek is information that would be relevant to making reproductive decisions and for those people to learn that you got information about their health status and that that information was withheld because there was no treatment for them but they might have made other choices in their life is what seems troubling to me.

And I would not want to establish criteria that say, "Oh, well, the reason I did not reveal it was that the National Bioethics Advisory Commission said that

unless there was treatment for you, I should not reveal it." That is all I am saying.

DR. SHAPIRO: Okay. Just a few more comments and then we are going to have to move on.

Alta, then Steve, and Arturo.

PROFESSOR CHARO: I appreciate the distinction that is being drawn here but I am finding myself not agreeing with a few things that seem to be floating in. With regard to, first, the category of people who originally personally consented to participation in research, the ones that are being discussed in 16 and 17, there was a suggestion raised at some point that they might be entitled to negotiate essentially the receipt of information even when the information is not considered to be very good information. And I am uncomfortable with that but I definitely heard it. I forget from exactly whom.

And I am uncomfortable with it because I can understand in the context of a doctor-patient relationship some degree of negotiation over the terms of that relationship but even there, there is an absolute threshold of medically appropriate that is used as a

baseline for what patients will be able to negotiate to receive. And I think in research they have even less of a call on these results.

In the context of those who have never been contacted and never given consent, I appreciate the dilemma that is creating. I mean, the case that I think of actually as paradigmatic is not even Huntington's, it would be things like apo-E in which there is no diagnostic test as Kathi was pointing out to me in notes.

In the course of developing a diagnostic test where there is no existing gold standard you are invariably going to have stages of research in which you have preliminary kinds of findings where it is looking at correlation with an important disease, Alzheimer's that has life changing consequences but maybe does not fall under threat to the subject's health.

I mean, I do not know, you may want to change the word to "importance" or whatever.

But I would like nevertheless to keep this fairly narrow and to keep the circumstances under which investigators feel compelled to go back to people fairly narrow because -- and this is purely anecdotal. It has

been my personal experience from a decade on an IRB that investigators want to go back much more often than an IRB would like them to. Our experience has been that investigators are so excited by their findings and so convinced that these are important findings that they want to share them with people and perhaps are over-estimating the importance they might have in people's lives and under-estimating the disruptive effects.

So I would like to urge that we keep these criteria kind of narrow and that the alternative to going back to people individually is going to be if the research is intriguing that with its publication comes the next stage for kind of open call for people to volunteer for additional testing in which they do have a chance to consent and knowingly accept results that are as yet not gold standard quality.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: While sympathetic to the thought Alex is putting on the table that there can be findings of importance, I actually would like to come down with Alta and that is to keep it narrow but the real animus behind this is more or less the Hippocratic Oath.

You find out something where you can help the person medically and you just cannot stand by and not do anything.

We find out many things in our studies that someone might consider important. It is not a question of it being just inconclusive. You can tell paternity. All right. That probably is important to a person. We do not go back and say, by the way, we learned something about your paternity. That is not the animus of it. As much as I can see your thought behind it, Alex, but the animus is something different here, and I would like to keep it narrow.

DR. SHAPIRO: Arturo?

DR. BRITO: When I read this for the first time in the revision I did not really think about it but now with Alex there is a lot of anxiety that I am feeling and I am not sure how much of that has to do with the clinician in me so I have to put a lot more thought into it but I just want to clarify something.

I am hearing two different suggestions from Alex basically or two parts of one suggestion. And that is when there is a threat to someone other than a subject

that is related to the subject that there is a readily available course of action to be taken and the other one when there is a threat to someone, another subject, when there is not a readily available course of action. It is like two different parts of the same thing.

And the first one makes -- the anxiety comes from the fact what if you find out not something like Huntington's, what if you found out something that could be a threat to potential offspring of the subject that there is a readily available course of action? Is it possible, with Alta's and Steve's suggestion of keeping it narrow, to include that in there somehow where we still keep it narrow by including only like offspring when there is a readily available course of action? You know, I could think of things like studies of cystic fibrosis or you find somebody has a sickle cell trait or -- and the -- or Tay Sachs or things like that where you can actually -- you know, the subject is the parent that can make an informed decision about their offspring.

So I think somehow in there -- I have to think more thoroughly through this but it is -- there is some anxiety there and something we are leaving out there based

on what Alex said.

DR. SHAPIRO: Okay. Let me just say something. Bernie is next on my list here. I do not want to lose track of two different things here. One is we are going to pay some attention to the word of a), b) and c) independent of Alex's suggestion, which we will continue to deal with. Right now we are going to deal -- that is going to happen during the break or something like that. Bernie may have already done it.

But in any case the -- but there is this issue, which I think is really a kind of well defined issue and we ought to see how we feel about it, namely whether really under -- we want to expand subject's health to something more than just personally involved with that subject's own health but the health of those they may concerned about like an offspring.

Bernie, then Steve.

MR. HOLTZMAN: But I have heard -- quickly. I have heard subject's health, I have heard subject's and other's health, and I have heard other important concerns of the subject. There is a difference. I am trying to imagine the case where I learn something about the subject

and it tells me something about someone else's health, not their's. It is very different than it tells me something that relates to a reproductive decision.

DR. SHAPIRO: It is the latter I think we are focusing on, not the former. The former is the example you gave, which is something I do not think we want to deal with or recommend. So it is the narrow version of what you suggested as I understand it.

Bernie?

DR. LO: My comment is along Steve's line. I would just ask, probably directed to Steve here, are there examples of genetic findings that would not affect the subject's health but would affect the offspring's health in a way that is predictable and does not depend on who the mate is. I think to find a serious auto recessive trait -- I do not think you can say that is going to affect the offspring's health. It just depends on whether the -- the partner is also a carrier. So I think that really is a reproductive decision and not sort of the high certainty of -- I think we are talking of both the serious condition and a high likelihood of that condition appearing.

MR. HOLTZMAN: Well, autosomal dominant.

DR. LO: But see but then the subject's health would also be implicated.

DR. BRITO: Not if it is X linked. I would have to think of a clear example but there are --

DR. LO: You are saying if you found out that a woman was a carrier for --

DR. SHAPIRO: Bernie, do you want to speak into the microphone?

DR. LO: I just think we may be talking theoretical. I am just trying to find an example.

MR. HOLTZMAN: Get yourself out of genetics. You could find out something about the subject which means that their child probably has it as well but the subject for whatever reason is not suffering the symptoms but the child is likely to, if exposed, get something. There is cases along those lines. You developed the immune response already so you are okay but likely your kids could --

DR. SHAPIRO: To me it seems that the issue is -- well, the finding and we may very well disagree about it -- but the question is whether we want to expand this

in some way. I think the clearest example is because it might, in fact, impact their reproductive choices of an individual because of knowledge that might be gained.

Now let's just take a straw vote on this and see where we stand. How many people think -- we do not have the language in front of us. Obviously that would have to be worked out. -- that we ought to find some way to expand this recommendation to include that possibility and, of course, even -- or just leave it as it is with the language changes? How many would like to at least try to work out a way to expand it?

(A show of hands.)

DR. SHAPIRO: Okay. Alex, do you favor expanding this or not?

PROFESSOR CAPRON: In favor of expanding it to reproductive choices?

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: Yes. I think it is a matter of finding the wording that keeps it simple. I do not think we should be writing a textbook on genetics and infectious disease here.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: But just to recognize that you have an interest in your own health and in the health of your children.

DR. SHAPIRO: Okay. Arturo and Alex certainly feel this way. Do others feel that this should be expanded in that direction?

(A show of hands.)

DR. SHAPIRO: Well, why don't you try some language and maybe you will convince the rest of the commission or not.

PROFESSOR CAPRON: I wanted to know what are we doing about the point that Steve raised, which I think is an enormously important point, and what I want to ask Steve is whether in the rewriting of a) your point would be encompassed by saying something like the validity and clinical relevance and reliability of the finding is comparable to that from approved clinical tests.

I mean, the idea being that we think researchers are so wonderfully smart and so forth and if they come up with a research result it is wonderful but as you point out, in fact, their research results may be less reliable than those from approved tests and is that really

the bench mark that we should be aiming for here?

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Well, they either have that or -- in which case they are an approved test more or less except for the approval process. I really think the intent of the language as it was, was to say to people that you are going to have to exercise judgment so just go and look and before you even think about revealing anything you better be pretty darn certain that the validity and clinical significance, which are two different things, okay, are high, are very high. All right.

Now whether they -- where you are going to the put the bar there and whether there is a gold standard and whatnot is very, very different. And so I think this was guidelines and guidance to IRB's. And so I do not think you -- I do not really even think it has to say more than it says at least under a).

PROFESSOR CAPRON: I think the point that you made, which is not really elaborated, in the preceding language should give rise to some commentary on a) to say that the concern is that research findings are not likely

to be at that level and that the decision to go forward should be based on the conclusion that these particular findings are close to that -- that are comparable to that level.

DR. MIIKE: By definition these are research results. They cannot be comparable to approved tests. You will never meet any standard if you put it in that phrase.

PROFESSOR CAPRON: No. As Steve just said, the kinds of results you could get would be the kind that you would submit to show that the tests should be approved.

DR. MIIKE: No.

MR. HOLTZMAN: No. There is a lot that will go in beyond that.

PROFESSOR CAPRON: I recognize there are technical requirements but you can have findings -- well --

DR. SHAPIRO: Bernie, do you have something?

DR. LO: Let me try some language that Arturo and I have worked on and see if it comes close to these concerns. a) would be scientifically valid and confirmed.

b) would be the finding indicates a serious and highly likely threat to the subject's health, and we can leave out whether it is health of others as well, but that would include the notion of scientific validity and confirmed. I think the highly likely threat would get at the clinically -- the reliability of a test in a clinically -- in the clinical sense.

DR. SHAPIRO: Let's proceed as follows: I think -- while I do not want to resolve this issue right this minute because there are still some people who want to think about it, maybe if we could work out with you, Bernie, Arturo and Kathi, some new language. Let's look at a new recommendation, a new a), b), c) if you like to this and let's try to take a look at that perhaps even later today some time. We will come back to it and then we will have to decide obviously on what you might call a reproductive choice issue that Alex has raised and we will just have to decide on that issue.

Let's go on to recommendation 16, which reads as follows: "The research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings to a subject,

as well as a plan for how to manage such a disclosure."

Comments, questions?

PROFESSOR CAPRON: Just a note. Alta described that a while ago as applicable to situations in which there is an informed consent process in advance. You did not mean that?

PROFESSOR CHARO: I did not mean that, no.

PROFESSOR CAPRON: Okay.

DR. SHAPIRO: Let's look at recommendation 17, which follows immediately on that. "When appropriate, persons should be asked whether they would be interested in receiving research results if such disclosure is deemed appropriate by the investigator."

There are a few appropriates in there but we will worry about that later.

Steve?

MR. HOLTZMAN: So this is just a question. With respect to the first appropriate -- okay. Well, no, there was an initial recommendation was of the form the person should be asked and the question was raised, well, maybe you do not want to in many cases be putting that even as an option in front of the people. So now we are

saying when appropriate. So clearly someone is determining when it is appropriate to offer this option to the subjects. Have we provided any guidance in that respect as to who and on what basis? And is that important?

DR. SHAPIRO: Kathi?

DR. HANNA: I would think that you would want to maybe change it to say, "When appropriate, the individual seeking consent." I mean, wouldn't that be a part of the consent process?

DR. SHAPIRO: Alta, and then Alex.

PROFESSOR CHARO: Steve, I am trying to remember a circumstance where it would not make sense at the time you are recruiting somebody into a study to simply ask would you like to receive research results that are in circumstances that are deemed appropriate by the investigator. Can we think of an example where you would not want to ask the question?

MR. HOLTZMAN: You are right. The second appropriate takes care of modifying the whole thing.

PROFESSOR CHARO: I guess at this point I would be suggesting we simply start the sentence with the

word "persons."

DR. SHAPIRO: Yes. I think that would quite easily. It takes care of the two appropriates.

DR. LO: Well, there is a problem that many of these persons do not know they have become subjects -- their materials have been used in studies. So we have to put some modifier in but there is a presumption there is an interaction before the study is carried out.

PROFESSOR CHARO: Okay. Maybe it is simply that in the text somehow this has to indicate this only applies when you are actually recruiting somebody. It is not the waived consent or no need for consent situation.

DR. LO: So it is when patients participate in a study --

PROFESSOR CHARO: Exactly.

DR. LO: -- they should be asked whether --

PROFESSOR CHARO: Sure. And they are not patients, they are subjects.

DR. LO: But people are being asked. They are not subjects yet, they are being asked.

DR. HANNA: Can I ask for clarification? Is it the person who is seeking consent who is supposed to

ask this question?

PROFESSOR CHARO: Yes.

DR. SHAPIRO: Bette?

MS. KRAMER: So does it appropriately belong then in the section on informed consent? Is part of it why it is confusing is location here?

DR. HANNA: We can cross reference it.

MS. KRAMER: Yes.

DR. SHAPIRO: Other comments or questions on 17? We will look at that issue.

PROFESSOR CAPRON: Do we want to have any of the discussion in the text that Steve suggested that we have or have you withdrawn that idea entirely? There still is some concern about on what basis we might suggest investigators would deem it appropriate or not to reveal results. Is that just the circumstances that are covered by the criteria under recommendation 15 or are there additional things that a person making an appropriate decision should take into account? I thought that was the question, in effect, that you were raising.

Yes, it is a question to you. Do you -- in light of your raising it you were sort of saying, well,

shouldn't we spell something out and the question would be what would we spell out then.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: In my mind 15 is covering the issue of you make a discovery that is medically relevant. Let me just use that short term. You have to feel like you are compelled to go back. I think in 17 we are dealing with maybe a broader set of issues which have to do with research design and disclosure and the consent of the individual.

Now you could have results that are not medically relevant results but you could decide that it is fine, that these people were participating, we know they are interested, and we say at the end of the study we will give you your individual results, you know, as to whether you have the allele for brown or blue eyes.

So I think what I am struggling with here is maybe the emphasis seems to be on asking the individual whether they would be interested as opposed to the protocol specifying and the consent specifying whether or not they will have results made available to them, whether or not they will have them optionally available to them.

I do not -- I am not being clear. I am sorry.

DR. SHAPIRO: I think -- let me go to Alta first. I have a concern here.

PROFESSOR CHARO: Sorry. I did not mean to cut you off at all, Harold.

You know, I would not like to see in the course of re-examining these a move towards encouraging researchers to be offering up their results to people. I think it only enhances the therapeutic misconception that runs throughout research. When people volunteer for research and/or are paid to be in research, I think it is quite appropriate to say, "You are doing this for money. We are doing it to test a theory. We are not planning to give you any of the results." And I would not like any of this language to cut out that option for investigators.

I only wanted originally myself when this discussion began to acknowledge that there will be extraordinary circumstances, not routine, but extraordinary circumstances where in the course of research an investigator comes across something that he or she feels absolutely must be communicated.

For example, they discover for the very first

time the presence of an infectious agent and really feel compelled to go back and tell people because it is serious and it is treatable, and has consequences for themselves, it might have public health consequences, and those of us on IRB's have all come across the occasional question about whether something like that has arisen.

But in no way would I want us to be moving toward the idea that it should be routinized and that just because you are in a study you should not be routinely getting the results. All right. If you really want results on things you should be seeing somebody in a clinical context, not in a research context. I would love to keep them as distinctly separate spheres as possible.

DR. SHAPIRO: Bernie?

DR. LO: What Alta just said could get out from the transcript into the text accompanying this. I think that would be very helpful.

DR. SHAPIRO: I have the same perspective as Alta does. I am really wondering about recommendation 17 all together myself. It seems on reflection to be a problem.

PROFESSOR CHARO: There is a little history to

this. I recall -- I hope I am recalling it accurately -- that it began really with something about persons should be allowed to refuse to receive research results. In other words, that there also should be the option to say even if it is in your opinion overwhelmingly important I do not want to know from this. And that language was changed to something seemingly more neutral of would they be interested because it was perceived -- it might even have been me for all I remember, on this point I am weak on the history, as having kind of presupposed the right answer to that question.

But looking at that neutral language now I think actually it is encouraging an activity that should be discouraged. I would love to simply -- if we are going to say anything at all, that people should be allowed to say I do not want to know even the most dramatic stuff.

DR. SHAPIRO: Well, that was along the lines of the suggestion I was going to offer in a moment and that is whether we ought to eliminate recommendation 17 and deal with the issue you have just raised, that is people who just do not wish to know, in 15. But I have not thought this through carefully but now I think 17

really is a problem. I think it raises many more -- it does not solve anything I can think about and it may raise some issues.

Bernie and then Eric.

DR. LO: I agree that stating 17 in a positive frame is less helpful than stating it as a right to decline to receive information the investigator thinks is pertinent to you. But again I think we are thinking primarily in the genetic context. Someone in the audience, I do not know your name, told me the break yesterday that if we are actually thinking about other kinds of research on stored biological materials such as the emerging infection example that Alta just used, I am not sure there should be an opt out in a public health context where there is both a serious threat to your own health and to the threat of third parties in the classical contagious disease sense. Now in the genetic sense they should have an opt out.

So I think we are getting more complicated here and I am just wondering if this -- if we are sort of -- we are getting mired in too much detail and maybe we should just strike 17 and have language that -- as Alta

suggested a couple of rounds ago -- that this should be a rare exception because of the high likelihood that findings that the researcher thinks are really terrific can pan out to be a lot less and not get into sort of the level of detail I think we are getting ourselves into.

DR. SHAPIRO: I think we are agreed that 17 is a problem so we are going to have to either strike it or reconsider it.

But, Eric, I am sorry. You had your hand up.

DR. CASSELL: Well, I want to vote for striking it. I think Alta is correct about what the presumption should be. And coming up with ideas about certain infections which will threaten the whole of the -- I mean, there is a biology remember and so far the -- we -- Ebola, hidden Ebola virus, you know, it just does not make sense and it does represent a danger telling people things when we do not really know what they mean or -- I think we just take it out and leave what we have here, which says exceptional circumstances. That is what it is all about.

DR. SHAPIRO: Any other comments?

PROFESSOR CAPRON: Well, I am trying to

understand how what we are talking about relates to what is already in 15. 15 says that the guidelines developed by IRB's should presume that it is an exceptional circumstance in which this information will be revealed and that it should only be revealed when three or more high criteria are met. Now we are dealing with -- and that applies across the board.

Now we are coming to the case where there has been a direct informed consent process with an individual and the question is as part of that process should individuals usually be told we are not going to reveal results because they are research results to you? And if that is the case, when we -- when it would be deemed appropriate is really the very things we say under 15.

Or are we going to say, well, researchers could take a somewhat different view of this and some of them could offer subjects, and we ought not to preclude them having that as an option. Do we accomplish that by saying nothing about it and leaving it open or having some discussion in the text, in the commentary?

I am not clear why -- I mean, there are people like Bob Veatch, who take the very strong view, and it may

be wrong, that if someone else has data of any validity about you, you should be offered the opportunity to get it and also to decline it but to get it if you want it. That is a very strong patient-oriented thing.

Now Alta says that does not apply here and it might well be that we say that the person says I am not going to reveal that to you. If you want that do not enroll in my study.

There is an easy answer to that, Alta. He just says that is my rule for the study. Do not enroll if you want that. Go see your doctor. By the way the doctor does not have a test because I have not developed it yet but go see your doctor. He will give you whatever information you can get under present testing methods.

But I am not clear that we can just sort of brush off 17 and say the issue goes away. I do not think the issue as to consenting subjects as opposed to people who do not know this is going on just disappears.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I would like to suggest that first this probably cannot be worked out until we have had a chance to go back and do some writing. But, second,

that when we do that -- as we all attempt to do it -- that we consider whether recommendation 16 offers an avenue for handling this problem. 16 speaks quite specifically to both situations where people were recruited knowingly, where they know they were recruited and those where they do not know, to the problem of anticipating circumstances where you might want to go back and having a plan for how to manage a disclosure.

And it allows an IRB on a very individualized case-by-case basis to consider what is at issue here. The plans are going to differ depending on whether or not people know that they have been recruited. We have had circumstances where we have had to send "tickle" letters to people saying, "Well, so you remember that you were in research years ago and from time-to-time we check with people to see if they would like to be kept up-to-date with those research findings. Would you want to be kept up-to-date?" It was all very disingenuous.

We were trying to get them slowly to step through a process where we could elicit from them a willingness or a refusal to get specific information because it turned out that what had been tests before --

there were sweat tests on CF -- now had genetic mutation tests made available and we had information, and we did not know whether or not they wanted to be told. That was handled very delicately.

There are other circumstances where Jacob Kreutzfeld, which has been an issue around the country where nobody thinks it is a serious medical threat but everybody knows that it can be perceived as one. And if we focus our attention on how to incorporate in 16 and the tests accompanying it a directive that researchers should -- when dealing with people who have been recruited, identify for them the problem -- you know, the likelihood that research findings are going to be revealed. And for many investigators the answer is going to be rarely and their IRB's will encourage that.

And for those that have not been recruited a more generic set of concerns about what the criteria are and those criteria could be the same for the recruited people or different but that is all individualized by the IRB. It would also include then the standards for revealing it, how one would deal with the IRB to decide whether or not the standards have been met and then the

series of letters or calls that would be used to let people know.

DR. SHAPIRO: Okay.

PROFESSOR CAPRON: Could we get a box here with an illustrative case? I mean, if you have a documented case of such a process I think it would actually be informative.

DR. SHAPIRO: Okay.

PROFESSOR CAPRON: It may belong in another chapter, I do not know, as an existing practice but I think it would be informative.

DR. SHAPIRO: We are going to have to rework 16 and 17 and so on and their connection to each other. And so we will just have to produce the new material on that.

DR. LO: Can I just ask another question about sort of when the IRB comes into play here? I mean, we are sort of talking about situations where the scientist thinks, "Gee, I have got results that maybe I should be telling the subjects about," and these people do not even know they're subjects. Is it conceivable that the IRB never saw that protocol in the first place because it got

through on a waiver but now we want to somehow say to the researcher you cannot just go back to the -- you, alone, should not make the decision to recontact patients without having somebody like the IRB review this process in 15 and 16 with you?

PROFESSOR CHARO: Right now, Bernie, if a consent -- the consent was waived, it means an IRB had to be present in the process. It means you had -- you had coded or identified samples and a consent waiver. The circumstance where an IRB under the current recommendations has never been involved has to do with unlinked or unidentified samples and for the unlinked ones you could go back to the class of people but you could not go back to the individuals, and that is exactly why there was the beginnings of a discussion yesterday afternoon about the issue of IRB involvement with unlinked samples.

DR. SHAPIRO: Okay. Let's go on. We will have to come back and rework this group here and we will try to do so.

Alta, at the break I will speak to you about this and see if we can formulate a plan for doing that.

There is recommendation 18, which is a very

short recommendation and easy to read. "When research results are disclosed to a subject, appropriate medical advice or referral should be provided." I think that is right. It goes in that -- these have to be reworked. I mean, I do not think any of us have any objection to the thought here but it has to be reworked in the context of these reworked recommendations.

Okay. We have probably about 15 or 20 minutes left here before moving on to the next part of our agenda so let's see how far we can get on some of these other recommendations.

The next section of the report deals with a consideration of potential harms to other groups, et cetera, and eventually we hit recommendation 19 on page -- 19 and 20 on page 139. So let's see if there are any comments or questions on 19 -- on recommendation 19.

Bernie?

DR. LO: Nineteen, I wonder if we can simplify it by collapsing down coded, identified, unlinked and unidentified? I mean, aren't we just trying to say that, "Research using stored biological materials, even when not potentially harmful to the individuals from whom the

samples are taken, may be potentially harmful to groups associated with the individual." And just go to the last sentence? So, I mean we are saying in --

DR. SHAPIRO: Right.

DR. LO: -- it can happen with code and identified and saying, yes, it may happen with identified and unlinked as well.

DR. SHAPIRO: That is right. The difference in wording is trivial in those two sentences. It just changes the location of words but otherwise has the same -- at least that is how I read it now looking at it.

PROFESSOR CAPRON: The reason it was written that way was originally we had only the first sentence.

DR. SHAPIRO: That is right.

PROFESSOR CAPRON: And it was pointed out at the last meeting, well, but it could also --

DR. SHAPIRO: The obvious solution --

PROFESSOR CAPRON: Your solution is a better one.

DR. SHAPIRO: Other comments or questions?

Thank you very much, Bernie.

Other comments or questions?

Recommendation 20. All right.

There is then a short section following recommendation 20, which is publication and dissemination of research results, and that leads to two recommendations, recommendation 21 and 22 on page 140.

Recommendation 21: "Plans for disseminating results of research on human biological materials should include, when appropriate, provisions to minimize the potential harms to individuals or associated groups."

Comments or questions on 21?

All right. Let's now consider 22, which in the past has been something -- I am sorry. Is this on 20 or 21? 22. Let me just read out 22, which is the area where we have had more discussion in the past.

"When accepting results for publication, journal editors should require investigators to indicate whether the research was conducted in compliance with the substantive requirements of the Federal Policy for the Protection of Human Subjects in Research, even if the study was privately funded and exempt from the federal requirements for that research."

That is how 22 reads now.

Bernie?

DR. LO: I would like to raise the question as to whether 22 should say in addition to this that they ought to publish with the study a sentence saying this was or was not conducted in compliance with federal requirements. I mean, right now for -- I mean, if it is federally funded, many journals that I publish in require you to have a sentence in your methods gets published. So I am just saying it is one thing that the journal editors have to know but shouldn't the readership that is reading the study also know and it seems to me that would be more of an incentive to researchers to comply with the regs even if they technically do not have to.

PROFESSOR CAPRON: I would be in favor of including that language in the commentary by way of example that many journals require that sentence that you described be present.

DR. LO: Should we also encourage journals that now do not do it --

PROFESSOR CAPRON: I think we should encourage it and say that is a good development. I am uncomfortable going beyond the notion of this research should not be

published to start telling -- as part of our recommendations as opposed to a comment on it, that journal editors should run their magazines in some particular way.

DR. LO: I am not saying they cannot publish it but there would have to be a sentence -- there would be a missing sentence that a savvy reader could look at and say, "Oh, Bernie is not complying with federal regs."

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Two points on this. First, by its language it applies to research other than research on human biological materials. This is now a general recommendation for all research of any type. I actually support that sentiment but I want to make sure that we all really do agree that we are going to use this report as a vehicle for a more generalized statement.

It actually could be the beginning of a pattern of putting that recommendation into every report and reiterating every time that no matter what the field of research that we think that the journal editor should help out in the unofficial extension of the common rule. And like I said, I am in support of that sentiment but I

do think we should know what we are doing.

The second is that in the latter half where it talks about in compliance with the substantive requirements of the federal policy, I find myself wishing for somewhat more precise language either to say that the research was conducted -- that the research was reviewed by an institutional review board.

In which case we can presume that they are applying all their usual standards to it. Or that we say that the research was conducted following independent review and provided for informed consent from subjects except where the research had minimal risk, which I think of as being the two real kinds of central substantive requirements, that is consent and independent review of the federal regs.

But as it is it seemed to me to be a little bit vague on what the journal editors need to determine was done in order to qualify for having met this recommendation's goals.

DR. SHAPIRO: Steve and then Larry?

MR. HOLTZMAN: I agree with the spirit of this but the devil is going to lie in the details. So if you

are doing work with unlinked samples you do not need an IRB review or with unidentified. You would not write in you had it IRB reviewed, yet you are in compliance with the substantive requirements.

PROFESSOR CAPRON: That is the reason for --

MR. HOLTZMAN: Yes. So I recognize that but we are trying to provide some guidance as to what the heck this means.

PROFESSOR CAPRON: Couldn't we turn to commentary at that point and explain what that mean that for research which, if federally funded, would be subject to IRB approval, the IRB approval process, that process would apply here for research that was exempted? Then it would be treated in the same fashion as if it were.

DR. SHAPIRO: Larry?

DR. MIIKE: Just on the suggestion that Bernie gave, I think it is more straightforward. Instead of adding that thing or putting it into a commentary -- instead of saying that journal editors should, et cetera, et cetera, just be straightforward about it and say that accepted and published articles should have an indication of whether it was done in compliance with the federal regs

and so on rather than go into this multiple step process because that is the result that you want to communicate out.

Because in order for the research to be published in a journal with or without that indication, they would have done what is in the current recommendation now.

DR. SHAPIRO: Bernie?

DR. LO: I want to suggest that Alex's comments actually be -- and Alta's be incorporated into the recommendation. So what I would like to see is a statement from the investigator that either the research was reviewed by IRB or was exempt under the federal common rule and also whether consent was obtained or whether there was an exemption for that under the federal guidelines. You know, it is two separate sentences but not to put it into the recommendation, which just gets too complicated.

DR. SHAPIRO: Okay. I heard something different in the beginning than at the end. I think substantive requirements is an understandable phrase actually. And if in the commentary the committee feels in

the commentary we ought to identify what this means just because of purposes of emphasis and reminding people what these substantive requirements are, that seems perfectly reasonable and that seems like a very good idea. But I would not like to build that into the recommendation. This is going to be a page long, this recommendation, by the time we get through if we are lucky.

And so that I think substantive requirements does work but I think we ought to have some commentary regarding just what this means along the lines, Alta, that you and others here have suggested.

On the other hand, to go to the first issue that was raised, that is whether we are asking journal editors not simply to inquire or require investigators to indicate but whether they must publish, in a footnote or any other way that they would work out, what the response to that is, is an issue which we have not resolved. That is Alex had one and you, Bernie, I think you had another.

I also am a little hesitant myself to give -- tell people how to run their journals and so on but this is an important issue so I could see the -- I certainly see the argument.

How do people feel about that issue? Not the way we write the recommendation but the equally substantive issue of whether we want to ask -- want to recommend that journal editors make a note of the response essentially? How do people feel? How many of you would -- along with Bernie, as I understood your notion -- like to require an indication in the journal itself? How many feel that way?

(A show of hands.)

PROFESSOR CHARO: I am sorry. I apologize. I was scribbling notes. How many feel what?

DR. SHAPIRO: Pay attention in class, Alta.

PROFESSOR CHARO: I am sorry.

DR. SHAPIRO: Pay attention. The question here is we are trying to see how the commission feels on whether we would recommend that journal editors not only require people submitting articles to indicate whether they follow these policies but have some way of indicating the response, namely whether these policies are followed or not where appropriate.

(A show of hands.)

DR. SHAPIRO: We have not got the language

here but I think the idea is --

PROFESSOR CHARO: I just raised my hand --

DR. SHAPIRO: Yes. You favor what?

PROFESSOR CHARO: That they should have --

DR. SHAPIRO: All those in favor of requiring -- making it a more stringent requirement here say yes or --

(A show of hands.)

DR. SHAPIRO: Okay. We will have to write something up on this. There is some disagreement on it but I think the overwhelming majority is here.

Kathi, do you want to write that, some proposed language there for that?

Okay. We now have a section and we only have a few minutes left this morning. Obviously we are going to have to come back to some issues and I want to turn to Jim before we wind up our discussion of this report because there are other issues. Most importantly, chapter 4, which we really have not had an opportunity to read carefully yet and some work continues to be done.

I want -- Jim had some things he would like to say along those lines. Let's just look at some of these

remaining recommendations to see what thoughts, if any, people might have on them if we can do so quickly.

Recommendation 23, which is on page 141, "The National Institutes of Health, professional societies, and health care organizations should continue and expand their efforts to train investigators..." et cetera, et cetera. You all know what that is. I will not bother reading it.

Any comments or questions or concerns?

Okay. Recommendation 24 is the recommendation of a type we have made before. I think it is important. "Compliance with the recommendations set forth in this report will require additional resources. All research sponsors (government, private sector enterprises and academic institutions) should work together to make these resources available."

All right. So there is no further comment on that.

Now we come to two recommendations where it might be difficult for us to have the kind of discussion we want in the time we have available. We will have to try to come back to that. In fact, I will not even attempt to deal with 25 and 26 right now. Hopefully, we

might be able to carve out some time late in the day, depending on our discussion, to come back to those. If not, we will have to find some other ways to focus. That is obviously a very important set of -- a very important set of issues.

But let me now -- I want to give a few minutes before our break to Jim to talk about chapter 4.

DR. CHILDRESS: We had planned, Eric and I and Kathi, to do a thorough revision of chapter 4. I failed to contribute my part. Eric did his part. I think not as much as he wanted to as well. I think that the chapter is still some distance from being where we want it to be and what I wanted to do is just throw out just a few things very quickly in the hope that even informally here and over the Belmont session and by e-mail then we, together, can begin to move the chapter a little farther along than it currently is.

And I think the big question I have for the chapter is whether we can actually get by with a conceptual framework that focuses only on, on interests, individual interest and group interest, or whether it is already going to basically keep us from getting out what

we need to get. And what some of the critics have noted, that this chapter might even set back the ethical discussion of protection of interests if we use that language of individuals and groups in this context.

One other preliminary point. I think that the language of specter (sic) that we have that we change that to philosophical because it already creates certain kinds of impressions in the public mind. I do not think it is a problem for us but it would create certain kinds of impressions.

But in terms of the approach itself, I think that folks know, we ended up only talking about harms and let's bring all other things like all the other wrongs that could be done to an individual would get subsumed under harms. So we have harms to dignity. It seems to me that is one thing we need to do. We need to sort out in this chapter the difference between harms and wrongs that could be committed.

Second, I think we -- if we are going to stick with the interest language that we are going to have to say something more about weights because here we are talking about balancing and yet we just throw in almost a

kind of laundry list of interest and really do not provide any kind of coherent approach, and some of the particular parts are very superficial.

There would be alternative ways to go about it. We could talk in terms of, for example, since this is an enterprise in trying to think about public policy, including professional practice in this area, talk about societal and professional values, principles, rules, et cetera, that set certain kinds of presumptions becasue it is not as though we just start fresh from interest. We do have rules pertaining to privacy and confidentiality that already presumably embody and express certain kinds of interest where we can talk about societal duties or individual rights.

I guess the big question is how we can make this chapter, and this really is a plea for input for Eric and me and Kathi as we work further on this, to improve the quality of ethical discourse in this chapter and -- this is important given the discussion we have just had -- to make sure that it will actually connect with and further contribute to the support for the recommendations that we have come up with. So, in effect, now it is

taking that chapter and thinking about it in and of itself but also in relation to the recommendations.

I do not know, Eric, whether that fits with your sorts of concerns, too.

DR. MESLIN: Absolutely.

DR. CHILDRESS: So if you could give us feedback here and at Belmont and by e-mail then we will try -- and I will try to be of more help to Eric than I have been to this point.

DR. SHAPIRO: Okay. This is in my view the biggest outstanding issue on this report and the most important one so I do really want to join with Jim in encouraging all of us to provide input and reflection on the issues he has raised or others that you might think are appropriate in dealing with those issues.

Do other people have page 71 missing? I have page 71 so I do not know what that means about everybody else. Okay. Okay.

We are going to take a break now. Let me apologize to Dr. Marshall. We are running about 15 minutes late. We will have to see what additional time we can carve out for this at the end of today but let's take

about a 15 minute break and try to reassemble at 10:30.

(Whereupon, a brief break was taken.)

DR. SHAPIRO: I would like to call this part of our meeting to order.

It is my pleasure to welcome to our meeting Patricia Marshall, who is associate professor of medicine and associate director of the Medical Humanities Program at Loyola University of Chicago and at the Scripps School of Medicine. It is a great pleasure to welcome Professor Marshall here. She is doing some work on NBAC's behalf, especially regarding informed consent in different cultural contexts, and I want all my colleagues on the commission to know how especially appreciative we are since I think Professor Marshall is here today directly from Lagos, which means -- so there is -- I do not know, a ten hour delay or a ten hour difference.

DR. MARSHALL: A million.

DR. SHAPIRO: A million. A million hours. So thank you very much for coming and we look forward to your comments.

DR. MARSHALL: Thank you. Where would be the best place for me --

DR. SHAPIRO: I think it is perhaps if you -- could you sit? Because using the mike really makes it a lot easier for everyone, if you do not mind. You could pick up these things and carry them if you like.

CONSULTANT REPORT

DR. MARSHALL: I think the first thing that I should say is -- and I am going to stand up for this. I think the first thing that I should say to everyone is --

THE REPORTER: If you want to stand you --

DR. MARSHALL: You know what? I will sit but it is just -- it is a greeting for hello to everyone and welcome to everyone, and I am very happy to be here. It means more than welcome. It means let's celebrate this beautiful day.

I did just arrive from Lagos, Nigeria, last night and, in fact, the time difference is not so great but I was up for approximately 48 hours. I thought that I was making sense last night. I left -- this morning I spoke with Alta. I thought I had slept well but not apparently.

DR. SHAPIRO: A replay of the conversation indicated otherwise, right?

DR. MARSHALL: Exactly. So I apologize in advance if my words spill over each other as I give my report.

This morning in my brief presentation I want to do two things. First, I want to review the primary goals of my consultation for you and, second, I thought that it would be interesting to share some of the data that I have just collected in Nigeria.

The primary goal of my consultation is to review the cultural relevance of informed consent in the context of U.S. funded international research and I have three specific aims.

The first aim is to do a fairly systematic review of the nature of personhood, definitions of personhood, from both a philosophical and a cultural perspective. I believe that all of you were given a copy of a draft outline of my final report and you can see some of the issues that I will be addressing.

If you look on page 2 you can see some of the issues that I will be addressing and the background of my report, including the problem of cultural versus ethical relativism. I want to look specifically at factors

related to informed consent in a cross-cultural context.

I -- and here I will be addressing especially the location of decisional capacity for consent, the impact of language differences, including the use of interpreters. I also want to look at socioeconomic influences on the informed consent process in cross cultural research and, in addition, political and economic issues and the implications of these for the ethical review process and the application of consent.

Finally, in this background section, I want to take a close look at the relevance of different types of research methods for the consent process and ethical issues that come up in international settings. It does not make a difference, for example, if you are using quantitative methods or qualitative methods where it might be more difficult to get consent.

What happens when you are collecting -- when you are involved in a clinical study, for example, and you are collecting specimens from individuals?

So that will form the background of my report and I would appreciate any feedback that any of you might have if there are issues that you would like to see me

pursue that I have not included, any topics that you think that I may have missed. What you have here is basically an outline of what I intend to do and what I have been working on.

The second aim of my consultation for you is to report the findings of in-depth interviews that I have started to conduct with U.S. researchers who are involved in studies in international settings. And in my interviews with these individuals I am particularly interested in the challenges that they have faced in the process of -- in the ethical review process for protocols. What happens in that process when they are working with Washington, when they are working with the ethical boards in other countries and so on? And then, also, I am talking with these individuals about again the application of informed consent.

My final aim, the final aim of my consultation, is to conduct a case study on the implementation of a set of related studies that are being conducted in Eastern Nigeria. These studies are looking at the genetic and epidemiological determinants of hypertension, type 2 diabetes, and breast cancer.

This case study has two goals really. One is to work with Dr. Jeremy Sugarman, who I believe was at your last meeting. As you know, Dr. Sugarman is involved in -- his consultation on this initiative involves looking at ethical review processes in a number of different countries and the data -- some of the data that I am collecting in Nigeria will be used for -- to inform his consultation on general issues. So he will have nine country sites instead of eight.

But then what you will be getting from me in my report is a more specific and in-depth look at what happens in a particular context with particular studies. In this case, a developing country, one in which many people live in abject poverty. I believe the average income is $200 a year. Does anyone know by any chance? In some cases I am sure that it is less than that.

Nigeria is a little bit more stable right now than it was several years ago but I can tell you -- I have mentioned to a few people here -- when I went from Ibada, an urban center, back to Lagos to go to the airport I was escorted by two Nigeria policemen with submachine guns. So I was driving in a small van back to the airport under

escort. It is very problematic to be on the roads at night. There are many bandits along the roads. There is a lot of corruption. People are -- basically people are poor so they want your money, not necessarily your life. So it is an unusual setting in which to be conducting these studies on the genetic and epidemiological determinants of a set of diseases.

One of the reasons why I was -- why I took advantage of this opportunity to work on this set of studies is because it gave me an opportunity to look at a range of illnesses based on their severity and also based on the treatments that are available for them.

For example, hypertension is something that people live with every day. It is very much a chronic disease. It is not nearly as life threatening as something like breast cancer, which has a symbolic load that is much more powerful. And just as in any setting in the world, these two different diseases, breast cancer and hypertension, various -- different resources are available to treat them and people have different kinds of access to those resources. So it was a beautiful opportunity, I think, for me to do this -- to focus on this situation.

And I have to tell you I am having so much fun with it even though it was -- being in Nigeria was pretty intense. You can imagine.

DR. SHAPIRO: We will not charge you for that?

DR. MARSHALL: What?

DR. SHAPIRO: We will not charge you for all that fun you are having.

DR. MARSHALL: Oh, we all work too hard. It better be fun, part of it.

I think what I would like to do right now is just move directly into some of the data that I brought back with me from Nigeria because it will really give you a sense, well, I think of two things. First of all, it will give you an idea of the kind of work that I do as an anthropologist. The importance that I place on letting people speak for themselves, the importance I give to trying as much as possible to get information verbatim.

So my -- the excerpts of these transcripts will give you a sense of how I do my work and also I have just pulled out some data that relates to issues that will definitely be of interest to you. Things like, for example, community consent and how that process works in a

situation where you have got to interface with tribal chiefs and local villages.

Does everyone have a copy of my notes? I did this last night when I came in. I knew this morning I would be too tired probably to do it correctly. But you can see -- and usually when I take notes -- on my diskette I have -- each line is numbered so that I can refer to it easily in my analysis. But when I gave the people here my diskette to print the format came out differently so I apologize for that. It is a little easier to refer to the transcripts when you have numbers along the side but in any case I think that this data will be fun for us to work with.

In Nigeria, let me tell you very briefly, I was able to speak with actually more than 25 individuals but I had formal or informal discussions related to the specific issues that I am concerned with, with 25 people, both individually and also in group settings.

In my transcripts, if you look right at the brief introduction you can see I have said that excerpts -- these are from interviews with researchers, individuals who actually have obtained informed consent, and

participants. I was very grateful to have the opportunity to speak with three participants in these studies.

Usually I use a tape recorder but because of the sensitivity of the topic, ethical issues in research, I did not bring my tape recorder with me but I used my field style of taking notes. I have a shorthand way of documenting. I am pretty good at this so you can -- if it is in quotes, that means it is a verbatim statement. If it is in parenthesis, that means that it is paraphrase.

Let's go then to the first description here. I was in three centers -- at three sites in Nigeria, Lagos, another urban center Ibadan, which is about an hour-and-a-half, two hours away from Lagos, and then a small rural village called Igbora. These are -- I was with primarily Yoruba people. There are three main tribal peoples in Nigeria, the Ibo, the Hausa and the Yoruba. I believe there are more than 250 languages in Nigeria, distinct dialects, so you can see that language is a definite -- represents a definite challenge to the process of implementing informed consent and you will see some of that in these particular transcripts.

Okay. April 9th. My birthday. I turned 47

in Nigeria. That was interesting.

You know what just occurred to me, also I actually left in the University of Lagos Teaching Hospital. Does that represent a problem in terms of confidentiality if this is a public record? I did not think about that, Eric.

DR. MESLIN: It is too late now.

DR. MARSHALL: It is too late. All of you -- all of you here will respect the confidentiality of the location I am sure, right. Let me see your faces here.

This is not -- this first part is not an interview. It is an observation of a team meeting. It is part of an annual site visit and the U.S. representative, his initials are R.T., he was working with the research team on issues of recruitment, recruiting the control sample, and also issues of informed consent. I included this segment because it shows you some of the unusual circumstances that you might confront.

For example, if you go down to R.T. in the larger phrase there, the question here had to do with what happens if you go to someone who has more than one wife, and this is, in part, a genetic study and so, of course,

they are looking at family lineages or, you know, family trees in relation to the expressions of disease.

So you go to a family and -- R.T. says, "You go to a family and a man has three wives and you go to the youngest. She does not have kids yet so theoretically she is not genetically related." So according to our requirements it is really not necessary to recruit her. But you create a social problem because you see she would be left out and there might be some jealousies or some misunderstandings about why you would exclude the youngest wife but include the older wives.

So we do it.

R.T. says, "We do it as a service. We test her for diabetes." So he says to the team, "If there is a perception that it will be a problem for the family if the youngest one is left out then just go ahead and include her." And one of the -- one of the team members, Nigerian team members says, "Okay, but what about the issue of the senior wife?" "The senior wife," he says, "may refuse because of her age or her husband may not allow her to participate because of a concern about her health, her age and so on." And R.T. says, "Well, try to explain why she

is a better control than the younger wife. She may understand why it is better to have a 60-year old rather than the younger wife." But R.T. says, "No arm twisting." And he said this in a very -- made a very strong statement.

I wanted to call attention to that becasue of the issue of implicit and explicit coercion, especially as it relates to this context. So here you can see the U.S. researcher is trying to give a very strong message about, "Look, this is what we want. This is the type of person we want to recruit to the study but, you know, no arm twisting."

Let's go to the next interview. I am trying to keep this -- I am going to go through this fairly quickly because I think that some of you may have questions and we can have a discussion and then you can take a look at the notes more carefully on your own.

Okay. This is an interview with a researcher and with a patient participant. I -- these really are my notes. These are raw, unedited field notes that you are seeing here. So it is lunch time and everyone goes out for lunch but at that moment the patient shows up so I

stayed and talked with him and the researcher did not eat lunch that day.

Now here I am asking about key dimensions of informed consent and the researcher is speaking about this and he says, "Confidentiality is very important." But he says, "First, the most important thing is patient care."

I think this is important because what he is -- you know, we think about informed -- we have this template in our minds in relation to informed consent. I mean, all of us here can say, you know, what is important. Confidentiality, voluntary participation, comprehension and, at least in my mind, those are foundational. But this Nigerian researcher says, "No, the first thing is that you must care about your patient," and I think it speaks to the concerns that this physician has about protecting individuals who are involved in his research.

Let's see. If you go to page 2 -- hold on a second. I am going to get some water.

Go to the first PT. "P" stands for patient by the way. When you see "PM" I am always PM for Patricia Marshall. In this case PT is patient. I was asking about the patient, what was the purpose of this study and the

patient was able to give me, I thought, a pretty clear rendition of the nature of the study. He says, "Some people in America are suffering from diabetes, too, and they, the researchers, are trying to understand how it works in families."

You see now, I mean, that is a -- conceptually that is important because it is not just that they are looking at diabetes but he understands that they are interested in the expression of diabetes within families and he says, "I would go to great lengths to be a participant in this study to help my fellow Nigerians and beyond so that the doctors understand more about what is happening here."

And then you can see I said, "Well, what else did Dr. J.N. do," and the patient described to me the types of studies that would be done on him and the types of procedures that would be performed on him. And then the physician says, "Well, you know, the consent form has all of this information and I go through it."

This consent form, by the way -- in the U.S. the consent forms are approximately five pages long but they have all been modified in Yoruba, necessarily so, for

a number of different reasons as we will see later.

Let's see. If you go down a little further you can see that it -- I asked about how long it takes to get consent and the physician says, "Well, it really depends on who I am talking with and their ability to understand."

I am asking the patient now about the risks that he might have if he participates and you can see the patient says, "Nothing will happen to me." He says, "I have nothing to fear in this study."

I asked about how they explain genotyping. When I asked the patient directly about the genetic information he looked at me with a blank expression on his face and the physician researcher says, "It was explained but he just blocked it out," he said, "Because it is not meaningful to him." And I say, "How do you explain it?" And he says, "I say genes are what you inherit from your mother and father and they understand that genes are what you get from your mother and father to make who you are." And he says to me, "If you ask him that way then he will know what you are talking about."

And I asked then, "Well, does anybody ever ask

what a gene is?" And he says, "Yes." The physician says, "Yes." And I say -- well, he said, "It is -- I tell them that is what happens. It comes from the parents when you are born." I asked the researcher, "What do you say if a patient asks if this information will help them?" And the researcher says -- I am at the top of page 3 now. The researcher says, "I say I do not know."

And, again, I think that this is significant here because instead of trying to run through a list of benefits that the patient might get, you know, if you say how is this information going to help you, this physician tells his patients, "Well, I do not know." But this physician also -- look at what he says. "Look," he says to me, "I am in a commanding position here because I am their doctor." And so many of the researchers called attention to the power that they have because they are in that unique relationship with these patients who are also participants in their study. They absolutely understand the nature of that power relationship and the implications for the vulnerability of patients.

DR. SHAPIRO: Ms. Marshall, could I just make a suggestion because we have a particular problem. I

should have told you about it before. We had scheduled our public comment session at quarter to 11:00 and I do not want to keep them waiting too long. So perhaps we could deal with your presentation in two components. If you could take another five minutes now and then we will go to public comments and then we will come back.

DR. MARSHALL: That sounds great.

DR. SHAPIRO: Is that all right because I just do not want to keep people who signed up waiting.

DR. MARSHALL: That sounds fine to me.

DR. SHAPIRO: Thank you.

DR. MARSHALL: You know what I would like to do then just for the sake of -- just because it is interesting. If you -- I want to share with you some of the data on community consent. What they have to do is get -- when they are working in rural villages -- is get consent from the local chiefs and I was very interested in how this process actually works.

If you go to page -- let's see -- okay. -- 6. Thank you. 6. And then again there is some other data later. Go to the -- kind of the middle of page 6. This physician says, "To enter a community you need to carry

that community along with you. There are imperatives. You must communicate with the chief and his council and some others from the community like community leaders. The individualism that exists in the West does not exist here. I cannot go to a village and start doing something. I need to go to the local leader and give them what they need. Gifts." Usually the gifts that are given to the chiefs are kola nuts or whiskey. So he makes this analogy to going on a date. You know, if you go to a date in the United States you bring a woman flowers and so if you go to a chief in a place like Igbora or Igdire then you go with kola nuts or whiskey.

Go to page 8. This is a part of an interview that was done in Igbora and here there is a description of how the -- I asked how the chief gets the information out to the community itself and this excerpt deals directly with that. The chief goes to the subchiefs. They go to the local household heads who then communicate the information to the individual families.

I said, "Is there any other way?" And I was told, "Yes. There is a town crier who might be involved." A town crier goes to as many as 20 to 30 places in the

neighborhood and the town crier is given an instruction from the chief on what to say and the town crier will carry a bell. It is a gong. He bangs the gong and people come out of their houses and he makes this announcement and then relies on those individuals who have heard that information to spread the news around and then he will go to another site in the village.

How is that?

DR. SHAPIRO: That is fine. I appreciate it and I want to apologize again --

DR. MARSHALL: That is okay.

DR. SHAPIRO: -- for interrupting you, especially given your great efforts to be here, but we will return. I do not know what your own schedule is but if you allow us, we would like to return so we can have questions and so forth.

DR. MARSHALL: Oh, that is fine. I am fine.

DR. SHAPIRO: Okay. Thank you very much and you are certainly welcome to remain with us.

DR. MARSHALL: Thank you.

DR. SHAPIRO: I do now want to go to the public comment session. Let me just remind everyone who

will be participating in the public comment session the rule of the commission is to try to ask everyone to restrict their remarks to five minutes or less, especially today since we seem to have quite a few people and we want to give everyone who wishes to speak to be able to speak before us. So I really would very much appreciate everyone trying to stick to that time interval. When five minutes is past I will have the impertinence to interrupt and let you know that five minutes has past and hope you will then draw your comments to a close.

PROFESSOR CHARO: Harold?

DR. SHAPIRO: Yes.

PROFESSOR CHARO: If I may, because I have been asked to recuse myself from the stem cell discussions due to my Wisconsin connection, I am going to also recuse myself from this portion of the public testimony since it is entirely about that topic but I did not want people to feel insulted if I just walked away from the table.

DR. SHAPIRO: Thank you very much. I appreciate that.

We have a list here. I hope it is in the appropriate order. The first person to speak to us -- to

address us today is Richard Doerflinger, the National Conference of Catholic Bishops in Washington, D.C., on embryonic stem cell.

Welcome. It is very nice to have you here today.

PUBLIC COMMENT

RICHARD DOERFLINGER

MR. DOERFLINGER: Thank you very much.

The Catholic Bishops of the United States welcome the prospect of obtaining ethical review of recent proposals for embryonic stem cell research. We think that is both a timely and important task.

Last week, of course, a working group at the National Institutes of Health discussed draft guidelines for research into what the working group called pluripotent human stem cells. Tragically the administration has narrowed this discussion to explore only research on stem cells obtained by destroying live human embryos or by harvesting tissue from abortion victims even though, as expressed by Dr. Michael West at your own November meeting, the words "pluripotent stem cells" have a much broader range and include many adult

stem cells.

The NIH has narrowed its discussion to avoid what we believe is a very morally significant topic, that of the less controversial alternatives to this research.

We urge this commission to have a more expansion vision and to explore the serious moral problems in these proposals, as well as the alternatives that can advance medical progress without demeaning human life and dignity.

I have a longer witness statement. I would just like to summarize three points from that for you.

First is the significance of morally acceptable alternatives. When the commission issued its report on cloning human beings in 1997 I thought it made a significant contribution by placing somewhat exaggerated claims of embryo researchers in a broader perspective. The commission said, "Because of ethical and moral concerns raised by the use of embryos for research purposes it would be far more desirable to explore the direct use of human cells of adult origin to produce specialized cells or tissues for transplantation into patients." The commission even mentioned the prospect of

identifying methods by which somatic cells could be dedifferentiated and then redifferentiated along a particular path without creating a human embryo.

The commission's observations two years ago were prophetic. The last two years have seen startling advances in isolating and culturing adult stem cells and even in the possibilities for dedifferentiating and redifferentiating them to produce a broader array of cells and tissues. Advances in the use of growth factors to grow new blood vessels and nerve tissue, the use of enzymes such as telomerase to immortalize useful cell cultures, and other advances also offer enormous promise.

In our view the moral problem of encouraging the destruction of human embryos for their stem cells is independent of claims about their possible expected benefit. We believe that ethical norms on human experimentation, which forbid inflicting death or disabling injury on any unconsenting individual of the human species simply for the sake of benefit to others applies to the human embryo and fetus.

Even if the commission were not to hold that view, it would be of enormous moral significance that the

same goals may be reachable without transgressing this moral and legal line, relying on the destruction of a developing human life to advance medical goals.

Point number two, the proposal that the commission make a morally substantial distinction between spare and research embryos. We believe that distinction cannot bear the moral significance that some have imported to it. In fact, if it is wrong to create a human embryo for the purpose of destructive research, that is largely because destroying embryos from whatever source for research purposes is itself wrong on the same grounds.

In short, the decision to treat a developing human life as a mere object of experimental manipulation is wrong. It is wrong whether planned in advance or decided on later in the process.

As a practical matter, fertility experts have testified that the distinction will be largely meaningless in practice because researchers can always make more embryos at the beginning of some couple's fertility work ups to ensure a sufficient supply of so-called spares for destructive research down the road. The NIH's efforts to make that distinction in practice will likely only succeed

in entangling the federal government further in discussions about creating and destroying human embryos. Decisions in which this administration claims to want no involvement.

The third and last point is what we believe is HHS's untenable interpretation of the current statutory embryo research ban which allows for the funding of research that depends upon and, in fact, commissions the destruction of embryos for their stem cells as long as the federal funds are not used for the particular act of destroying the embryo. We believe that ignores the will of congress. 75 supporters and sponsors of the statutory ban have already protested this misinterpretation. In fact, I know of no supporter of the current law who has welcomed the HHS's interpretation. Only the opponents of the ban have welcomed this interpretation of the ban.

It violates well established principles of statutory construction because the congress clearly intended to ban the use of funds to create human embryos but took great pains to separately ban funding of any research in which human embryos are destroyed. Clearly excluding any possibility that the congress intended only

to ban funding of a particular act of destroying an embryo.

Even the NIH draft guidelines show in a very dramatic fashion that once you begin to fund research that is so-called downstream from the destruction of these embryos, you end up in federal monitoring of the entire process of donating and destroying the embryos. That donation and destruction is an integral part of any research protocol that the NIH would be funding.

This interpretation, also, reverses NIH's own earlier practice of enforcing the embryo research ban, which it has earlier enforced, to the chagrin of at least one researcher by the name of Mark Hughes, to ban the use of NIH funded equipment even for the analysis of genetic material after a cell has been taken from an embryo.

And this policy also ignores the precedence of earlier congressional policy on the use of fetal embryonic tissue from abortions, which despite the inadequacies in our view in the current law in fetal tissue, does ban any influencing of an abortion decision or the timing or method of an abortion to obtain tissue and certainly would forbid the harvesting of tissue or the use of tissue after

harvesting when the harvesting is itself what destroyed the embryo or fetus.

And finally the HHS interpretation contains a new and arbitrary definition of the word "embryo," which is not found in the statute and, in fact, would allow researchers to engineer lethal defects in advance into embryos or to use only those which are already diseased or damage on the claim that this would not be embryo research because those embryos could not have survived to live birth. We believe that is inconsistent with what congress intended and is really an effort to evade the law.

In short, we believe the proposed HHS policy is seriously flawed on legal and scientific, as well as moral grounds. To build a research policy on this foundation risks discrediting NIH's legitimate research goals by forging a bond between pursuit of those goals and the deliberate destruction of human life. A bond which we believe is entirely unnecessary. We believe this commission should urge the NIH to divert its funds to stem cell techniques and other promising avenues of research that in no way depend upon such destruction.

I also have a rather substantial compendium of

literature on what I am describing as the promising alternatives, which I would be glad to provide copies of to the commission.

DR. SHAPIRO: Thank you. We would very much appreciate copies and we already appreciate the copy of your remarks that you have provided us and we will provide to all the commission members.

I would say for anyone else in public comments today, if they have any written materials today or would like to supply some subsequent to today's meeting, we would be very glad to distribute it to all members of the commission.

Thank you very much for your remarks. We appreciate you being here.

PROFESSOR CAPRON: Are you accepting any questions?

DR. SHAPIRO: Yes. I think --

PROFESSOR CAPRON: One question.

DR. SHAPIRO: If the question and answer are brief.

PROFESSOR CAPRON: Yes. Very brief.

You say at the bottom of page 3 and the top of

page 4 -- you make an empirical statement, Richard, that fertility experts have announced that they or their colleagues in the industry will easily evade. Is this something which is documented?

MR. DOERFLINGER: There should be a three page facts sheet attached to the written statement which has quotes and citations from some of those.

PROFESSOR CAPRON: Thank you.

MR. DOERFLINGER: Some from the United States and some from Australia.

To give just one example, Dr. Jonathan VonBlerkon (?), who was actually commissioned to testify on the scientific state of human embryology to the Human Embryo Research Panel back in 1994, was asked once at a public forum in which he and I were debating, "How many spare embryos are there right now in the United States," and he said he was not quite sure what the number was now but he was confident that whenever research was approved, when funding was approved for research requiring only spare embryos, he was sure that suddenly sufficient numbers would appear.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I would like to ask an additional question. Thank you for coming and providing us with this material.

I take it you are arguing that there are other alternatives to pursue the goals of research that do not involve such, in your view, morally objectionable procedures.

MR. DOERFLINGER: Yes.

DR. LO: Can I ask you -- can I infer that you believe the techniques to reprogram adult cells to a pluripotent state would be an acceptable way to pursue the sorts of therapeutic goals that people are talking about. What I would like to do is ask you -- there have been concerns raised that a cell that is dedifferentiated may, in fact, not just be pluripotent but may be totipotent and that, therefore, perhaps those cells should be considered in the same way we consider embryos as having the potential to develop in utero to a fetus that can be delivered as a child.

I was -- I would be interested in your views on this question of whether you can tell a

dedifferentiated cell is only pluripotent and not totipotent because some of the ways we are trying to find out would -- may, itself, violate the respect that might be due those cells.

MR. DOERFLINGER: It is, as you know, a very complicated question because I found a number of different definitions even of the words "totipotent and pluripotent." My understanding is that currently some congressman have expressed a concern that some of this research when the stem cells are cultured may lead to the stem cells reaggregating and forming embryonate bodies which may or may not have any sufficient characteristics to actually undergo some early embryonic development. In which case the culturing of the cells may run afoul of federal law in some way.

My understanding is that when the experiments have been done, for example, to allow stem cells in the adult mouse to reprogram, and they have succeeded perhaps in having a neural stem cell be able to produce blood cells, this is a reprogramming that happens still within the range of pluripotency. Nobody is talking about these being put into oocytes, for example, which I think would

be a very significant change and that this is all along the spectrum still of somatic cells even though there is dedifferentiation back to the kind of pluripotency that might have been obtained at the blastocyst stage or a little later but that this does not involve creating a new organism that would be capable of developing as an embryo.

Certainly the -- we do not have the objections to that kind of work that we do have to the somatic cell nuclear transfer work of Dr. West, which to our -- in our interpretation does require first creating an embryo growing into the blastocyst stage and then harvesting out the stem cells.

DR. SHAPIRO: Dr. Cassell?

DR. CASSELL: Are there any moral differences between embryos at all and whatever age, excess, aborted? Are they all morally the same? Does anything affect their moral status?

MR. DOERFLINGER: I think in terms of fundamental dignity and rights simple membership in the human species, as an organism in the human species, is the only principle that is really convincing to us. There are differences in the moral status of different actions one

might take with regard to human embryos or to humans after birth. We are particularly convinced that the effort of the Human Embryo Research Panel back in 1994 to try to tease out that question was a failure.

The commission -- the panel ended up deciding on a pluralistic approach in accordance with which basically the question of human dignity and the question of personhood was put into a circular argument. In effect, certain embryos are potentially -- other people after birth as well could be denied the same moral status as other human beings based on whether destructive research on them would have yielded medical benefits.

So we would make a conscious decision to grant or deny the status of personhood to members of the human species based on how useful it would be to be able to deny that status. That seemed to us just completely circular. If there is a difference between these different classes of human beings, it has to be determined on objective grounds and not because we really want a particular answer.

We would say no. There is no fundamental difference. There is a difference in capacity and

abilities. We do not believe those differences and abilities and stage of development make a difference in terms of the fundamental character of the right to life.

DR. SHAPIRO: Thank you.

Eric, anything else?

All right. Thank you very much. Once again we appreciate your presence here today.

The next person to appear before us is Dr. Edward Furton, an ethicist for the National Catholic Bioethics Center in Boston, Massachusetts.

Dr. Furton, welcome.

EDWARD J. FURTON, Ph.D.

DR. FURTON: Thank you.

Our center has been in existence for over 25 years. We offer moral analysis on issues in medicine and the progress of the life sciences to interested catholics and noncatholics. My testimony here today reflects the considered judgment of our staff of five ethicists at the center.

In keeping with our intellectual tradition, our center is dedicated to the unity of faith and reason, to the compatibility of science and religion. Our's is a

tradition that supports the progress of science. Catholics have contributed major scientific thinkers to Western science, including Gregor Mendel, a monk and the father of genetics. We are comfortable with the modern evolutionary theory.

We do not believe that there should ever be conflict between science and religion so long as they are in the service of the human being.

Our center, also, holds that morality is objective, that the good exists in nature, and that reason has the task of seeking the good through reflection on nature. This view is widely held. We emphatically reject any claim that we bring to the public discussion the specifically religious teachings of our faith. We hold morality to be evident to reason.

We recognize that embryonic stem cells have great potential for the cure of seriously debilitating human diseases. We do not agree, however, that retrieving these cells through the destruction of human embryos can be justified on the grounds that the resulting research will provide many medical and scientific benefits.

We do not believe that one life can be

expended to benefit another.

In the view of the National Catholic Bioethics Center an individual human life comes into existence immediately at fertilization. It is surely human although not fully developed. From a strictly scientific standpoint there would be appear to be no reason to think otherwise.

The zygote functions as a unified organism and the genetic code of the zygote possesses all that is necessary for complete human development. If allowed to develop the human embryo can and will become an adult human being.

This is the basis of our opposition to the destruction of human embryos for the sake of obtaining pluripotent stem cells. To dissect a living human embryo in order to obtain cells for experimental research conjures up images of some of the worst abuses of human rights within recent history.

We understand that not all scientists share our point of view. Some hold that personal human life comes into existence at a later point in the developmental process though they often cannot say clearly when that is.

You may or may not share our outlook. You may have no particular view on when human life begins. But whatever your views as members of this commission and whatever the views of HHS and the present administration, please remember in your deliberations that millions of your federal citizens hold that a human embryo is a human life worthy of the protection of law. This is certainly a reasonable point of view.

As a nation of many and diverse viewpoints, the view that life begins at conception deserves the same respect accorded to any other reasoned physician on this very important topic.

The research that HHS has chosen to permit with federal funding will allow the establishment of permanent stem cell lines from which all future research and new therapies will derive. Unlike other cell lines, embryonic stem cells show the capacity for immortality. If permanent stem cell lines are established that derive from the destruction of human embryos, in our view all future research and all derived therapies will be similarly tainted. As a result of this tainted origin, many Americans who have deeply held moral objections to

embryo destruction may choose not to receive any benefits from the new research.

Consider what HHS is presenting to those who oppose the extracting of cells from human embryos. As the promising new therapies become available, these people will be forced to make a choice. Either live in accord with the conviction that life begins at conception or alleviate the suffering of loved ones. This is a tragic choice that should not be forced upon any citizen.

We all agree on the need to fashion the best public policy for medicine and scientific research. From our point of view, however, we wonder why the federal government does not try to foster the kind of research that is morally acceptable to all of its citizens.

Science is the universal instrument of reason. The benefits of scientific research ought to accrue to all people. Short of this possibility, however, we would at least hope that the government would not support research guaranteed to cause moral division among the people. Nor does the rush to take stem cells from destroyed human embryos seem a necessity for scientific progress. There are many promising alternatives to the use of embryonic

stem cells regularly cited in the literature. Recent research suggests that differentiated precursor stem cells from a patient's own body may be more useful than embryonic stem cells.

I understand the Journal of Science is reporting that Cyrus Therapeutics of Baltimore, Maryland, has isolated the mesenchymal stem cell. So new things are happening every week in this area.

From a medical point of view, therapies derived from cells such as these would not suffer the disadvantage of possible immune rejection. From a moral point of view they do not suffer the disadvantage of coming from destroyed human embryos.

Thank you.

DR. SHAPIRO: Thank you very much. I very much appreciate your comments.

Any questions from members of the commission?

Thank you for the material which you distributed, also.

Eric?

DR. CASSELL: I would ask you essentially the same question I asked before. Does the spare embryo that

is going to be thrown away have the same status as the implanted embryo of the same age?

DR. FURTON: Yes.

DR. CASSELL: It does. So that there is no moral difference between that and an implanted embryo?

DR. FURTON: No. There is no moral difference.

DR. CASSELL: There is no moral difference between the aborted embryo and the implanted embryo?

DR. FURTON: The aborted embryo is dead as a human being. That does give it a different standing from that respect.

DR. CASSELL: And is that relevant to this issue?

DR. FURTON: I would say that retrieving materials from a dead human being does not have the same moral standing as retrieving human beings through the dissection of a living human being.

DR. CASSELL: Okay.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Could I follow up on that? That suggests to me that you might be willing to draw a

distinction, moral assessment, of a policy that allowed the use of cadaveric fetal tissue to develop these stem cells as differentiated from a policy that allowed the destruction of spare embryos as a part of the process of obtaining the stem cells. Is that correct?

DR. FURTON: We would be very concerned that any pressure be put upon those who provide abortions or in any way -- we would be opposed to any policy that would promote abortion in any way. So there is a moral distinction between those two. I think practically speaking from our perspective. I am not sure how much difference it makes.

DR. CHILDRESS: Thank you.

DR. SHAPIRO: Thank you very much. Any other questions?

PROFESSOR CAPRON: A question.

DR. SHAPIRO: Question.

How many of you need copies of this material? Okay. We will make sure we get you some. I apologize.

Alex, you have a question.

PROFESSOR CAPRON: Well, I guess, the follow-up is if there were the same sorts of protections in terms

of no financial inducement or no moral inducement for that matter to the couples deciding that their own reproductive wishes had been fulfilled and having been given the option of donating the embryos for implantation with another couple seeking reproductive, and having rejected that as an alternative, and then being given the alternative that remains is to destroy the embryos, granted that you would not want them to do that, you recognize the moral diversity that some people choose to dispose of spare embryos.

If at that point the researchers could only obtain an embryo which had through a process by the clinic, the fertility clinic, been destroyed, that is to say rendered into the same state of death as to its own ability to live further as an aborted fetus, if that material was still usable for research purposes and the donation decision was made then again with protection against any inducement to the fertility center, any payment to the fertility center to enter into that process, wouldn't that now dead IVF embryo be in the same status as the aborted fetus as a source of transplant or research material?

DR. FURTON: Professor Capron, your question is very difficult for me to answer kind of on the fly here. There are many factors involved in it.

I would say that the principles -- these are longstanding principles that Catholics have had in place for centuries. Formal and material cooperation with wrong doing would come into play and I would want to sit down with my colleagues, as we do all of our work together in a consensus format, and consider that.

We would be happy to give you our opinion of any model or ideas that you have along these lines. I think there is a distinction between a living human being and a dead human being but I think that is all I could reasonably say at present on that issue.

PROFESSOR CAPRON: Well, if you would like to follow up, I am sure we would be happy to receive an addendum to your statement. The point being as I now understand it, the IVF embryos are still intact at the point that the researchers begin their work on them in terms of extracting the cells that would become the cell lines. I am just asking if it turned out that were technically possible for the IVF clinic as part of its

process of discarding spare embryos to put them into a condition where they were not viable and could not be implanted and so forth, would you then consider -- and will you give us your opinion then -- with your colleagues on whether that would render them in the same status as an aborted fetus?

With the clear understanding in all of this that you remain skeptical about whether there can be adequate protections to keep inducements over reaching from existing. But it is the comparability of the status of the two, not your agreement that the procedures are adequate that I am interested in.

DR. FURTON: Though I am very skeptical about the approach you are suggesting, I will try to speak with you privately and get your question exactly and bring it to our group.

PROFESSOR CAPRON: Okay.

DR. SHAPIRO: Thank you. I very much appreciate your willingness to be responsive in that respect and pass it on to your colleagues as well.

Larry, you have a question? Any other questions? Okay.

Well, again, thank you very much and thank you for coming down here to Charlottesville.

The next person who will speak to us is Dr. -- you will have to excuse -- I am going to mistake the pronunciation -- Karen Poehailos. Is that correct?

DR. POEHAILOS: Poehailos.

DR. SHAPIRO: Poehailos. Thank you very much. I really apologize for not being able to --

DR. POEHAILOS: That is okay. It is frequent.

DR. SHAPIRO: Thank you very much and welcome.

KAREN D. POEHAILOS, M.D.

DR. POEHAILOS: Thank you.

Good morning. I hold a doctor of science degree from the University of Virginia and completed my family medicine residency at the UVA health sciences center here in Charlottesville. I am currently certified by the American Board of Family Practice.

I would like to welcome the NBAC members to Charlottesville and as a graduate of Mr. Jefferson's university feel compelled to open with a quote from him.

"The care of human life and happiness and not their destruction is the first and only legitimate object

of good government."

I appreciate this time to share my concerns regarding embryonic stem cell research. In this instance we are truly discussing the destruction of human life as an object of government, as evidenced by support for this with federal funding.

Clearly I am not a researcher in this area. However, the basic principles of human development called into question here are easily understood by any student in the biomedical sciences, as well as by any high school biology student. From the moment of fertilization a zygote has all the genetic material to identify it as a unique human being and is defined as such by prominent human embryologists in their textbooks.

The progression through the stages of embryo and fetus to live born infant is a continuum, though, lawmakers and some ethicists seem determined to create a step-like progression in order to make arbitrary distinctions on the rights to constitutional protections.

Federal laws, which regulate the use of research of fetal tissue and the use of live fetuses in research, if applied to preimplantation embryos, which are

simply earlier on the continuum, are flagrantly violated by research that is proposed.

The federal tissue research laws permits only the use of cells obtained from a dead embryo or fetus. These may be used for therapeutic purposes only as safeguards ensure that the researcher avoids participating in abortion and that the researcher has no effect on timing, method or procedures used to terminate the pregnancy.

How can intentionally removing the inner cell mass of embryos to cause their death be consistent with this? The embryo is not dead until the tissue was removed via a procedure that is a direct result of the researcher's needs.

Live fetal research laws treat the preborn human as worthy of protection from the time of implantation onward to the time of viability at delivery. Since the unborn child is incapable of giving informed consent, federally funded research involving this child is permissible if it is potentially therapeutic for this child or if it would not subject the child to significant risk or harm.

Surely nobody would propose that destroying an embryo by removing its inner cell mass is either benefitting the embryo or that this action carries no risk of harm.

Under these laws unborn children planned for abortion are afforded the same protection as those intended to be carried to term. This would predicate against the use of so-called spare embryos from in vitro procedures.

Congress addressed this lack of protection for preimplantation embryos in its HHS appropriations riders, most recently section 511(a). This bans the use of federal funds for creating of a human embryo for research purposes and bans the use of funds for research in which, I emphasize, a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death.

My interpretation of this, shared by members of the House of Representatives in their February letter to HHS Secretary Shalala, is that what is banned is the funding of the research which uses them. This contrasts with the HHS general counsel's interpretation, which is

that federal funds can be used to do research upon embryonic cell lines as long as they were developed using private funds.

The ultimate tragedy is that so much energy has been expended on the most morally reprehensible method of doing this potentially valuable research. Ongoing development would indicate that the use of embryos to obtain stem cells for research in clinical use is likely unnecessary. An opinion shared by stem cell researchers, including one from the NIH.

Recent issues of science journals have described many advances in manipulating genes, stem cells and organ cells to obtain the same results ethically. These include the angiogenesis studies and the telomerase studies referenced by Mr. Doerflinger. As well, it includes culturing stem cells from placental tissue to treat leukemia, creating functional bladder neo organs by using (eurythelial) and smooth muscle cells in the mouse, and the use of mouse neural stem cells to be transformed into hematopoietic tissue, demonstrating that one need not be restricted by the initial cell line.

Your own draft statement of April 1st of this

year from chapter 4 of Ethical Perspectives on the Research Use of Human Biological Materials expresses my position. I quote, "To ensure that patients and research objects are treated respectfully as agents, not as passive objects to be used for the ends of others."

You echo by 200 years my opening statement by Mr. Jefferson that the care of human life and not its destruction is the first and only legitimate object of good government.

Thank you for your time.

DR. SHAPIRO: Thank you very much for being here today. We would very much appreciate the opportunity to distribute your statement to the commission. I do not believe we have a copy.

DR. POEHAILOS: I will be glad to provide one.

DR. SHAPIRO: If you could provide it to Ms. Norris, who is sitting right here, we would appreciate that.

DR. POEHAILOS: Okay.

DR. SHAPIRO: Or we can get it Xeroxed, I am quite sure, if that is convenient.

DR. POEHAILOS: Okay. That is fine.

DR. SHAPIRO: Are there any questions from members of the commission?

Yes, Professor Capron?

PROFESSOR CAPRON: Have you studied the origin of the provisions that you cite on federal research with -- federally supported research with fetuses because I believe that if you look at the record of the National Commission the strong prohibition on anything that would not be therapeutic for the fetus arose from the notion that it would be improper with an abortion contemplated by a woman to do tests which could be harmful to that fetus precisely because the woman might change her mind and then you would have harmed the child that the fetus would become. And that the fact that that decision ought never to be made irrevocable for the women.

In other words, you ought not because you have agreed to be in research be in a position in which you would feel morally obligated to go ahead with an abortion which you changed your mind about, most people do change their mind and decide not to have an abortion that they thought they were going to have.

I think that historically explains why the

prohibition on nontherapeutic research on the living fetus in utero was adopted but if you have looked at the record and see something else I would be interested to know.

DR. POEHAILOS: No, I have not.

DR. SHAPIRO: Thank you.

PROFESSOR CAPRON: That does not disagree with your other points. It is just on that particular assertion as to the conclusion we ought to draw from that as to in vitro embryos that are in the deep freeze. It does not seem to me it follows the same way because they are not at that point irrevocably committed by being implanted.

DR. POEHAILOS: I might raise a point that referred to the last speaker, that came to me when the question about changing -- about if you had an embryo, a spare embryo that was not being used, and what if you could somehow change it that it then was somewhat equivalent to being dead.

My opinion is you have killed it. If you have somehow changed the embryo that would be viable if you tried to implant it, whether you kill it before you do the research upon it or kill it by doing the research upon it,

I think is arbitrary.

PROFESSOR CAPRON: Well, that is the distinction, however, that is drawn with fetuses, which are actually obviously a much more developed form of the human organism and researchers are not prohibited from using those fetuses for research purposes if the fetus has been aborted and is dead.

In the same way -- I mean, it is a separation and it is an insistence that there is a separation between the decision that goes to the death of that organism happening before any decision is made or any steps are made to use it for research. It may be that it is technically -- that the hypothetical that I have raised is technically impossible and that you cannot destroy an IVF embryo and still use it, its inner cell mass in the way in which it is being done.

I raise it as a hypothetical but I do wonder if it were possible to do that, if technically it were possible, wouldn't we be on the same moral ground as we are with a dead aborted fetus where our country has accepted the notion that if those processes are separated it is all right to use the fetal tissue for

transplantation or research purposes.

DR. POEHAILOS: I think if it is -- if the embryo -- if the embryo is being -- what my impression was of the initial question when it came up with the last speaker was that if the embryo was going to be destroyed and then used by the researcher as opposed to being destroyed in the research, my feeling is that the embryo -- I mean, and defined by embryology textbooks, this is not having to do with my personal faith, experiences or feelings on it, that embryo -- textbooks define the embryo as the beginning of a unique human being. No, I do not think we should be destroying frozen ones either and I do not care for what purpose we are destroying them.

PROFESSOR CAPRON: I understand that but you recognize that neither law nor broadly accepted morality prohibits people from doing that now. They go to IVF clinics. They produce a bunch of embryos. Some of them are implanted. Some are frozen.

And then at some point they end their reproductive process. That is to say they either have the children or they have abandoned hope of having children through that process.

They are then offered the alternative would you like to give those embryos to another infertile couple that has difficulty in producing an embryo? They say, "No, we do not want our biological child to be born to somebody else." "Then you realize the alternative is to destroy them." "Yes, we do." They destroy them.

Now what I -- what we are asking is, if at that point as they are now asked by some clinics to allow the use of those embryos for research on fertility purposes where they may be used as living embryos, I guess, I was asking whether if the process of discarding included a step which "killed" the embryo at that point. You would object to that. I understand.

DR. POEHAILOS: Yes.

PROFESSOR CAPRON: I have problems with it, too. But if that were the case, doesn't the end result very much resemble the dead aborted fetus? And, if so, shouldn't we apply the same model even if we then say the model is full of problems and --

DR. POEHAILOS: I was going to say I question the model in the first place.

PROFESSOR CAPRON: I understand you question

whether or not you can separate out the decision to have an abortion and the decision to donate for research or whether there will be corruption of that process but that applies. I am just asking wouldn't that logically apply to both?

DR. POEHAILOS: I would need to think about that. I could add it to a statement.

DR. SHAPIRO: Thank you.

Eric, do you have a question?

DR. CASSELL: Yes.

DR. SHAPIRO: And then we ought to go --

DR. CASSELL: At present we allow parents to consent to autopsy on their children.

DR. POEHAILOS: Yes.

DR. CASSELL: And even though in the course of that autopsy some of the tissues may be used for research.

DR. POEHAILOS: The child is already dead.

DR. CASSELL: Yes, I understand that. Just like the aborted fetus is already dead. At what point do you think the IVF embryo that is not used is no longer viable? When do you think that happens?

DR. POEHAILOS: I do not think it happens.

DR. CASSELL: You mean they are viable straight through, continually viable? You have found a way to keep things immortal. The IVF fetus is -- the IVF embryo is not used, at what point is that embryo no longer alive?

DR. POEHAILOS: When it can be proven that it cannot develop. I am not aware of any studies where someone has decided what the life span in a freezer is.

DR. CASSELL: I see. So you have to prove that it cannot be implanted?

DR. POEHAILOS: Except trying to prove it probably would be an ethical problem in itself but this problem can go back to something far bigger than this that I am sure I do not have time to go into now but basically whether we should be creating these embryos in the first place. That is another issue.

DR. CASSELL: Yes. But that is not where we are, is it?

DR. POEHAILOS: That is not where we are.

DR. CASSELL: Right.

DR. SHAPIRO: Thank you very much. I very much appreciate your statement and your responses to

questions. Thank you very much for taking the time to be here today.

The next speaker is Sidney Gunst, Jr., from Richmond, Virginia, also on this subject.

SIDNEY GUNST, JR.

MR. GUNST: Ladies and gentlemen, good morning. I have a big problem. A life or death problem. My four-year old son, Sidney -- my greatest value -- required open heart surgery on his aortic valve in 1996. He was two-years old. It was only a temporary fix. His pediatric cardiologist predicts Sidney's heart valve will fail again during his teenage years. Today, his options are limited to mechanical valves, animal valves, and cadavers, each with their own set of potential problems.

Fortunately, there is a far-superior alternative in sight. An alternative that could save his life by making his heart as good as new. The alternative is a regenerated or cloned valve. The development of such a valve is now conceivable through the advancement of human embryonic stem cell research.

Yes, I am an advocate of this research and of the cloning of body parts. Why should you advocate it?

Becasue it promotes human life.

But is it ethical? If ethics is a guide to the choices and actions that promote human life then the answer is yes.

I believe there are essentially four unwarranted fears driving the opposition to this next advancement in medicine.

Fear number 1. And I have heard these comments. What about evil people being cloned like in the movie "The Boys from Brazil?" Evil people cannot be cloned. Character is not genetic, it is chosen. Hitler was evil not because of his physical characteristics but because he chose to be.

The second fear: What about rampant irresponsible cloning? No matter the form of conception, whether traditional, in vitro, cloned or any future method, parents have the same responsibilities. If a couple gives birth to one child, or to nine of them, then they are responsible for raising that child, or all nine, to adulthood. If someone clones one child or 99 of them they still have the responsibility to care for that child, or 99 of them, just the same. What the children look like

is irrelevant.

The third fear you hear: We must not play God. That seems to be the primary thing today. Nonsense. We do and we must, especially in the field of medicine. Every time a surgeon removes cancer from a patient rather than letting him die, he plays God. Every time penicillin is prescribed to combat infection, or anesthesia is administered to protect a patient from suffering needless pain or suffering, or a C-section is performed to ensure a safe delivery, or a human organ is transplanted rather than allowing nature to take its course, a doctor is playing God. Now, science and reason and religion and faith, the compatibility, in the case of human organ transplants, 30 years ago was fought by the church.

It is a doctor's job to play God.

Historically, religionists have opposed these and other medical advancements, many of which have saved millions of lives, maybe even someone you love.

And not only must doctors play God, we all play God. Every choice we make, every action we take, changes the course of nature. When we cut down trees, plant crops, build houses, bridges, cities, power plants,

computers, we are playing God. Every alteration we make is an example of our playing God. This is how we survive. We reshape nature to suit our needs, to sustain and enhance our lives. If we did not, we would die. The history of human survival is the history of man playing God. It is as simple as that.

The last one: But we must not go too far. Too far? According to what standard? The standard of moral value is human life. The standard of ethics, which is what we are here to discuss, is life.

There are only two alternatives in this debate; there is no middle ground. If life is the standard of moral value, then the only ethical position of the Bioethics Commission is to advocate human embryonic stem cell research and all the procedures that promote life. The alternative is suffering and death. Where do you stand?

I am eager to take questions and would be delighted to further participate in this most vital matter.

Thank you.

DR. SHAPIRO: Thank you very much. I do want

to remind the commissioners that I think you all have copies of this statement at your places but let me see if there are any questions at this time.

Jim?

DR. CHILDRESS: Thank you. I wondered in terms of your global statement about religionists where you were perhaps over simplifying the views in terms of talking about opposition to organ transplants and so forth because at least as I read the history of various religious traditions in the United States, in particular, there are considerably more nuances than that and many of the points of opposition say to organ transplants would come at the point of trying to determine brain death or something like that but would not be as generally opposed to progress that would promote life as your comments seem to suggest.

Any further reflections on that?

MR. GUNST: You had that exact equivocation from this gentleman over here in the discussion with the lady preceding me regarding frozen embryos and whether that was morally correct or not. This country was founded on the principle of separation of church and state and

that -- I do not want somebody else's emotions or opinions dictating the choices and rights that I have, the inalienable rights that my son has to his life.

Now obviously my position is that life does not happen at conception. That is a potential child. No question about it. But it has not been individuated. It is not an individual and it does not have the same rights. That is the current law in this country, "Roe versus Wade."

DR. CHILDRESS: Thank you.

DR. SHAPIRO: Thank you. Any further questions from members of the commission?

Again thank you very much for being here.

MR. GUNST: Thank you.

DR. SHAPIRO: We very much appreciate your views.

We have -- the next person who has signed up to speak to us today may or may not be here at this time and that is John Cavanaugh-O'Keefe.

Is Mr. O'Keefe, Cavanaugh-O'Keefe here?

DR. _____: Can he add a statement in the record?

DR. SHAPIRO: Yes, he certainly can.

Thank you very much.

The next person is Ida Chow from the Society of Developmental Biology in Bethesda.

Ms. Chow, thank you very much for being here today.

IDA CHOW, Ph.D.

DR. CHOW: Thank you.

"Dear members of the commission:

"On behalf of the board of trustees and the public information committee of the Society for Developmental Biology, we should like to comment on the importance of research with human pluripotent embryonic stem cells and express our support for the ruling that NIH funding can be used for research for such cell lines.

"Many diseases that exact a heavy toll on our society involve damage, degeneration or functional failure of cells or tissues. This list would include diseases such as Alzheimer's, Parkinson's, diabetes, congestive heart failure, liver diseases and many others.

"The possibility of treating such conditions by implantation of cells with the capacity to repair the

damaged tissue is an exciting one that deserves to be explored from all possible angles.

"Studies have shown that adult organs contained so-called stem cells which have the capacity to proliferate in culture and differentiate into a number of different cell types. Indeed, such adult stem cells may have a greater capacity for making different cell types than previously and generally thought.

"Judging by a recent report suggesting that stem cells obtained from the nervous system of the mouse can generate blood cells after bone marrow transplantation, more research on the capacity of adult stem cells is clearly warranted. However, it is not clear that those stem cells will ever be capable of making all cell types of the body, which is the property possessed by pluripotent embryonic stem cells.

"In a mouse, embryonic stem cell lines can proliferate indefinitely in culture and can differentiate into a wide variety of cell types when given the right inducing signals. These properties suggest that embryonic stem cells hold enormous potential for future cell based therapies.

"The recent derivation by two groups of human pluripotent stem cell lines that appear to have many of the properties of mouse embryonic stem cells has brought this possibility closer to realization. There are still many obstacles to be overcome.

"We need to understand better how to regulate the differentiation of stem cells into different tissue lineages. Suitable modes of delivery of the cells to the requisite organs need to be developed and the grafted cells need to be protected from immune rejection.

"If the potential of stem cell research is to be rapidly translated into therapeutic reality, it is critical that all aspects of stem cell research, including research on both adult and embryonic stem cells, in nonhuman mammals and in humans, be a high priority for federal funding.

We need more of the best scientists doing world class science to move this area forward.

"The stringent peer review and oversight mechanisms of the NIH will ensure that this occurs. We support the recent ruling by DHHS and NIH that research on human embryonic stem cell lines is not covered by the

prohibition of use of federal funds for human embryo research.

"Mouse embryonic pluripotent stem cells cannot give an embryo alone. They have to be deliberately and with forethought combined with normal embryonic cells and reimplanted into the uterus to contribute to a live born mouse. The human embryonic cells provide vital information for the development of the embryo and they contribute to the placenta. It is clear that both the derivation and the potential future use of human embryonic stem cells raise difficult ethical issues relating to the use of human embryos or fetal material for research purposes.

"We are confident that the NIH with the assistance of NBAC will set in place suitable mechanisms to ensure that all research funded on human embryonic stem cells abides by the highest ethical and scientific standards.

"We are entering an exciting era in biomedical research where our understanding of human genetics and cell and developmental biology will soon translate into real advances in our treatment of diseases. A balance

between ethical concerns and the potential benefits for humanity must be reached so that the incredible expertise and creativity of the biomedical research community can be brought to bear on the task of ensuring that the full potential of advances and the development of human embryonic stem cells is realized.

"Yours truly, the Society of Developmental Biology, board of trustees, public information committee and executive officer."

Thank you.

DR. SHAPIRO: Thank you very much. We would also very much like a copy of the statement if you would not mind so that we can distribute it.

DR. CHOW: We sent in an earlier version but I will send in this updated version plus some supporting material.

DR. SHAPIRO: If you could that as soon as possible, it would be appreciated and distributed to the members of the commission.

DR. CHOW: Yes.

DR. SHAPIRO: Professor Capron?

PROFESSOR CAPRON: Dr. Chow, when we were

deliberating on our report on cloning human beings, we heard from some leading developmental biologists that while it would be interesting, and there would certainly be some people who might be interested in doing research on cloned human beings, that there was a great deal of research which could be carried out in animals and not in human beings and that, therefore, the kind of moratorium that we urged and that the president urged would not stand in the way of a great deal of progress being made that probably sensibly would have to be made before one moved into human beings.

And I wonder whether there is any way of inquiring and establishing, and maybe your supplementary document does this, whether or not the other avenues of research in this field, using human cells that are not derived directly from living human embryos, also would offer for a period of time avenues of research, which if they proved successful, might obviate the need ever to use human embryos. And how would one go about determining this?

I mean, it is not a question would somebody find some interest in doing it? The answer is always yes.

But really isn't there a great deal that can be learned from other animals and their embryonic and nonembryonic cells and from cells, somatic cells, as opposed to embryonic cells from adults?

DR. CHOW: Yes. First of all, I would like to let you all know that the Society for Developmental Biology was the society who polled its own membership about the moratorium on cloning of human cells and this moratorium was later adopted by the Federation of American Society for Experimental Biology as well as other biomedical associations.

So, as you see, we do have a stand on not using and not cloning human beings.

Also, in the past hearings you have heard from Dr. Bridget Hogan that many of this research is being done and there is really no use to use a lot of human tissues to study some of the basic questions. However, since we all know different species may have different properties somewhere along the line there is going to be a need to use some human tissues and so although we are supporting the use of human embryonic stem cells, we know the need of using them, we are very cautious in the sense that they

should only be used once all the supporting materials and supporting studies have been done prior to requesting the use of human tissues.

And so it is not just going, "Oh, there are all these extra embryos sitting around. Why don't we use them." It is not that. We have to consider the real need and only -- that is why we mention the high and stringent standards used for peer review for the need -- that NIH -- and it is only achievable if federal funding is allowed because otherwise it is going into private industry and some private industries are very, very conscientious but we cannot guarantee it for everybody. That is another reason why we think the federal funding issue is going to be important in really regulating the propriety and the appropriate use of human tissues.

DR. SHAPIRO: Thank you. Larry?

DR. MIIKE: Let me just ask you a technical question, which I assume is going to be correct, which is that when one looks a pluripotent stem cells and the great promise about getting very differentiated and organized tissue, the research does not go in just that direction but to take a look at the very differentiated tissue and

see how you can go backwards because that is what I understand in the whole thing.

DR. CHOW: Right.

DR. MIIKE: So that part would go on regardless of what happens in the political and moral atmosphere that we are talking about.

DR. CHOW: Right.

DR. MIIKE: Thank you.

DR. CHOW: Correct.

DR. MIIKE: Do you have -- could you provide us with some description or some summation about that kind of research?

DR. CHOW: Well, based on some of the -- I am not sure whether too much of that has been published yet but I hear within the community that quite a lot of this research is done using oocyte cytoplasm because as you know the nuclear transfer technology has given us a lot of insight in what is in the oocyte that is providing this mechanism for dedifferentiation and so I think that in this particular case, of course, it is not using only human oocytes because people are using mainly other mammal oocytes to try to find out what is inside of the oocyte

cytoplasm to differentiate and find out what this de-differentiating factors or combination of them could be.

So if that is possible then it is quite possible to go back to somatic adult -- somatic cells from adult individuals, any animal, and try to de-differentiate them and then use what is known now as some of the signaling factors trying to redirect the cells to differentiate into various cell types.

So we are not going to be going back to the whole issue of making a full human being or embryo but if we know the various steps then we will be able to interrupt step by step and progress from that step on. This is still in its infancy. So I think that we do need to make use and give the opportunity to all the scientists, especially many of them are federally funded, who can probably contribute a lot to this research if they are allowed to -- it does not necessarily mean that they will be using it. If the potential is there they can be allowed to use it.

DR. MIIKE: My only point was that I do not want to get lost in the debate but part of the research process is the backward steps.

DR. CHOW: Right, exactly. Exactly. And it is being done right now.

DR. SHAPIRO: Thank you. Any other comments or questions from members of the commission?

Again thank you very much for being here. We look forward to the other materials that you will provide.

Let's now reorganize our schedule today. We are running probably three-quarters of an hour late or a little more than that. What I propose now is that we do break for lunch and we will reconvene at 1:15 here. We will try to wrap up at that time our discussions and testimony from Dr. Marshall and then proceed immediately to our afternoon agenda as put in your books.

So thank you all. Let me extend once again my great thanks to those who came to address us during public comments, especially for those who had to travel to be here. Thank you all very much.

PROFESSOR CAPRON: Mr. Chairman, do we acknowledge the receipt and enter into our record the statement from the Ethics and Religious Liberty Commission of the Southern Baptist Convention, which I believe was also distributed today?

DR. SHAPIRO: Yes. Thank you.

PROFESSOR CAPRON: I gather the authors are not here.

DR. SHAPIRO: Not as far as I know, yes. We will certainly put it in the record. Thank you very much and we are recessed until 1:15 this afternoon.

(Whereupon, luncheon break was taken from 12:07 p.m. until 1:28 p.m.)

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A F T E R N O O N S E S S I O N

DR. SHAPIRO: Okay. I would like to call the meeting back to order otherwise we are going to run much too far behind. The schedule is already delayed.

As promised, I wanted to go back to two things before we get to our discussions on stem cells. Both, hopefully, will be relatively brief. One, of course, will be brief, which I will talk about in a minute. It has to do with the HBM report.

But I also wanted to give Professor Marshall an opportunity to have a few more words about the material that she was presenting to us. I think we have all had an opportunity to read the actual document. And then I want to allow some time for questions of Professor Marshall.

So let me turn to you with apologies that we have had to split up your work in this way.

CONSULTANT REPORT (Continued)

DR. MARSHALL: No problem. No problem at all.

What I would like to do right now is perhaps summarize some of the findings from Nigeria and this is a very quick assessment based on the interviews that I just finished within this last week.

I think there are four dominant problems. Two are substantive and two are practical. Four challenges to the obtaining of informed consent in a cross cultural situation like you have got in Nigeria with these genetic epidemiological studies.

The two substantive challenges are, first, cultural and, second, translation issues in relation to the language and within the cultural challenges I think there are three issues. The first one has to do with the problem of authority and consent, the location of decisional capacity. It is important to tease out the -- how an individual provides consent within the context of being absolutely imbedded within the fabric of a community. I am just going to go over these very quickly.

DR. SHAPIRO: That is fine.

DR. MARSHALL: The second issue in relation to a cultural challenge has to do with concerns about the procedures that are done during the course of the research. For example, in Nigeria there are concerns about drawing blood and it is because of the beliefs about blood. Blood is thought to be a part of your -- the -- it is a piece of the goodness of your heart, the goodness of

your soul, and it is such a precious commodity you do not want to give it up. Also, if someone takes your blood it could be used for sorcery. It could be used for -- someone could sell it and it could wind up coming back to you in an evil kind of way. So that would be a second cultural concern.

The third concern has to do with -- the third issue related to a cultural challenge has to do with the presentation, the portrayal of risks and benefits. In the United States, we are very careful to portray risks in a very negative -- I mean, a robustly negative way. We say things like "you may die if you participate."

I had more people tell me essentially, "What? Are you out of your mind? How am I going to tell my patient that she may die?" I mean, you know, they thought we were crazy to go to that extent and that instead we should emphasize the positive.

So there is a strong feeling that we over emphasize the risks, we dramatize, we make mountains out of mole hills, and if they did that nobody would participate in studies.

And the other issue is not representing enough

about the benefits of the study. Either benefits that would come to the individual or benefits that would come to the group, the community.

So those are the three cultural factors.

In relation to the issue of translation, this is the second substantive challenge, the translation of documents from one language to another presents, I think, two problems. First, the language itself and, second, conceptual issues related to the substance of the document. In relation to the language, it is problematic. There is no comparable word. For example, genotyping, gene -- there is no -- there is not a Yoruba word for gene or genotyping so there is -- I mean, you just practically have to work your way around that.

And the other issue has to do with conceptual things. I mean, if you do not have a concept of a theory it might be difficult to communicate something about infectious disease. That is a -- I mean, that is just an example. That is not necessarily true with the Yoruba but it is an example of that kind of -- what I mean by conceptual issue.

Now the two practical issues have to do first

with the amount of information. The people that I spoke with in Nigeria, they just shake their heads at the length of the informed consent documents that we use. They were trying to work with five pages of informed consent material and they said that if they took a consent document like that to their participants, potential participants, they would spend half their time dealing with trying to recruit people and they would never get on with the business of caring for patients or conducting research. This is a practical issue.

The other practical issue is dealing with the administrative requirements from Washington. A physician, with whom I spoke, complained strongly about the fact that he had to use his -- money from his department when he had no resources to make nine copies of the entire study for his IRB instead of being able to simply summarize the study.

Why don't I stop there. There are so many interesting compelling issues to talk about but really I think those four are the primary challenges.

DR. SHAPIRO: Thank you very, very much and we certainly look forward to your report, which sounds really

fascinating, indeed. But let's see if there are any questions from the commissioners at this time.

Jim?

DR. CHILDRESS: I guess one would be whether in the process of this research since you are very familiar with this context and environment, were there any surprises? Were there certain things you have gone in with, preconceptions, and it turned out to be mistaken when you started looking at these particular issues?

DR. MARSHALL: I think that I expected -- I did not expect the participants to be so knowledgeable about the purpose of the research. I mean, the research is on the genetic and epidemiological determinance of hypertension, breast cancer and type 2 diabetes. And I was amazed at how articulate some of them were.

However, I only -- I did not speak to -- these participants were chosen for me. So it is not like I am going in blind talking with people that, you know -- with just any participant. I mean, this is an exploratory study and the people with whom I did speak I talked with them in depth. But that surprised me that they would be, you know, so articulate.

DR. SHAPIRO: Did you get any sense from the discussions you had that this process of going to the chief, who then had a mechanism for -- I mean, beyond the gift giving and so on, had a mechanism for informing others? Did you have the sense that it can stop right there? That is that beyond the gifts he was just serving as a method of reaching the community or was he or she evaluating this and deciding whether it would be good for their community members to participate?

DR. MARSHALL: Absolutely they evaluate whether or not it would be good for the community. And that is a big consideration that plays into, I think, their decision about whether or not to provide approval. Usually if -- because of the health -- because it is related to the health of the community I think there is an inclination to provide approval as long as there are not any red flags going up.

But let me tell you recently there was a publication -- an article published in Social Science in Medicine. I believe Leach was the lead author on that, an Englishman, and this was a study of informed consent in Gambia. The point of this article was that people

involved in this -- it was, I believe, a malaria vaccine that they were looking at so they were getting consent from parents and everyone was providing consent and they were saying, "You know, we have people making autonomous decisions here and really every one is more or less with the program."

But they mentioned one community that totally refused to participate in that study and I believe, although it is not communicated, I believe that what happened is the person -- the community representative, whether it was a tribal leader or maybe a religious figure, they said, "No, this is not going to happen. We will not allow the study to be done."

Also, I heard -- people were telling me this last week -- people were telling me about instances where studies failed because the chief may have given approval, they started to do the study and then something happens to one of the participants and words gets out, and the study has to stop becasue people back out of the study. They say, "You know, what are you doing to us?" Even if what happened was not related to the participation in the study.

DR. SHAPIRO: Thank you.

Arturo?

DR. BRITO: Your comment about the fact that in Western medicine, Western research, we emphasize a lot on the risks and the feeling that maybe the benefits need to be emphasized more, makes me feel like maybe there is a lot of -- could be a lot of potential problems with the therapeutic misconception like with a lot of the community leaders as well as individuals. Is there a method in place to get around that to make it very clear that there is a difference between a research study and a therapeutic -- or a therapy basically?

DR. MARSHALL: Good comment. No, there is not a method in place to do that. I think that really depends upon the negotiation of informed consent. That conversation that occurs between the individual obtaining it and the person giving it. I can tell you my own opinion is that a lot depends upon the integrity of the researcher, the integrity of -- and the integrity of the person obtaining consent. I believe there are two issues that infuse that negotiation of consent, trust and power.

And I think that for the most part people

participate in studies because they feel that they are going to get something out of it either in relation to their health, certainly even in the notes that I gave you I think that there is a comment about -- from a participant where he says, "You know, I am going to get drugs. I want to participate because it will help the Nigerian people and it will help Americans, too, but also I will get my health care paid for and I will be given drugs."

It is very important for people who have nothing, who are not able to obtain those drugs in any other way, but there is -- in answer to your question is there, you know, a formal way to deal with the benefit issue, no, there is not. It is really a matter of how it is presented.

DR. BRITO: Thank you. A question related to something Harold mentioned or was asking about, is there also a formal way to limit the ability to coerce the community leaders? It struck me that when you were speaking about the whiskey and the kola nuts as a method of engaging and bringing up with these issues with community leaders, but I could also see a potential for

the community leader to be bribed or coerced to include his community. Is that an issue at all or is that a concern?

DR. MARSHALL: First, I think that it is important to understand that this practice of providing gifts to a local tribal leader, that is normative behavior not just in relation to the implementation of a research study in a community but it is behavior that occurs for any event that will take place within the community. And the providing of gifts really is the kola nuts and whiskey. It is like a -- we are not talking about a bribe or what could be conceived as a bribe of building a new -- you know, building a structure, a health care clinic, say, for example.

I do not really have so many problems with that personally with that interaction that takes place but for me the paradox that we are saying -- is there something the matter with this? Am I talking too close?

DR. SHAPIRO: Arturo, why don't you turn your's off and see how it goes.

DR. MARSHALL: I was talking with Bernie during the break. For me the real paradox is here you

have this infrastructure of community that is so powerful and so compelling and I believe that they are looking out for the most part for the good of their community. But on the other hand, you know, I said, "Well, okay, so you have got this approval. How many people actually refused to participate?" Very few people, in fact, refused to participate if a study is -- has the -- someone even called it an imprimatur. So, you know, there is a delicate balance there.

DR. SHAPIRO: The last question because then we are going to have to move on.

Bernie?

DR. LO: In your notes and your comments I was struck with some of the implications for our other discussion on research on human biological materials. We would assume that to use stored tissue samples involves low physical risk and that drawing blood is a pretty harmless procedure. And your example suggests that in some cultures it may be conceived of as very risky in metaphysical terms, that taking my blood opens me up to the risk that someone is going to practice sorcery or something. It is conceivable to me that the same protocol

that was deemed low risk, minimal risk, whatever we want to call it in the U.S., may not -- it may not be appropriate to apply that same risk analysis in another culture.

To what extent are the researchers sort of aware of both the approach or paradigm we are sort of putting forth, for example, here and how that really may not apply in a culture where risks are evaluated in a very different way and what is considered risky is something totally alien to this --

DR. MARSHALL: The researchers are absolutely sensitive. Not just the researchers but the people who are obtaining the consent. I mean, they may be research assistants. I spoke with a number of those individuals also. They are very sensitive to what the potential subjects might consider to be risky.

Forget about the issue of, you know, what will happen -- what can be used in the future in relation to developing some other material from any bodily specimen you take from me. That is not a concern for these people. What is of concern primarily was the drawing of the blood and they have developed some strategies to talk about

this.

I have to tell you again this was raised independently to me by almost everyone that I talked with so I -- it was an across the board concern, this issue of drawing blood, and they -- the way that they deal with it is by emphasizing that it is a small amount. They say, "Look at how much blood you have in your body. Think about how much blood you have. We are taking just a small amount."

I had one person tell me that she had a patient involved in the study who became very upset when they were drawing blood and a little bit of the blood spilled on the floor and the blood spread. You know, I mean, it just -- it became -- it appeared to be a pool of blood. And it was this idea of spreading that gave the appearance of largeness and in that case the person obtaining consent had to do a lot of explanation.

So they are aware of that -- the perception of different kinds of risks but most of the people that I spoke with they -- they told me, "We do not like to tell patients that bad things may happen to them."

I think you have one of the quotes from

someone who -- one of the docs who said, "You know, I cannot tell someone..." this is so true for Nigeria. He said, "I cannot tell someone I am going to provide them with transportation to get to the clinic." He said, "You know, they could die on the road," which I mean -- you know, that is true. There are skeletons of cars and buses and burned out cycles littering the median strips in the country side. He said, "I cannot do that. I have to say, 'I will drive you.'" Is that how he said it? "I will bring you to the clinic." He said, "And maybe what I will say is 'I will get you to the clinic safely.'" Isn't that what he says in there? I think that is the part in the quote. "I will bring you there safely."

And then finally he says, "And maybe the last thing I will say is, 'And God forbid, an accident will not happen.'" You know, it is like -- so there is a real sense of protectiveness about how you communicate danger to potential subjects.

So this notion of risk is an interesting one and I would love to explore it more to tell you the truth. In the end, all I will be able to give you is the results of a number of in depth interviews. So, you know, it will

be a great time to think about what sorts of hypotheses we can generate but it should be a very good case study.

I think it will be.

DR. SHAPIRO: We think so, also.

Thank you very, very much and thank you especially for being here today. We very much appreciate the effort you went through to come.

DR. MARSHALL: I am glad that I could be here and, you know, I think that I am going to leave now so I can unpack my bag.

DR. SHAPIRO: Okay.

DR. MARSHALL: Thank you very much.

DISCUSSION OF DRAFT REPORT CONTINUES

DR. SHAPIRO: All right. Do you want to press your button there before leaving?

Okay. I want to now just go back extremely briefly to a particular aspect of the human biologicals materials report, which was the object of some discussion late yesterday afternoon, with respect to recommendation 2. I am going to turn to Eric to describe this situation. We just want to get a sense from the commission so we know how it is we want to go about writing what will replace

recommendation 2.

Eric?

DR. MESLIN: Well, very quickly, we wanted to get a sense of the commission as to whether you wanted to divide up what is currently recommendation 2 into two subpieces. The first relating to the principle issue of research conducted on unidentified or unlinked samples and then the second issue relating to the independence of the individual who would be -- is that me?

DR. SHAPIRO: I think it is maybe me from this.

DR. MESLIN: So we will be happy to bring some people together by a call or to get some writing done but we want to get the sense of the commission as to which direction they would like us to go.

PROFESSOR CAPRON: I thought that the division that was being contemplated was between the present section, which would be described as research conducted on unidentified samples without the language of -- with whether the specimens are, et cetera, et cetera, unidentified samples.

And then a separate description of research

conducted on unlinked samples in which we could address the mechanism by which the adequacy of that unlinking process was addressed. And if there is adequate unlinking then the samples would not be subject to the requirements of the common rule but that the process of determining that that had occurred would be a predicate.

And there was some discussion as to whether that should be an IRB or some other -- the department of pathology or some other mechanism at the university or the research institution or the repository or wherever it is.

And I thought there was wide agreement with Steve's point that we are really concerned with the objective which might be achieved through several different processes and that we did not want to bind ourselves to the one process which is described here, although that would be an appropriate part of the commentary.

MR. HOLTZMAN: I am going to try to -- it is going to sound like I am going to make this more complex but I think I -- as I have been thinking for the last ten minutes about this since I talked to you, it is along the lines of Alex and I think we can simplify it.

And that is if you read this recommendation -- let's put aside the issue about how you ensure the unlinking. What this recommendation is about is asking OPRR to provide some clarification and I think what we want to do, therefore, is to ask OPRR to provide clarification that under current regs research conducted on unidentified samples does not involve human subjects and research conducted on unlinked samples does not involve identifiable individuals. In both cases such research is not subject to the common rule. That is one bucket.

The second has to do with how do we ensure that unlinking is real unlinking? And as I was writing that and thinking about it, I think we probably have the same concern with coding. So I found myself then writing a second recommendation that is totally distinct along the lines of institutions and organizations that participate in research conducted with unlinked and/or coded samples should institute policies and procedures. For example, the use of independent third parties to code and unlink to ensure that the coding schemes and unlinking procedures are robust and I did not get far enough.

I think those are the two very distinct issues.

PROFESSOR CAPRON: I think we introduce confusion by putting together the unlinked and the coded here and I think we also introduce complexity in the expression of the idea by putting together the unidentified and the unlinked. So I think I do not agree with your solution there because the point of having a separate statement on unlinked is precisely to identify the adequacy of the process and to recognize that while unidentified just fall below the radar screen entirely, it is -- you know, sort of stealth research as it were.

The other, we have to determine whether or not it is below the radar screen and so it is necessary to fix a lacuna in the present process and I think that the recommendation there is not just for clarification by OPRR, which is what we urge in recommendation 2 on the definition of identifiability, Steve.

It is really suggesting that we need an assertion of a procedural step which would be required in order to fall into that category. So it is sort of the ironic thing. Once you pass it, you are back out of the

system.

Now earlier today we identified another circumstance where the -- I think you were the one who identified it, right? -- where the problem of research falling -- you know, that we were presuming a process which would not occur in the way that we were presuming it. I am forgetting which recommendation it was. I am just looking for it. Was it 14? Yes. It is the stripping where we are talking there about stripping the identifiers.

In 14 we recognize that you would not be explaining this to the IRB unless you had a process like this to unlink it. It is the very same category and that is why that recommendation 14 could be folded in to a new recommendation following 2. But it seems to me it would be very complex to try to package that all in with unidentified samples, which are much more straightforward.

DR. SHAPIRO: Larry?

DR. MIIKE: My recollection of the discussion is very simple in the sense that if we are talking about unidentified specimens, which nobody knows who they are anyway, it is not an issue to say that there they are

exempt. What we -- what came up in the discussion was that for the unlinked there was no oversight over that so that was the issue that was facing us, whether we want to only keep 2 for the unidentified specimens and then develop some means of -- some way of a check to see whether the unlinking, which removes it even from any kind of scrutiny, is something that we would want to develop. I mean, that was my understanding of this morning.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I am not sure if we are in disagreement, Alex. Is it or is it not the case that if something is genuinely unlinked that it is not -- that it is exempt? I think we have said that it is.

PROFESSOR CAPRON: Yes. I think we have -- I think there is agreement that if it has risen to the level of being extremely difficult for the researcher, et cetera, to figure out who these people are, we consider it the same as if it is unidentified.

MR. HOLTZMAN: Right. So to me the first step of the -- if we are going to say, OPRR, let the world know that the following class of research is exempt, I think we should state the classes that are exempt. So that is why

I said take -- in the simpler form rec 2 would simply say these two classes of research are exempt.

Now it is another step then to say in order to be exempt what are the kinds of procedures we want to do to ensure the sanctity of the unlinking process. So that was -- now whether in that latter we also want to get into recommendations about sanctity of coding. We could go there as well.

PROFESSOR CAPRON: I would not urge that we go to the coding thing because the coding thing is already covered by recommendation 3.

MR. HOLTZMAN: That is right.

PROFESSOR CAPRON: And while I -- I mean, I agree with your analysis. I see -- I think it is clear but I would just say at this point we probably want to leave this to the drafting process and see if we can do it. I will help with that to make this two statements of categories A and B where both of which fall below the radar screen.

DR. MESLIN: Larry? It will be the last comment.

DR. MIIKE: I would just like to introduce

another thing, which is that I do not think we need 14 at all. I mean, if we can deal with the issue about the legitimacy of unlinked I do not see why we need to ask the question that 14 asks.

PROFESSOR CAPRON: Well, 14 was this sort of ironic thing that having stated that there was a category of unlinked which was not going to be subject to review, it was almost a statement of principle rather than a recommendation that researchers should be pressed to say if you have data where the research could probably be better conducted with coded or even identified samples for some reason but particularly coded samples, why aren't you doing it that way. Why are you going to unlinked? Are you going to unlinked simply so you will not have to go through the review process? That is a bad reason to go to unlinked.

Now it is sort of the flip side. And if we have a process in which you have to explain how you unlinked, it would be appropriate at that time to say why are you unlinking.

DR. MIIKE: I am just saying it is not an appropriate question or a recommendation for us to ask it.

DR. MESLIN: I am going to suggest given that we have all taken notes, one of which is that we could be linking 14 with 2, that Steve and Alex and Larry, if you would like to join a quick e-mail conversation to produce some language and circulate it fairly quickly, if that is acceptable to everybody.

PROFESSOR CAPRON: Do you want to resolve the issue that Larry raises? I mean, Larry -- because it does not make sense to redraft this and include that, which would be more complicated, if most people agree with Larry.

DR. SHAPIRO: My feeling is that -- I mean, I think the reason we have 14 -- I am not sure it is in its right place and it might need to be redrafted in some way -- but I think the reason we have 14 is still there as far as I understand it.

PROFESSOR CAPRON: Well, I agree.

DR. SHAPIRO: That is that we wanted to put some impedance mechanism in the system to -- because there were benefits that might be foregone by unlinking or making them unidentified and we wanted to make sure that people did that thoughtfully. That is all.

DR. MIIKE: But, Harold, if researchers want to do lousy research that is their problem. It is not our's. I mean, there are boards and there are peer review people to decide whether it is a worthwhile project or not. It seems to me that is what we are getting into here.

PROFESSOR CAPRON: But the point is that one of the foregone benefits is foregoing the benefit of IRB review and the incentive for someone to do that should be at least explicitly addressed.

DR. MIIKE: Well, what I am saying is that the revisions that we are going to do would not address that issue.

DR. SHAPIRO: I understand what you are saying.

Steve? And that is the last question. We have to get off this subject.

MR. HOLTZMAN: I think there is actually a very deep question that is at stake here because there is a view that says you are unlinking them to get around IRB, to get around doing human subjects research, to get around consent, and that is a bad thing to do. Put aside whether

or not it is good or bad research, that that is the bad thing to do.

There is another view which says IRB human subjects projection in research, et cetera, is a very good thing but it is only in play where there is personally identifiable samples of people and in taking that -- unlinking them it is no longer in play so that you have not done anything bad. All right. It is just that it is a different view of when those considerations come into play. So in that sense this is a very substantial recommendation in terms of a judgment on that issue.

RESEARCH INVOLVING HUMAN STEM CELLS

DR. SHAPIRO: All right. We will redraft those and then pass them around to the commission for review.

All right. I want to go on now to something we had hoped to get to at 11:30 this morning and have not managed to reach yet and that is to return to our ongoing discussion regarding our stem cell report that is in process in our own thinking on this issue.

Let me just say something about the timetable that is in front of us in this area. We hope by sometime

before the end of this month, that is before the end of April, to really have completed a draft of what I will call for the moment the science chapter. And send it out to review by external readers, other scientists who may look at it and so on, as well as sending it to members of the commission.

This is in my mind a really quite important chapter of the report as I see it because it is not simply a recitation of where the existing science is on the isolation of human embryonic stem cells or just how that -- recent developments in this area and how that has raised a new set of issues for some people.

But I also aspire that this chapter shall look at the science that is before us and what the road map seems to be as we look ahead and what kinds of issues we are going to be faced with, if not tomorrow then the day after tomorrow, because I think that may very well impact how we think through and what kind of framework we want to provide for whatever recommendations we come to or for any issues that we might wish to highlight even though they may not come forth as a recommendation.

So, for example, depending on how we think

about or how we might anticipate scientific developments, we might think that there are certain types of new language that will have to be used to be able to deal with an entirely new understanding of what is going on in the basic biology and while we may or may not use that language, they may or may not generate any recommendations at this time, it may very well enable us to set some groundwork for issues that are going to have to be addressed in the years ahead.

So I think this chapter is important not only for whatever educational function it may have to outline for people where the science is today and what it is that has caused us to come back and look at this subject but because it may, in fact, lay some framework for the way all of us will have to think this through in somewhat different ways as we go forward. That is speculative at the moment but at least that is what I would aspire to here in this chapter.

So that will be an important thing for us to look at carefully and, hopefully, we will be able to do so around the end of this month to the beginning of next month. And having some external review of this is going

to be really quite important because I really want to be sure that whatever we produce, and those of us -- those people who help us produce it -- really stands the scrutiny of other people who are independent of the commission and its work.

Now we will also in that time frame, that is end of this month, beginning of next month, probably on April 29th or May 6th, is -- as you know from the e-mail that we have distributed, we are going to try to put together another meeting of the commission, although I understand that that will be really very -- it will be difficult for all our calendars and I do not know how many commissioners will be able to make it but we will probably have a one day meeting to deal with at least one issue and perhaps other issues.

We want to provide an opportunity for the commission to hear about religious perspectives, various religious perspectives on the issues that are before us. We, of course, heard some very important testimony here today but there will be -- we want to provide an opportunity to hear additional testimony on this issue and perhaps by that time there will be other issues, which as

we work through our report, we may want to at least run through at that time. But that will be -- you will hear more from the staff on that issue. That will also occur at the end of this month, the beginning of this next month some time.

Our objective right now, and it is regarding the actual report itself, we have a lot of material here that provides a lot of background and some ideas regarding ethical and other aspects of this issue but we have to begin drafting the report itself and we probably will not know just where we stand until we actually look at a coherent framework.

I hope that we can by the first week or ten days of May begin to have drafts of some chapter. We will, of course, have the science chapter I just described. We will have some introductory material. Perhaps some material building on the regulatory and legal issues that are involved here. Perhaps even by that time, although it may be pressing our luck a little bit, something or at least some initial ideas of the structure of what we will do on the ethical issues that are particularly relevant to the kind of recommendations we

will be discussing.

That is a lot to get done. I am not sure we will get it all done but we are trying to provide some really meaningful additional material by the time we meet in Chicago on May 11th and 12th. I think that is the date for our Chicago meeting, on May 11th and 12th.

Now as you think about that schedule, by mid-May, as I understand it, the NIH Guidelines will be distributed, whatever guidelines they are going to develop, will be distributed for public comment and I believe for a 60-day period. That is my understanding. I do not want you to hold me to that.

That is NIH's decision but my understanding is that they are at least aiming to distribute for public comment in mid-May, which means that it will be a couple of months after that. There will be a couple of months for the public comment and then some -- perhaps they will move to some final resolution of their judgment. I really cannot speak for them on that issue at all.

But in late May the AAAS will also be issuing its own guidelines. As you know, the AAAS has also engaged itself in this subject. And so we will have

between the time of the first draft materials that we start producing, it will be somewhere in the beginning of May, and certainly for the Chicago meeting, and the end of May, we will have the benefit so to speak of seeing what some other organizations think about this and how they are trying to pursue these matters.

I have no idea in the case of just how broad those guidelines will be either for the NIH or AAAS. We will just have to wait and see how that develops.

I am hoping that not long after that, somewhere towards the end of May, we will have a pretty good fix on our recommendations. We may not have them all in place and we may not be able to feel completely comfortable but we really have to by the end of May, which is roughly six weeks from now, have a pretty good fix on our recommendations because that will enable us to produce a coherent draft report for June, our June meeting, and I hope actually in June to get a turn around.

That is my aspiration, is to have a report ready to distribute to the committee, a draft report, early in June, send it out for comments, bring it back and send out a version that will reflect some of those

comments, at least, that we can then discuss at our meeting at the end of June.

That will enable us to report roughly in that time frame, shortly after our June meeting, which as you might recall will occur on June 28th and 29th. That is a very ambitious schedule since this is such an important and difficult topic to deal with. As we know, every time we have discussed this there are a complex set of issues for us. Some of which, if I had to make a guess, we will not be able to deal with them all. We will probably find ourselves -- but I hope we will be able to deal with a coherent set that will add and make some contribution to the ongoing public debate on this issue.

Indeed, I think my own view is that our discussions already have made a contribution even though we, ourselves, have not resolved where we stand on a whole series of issues. It is quite clear to me from the feedback I get from those people, both the AAAS, NIH, other places and Congress, and elsewhere, that our discussions, even though we may all change our minds about something, are already beginning to have some kind of impact on the way others think.

So that is the overall agenda. It is extremely demanding. We are going to try to be working very hard in the next little while and, of course, while we do this we have to complete our HBM report and in that area I am -- I want to reiterate what Jim said just before lunch. I think the biggest outstanding problem is to get chapter 4 right. We have some times to resolve in the recommendations which are important enough but I am fully confident we can resolve that in some satisfactory way and I am fully confident about chapter 4 also but nevertheless that is, in my own mind, conceptually the biggest job we have in the next month or so.

But, hopefully, at our next meeting we will have something for us -- by next meeting I do not necessarily mean the special meeting we are going to have. I do not know how fast we can get material for that. That will be around -- especially if it is around the end of April we certainly will not be there. But we do have to come back to chapter 4 in a very careful way as Jim indicated.

So that is roughly the framework in which we are operating. Despite the fact -- it is always difficult

and challenging to have to deal with issues like this under deadlines of any kind because no matter how often -- how hard you think about this, you always at the end of the day want some more time for reflection. I do not mean you. I mean myself in that respect. Many people. On difficult issues you just want to have more and more time for reflection on what are, everyone would say, very difficult and sensitive issues.

But we are committed to reporting roughly in the time frame of the end of June and that is what I would like to continue to aim for if we can all -- if we can all get there and only time will tell.

Now I would like to go back to our last meeting. If you recall, we had after some initial discussions, we had realized that all of -- many of us were using different kinds of reasoning and different kinds of propositions to get ourselves to recommendations that we seemed, at least in a very initial way, to either be comfortable with or if not comfortable with, at least thought of them as a good place to start our discussions and to see how those recommendations might be supported if they could be. And I want to go back to that discussion.

We had partly, I think, in response to a very helpful paper by Professor Fletcher, who has now given us -- I do not know which version this is. This is his third or --

DR. FLETCHER: You have Draft 3, Part 1.

DR. SHAPIRO: This is -- all right. Draft 3, Part 1. It is beginning to sound like a federal regulation but in any case it has been very helpful to us and we are very grateful to you for your ongoing care with which you are providing a coherent way for us to think through this problem.

We had thought that we might at least begin by looking at these different cases. You recall from Professor Fletcher's paper those cases one through four. I am not going to bother describing those. I think you all know what they are. And we really focused our discussion last time on cases one and two. This was a case of what you might question the use of aborted fetuses as a source, at least indirectly, to produce cell lines. The so-called Gearhart research program. And the case two is really is the so-called spare embryo case where you might think of that as the Thomson research project.

And we talked about whether we felt it might be reasonable to think that that was permissible. What we are talking about here, let me remind everybody, is not simply whether it is legally permissible. We know in this country right now this is all legally permissible. We were focusing our attention on whether this should be -- such efforts should be appropriate -- is an appropriate thing to be supported by federal funds. That is really the focus of our attention. And whether the moral arguments one way or another would lead us to indicate that, yes, it would be appropriate or, no, it would not be appropriate.

And I think, if I am recalling correctly from our last meeting, that the sense of the commission at that time, initial as it may have been and tentative as it may have been in many of your minds, was that we probably might move in that direction, to think that both for cases one and two that this might be something that was appropriate for the federal government to support for different reasons. Also, we then discussed the issue of whether it was disingenuous or not to separate use from derivation. That is less of a problem.

Case one obviously where you are dealing with a fetus that is dead, the issue is the so-called firewall that you erect between the decision to abort and the use of this for this purpose, use of the tissue for this purpose. That was case one. I think we came rather more easily to the idea that both for the purposes of use -- that is using the cell lines -- federal funds for the use of these cell lines and for the derivation seemed to most members, I would not say all members, of the commission to be appropriate.

And then we went to case two and it is at least my recollection, and some people who have been reading the transcript can correct me, that at least many members of the commission, certainly probably not all, thought that in that case as well that we ought to be considering the recommendation that federal funds were appropriate both for the use of these cell lines, existing cell lines one way or another and for the derivation of these cell lines under the grounds that it was, as I said a few moments ago, disingenuous to try to make a distinction between the two.

Now, I guess my first question is, one, have I

described something which seems like another meeting to you, another commission, or have I described something that was, indeed, a reasonably accurate reflection of our discussion? And I will ask you to answer that in a moment.

I think today that we ought to see -- first of all, revisit that issue. Is that where we were? Do people think that that is still a viable position at least in a tentative way? Because, of course, we will have to develop the reasoning for this and I think each of us did that as a matter of fact the last time but we did it in somewhat different ways and we would have to find a framework on which we could agree.

But we, also, at least look at -- and think about for some time the -- what Professor Fletcher has called cases three and four, and see if we are comfortable creating a distinction there and saying that in three and four there are morally relevant differences between three and four or other relevant differences between three and four regarding public policy and the expenditure of public funds for these purposes.

So perhaps we can start by focusing on those

two issues and let's see where our discussion takes us. Let's go to the first part of that, namely whether in your mind I have adequately summarized the initial stages of our discussion last time.

I am going to take -- incidentally, I am going to take silence to mean not that I am incorrect but I am correct. But people may want to add things or perhaps I have left out some part of the -- our discussion that you consider important and relevant and I certainly would like to understand that.

Alex?

PROFESSOR CAPRON: Just as to category two that all of the kinds of protections and perhaps more attached to category one would have to be customized for that category.

DR. SHAPIRO: That is correct. I should have said that. I apologize. I think it was the direct sense of the commission that those protections, both in cases, but it would be more difficult and more demanding to construct those under case two than case one, but I think it is exactly as you have indicated. The sense that those would be very important to any recommendation we might

consider in this area.

Bernie?

DR. LO: As we originally sort of thought through this approach my recollection is we were thinking there was sort of a gradation of acceptability, that there is going to be more acceptance for things at the top of the list and a lot more controversy and a lot more objection to things at the bottom of the list. And that we might choose to draw the line at various places as individuals and as a commission it was not clear where we were going to draw the line.

I guess one question I have is are we prepared yet to think about is there a line that we would draw that allows some research to be federally funded? So are we, as a commission, willing to draw the line at a place where some category of stem cell research will be permitted and then the question is where is the line or are we still considering the possibility that no research will be acceptable for funding because we think that even in number one, which is the least objectionable in the hierarchy, still is objectionable enough to not merit federal funding? Because then it seems to me the report

takes a very different tone that some research will be funded. It is a matter of what is included in that as opposed to no research being done.

DR. SHAPIRO: Well, I will just again reflect on my own recollection of our discussion last time. It was in the -- I think the category you just described, and I do not want to speak for every member of the commission but for the commission as a whole -- that there was, I would say, very definite feeling that some research should be funded. And then the question is where to draw the line and what reasoning you would have and how persuasive could one be in that connection. That is certainly my very strong recollection.

But if someone -- you know, if others disagree -- and again I do not think there is probably any issue in any of this that all of us feel the same way about so I am not trying to implicate any single member or every member of the commission in that view. Just the overall perspective that we came to.

All right. Let's go on. We will have to come back to this. There is an extraordinary amount of detail to work in here, which we will certainly come back to.

But I think I would like to have -- hear some discussion from the commission, commission members, regarding what is known as case -- what are known in our lingo right now for the moment in the shorthand we use -- as case three and four, and see how people feel about them without -- whether you think they are really morally relevant or otherwise relevant distinctions. Or do they definitely either fall above the line or below the line wherever we decide to put this line at some stage?

Steve?

MR. HOLTZMAN: Just a quick question so I am clear on what we are discussing. Are we talking about federal funding for the derivation of ES cells from three and four, and for that matter for two -- from two? Or are we talking about federal funding of ES cell research where we are now going to look at what was the origin of those ES cells and say that that may or may not make a difference?

DR. SHAPIRO: My understanding is in our discussions of case one and two we were talking about the use and derivation. That was certainly the way we talked about it last time, leaving open the issue if we are going

to stay there or not. But that is certainly -- on three and four, I do not think we had any careful discussion on that issue, and that is open. It is open.

MR. HOLTZMAN: So again for clarification, you take the sense of the commission to be federal funding of ES cell research where the ES cells were derived from spare embryos and also federal funding of the derivation of ES cells from spare embryos?

DR. SHAPIRO: I would say that was where our discussion was when we left it. Whether it will stay there and what will happen and how we will come out, I was not making any predictions on that.

Larry, and then Alex.

DR. MIIKE: Cases one and two are fairly straightforward in the sense that we are dealing with existing sources. We were not talking in case -- in case two, if we are talking about creating sources then we are into four because if we are talking about creating embryos and we are creating embryos for a research purpose it is --

DR. SHAPIRO: Yes.

DR. MIIKE: Well, let me finish.

DR. SHAPIRO: I am sorry. I apologize.

DR. MIIKE: I understand. But what -- in case two we do not -- we are not dealing with creating the embryos. We are talking about using the spare embryos in terms of creating ES cells. Cases three and four are quite different, of course. The derivation and the creation is one and the same in the sense that we are talking about creating through somatic cell nuclear transfer or we are talking about creating embryos in the usual way of IVF fertilization for research. Then the creation and the derivation is part and parcel of the same process.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I do not think I do agree with Larry's analysis. If it were possible to separate derivation and use for categories one and two, it is equally possible, it seems to me, to separate them in categories three and four.

You described before something, which I agree, which was that we had concluded that it was disingenuous to say that you could support use and not support derivation because you are simply passing the money, which

will lead to the derivation through the people who are using it. The price that they pay to get them.

And I think, Larry, that you could equally have in three and four, if you did not accept that position that the two really amount to the same thing, you could have someone claiming that they produce their stem cells from embryos that were created from research but they are not the people who are using them and it makes equally good sense -- if it made any sense, it makes equally good sense in that case. The researcher does not have to be the person who is using them in his research or her research, the person who derived them in the first place.

So I believe that we should say that it is justified to fund the use only when it is justified to fund derivation because I do not think they can be separated but I would apply the same logic to all the categories.

As to the difference between category three and category four, both of those would be -- have the similarity of being embryos that are derived for research purposes. Since you cannot now under the kinds of

recommendations that we have put forward at least, and the logic that we support, create a cloned or somatic cell nuclear transfer embryo for the purpose of reproduction. The only reason to do it would be for research purposes.

The reason for having a separation between categories three and four, as I understand it, is the argument that category three, somatic cell nuclear transfer, aims towards a particular therapeutic modality that has special arguments in its favor.

And it seemed to me that the one thing that was left out of your summary, Harold, was the notion that for all of these categories, but particularly for those that we were not prepared to say were suitable now for federal funding, we imagined that there ought to be a mechanism for ongoing review of this area of research that could reach determinations as to whether or not the argument in favor of such research is ever made out.

We have heard speculation today that it will not be necessary in the somatic cell nuclear transfer area to use embryos once the process of dedifferentiating adult differentiated cells has been perfected. And if that is the case, then such a panel could well say given the

obvious moral problems in going ahead with making embryos for this purpose, and given the existence of a perfectly good alternative to that, there is no reason to approve it for federal funding.

But I think we ought to in a certain way ask ourselves questions about category two in the same way, which is, is this something where it is necessary for research to go in this area with human cells now or is this for a period of time, not as a new moratorium but really as a continuation of the existing prohibitions, something which deserves to be looked at in the context of need? Is it necessary to achieve important scientific results, which I think are regarded by everybody, whatever their view on how we should go about it, everybody as legitimate and important results?

Is it necessary now to take this step or not? And we could make that determination and I think you have suggested that tentatively we have. Or we could say if our primary emphasis is going to be on a process that that determination in which we are inclined in a certain direction really ought to be made by a body that gets more deeply into all the science and the arguments for clinical

need and so forth. I just want to put that on the table as well.

DR. SHAPIRO: Thank you.

Other comments or questions?

Bernie?

DR. LO: This morning before the break two of the public speakers suggested sort of an additional item on table one, which was to derive pluripotential stem cells from dedifferentiation of somatic cells that did not pass through a totipotent stage but were merely pluripotent.

I guess one of the issues that it seems to me we ought to think about is, first of all, what is the scientific likelihood of that happening so that it should be -- is it plausible enough that it should be considered? Should it be -- if that is an option, where should it be on our table? Does it go to the top of the table as being the least objectionable of these alternatives?

And then there is the implicit argument, I think we were presented, that given -- if it is, in fact, significantly less controversial or objectionable morally, should it be preferentially supported for public funds and

what is the scientific cost of doing that?

I mean, it seems to me those are some of the questions that are being posed to us. If there is an alternative that is not morally objectionable and may or may not be as scientifically promising, should it be preferentially the way we should pursue things? I do not know if there is enough in the science realm to be able to really address that or is that just too speculative at this point?

DR. SHAPIRO: Larry?

DR. MIIKE: I look at that as a different issue and not before us for making decisions on. I think that is a given that there is no controversy or we are trying to go that route. The question for the panel here and for those who object to this is that -- should we put all our eggs in that basket and should we -- if we go that route until we -- we would narrow the choices to that. So I do not think that it is for us to think in terms of the four cases as our options, as us having to deliberate about where that stands in that. It is a background issue and it would influence how we make our selections in the four choices before us.

DR. SHAPIRO: Eric?

DR. CASSELL: This may be a little going backwards a step but one of the things I noticed in this morning's discussion in talking about the spare embryo situation, the discussion is so abstract that there is no sense of what is this object and what happens to it if it is not implanted and how -- and it is not frozen, and how long does that take, and what is that like in other biological systems that we care about.

Like in organ transplantation where if you do not use the organ soon enough then it has still got cells but it is not good for implantation in another -- I mean, somehow we have to take this away from the abstraction called embryo and get it down to where we know exactly what it is we are really talking about.

And I think that that will make it easier to make these things morally distinct as well as scientifically distinct.

DR. SHAPIRO: Thank you. I think the issue of, you know, what is the state of science and what does that mean is actually in my own mind pretty important for us. I think there is going to be a limited amount that we

can find out. That is I do not believe we know everything or everybody knows everything that we would need to know right now to make very fine distinctions.

But on the issue of how one thinks about the embryo and its moral status and so on, I think there is more or less uniform agreement amongst us, at least that is what I sensed the last time, that at the very least -- and this would be saying something very minimal for some members of the commission -- it is something that we -- that it has some moral status we have to care about and we have to respect and that -- to use the kind of language that has often been used in this area. And, therefore, if there were alternatives this would be a very serious matter. I mean, if you could -- if there were viable well-known alternatives today, there would be very little reason to move in this direction.

And so while I do not think we can -- my guess is we will not get conclusive scientific evidence on this. I do not think we know enough yet. At least that is my understanding. We will know more in a little time from now. But I do think that is relevant for us. At least it is relevant for me. Let me put it that way. I do not

want to say it is relevant for everybody. It is relevant for my own consideration of these issues.

Moreover, you recall that the testimony that we had -- I guess it was testimony of some kind -- that when Dr. Varmus visited the commission's meeting at, I guess, our first meeting after the Miami meeting he attended -- I think it was in Washington. We began talking about moving up and down the cell lineage map and what that meant for how we could think of the moral standing of all kinds of biological materials.

And this is changing in such a radical way as I tried to say early on in my remarks and it threatens to change in an even more radical way as we begin to move up and down that cell lineage map to say nothing of whether we can at some stage of the game provide alternatives to the oocyte and so on. I just have no idea myself but I mean given where things are going it does not sound so totally outlandish.

It is my strong feeling that there is just so much that is happening here, so much that is changing in our concept of the way things are and how they might work that we are going to have to be cognizant of as we begin

to formulate our recommendations in particular because however they may appear right now and however useful they might be for the next few years, if any of them would be accepted. I am quite sure that they would have to be modified. And we want, you know, some years down the road from now we want to prepare for that as well.

So even if we make no recommendations -- for example, on three and four, we say on three and four that these should not -- would not be appropriate for federal funding at this time or whatever recommendations, we really want in my view to lay some groundwork for how you might think about this as we go ahead. And I think if there were not any benefits from this we all would agree that, you know, this would probably not be in front of us if there were no benefits.

So we have to have some view of what these benefits are. The issues that were raised this morning in some of the public testimony is asserting, and perhaps correctly, that there are alternatives to this that are sufficiently close and real.

We heard opposite ends of that here this morning from different people who spoke. Some of them

spoke to the fact that there were alternatives they believed that were viable and important and, therefore, there was no need to go in this direction right now. And we heard exactly the opposite of that from other testimony here this morning. So we are going to have to make our own judgments on this on the basis of the evidence that we will be able to put together.

Bernie?

DR. LO: I would like to raise another issue that sort of runs through and try and get a clear sense how it applies to these four situations.

I think most people would agree that embryos are deserving of special respect more than is due to sort of other conglomerations of cells. I think people disagree very, very strongly of how to interpret that and what it means. Some people, as we heard this morning, said it means you cannot do any research that denies the embryo the chance to develop into a fetus and a child. And others may take the view that it means that you should use the fewest embryos needed to do the research.

I guess what I am not clear about is if you have an embryonic stem cell line where you do not need to

sort of use more embryos to create more embryonic stem cell lines to carry out the research program, is it better to just sort of use what is there as opposed to continue to make more cell lines? Is that a sort of point where people would think that there is less objection to sort of using a stem cell -- an embryonic stem cell line that has already been derived and set up and growing in someone's lab as opposed to taking more "spare" and excess embryos and creating more embryonic stem cells at least at this point in the research?

DR. SHAPIRO: Steve? Trish, did you have your hand up?

MR. HOLTZMAN: This is just a real quick --

DR. SHAPIRO: Okay. Steve and then Trish.

MR. HOLTZMAN: -- which is if you look at what has taken place in the history of embryonic stem cell research with mice, after a certain number of passages, right, cells do not work as well and so for the -- you know, we have had ES cells in mice now for like 17 years or so and they are continuously making new cell lines in order to have the properties that you are going to look for in terms of being able to control differentiation.

DR. SHAPIRO: Trish, I am sorry.

MS. BACKLAR: I think that actually I said this last time. Bridget Hogan, I think, told us at our meeting in Princeton that it is very difficult to keep these cell lines going.

DR. SHAPIRO: I cannot speak as a scientist on this issue at all as you all know but I have -- we will know more when we review our science chapter and put more credible information in front of the commission so I am not -- this is not by any means an assertion but only my understanding of what I have learned from speaking to scientists about this, and others about this, namely that to take the extreme, a single cell line reproducing forever and ever and ever is just not viable and not -- even if you could do it, which is very unlikely, there is -- it is too specific and too specialized and too much of a single case to really solve most problems is what I am told.

Now we will get better and more credible statements than I could possibly give on this for the commission but I think it is -- my understanding so far is that while, of course, in some sense -- now I am giving my

own opinion -- it is better to use existing cell lines if you have the choice. If that is sufficient that seems quite the right place for me to be -- for one to be. If it is not then one has a harder decision to make.

Let me get -- excuse me, Steve, I am sorry. I did not see your hand. I apologize. You have to throw your hand in the air here and catch my attention or just start speaking.

MR. HOLTZMAN: The statement was made that we all believe that embryos deserve a certain kind of respect distinct from that which is attributable to other clumps or cells or somatic cells. And the line of thinking reflected in this whole conceptual scheme, as well as the point you were just making of the all things being equal, better not to generate new cells if you do not have to, reflects a certain view, which at least in my opinion the changes in our knowledge and technology are starting to challenge what it means to respect an embryo.

And what is an embryo in the sense of where we run into them in the world? The world used to be a lot simpler. We only ran into embryo in women's wombs and respecting it meant respecting and taking care of it and

letting it come to term.

And when we ran into somatic cells, they were simply things that flaked off your skin and your hair.

And what has taken place in the last few years is a great blurring of where we are running into these things. Again I said this at the last meeting that the great lesson of Dolly, at least to me, is that the clear bright line distinctions between an embryo and a somatic cell, and where and under what conditions a somatic cell can become an embryo is up in the air.

And I think that ought to raise questions about what is the nature of respect and I think, Harold, when you said we need to look to where the science is going in the sense of what is the world we might be inhabiting and that reflect in our moral judgments at least an awareness of that or at least our scheme I think is very, very important.

And we may find that certain ways of thinking, which given where we used to run into embryos and only run into embryos that made sense, may be changing.

DR. SHAPIRO: Thank you.

Alex?

PROFESSOR CAPRON: There is a core of what you have just said, Steve, which I agree and we have to be clear in our discussion as to what we are talking about but I think it is an over statement to suggest that we are left with no line here and that, in effect, all the cells of my body are equivalent to a human embryo.

The method used in Dolly produced a viable embryo and became Dolly using an egg. There is no indication yet that it would be possible to take a somatic cell and create from that cell without the use of an egg a viable organism.

At the very least it could be said that until that manipulation has occurred you do not have a situation that is equivalent to what concerned us about the embryo. If we get to that point then being clear, which I agree with you, this is the point which I do agree, if we get to that point then being clear why we cared about the embryo in the first place becomes important. It is not just the adventitious fact that embryos were equated with babies because they were always in the form of babies to be, shortly to be, by the time we knew they were there.

The same issue after all has already been

raised by in vitro fertilization and the existence of embryos in freezers or in petri dishes or whatever.

So I do think we have to be clear about why we care but I think it is obfuscatory now to say the lines are all blurred and we do not really know -- how can we rely on the old standards about what are -- why we cared about embryos until we are at the point that some other cell, a somatic cell, goes all the way back to becoming something which could become a human being if implanted in the uterus.

We have no reason to think that that is true of ordinary somatic cells absent their being inserted into an enucleated egg or with a chimera process, maybe not even an enucleated egg. So I -- I think we do not serve clarity of thinking by over emphasizing how blurred the lines are now.

DR. SHAPIRO: Okay. I have a number of people who want to speak. Jim, then Arturo, and then Bernie.

DR. CHILDRESS: As we work on even the ethics part of this, as well as the broader conceptual part, I think the kind of question we are asking is going to be exceedingly important to keep in mind, and let me -- for

example, I note I agree with Alex and am largely against Steve at this point, but if we are trying to think about whether we should have policies of respect that say do not use if you can avoid using embryos in cases two, three and four. Do not use -- many of you can use only a few, et cetera, et cetera, and setting certain kinds of presumptions.

But we need not actually all agree that -- on the status of the embryo and exactly how much respect should be deserved in some larger philosophical sense. But actually recognizing the kind of moral controversy that exists in a society about the embryo may still lead us to support certain kinds of policies that embody this sort of respect. I think that we may end up without -- as we have in some other areas -- getting a consensus on certain levels without getting the consensus about the status of the embryo.

There are certain things -- that understanding the terms of respect that may for some of us be justified by strong convictions about the status of the embryo and maybe for others justified by a recognition of the serious moral controversy in the society about the status of the

embryo but still I think we may come to the same point in terms of what the respect might involve.

DR. SHAPIRO: Thank you.

Arturo?

DR. BRITO: I agree largely with what Alex said and I think where a light bulb goes off in my head is when I hear the word "viability" and I think that is very, very -- I mean, I have said this before but this is the key word here for me at least because I find it more reasonable and more acceptable to derive the cells that we are going to be investigating from somatic cell nuclear transfer techniques because at this point we do not know if that embryo or embryo-like structure is totally viable.

Whereas, I find it more objectionable to use the cells from elective abortion. I know I have said this before but I am saying it again because the key word here is viability because we know that those cells came from a viable fetus or embryo. So that is where I feel that there is some sort of -- and I have not put it all together yet and once again it is obviously a difficult issue. That is where I feel there is some hypocrisy and some -- where the controversy lies.

I would feel more comfortable personally creating an embryo and utilizing those cells versus one that is already existing that we know has a potential for human life.

DR. SHAPIRO: Bernie, and then Eric.

DR. LO: I wanted to go back to Steve's question on whether these sort of new scientific events are sort of rough outlines that have been part of sort moral discussions.

I think it is important to raise those questions and to ask them and we probably should provide some guidance on how to think through it and I think Alex's comments and Jim's comments are ones that I by and large agree with.

I think we have to also make a distinction between what -- a somatic cell may be cloned if a scientist manipulates it in certain ways in the laboratory versus what it can do with relatively simple things like implanting it in a human uterus.

I mean, to some extent, you know, all sperm and oocytes then are a lot closer to being potential human beings than somatic cells because what you have to do to

make them totipotent is a lot less. And yet we felt very comfortable saying, you know, there is a line between gametes and zygotes. So I think that has to be part of the discussion. Yes, it is theoretically possible but the types of manipulation really sort of -- are not the sort that you can say that the somatic cell is equivalent to, to an embryo.

DR. SHAPIRO: Eric?

DR. CASSELL: Arturo, I want to pick up on what you said before because I think that that viability issue is important but I take it that that aborted fetus -- is that viable in your sense? That aborted embryo, three-month aborted embryo, is that viable? It has been aborted.

DR. BRITO: It has been aborted, no. But then it raises the complicity issue. It raises the issue of if you are a scientist utilizing the cells from an electively aborted fetus then what you are -- in my mind you are agreeing to the fact that it was okay to abort that fetus.

DR. CASSELL: I see. But the fetus -- so we can keep separate the acts of individuals for a moment. The fetus itself is not viable.

DR. BRITO: We can keep it separate but I am not -- that is my fear.

DR. CASSELL: Well, I understand that but for the moment, though --

DR. BRITO: That is right. I do not have any problem with the spontaneously aborted fetus.

DR. CASSELL: Right. And the same thing with the excess embryo. The minute it is not viable, what is that?

DR. BRITO: Okay. We go back. I agree with one of the -- the lady with the public comment. I am sorry I do not remember her name earlier. I have issues with the production of excess embryos through IVF. So -- and that is not where we are at. I understand that. So in this case I guess an excess embryo that is going to be discarded --

DR. CASSELL: Yes.

DR. BRITO: -- from a legal point of view it would be more useful to utilize that for scientific purposes. So I would be, I guess, willing to agree with that. But we do not know at what point an excess embryo no longer becomes viable. I do not know.

DR. CASSELL: But that is the determinative thing. I mean, we are --

DR. BRITO: Right.

DR. CASSELL: -- I mean, that is an issue of -- a fact that can be determined.

DR. BRITO: Yes.

DR. CASSELL: Okay.

DR. BRITO: Okay.

DR. SHAPIRO: Thank you. Do you want to turn your microphone off, Eric, for a moment at least?

Jim?

DR. CHILDRESS: Arturo, let me just raise one question. As I understood your position, it is that if we agree to use the material from a deliberately aborted fetus then we, in effect, approved of the act that produced the -- the act of abortion.

And yet -- and this is the sort of issue that was discussed a lot around the human fetal tissue transplantation research -- and yet if we use tissue or organs from someone who has been killed in a homicide, let's say, we have managed in some way to draw a line between the use of those biological materials or organs

and the acts that --

DR. BRITO: The difference there -- the difference -- yes, and this has been brought up and I have thought about this and I have thought about this. The difference there is when we use the collective "we" or the community that is using this, it is not the same community that committed that act of violence that killed that individual versus the scientific community or the medical community is the one that theoretically produced the elective abortion or was involved in the elective abortion. Therefore, there is more of a risk and more of an association with that. Does that make sense to you?

DR. CHILDRESS: I can see some logic to it but I am not persuaded by it.

DR. BRITO: I do not expect --

DR. CHILDRESS: Not everyone in the scientific and medical community, for instance, is performing abortions, et cetera. So the way you draw a line with the community it seems to me to be --

DR. BRITO: It is illegal to kill --

DR. CHILDRESS: That is a separate issue.

DR. BRITO: Right.

DR. CHILDRESS: The question of legality.

DR. BRITO: But it is -- no, it is not a separate -- it is a separate issue but that is the point. It is not -- then the government or legal -- or legal community and the scientific community are saying it is not illegal to have an elective abortion. Therefore, the next step is -- but is it unethical? No. And no one is going to argue it is ethical to kill someone for no reason or what have you, and it is not legal to kill someone. Therefore -- do you see my logic? I know you are not persuaded but --

DR. CHILDRESS: No, I see it but I am not -- I see the --

DR. SHAPIRO: Could I just ask a question that just comes out of this interchange? Arturo, if I misunderstood, please forgive me. I am just trying to understand carefully what your own thinking is.

An abortion a woman might choose to perform herself. How would that strike you? It is not the community involved. You do not have to answer now. Just that as you think about it -- because I am very interested in your views and hope that you will take some time to

write them down because I really find that very helpful.

Again this is on the periphery of what we are discussing in some sense and so I do not want to -- Kathi?

DR. HANNA: I just wanted to -- for the record -- clarify the issue of viability in terms of the blastocyst or the embryo because in our questioning of IVF clinics and my talking on the phone with people who routinely practice IVF procedures I think it is probably worth the commission being aware, at least if you are going to try and expand on this viability issue, that some of the more progressive clinics have now started a practice where they do not even store what they consider to be nonviable embryos.

So, for example, they might have several embryos in culture that they are watching over a period of 24 hours or so and they now have some fairly good indicators of which of those embryos are likely -- more likely to implant successfully.

Now they do this for obvious reasons, which is that they want to choose the most viable embryo. They want their success rates to go up and they want to have a successful pregnancy achieved. But what happens with

those that do not meet the test, they used to get implanted or they got stored. Now they get discarded.

So I think you just have to think about the fact that it is not just that all of these embryos get stored now. Many of them are discarded prior to storage. So when you are talking about viability I think the definition of viability is also something that is evolving.

DR. CASSELL: Just to intrude for just a moment, that is why it is important for us to move from the abstract statement to the science of exactly what happens with those embryos.

DR. SHAPIRO: Trish, and then Alex, and then Larry.

MS. BACKLAR: Then, of course, one might find that those embryos that are not viable are also not going to be useful to make cell lines out of so that is an issue that must be faced as well.

PROFESSOR CAPRON: I was going to comment on that point. I mean, it depends, I suppose, on whether it is an aneuploidy that is the problem or something about the cytoplasm of the egg or whatever, and one might be a

useful source and one would not -- I also wanted to comment on two things.

I think Arturo introduced the word viability particularly around the fetus in a way which is somewhat confusing in that by viable at say three months of pregnancy or something we mean that if the pregnancy continues there is every reason to think there will be a live birth.

But if you mean by viable the way the term has been used in the context of abortion then those are the very abortions which are almost impossible to do becasue the states are free to regulate and many have to preclude in any, except the most extreme cases, the abortion of a viable fetus, meaning one which could at that moment survive independently outside the uterus.

So I thought for a moment -- I am not sure that was the point Eric was getting to but I think that was part of the confusion.

To underline the point that you were making in your exchange with Jim, both in the examples of some of the early work of America's most preeminent euthanasiest, Jack Kevorkian, and his original proposals of using death

row inmates as sources for research and then later for sources of transplanted organs, and in the alleged practices of the Chinese today in exporting organs from death row inmates, both of those cause concern.

Jim, I would say that a little bit of our reaction there about using that particular source of organs I think is behind Arturo's comment and that it is understandable for people to say where the woman who is choosing to do the abortion is then choosing to donate the fetus afterwards, we can have all sorts of protections so that her decision is not manipulated by the researchers either to say, well, why don't you have an abortion because of the wonderful goals of research or we will pay you in this way or we will give you this or that incentive to do it.

But even absent that, there is a connection which causes in his mind the kind of alarm, which I think you might find if we were talking about organ transplant in the Kevorkian death row U.S. context or the Chinese exporting of these organs that they seem to have available, which is debated whether they come from their death row inmates.

So I think that there is a little bit of a bell that goes off in my mind, although I basically agree that the use of an aborted fetus is like the donation of any other cadaveric tissue.

DR. SHAPIRO: Larry?

DR. MIIKE: I will just wait because my comments are not related to this discussion.

DR. CHILDRESS: Could I just respond? It seems to me that in terms of the use of death row inmates, after they have been executed as a source of organs, that there the big concern is that, indeed, the number of executions will increase. That is also related to the abortion issue but that is not the issue that Arturo was raising. It is primarily a complicity issue with what has already occurred. That was the important point of differentiation.

I think most of the opposition again of the death row -- the use of executed prisoners has to do with -- especially in China, sort of a social cultural context, it may lead to additional executions and that is a parallel that is appropriate, I think, with the abortion one.

DR. SHAPIRO: In any case, Arturo has agreed that he will try to write what he thinks so we will not have to imagine but we will actually have an opportunity to look at that extremely carefully.

Larry?

DR. MIIKE: It was just a comment and I think it is probably more directed to the AAAS and the NIH working group that is going to come out with recommendations.

We are after all talking about the promise of stem cell research and so I would be disappointed if their report and our's do not put it in the context of the research promise because obviously the sticking point is the embryonic source of some of these. So if one talks about a legitimate research agenda in this area, embyronically derived cells are just one part of that overall picture, and I think that it would advance understanding of these issues within the overall scientific enterprise if that is placed in that that context and that is why we get into some of the other issues that Bernie raised about alternatives.

So I hope that we do not just sort of focus

blindly on the four choices and talk just about the embryonic issue.

DR. SHAPIRO: I think we have every intention to look at the broader perspective here even though the request is that we come down with some recommendation in this area and we have to answer that directly but I hope our report will speak to certain broader issues that not only will be useful now but might even, if we are careful enough, be useful as things unfold in the years ahead in ways that we cannot really fully predict.

PROFESSOR CAPRON: Arturo, one question. Do you intend in what you are going to write up to explain why you thought somatic cell nuclear transfer embryos were a more acceptable source because as I understand the argument, it is that viability there in -- suppose you could produce such an embryo and divided normally, and looked on Kathi's criteria as though it was going to be a "viable" but we have not -- it is a question of we have never had one of these born because there is a prohibition on their being born ergo we can regard them as in a different category.

That -- I have a hard time following that

because the notion of nonviability there derives from a different source, not a lack of theoretical precedent but a lack of actual historical precedent and it just seems to me it would be sort of exploiting the fact that we are unwilling to allow implantation and I just would like to have you spell out your reasons when you write up your document.

DR. BRITO: I will. And it is also contradicting an e-mail message I sent about two months ago so it shows -- a lot of these issues, you know, the fact -- at what point you consider this process as a continuum. Is it 14 days? Is it at fertilization? If you worry about the gametes -- I still have not decided on that. So I will try my best to outline them and maybe in doing that I can -- but I know where you are coming from there.

DR. SHAPIRO: Larry?

DR. MIIKE: Just to revisit a topic that I think Bernie introduced. When we look at the four broad choices that we are dealing with, I think in our initial discussions earlier I said that I really had basically no objection to three or four from an overall conclusion

side.

The issue was federal funding and I think that that is the -- do we have to come up -- and I think -- I know several of you will have differences about what you would feel morally and comfortable about in supporting but feel uneasy about federal funding in those areas.

So I think that is an issue that we have to be very clear about, about why we feel one way on one end and the other way on the other.

DR. SHAPIRO: I think that is right. That issue has come up a number of times and we will have to clarify that. I want to come back in a little while, and perhaps we will probably take a break in five or ten or fifteen minutes, and then we will come back to some of these issues because I want to also revisit with the commission if we are going to draw the line somewhere, where people's feelings are at least at this morning, regarding where that line should be drawn. Is it one, two, three or four, and the use versus derivation, and so on.

There is another issue, which I think is important, if any of you -- any of the members of the

commission have any views on it, it would be very helpful as we begin to develop or produce the ethical framework that is going to underline -- that will eventually have to underlie our recommendations.

And that is if we are going to recommend that there be some situations where a derivation of stem cells would be appropriate for federal funding, particularly let's just take the case two just as an example. We have to be able to articulate and should be able to articulate on what basis we think this may be so. Of course, we have the issue of a scientific promise and so on. We think that is important but we do not think that is sufficient all by itself.

And, therefore, inevitably one is drawn to the -- in my judgement, inevitably one is drawn to asking one's self the question that has been around for a long time and no one has been able to resolve -- I mean many people have resolved it in their own minds but have not convinced others -- and that is the -- how we are going to think about the moral status of the embryo. There is lots of commentary on this -- on every conceivable point in this spectrum here. People -- different people feel

strongly about their own views.

But there is no way of escaping the fact that if we are going to say that it is legitimate or it is a legitimate object or project for the use of federal funds that one has to have a view of what the moral status of this is and more important than that how does one go about -- not arguing that so much but how does one go about supporting that? How does one articulate that in a way that is satisfactory to one's self and one's own view of why it is this seems to be appropriate?

We have heard this morning, and these arguments have been raging around the world for a long time, there is nothing new here between those who have a very definite view about, for example, the moral status of a fertilized egg or the embryo, and there are alternative views of that -- what that moral status is.

But that is as we have just -- as I just try to think ahead and try to imagine how we are going to develop our thinking on this and how we will develop our arguments on that, the framework by which one reasons here is really quite important. And so if any of you have any views of that -- we, of course, will be working on that

but if any of you have any views on that, that will also be very helpful to us as we think through drafting material for your consideration.

So if any of you have something you want to think about for a little while before -- a little while, in this case being ten minutes, not weeks -- that is really going to be quite important. I do not think we -- I do not think we should sidestep that issue and just issue sort of a declaration on the matter.

So, Larry?

DR. MIIKE: The other issue is whether we take a narrow focus about the derived issue for stem cell research or we deal with the embryo itself. I do not think we have reached any conclusion on that and obviously some of our contracted papers tell us that we must address those issues.

DR. SHAPIRO: Yes. Other comments before we break?

Okay. Let's take a 15 minute break. It's 3:15. Let's reassemble at 3:30.

(Whereupon, a brief break was taken.)

DR. SHAPIRO: I would like to get our meeting

started again if I could have the attention of the commissioners.

There are a number of issues that we are going to have to address as we work our way through this. I would just like to highlight some of them to make sure that commissioners as they try to think this through either provide us with their own views -- they may have some comments right now but in any case it is something that will be important to us as we write this report.

First of all, as has been said and as we have reminded ourselves a number of times, what we are trying to do is to come up with some suggestions with respect to federal funding in this area. That is a different matter. That is a somewhat different matter than just dealing with the issue as a general issue for society as a whole.

I think it will be quite important for us to be able to articulate what the benefits are for making -- if it is appropriate for federal funding. We could make all kinds of arguments regarding how good an idea this is for various people to pursue. It is yet an additional supplementary argument perhaps to say not only is that

true but for various reasons it is important that the federal government participate in the form of sponsorship of some of this kind of work. That is a very, very important element of what we are doing. That issue is discussed in a number of the papers that you have had in your book both this time and last time. I do not think that is an issue which would cause us any difficulty but nevertheless we will have to articulate that.

So if any of you have some ideas which you think are important for us to include regarding the special reasons or any reasons you might have why the federal government should participate in the sponsoring of this kind of research. It is very important for us to understand what your intentions are in that regard.

So let me just see if any of you have any comments right now. If not, that is something I certainly would like to hear from everybody or for those of you who have views on this matter I would like to hear from you. But anyone now want to speak to that issue right now or is that an issue you are comfortable with and so on?

Alex, all right, if you want to.

PROFESSOR CAPRON: As you say, we have heard a number of times that there are two advantages to federal participation. One, it involves the oversight mechanisms, whatever we are designing especially for this area and the general IRB type oversight mechanism, which may not occur with privately funded research. And I think our experience with the whole in vitro area having been excluded from federal funding and the way research is carried on with patient dollars on patients with much less supervision than would have been the case if it had been done at NIH is an example we can cite.

The second argument that was raised, and which I think has some merit but I do not think we heard all the evidence about it, would be that the sponsorship of this primarily or solely by Geron and other private corporations may lead to either -- to various forms of protection of intellectual property through patents or trade secrets or whatever, which are not conducive to the best development of science in this field and the accessibility of the techniques to the broadest therapeutic use. I think I would want to know more a la Blumenthal's and other people's background material on

that.

The point that I hope we will not confuse here is that we have to argue for the funding of this area compared to other priorities in science. I do not think we are in a position to make that judgment and anything that we say about the importance of the federal government should be, it seems to me, paying for this. That is it should be said in the sense of not having a prohibition on it rather than -- or the value of not having a prohibition on it rather than this is research that should be -- should be funded when there may be other more valuable research for those dollars that we are just not competent to judge.

DR. SHAPIRO: I think it is true that -- the very last point that you make. It has always been my understanding that we were not setting the scientific agenda for NIH or anyone else. We have views on this but that is not what this commission is about.

Would you -- in addition to the issues, the two items you raised -- there is a third item which comes up, I believe, in some of the material that has been prepared for us, which just deals not so much with the

exclusion of a very large proportion of the community that could work on this as opposed to the fact that it happens to be -- the part that does work on it is in the private sector and that may have certain characteristics.

Independent of that is another issue, it seems to me at least, that is the exclusion of any large group that might bring some vitality to the work in this area.

PROFESSOR CAPRON: Well, the difficulty with going very far with that argument is certainly some researchers in the in vitro field simply left the federal government and went to private clinics.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: And Thomson himself wore two hats. So he was able as a researcher both to be doing federally funded research in one lab and Geron funded research in another. So I am not sure that the latter argument is as convincing as it would be if we were faced with people sort of having to commit themselves to be federal -- I mean, I am not sure you can be a federal employee and do it that easily but certainly if you are a researcher in the universities you could --

with some difficulty. I mean, it is more cumbersome but it is not -- it does not seem to me it excludes a whole category of excellent scientists from ever working in this area.

DR. SHAPIRO: Bernie and then Eric?

DR. LO: To try and develop further the thoughts that Alex has been setting forth, I think there are a number of arguments that fall into the category of NIH support could arguably enhance the quality of scientific work, and there are things like the peer review process at NIH is a lot more thorough and a lot more rigorous than typically may take place in the private sector.

It is often investigator initiated research, which means there is sort of a broader base of ideas and it is thought that a lot of good ideas need to come from different people rather than one person or one company driving the research agenda.

I think this point that Harold and Alex were just talking about in terms of attracting a larger number of investigators, of which a lot would -- some would be of much higher quality -- it is a real hassle to set up a

lab to do this kind of research now. You basically have to set up a whole separate lab and have very strict bookkeeping and accounting to be able to demonstrate that no federal dollars were used even indirectly. You have to make sure that the paper in your Xerox machine was not paid for by federal grant. So you basically have to have two completely different labs.

And I think there are a lot of investigators who are not willing to do what Thomson and Gearhart did or institutions may find it difficult to do.

But more than that I think it is the younger investigators, not the established stars in the field, who just may not be in a position to do that kind of work and it is typically the -- you know, certainly under the current set up at NIH they are really pushing the R01 series grants for young investigators to sort of launch their careers in a long term basis and I just do not think that is the way -- Steve could contradict me but I do not think that is the way a lot of privately funded research works.

Finally, I think the NIH gives you a mechanism for long term support and that once you start

getting NIH grants, you know, there is the expectation that at the end of the grant if the work goes well you will turn around and write another grant. So people really view that as a potential long term support for an ongoing research program. Again, a lot of things you hear about public -- privately funded research is that if it does not really pan out, not in a scientific sense but in a commercial sense, the longer research may be cut off and you may be left scrambling.

So for a young researcher it is just harder and a bigger risk and I think not as easy to do so there are a whole lot of arguments that put together suggest that the quality of the research will be better if there is federal support for it.

DR. SHAPIRO: Eric?

DR. CASSELL: I think all those are good arguments and they are practical arguments but there is also the case that I have difficulty seeing us as a bioethics commission coming up with a partition that divides its ethical here and it is not ethical there.

If the arguments are good, and I think we have persuasive arguments, then, in fact, it ought to be

across the spectrum of funding for research and I would find it difficult, though I also understand there are practical reasons why that might come about.

But I would think that to some extent we would not have succeeded if there was a partition between the kinds of funding.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I would caution two lines of argument against -- or at least be careful about the two lines of argument I have just heard but encourage a third. The first -- Alex said he would tentatively -- this whole issue of the accessibility to the results of the research.

Under the Bayh-Dole Act, federally sponsored research, universities may license it under an exclusive basis and that can prevent others from getting at it. So, for example, it is important to know that the fundamental patent covering primate stem cells, including human stem cells, held by the University of Wisconsin licensed exclusively to Geron was from federally funded work. So I think when we look at this we need to look at it very carefully.

Second, I would caution against the whole issue of quality of the research. I am not sure I would want to say in any sense categorically that research going on by investigator X at Harvard on day T-0 is better in quality than when he moves across the river to Millennium and is conducting exactly the same research. Okay.

(Simultaneous discussion.)

MR. HOLTZMAN: With better equipment and with better reagents, et cetera, et cetera. Okay. And often because --

(Simultaneous discussion.)

MR. HOLTZMAN: No, there are no assigned parking spots.

So I just want to be -- we need to -- but I do not even think we need to go there because I do believe we have had a very, very successful biomedical, industrial, academic complex in this country which has produced the best medicine in the world and there has typically been a role for both.

What is disturbing in the current context is industry is being assigned the exclusive role to go back

and do the most basic kinds of research in this area and it would be much more effective if the academic community was able to do that on the basic processes of cell division on the basic factors that are involved in these differentiation processes and that the industry could focus on, for example, what does it mean to produce a QC'd stable cell line of a certain kind, and that you would have a better division of labor.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: I have said this before and it is -- I do not know whether it is true or not but to me from what I understand about this -- the potential in this area is so enormous that it would cripple NIH as a research institute if they shut off this. So I use the word "NIH" as a second class institution as a possibility.

DR. SHAPIRO: Thank you. Let me move our discussion. That is very helpful. Thank you all for those remarks. Let me move the discussion to another area, which in some sense is also -- maybe really a little more straightforward but maybe not. I am in any

case very anxious to get commissioners' response if they have any, and that is the question of oversight.

It has been mentioned a number of times as various people have talked today about case one or case two and so on but there is -- any views you have regarding what would be the appropriate level of oversight regarding work in this area, I think, would be helpful as we try to build the structure of an argument here together and some recommendations that we might put together.

So does anyone have any views regarding appropriate levels of oversight? Let's take case one and two for the moment that we -- obviously, analogous things in case three and four if we get there and so on.

DR. CASSELL: Just as a question of information. Could we hear more about what the British system of registry and so forth is some time even if it is just a brief --

DR. SHAPIRO: We certainly can. As a matter of fact, I have in my briefcase a description of it which I would be glad to give to you or have -- Eric, I will distribute it. Essentially you need a license is the

essential response. But, yes, I will give that to you and we will certainly supply it to everyone.

Bernie?

* * * * *

E V E N I N G S E S S I O N

DR. LO: Let me just sort of go back in time and set forth some of the recommendations of the much maligned 1994 Human Embryo Committee suggested in terms of oversight because I thought actually that was some of the most interesting things that commission -- committee did.

We were very concerned about how to provide meaningful oversight in a very complicated and very new situation and the proposal was made that there be a time limited national review of this research for a number of reasons. First, concerns about whether local IRB's were really in a position to sort through all the difficult issues both in sort of the large scale issues and specific issues having to deal with particular cases or protocols.

We also thought that in a new area there was a value to trying to sort of bring together experience on a series of cases to sort of derive or infer or bring forth a set of guidelines that could then be used by other -- together with case examples, which could be used in a more sort of decentralized way.

Pat King coined the sort of term sort of a common law set of cases of protocols involving human embryo research.

At the same time there were concerns about setting up an administrative body that could have a lot of drawbacks, including the situation of requiring approval from a body that if it was not appointed could never approve anything and, therefore, no research could proceed. So there is a lot -- some attention given to how you would actually make that work without either making it very cumbersome or providing the opportunity to stifle the research by just not providing the appointment of the members of an oversight committee.

But I think that the line of thinking that said that we were very -- given the newness of this work, the clear moral controversy surrounding it, if it were to be federally funded it would deserve oversight above and beyond the oversight that is now part and parcel of every sort of NIH review grant. We are not convinced that either the study sections nor the councils at NIH nor the individual IRB's was going to provide the level of oversight that would really persuade the public that this

was all being done in a responsible manner.

DR. SHAPIRO: Other comments regarding the issue of oversight? Alex?

PROFESSOR CAPRON: We have had at previous commission meetings analogies made to the Recombinant DNA Advisory Committee, which has some of that same kind of history, Bernie, of a common law in the sense of cases or situations being considered and then in light of a pattern rules being derived and changes being established in what can be reviewed without the national review and what continues to need the national review.

It seems to me that is germane here even if it is not a 100 percent match. I mean, after all, the Recombinant DNA Advisory Committee did come into being before there was any human gene therapy and it was, as in this area, dealing with issues of basic science. Now the reason for concern was not that there was something morally wrong about manipulating E. coli but rather that there was dangers of a physical sort to health workers, researchers and the community. But that is an example of federal regulation of basic research.

As it has moved into gene therapy there is

even a closer analogy because many of the same kinds of concerns arise and as the committee is now considering again the issues of germ line gene therapy some of the same questions come up about trade offs that have to be made. Is the justification for doing a particular kind of therapy on an individual which risks is very likely to cause a change in their germ line sufficient that it is justified -- that it would be justified to go ahead even though that change is one which, in effect, creates an experiment on an unborn child in future generations?

And that seems to me comparable in some ways to the question of is there a justification for moving, for example, to somatic cell nuclear transfer embryos as sources of germ line cells where there is now, let's say some years in the future, enough animal research to show that the therapy would likely succeed in human beings if tried in them, and if it turns out that our best hopes for the use of re-differentiated somatic -- adult somatic cells does not pan out.

I mean, you cannot create heart valves or livers from skin cells of people or whatever. And so it seems to me that that is worth having a body that can

react to changes in the science and we could use the RAC as a partial analogy just as we could also draw the earlier report as Bernie suggested.

DR. SHAPIRO: The suggestion here that I hear from both Alex and Bernie is that if we were to recommend proceeding, for example, with cases one and two, that a part of that should be some type of national oversight. It might be a RAC type group which issues certain rules which tell you when you have to come to the central -- or when you do not, so on and so forth. I am not worried about the details about this at this moment but just to whether you think we should try to construct some type of oversight of that type.

PROFESSOR CAPRON: I would love a word or two from Eric since he has the direct, I think, first hand experience of the Secretary's Advisory Working Group. When the RAC began, it was a fairly small group looking not at regulations at that point. It was just really giving guidance to the secretary. And within a relatively brief period of time its mandate and membership and form of meeting was broadened.

It seemed to me that what Harold Varmus had

come up with was more like that than I had expected. I had originally thought in his description he was really talking about sort of the heads of the departments were going to have an advisory group to him. But it is a group chaired by people from outside the department, et cetera, et cetera.

So it may already more closely resemble this and the question is, is it an ad hoc group to draft a set of guidelines which will then be self-administering or is it already conceived of as a group that would be a standing committee that could serve the very functions we are talking about?

DR. MESLIN: Well, maybe just very briefly I can direct you to tab I, 4-I, and that gives me an opportunity to just correct for the record there is a document that says, "Charge to the Working Group," which is a document that was not widely distributed so NIH wanted to let me -- wanted me to remind you that this charge to the working group, which is in your materials, was not formally sent out all over the place and apologies that it was given the impression that it was signed off on by everyone.

In any event, the working group to advise the advisory committee of the director, which met recently and has produced the guidelines, a draft set of guidelines, which I would say, if there are NIH people who may wish to speak to this, are now being worked on, has a statement that describes what they believe ought to occur and it talks about informed consent and it talks about areas of research that are ineligible for funding.

What they did not do extensively at that meeting was talk about the actual oversight mechanism that would occur. Discussion was not finalized and that working group to the ACD will be producing yet another document.

I would recommend that we wait to see what that document looks like when it is published in the Federal Register in the next couple of days but, unless anyone from NIH in the audience wants to speak to this issue, my understanding is that they are working on that particular mechanism.

It is -- I remember Jim Childress raised this at a very -- a much earlier meeting.

It is the point you just raised, Alex.

It has gone beyond just the administrative review type model. There has been concern about having public membership raised and certainly Dr. Varmus has mentioned that in testimony before the senate as well as in other materials.

DR. SHAPIRO: I do not want to take too much time on this now but I do not hear any negative reaction to the fact that as we think through oversight, regardless of who the body is and how it is appointed, which is of course very important, that some type of responsibility at the central part of this at a national level is appropriate.

Is that fair or unfair? Does anyone think that is inappropriate or somehow creating a monster of some kind that we will not know what to do with later?

PROFESSOR CAPRON: I hope we -- if we go this way, I hope we exploit --

DR. SHAPIRO: Of course.

PROFESSOR CAPRON: -- the strength of it for us, which is not every issue has to be resolved.

DR. SHAPIRO: Right. Exactly.

PROFESSOR CAPRON: Which is prudence rather

than cowardice in my view.

DR. SHAPIRO: All right. We will not poll on that issue itself but that is right.

Bernie?

DR. LO: Another point that we might want to think about is if such -- if there is federal funding and if such a national oversight body is set up, should they be allowed to review research funded in the private sector which would otherwise not have to go through review and should, in fact, such research be encouraged to go to that body to provide some assurance that all research, whether or not it was federally funded?

A couple of meetings ago we had the ethics committee from Geron come and speak to us and it struck me that that was really formed after many of the crucial decisions were made and they were sort of asked to sign off on something that happened and not provide really prospective oversight.

Again, I think the public could be very concerned about whether the types of "oversight mechanisms" set up in the private sector by some of the companies doing this research really provide the kind of

meaningful oversight that is desirable.

DR. SHAPIRO: Kathi?

DR. HANNA: I just wanted to get some input from the commissioners about whether you think it is worth us trying to find out whether non-NIH federal agencies are interested in this kind of work. I have raised this issue before. We tend to think in the NIH paradigm and the congressional ban only applies to NIH. Supposedly if VA wanted to do this work now, they could. Do we want to -- when we talk about some kind of national oversight, do we want to think about whether other agencies should feed into that system or do we just want to keep the recommendation specific to NIH?

DR. SHAPIRO: Bernie?

DR. LO: Well, I think again there is different levels. The general principle that this research is new enough and controversial enough that it deserves careful review, I think we should agree on how to do that if a lot of different agencies are doing it and having jurisdictional turf problems, I think, is a second order question but I would hope that we would agree that it does not matter who is doing it, it ought

to be scrutinized pretty carefully.

PROFESSOR CAPRON: And again the RAC experience is relevant here because -- on both scores that you have just raised. The RAC looked at privately funded research and, indeed, at first there was a very strong encouragement that private sponsors should use the RAC and the responsible thing to do was to use them. In later years, Dr. Varmus became skeptical of what was happening in the gene therapy area on the sense that the RAC was being used to give a false imprimatur of NIH level review to protocols that would never have made it through a study section at NIH and that this was -- the private sector really exploited this opportunity for publicity. So there is a tension there.

But, likewise, on the second point, Kathi, I believe we should get somebody to do a little of the history on this but work that eventually was spun off to the Department of Agriculture and so forth in terms of the manipulation of plants and to the Environmental Protection Agency was initially reviewed by the RAC. And it was only as they got to industrial scaled things that seemed to be sort of "me too" phenomenon where they knew

what they were doing or agricultural things that were in that same category then it became apparent that this really ought to be handled by an agency with more expertise on environmental issues or on agricultural issues and it was divested from the RAC. But that was stuff which -- I do not know how much of that was federally funded as such but some of it probably was.

DR. SHAPIRO: Okay. I think that I would like to go on to some other issues now but that has been very helpful and we will start to try to formulate in our minds some kind of process here which are going to be responsive to the kinds of issues that were raised here this afternoon.

I guess the issue I would like to go to next is really a question to turn our attention to the overall structure of how we are approaching this. Now we have been encouraged from the beginning to approach this in steps, i.e. from the most controversial -- from the least controversial to the most controversial, however you want to go up or down that scale, and that is legitimate.

I think -- I think that is a legitimate -- I think the point Jim was making before, I hope I do not --

have not misunderstood you, Jim -- was that one approach we could take would be that -- some people might believe that that is -- for their own moral and ethical reasons consider that an appropriate approach. That is they feel comfortable for their reasons with cases one and two again, for example, and not so comfortable with three and four. Or perhaps, Arturo, it would be one and three and not two and four. I mean, I have -- I do not -- I mean, not everyone would have the same ordering here. I think that is clear. But you could feel that way because of one's own consideration of the moral and ethical issues involved, however you understand them.

One, however, could also feel that way for another reason, namely that there are differences of opinion on these issues in our country and we might feel that we have to recommend or should recommend something that is responsive to that fact. Something that is sensitive to the fact that there are differences of opinion and people have strongly held views on different sides of this issue.

And, therefore, given the scientific agenda and given the benefits and so on that we see that it --

as a matter -- to use a word that Alex used just a few moments ago -- it is a matter of prudence to take a single step now or recommend -- I should say, of course, we are not in charge of any steps. We are just going to be recommending something now, allowing more time for further discussion, clarification and other issues, and not having to resolve all the issues right at this moment.

That -- it is really quite important if we are sort of comfortable with that general approach because how we articulate the positions will change somewhat. Rather than having to put forward, for example, a particular moral perspective that we would then have to argue dominates all the others, which, I think, as we all know, would be a difficult task.

We could look at the issues that are there from various points of view and then say, "Well, in view of all this, this is the kind of thing we think is appropriate at this stage."

So that is -- Jim, forgive me if I have sort of summarized or caricatured your point rather than do it justice.

But I think that is an important issue for us and I really would appreciate any reactions various committee members might have as to whether that might be a useful avenue to try to articulate in a careful and thoughtful way.

Any views about that?

Arturo?

DR. BRITO: In terms of ordering them, it seems to me that the most logical way and the least controversial way would be ordering them or ranking them -- not ranking, ordering them in terms of what is most allowable legally to least allowable legally and not phrase it in the term of morally or ethically. That way you avoid the controversy of what -- and approach it from that angle.

DR. SHAPIRO: That is one way. I will let Professor Fletcher speak for himself since we have tended to use the cases he suggested. I understood them to be from least controversial to most controversial, is the way I understood it. Have I misinterpreted it?

DR. FLETCHER: That is right.

DR. SHAPIRO: And that may also -- they may,

in fact, sort of relate to this other categorization also.

DR. BRITO: But most controversial and least controversial in whose point of view is obviously the question.

DR. SHAPIRO: Exactly.

DR. BRITO: My question, Dr. Fletcher, would also be does that -- I have not really thought about it in this way but does that coincide with what is most legal and least legal or least likely to be legal?

DR. MESLIN: Would you come to a microphone?

DR. FLETCHER: I had not factored in the legal aspect. I was thinking in terms of degree of moral controversiality. But case one is legal both federally and in the states. Case two is illegal federally but legal in every state except Louisiana. Case three is --

DR. SHAPIRO: It is a legitimate -- do you mean legally federally -- that just means that it is illegal federally, that is you cannot use federal funds?

DR. FLETCHER: Federal funding.

DR. SHAPIRO: It is not a federal crime.

DR. FLETCHER: No.

DR. SHAPIRO: But you cannot use federal funds.

DR. FLETCHER: I meant illegal to use federal funds.

PROFESSOR CAPRON: You are speaking derivation now.

DR. FLETCHER: Yes.

Case three has never been tested but is -- in theory would be legally permissible except with federal funds. And case four is like case two in the legal -- that is legally considered.

DR. SHAPIRO: From the point -- I am just trying to think through this quickly. I had not quite thought about it this way, Arturo, but case two, three and four are illegal in the federal sense the way you have been talking about them but there is no -- other than Louisiana, there is no other legal constraints.

DR. FLETCHER: That is correct.

DR. SHAPIRO: So there is -- in some sense, similarly legally although it might be hard to order them that way.

DR. CHILDRESS: But there are some state laws

relating to the creation of using human cloning to create a --

DR. SHAPIRO: Yes.

DR. CHILDRESS: -- child.

DR. SHAPIRO: In more than one state, right. Two or three. Two states.

DR. CHILDRESS: California. And which other?

PROFESSOR CAPRON: I cannot remember. Is it Minnesota, Maryland -- they are not close to each other but there is one other state besides California. California did it first.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: Michigan.

DR. SHAPIRO: Michigan.

(Simultaneous discussion.)

DR. CHILDRESS: It is Michigan, I think.

PROFESSOR CAPRON: Okay.

DR. SHAPIRO: I think that is correct. Some states.

(Simultaneous discussion.)

PROFESSOR CAPRON: No, no. This is cloning we are talking about. I think it is California and

Michigan. But the aim -- they are badly drafted perhaps but I think aim at reproductive cloning and so they would not reach except if they over reach -- that is to say if you are making it in the lab and you have an embryo that you have created in this fashion you might now take the next step and so we are going to make life difficult for you in some way.

Arturo, it seemed to me that a lot of the time in this area what we say is that the law ought to reflect considered moral judgments and so the question that I thought Harold was putting to us was, was there a way in which we could show that there is a large overlap as to what policies people, who actually reason somewhat differently ethically, would agree is a sensible policy translating that into law rather than in this area expecting the law to be the primary guide.

I mean, we are really at the edge of formulating a legal response to many of these things and certainly those people in the congress who have said that they, having agreed with prior bans on embryo research, are moved by the notion that stem cell -- the prospect of benefit from limited forms of stem cell research are

great, have seemed to indicate that they wanted us to consider, they would like a consideration of whether the policy ought to be changed in light of moral reasoning.

And I thought Jim's suggestion of the way to proceed was a sensible one because Harold says it may be extraordinarily difficult for us to say this one ethical view trumps all others.

DR. SHAPIRO: Just as a point of information, I do want to point out there is something, which I have not read carefully yet because I have just received it yesterday, what I think you all have is a draft of Lori Andrews' material on state regulation of embryo stem cell research and so on. My brief glance at it late last night seemed -- made me feel it really was quite a good compendium and might be very useful for all of you who want to, you know, check up on this and get a little more informed on this. I think this is -- I know we have not had a chance to read it because you all got it too late but it is, I think, a useful thing for us to have.

And when reading this if there is more information you want on this legal type issue, please let the staff know. This seems quite comprehensive but at

least let us know if you want more information.

Did we interrupt you?

DR. FLETCHER: About the recommendation that the commission adopt a legal basis for its recommendations about these cases. My own thinking about this is that a moral argument is necessary to discuss federal funding in any of these respects because of what Alex said about the law being a reflection, we hope, of broadly acceptable moral considerations.

The law expresses our values and our moral ideals. In my recent paper or draft of it, I discussed the concept or the relationship of law and morality and that law can be a floor for morality but not the ceiling. It is not the ceiling of our moral ideals.

So in that framework and where I am going with the main moral argument in the paper is as follows: That analysis of the cases shows that case two is more like case one than it is like cases three and four if you accept the argument that the discard issue makes it more like case one. It is true that is different because embryos die in a different way in case two than fetuses die in case one.

But even if you find that close similarity that is still not enough to make a convincing moral argument that federal funding ought to support interagency -- and I would say, Kathi, NSF activities. I think the National Science Foundation is quite interested in this issue and would probably fund some basic research here but a convincing moral argument is needed.

In thinking about this and in rereading Ronald Dworkin's work in Life's Dominion and a rereading of Commissioner Charo's work on her reflections on the ethical work of the Human Embryo Research Panel, I am considering, and I am writing about, a twin argument in terms to support the concept of federal funding of case two.

On the one hand rather than focusing exclusively on the moral status of the fetus -- of the embryo, as I think that you can be so focused on that issue that you freeze in terms of the two dichotomous views that are represented by the Human Embryo Research Panel's report on the one hand and the ban on the other. And whenever I think about Washington I do not think about it these days as divided by the Potomac. All

right. I think about the Human Embryo Research Panel's report and its pluralistic approach to the moral status of the fetus that brought many criticisms on the one hand and the federal ban on the other.

And I think the NBAC has an opportunity to push beyond that and using Professor Dworkin's framework I think it is a step deeper -- it goes a step deeper and it would go like this: That if what could unite conservatives and liberals on this issue beyond their differences about the moral status of the fetus is intrinsic respect for life and you look at what people on both sides of the issue -- how they would interpret that principle in this situation -- conservatives do not believe that the embryo is a person with full rights of a person, which include the right not to be killed.

A conservative thought admits that embryos have the potential to become persons rather than the full status of a person and it is in respect of that potential of the genetic and the environmental interaction that they believe society owes embryos protection.

On the other side, liberals do not believe that the embryo is mere tissue or nothing. People with

liberal views have respect for the embryo and that has been the main theme of the commissions and the panels that have dealt with this issue before. So that liberals and conservatives might interpret the claims of an intrinsic respect for life differently but you do have some moral ground there to unite both groups, which could yield important protections and processes for embryo research.

But this principle in my thinking is not enough and here is where Professor Charo's work comes into the main argument.

The other principle that we have to pay attention to is justice because when you are talking about federal funds you are talking about distribution of benefits as well as risks and there are winners and losers in terms of how these federal funds are distributed.

In my thinking about the justice issues and who wins and who loses, what it comes down to is if you have no federal funding -- you maintain the ban completely and have no federal funding for case two then it not only slows down the process of getting to clinical

trials with stem cell research but what it means is that you have to accept the increase of suffering or the delay and relieving suffering of very many people as well as tolerate early deaths. So there is a price to pay there for not recommending or not acting on the obligation to fund this research from the federal side.

If you permit federal funding there is suffering of the persons with views who believe that human life -- not only is human life being killed but embryos having status of human beings are being killed and there is a great deal of moral suffering involved in that. It is not just a perception. It is real.

As one of the speakers said this morning, I think quote eloquently, that he would be placed in the moral bind of watching a relative suffer from not being benefitted by this research as over against watching his fellow creatures and fellow human beings being extinguished and, of course, in order to do good that is a terrible bind.

But where you come out on the justice issues I think is very important and it seems to me that in the political process there is a strong argument here for

recommending federal support of case two in principle -- in principle -- and then letting the political process take care of timing. I do not think the NBAC ought to get involved in recommending at the level of when and how the political process ought to work in amending the ban.

I think there is some virtue in waiting to watch the NIH process in terms of funding uses of embryo -- of derived embryos with private funds, how that works out, whether they can really manage this well, whether it produces some clinically relevant results and especially having those who need embryos for research justify the need. In other words, just do not take it for granted that there is a need. There has got to be a demonstrated justification for the need for embryo research.

So if you put these two ethical principles together, which I would describe in terms of shorthand of Dworkin and Charo, then I think you have a much stronger moral basis for recommending federal funding. This is the direction of my thinking.

PROFESSOR CAPRON: The ethical principles would now read non-maleficence, beneficence, autonomy, justice, Charo.

(Laughter.)

DR. SHAPIRO: On some of the comments you made regarding the fact that we should not -- that you would not recommend just because people say they need something that they really need it. This is too controversial an area and they would have to demonstrate or convince.

That is an issue, of course, that has been also carefully addressed, Eric, in the British regulations which you asked about before and they have a series of conditions, which to me seems quite reasonable. I do not remember them all and I am not going to attempt to repeat them.

But really do sort of run along the line of exhaustion of nonhuman models, the actual need for human models, the human need, that really addresses a real human need. There is informed consent, et cetera, et cetera. I do not have the whole list in my head but it was -- I remember reading about it and it was really quite, I thought, a very thoughtful way of going about it and something we might incorporate in whatever we recommend.

Thank you. Other comments or questions about this? I am just trying to cover a number of issues here so that as we begin to draft material we are responsive to just where the commission is on some of these issues.

One of the issues which has come up a number of times -- let me start this another way. There is quite a bit of material in your books. Of course, there is Jim's paper, which is very helpful. Andy has done a number of very interesting things, I thought, with the materials in the book. I hope you all had a chance to read it. I think the Parens paper is in the book as well. I am probably missing some. I cannot remember all the ones that were in there.

But does anyone have any comments about those? About whether their approaches taken there struck you as useful, the advice useful or not very useful, and impressive or unimpressive? Were you moved by any of it? Were you offended by any of it? I will not ask you if you read it closely enough to decide on the Phyllis (sic) issues.

Eric?

DR. CASSELL: I just want to go back at the

step and ask if in Lori Andrews' paper about state law, what is the status of that law if the federal government approves the use of embryos for stem cell research? What happens to condemnatory state laws?

DR. SHAPIRO: My understanding -- well, I will let some lawyers speak to it -- is if you live a state you have to obey the laws there. That is my understanding. But, Alex?

DR. MIIKE: What we are talking about is federal funding. It is not a law that says that you must.

DR. SHAPIRO: Right.

DR. MIIKE: So just the funding issue and then the sort of state law would still apply.

PROFESSOR CAPRON: It is not like a federal civil rights statute that overrides a local property law.

DR. MIIKE: As a matter of fact, you make the point that that is where -- if there needs to be diversity of opinions and that gets played out at the state, you feel comfortable that some states may say, "No," and some states may say, "Yes."

DR. FLETCHER: Yes. I made the point in the

section about the law and morality on the embryo research that in the long run I prefer a state by state expression of values on the whole question of the status of the embryo in research and on the justice issues, too, rather than a federal ban and that this is the way democracy works best. And I think the states will have more energy about looking at this issue and will want to look at this issue, particularly those states in which a great deal of this research potentially could be done.

So we live in a democracy and I think we should expect that the electorate and an informed judiciary are necessary in order to ameliorate the differences that we have about moral questions.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: Harold, you asked sort of an open ended question. I want to respond on a topic that sort of has reached us in two different directions and that is the difference between case two and case four, the so-called spare embryos and the embryos expressly fertilized for the purposes of research.

A number of things we have read and some of

the testimony this morning suggests that is a meaningless distinction because the number of embryos created in a clinical IVF setting can be easily manipulated by the infertility specialist/researcher and so they will always be able to claim that the intention was to use them for assisted reproductive services but they just happen to be left over.

And then there is the interesting data that Kathi gathered by actually calling IVF centers and saying, "Do you have extra embryos? How many? What do you do with them?"

It seems to me that there are two different issues here. One is, yes, you can manipulate the number of embryos produced per cycle or per couple or per woman or whatever. I agree that depending on the IVF director that number can be either inflated or deflated. But it did seem at least from the data that Kathi showed us that women and couples make distinctions between various purposes to which they are willing to let embryos be used after their reproductive clinical needs are met one way or the other.

So I am just wondering what we all think of

this argument that that distinction does not hold up because it can be so easily manipulated by the researcher. That seems to me is attacking the wrong part of the situation. It is not how many are created but sort of what you do with them at the end as well.

DR. SHAPIRO: Any comments?

Alex?

PROFESSOR CAPRON: Yes. I think that there is a difference between saying that the distinction does not hold up because in principle there is no distinction, which is my view, for example, on use versus derivation. And the distinction does not hold up because practically it will be hard to enforce it. I take the latter view on this one that if there is a problem it would be hard to enforce. Not that there is not an in principle difference.

And I think that Kathi's example of people deciding -- the centers deciding that certain embryos will not be retained for reproductive purposes because the likelihood that they will create a child is so low that it is clinically not advantageous to the couple to implant them brings that to a focus.

Obviously that decision, what level you set your viability criteria at, also will influence the number of embryos that are available. At some point if this is really an in vitro clinic that we are talking about, there are incentives on its part not to discard and give away to researchers a lot of embryos which will be useful for couples.

I mean, not only is it a violation of their Hippocratic duty to the couples but it undermines their own -- it raises their costs. And if we at some point are able to construct a mechanism which does not give them any financial incentive and closes off any discussions and so forth, I am not convinced that it is not possible. I do not know that it is possible but I am not convinced that it is not possible to overcome the practical objections.

So I think it may be possible to construct something which makes sense between two and four but I recognize that it is a difficult task and it requires a good deal of ingenuity. I think there are some self-correcting mechanisms, however.

DR. SHAPIRO: Bernie?

DR. LO: If I could just follow up on that. Then if we think this is a distinction worth pursuing, would it be advantageous for us to try and get thoughtful IVF practitioners to come to one of these sessions to address this point of whether you can put in place the kinds of practical procedures Alex was talking about to make that theoretical distinction work out in practice?

PROFESSOR CAPRON: And Richard Doerflinger has promised that he will provide or has already given to the staff, I think, the background for his statement that people in the field themselves, in effect, say there is no holding us back. I mean, you cannot -- it will -- we will create them if they are out there. And I would like, therefore, to have first person testimony about that from, as you put it, some people in the field to assess where the risks are and if it is possible to overcome them.

DR. SHAPIRO: Rachel and then Larry.

DR. LEVINSON: As a point of information on this issue and also going back to whether or not you would consider an oversight process that in some way reaches beyond federal funding to the private sector, the

advisory panel that Dr. Varmus has put together is considering as one of the elements of their oversight process requiring certain documentation of procedures by the deriver.

In other words, the investigator that is coming in and applying for a grant must provide some documentation that certain policies and procedures were followed by the -- whoever it was who provided the stem cells to them to begin with. For example, it is not now required that certain in vitro fertilization clinics have an IRB. They may require IRB review and approval of their informed consent process. So that is something to think about when you are designing your oversight mechanism that you could reach back before federal funding and include that in the process.

DR. SHAPIRO: In part, I think -- I am glad that Rachel reminded us that, in part, that derives, I think, from reading that long points to consider document, which I think was central to their discussions -- but in any case, Larry?

DR. MIIKE: I just want to make sure that in the information on the practices in IVF clinics that

there is a comparison between the short window in which we are able to get embryonic stem cells from the developing embryo versus what are considered defective embryos that are being now discarded because I think there is a significant source in those defective embryos in terms of going to full-term and that can alleviate some of the issues that are being -- that we are arguing over.

DR. SHAPIRO: Thank you.

Alex?

PROFESSOR CAPRON: Could I introduce an issue that we have not talked about that was brought --

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: -- up by Mr. Furton this morning? He argued, as one of the claims against federal funding, that it was wrong for the federal government to create therapies which because they were derived from sources to which some people have strong objections would put those people in the moral dilemma of deciding between the bad choice of using this illegitimate fruit of the poison tree as it were and facing whatever illness they have or their child has. I must say I was not convinced

by that argument and I do not know whether we have an obligation to address in our report every argument that is put forward in good faith here to us.

If it were -- if it were the view of the commission that this is a view that more people than just Mr. Furton would likely hold I think we may need to address that and I do not know exactly how we would do it. I always look to Jim Childress on such matters. But I did not find myself convinced by that.

I mean, it seems to me there are any number of medical interventions that some people object to in society and the only reason they exist is that other people regard them as providing a solution to what is otherwise a medical problem and yet some people say, "Well, I cannot accept that." From Jehovah's Witnesses with blood transfusions to in vitro fertilization itself.

And I do not know whether, for example, some couples who use the so-called gift procedure to achieve fertilization or some people who would like to use it because it does not involve an in vitro fertilization would object to it if they realized that some of the techniques that allowed gift to work were actually

pioneered by people who were doing in vitro fertilization in terms of the potentiation of the eggs and sperm and so forth.

But, if so, and they are faced then with not having children, which they regard -- biological children, which they regard as a great loss, which I could understand that they would, I am afraid that life is full of these kinds of moral choices in my view.

DR. SHAPIRO: I think it is an interesting question.

Jim, and then Bernie.

DR. CHILDRESS: This has obviously, as you know, come up in several other areas. In the discussion of human fetal tissue transplantation research the main way that it came up there was to make sure that potential recipients knew about the source so they could make their own decisions if they felt that the transplantation in this case would be something that would be morally tainting.

There are two issues here, it seems to me, in trying to get at it. One would be the understanding of the religious perspective on which this is based and the

other would be -- I am not saying that we should try to get this information but, in fact, would -- many of who affirm this on the level of belief actually followed in practice if this kind of therapy were available.

That is kind of an empirical question we cannot really address but at least it seemed to me to be an interesting and important question the way it was raised and it would at least, I think, push us in the following direction as several other considerations have: Namely, if there is a way to avoid using that source, do so. At least it goes in that direction.

Now whether it goes farther than that, it seems to me to be a much harder question to address.

DR. SHAPIRO: Bernie?

DR. LO: In addition to what Jim said, which I agree with, I think that I would sort of urge that the commission bend over backwards to really understand and address the objections that people who are most concerned about this are raising. So as you put it and I think John Fletcher put it, I mean there is real moral anguish in that testimony this morning and I think that part of the respect we should give them as sort of sincere

critics of the projected federal funding is to take their arguments offered in good faith seriously enough to really address them because it comes out of such a deeply held position.

DR. SHAPIRO: Larry?

DR. MIIKE: Just an observation. I did have a chance to talk to that person and I did raise the issue about transfusion, and he did say it was different. So we could always ask them for why -- we did not have time to discuss why it was different. So we can always ask for a written answer to that.

DR. SHAPIRO: Okay. I think that -- you know, that obviously was an important argument. I think there are other stronger arguments. Myself, I was not convinced by this argument but I think it is an important one and something that deserves our respect and attention. I completely agree with that.

Okay. Are there other issues that people would like to address now?

Larry?

DR. MIIKE: Just one question on Dr. Parens' paper and the extension into what I guess would be the

gene therapy chimeric area.

DR. SHAPIRO: Yes.

DR. MIIKE: You know my opinion about that.

DR. SHAPIRO: You were anxious to do that, right?

(Laughter.)

DR. SHAPIRO: Bernie?

DR. LO: (Not at microphone.)

DR. SHAPIRO: I think it is an interesting -- my own view is that it is an interesting -- as a matter of fact, I enjoyed that paper a lot but I think we have only -- we have got enough to do is my view without going into that area and we may have too much to do but we are going to give it a shot.

Any other issues to come before us this afternoon? We have been at this a long day now. We have been here since 8:00 o'clock this morning.

All right. Thank you very much. I want to express my thanks to Jim. I know whenever we meet in an area where we have a member of the commission, it is actually time and effort and work for them so I appreciate it very much.

I think Jim may have some announcements to make.

DR. CHILDRESS: We are making a transition into Belmont Revisited for the commissioners and several in the audience who are participating in the conference that starts with a reception tonight at 6:00 o'clock in the Omni beyond the registration desk. Go on around and there will be a room where the reception and the registration will be held.

So you are invited to that and we look forward to interacting with you and I have detailed schedules of the conference sessions that obviously begin with the reception and registration this afternoon but we will really start formally with the working sessions tomorrow morning.

In addition, the reception runs from 6:00 until about 8:00 but for people who want to get dinner here in Charlottesville in one of the restaurants perhaps nearby, and there are several good ones, I have made several reservations in my name but check with me and I will need to sort out who will be going where.

DR. SHAPIRO: Is this a blind trial or is

this a --

DR. CHILDRESS: To make 40 reservations with one place is pretty difficult to do but I do have several scattered around so check with me and we can figure out which --

DR. SHAPIRO: Maybe, Jim, if you just assign people to --

DR. CHILDRESS: That is right.

(Simultaneous discussion.)

DR. CHILDRESS: But I look forward to sharing with you in that conference.

DR. SHAPIRO: Thank you very much and thank all commissioners. I look forward to our next meeting.

(Whereupon, the proceedings were concluded at 4:55 p.m.)

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