28TH MEETING

OF THE

NATIONAL BIOETHICS ADVISORY COMMISSION

JUNIOR BALLROOM
SHERATON PREMIERE AT TYSONS CORNER
8861 LEESBURG PIKE
VIENNA, VIRGINIA

March 2, 1999

EBERLIN REPORTING SERVICE
14208 Piccadilly Road

Silver Spring, Maryland 20906
(301) 460-8369

I N D E X

I N D E X (Continued)

P R O C E E D I N G S

WELCOME AND OVERVIEW OF AGENDA

DR. SHAPIRO: All right. I would like to call our meeting to order, please.

Welcome. Thank you all very much for being here today.

Our agenda, of course, has been distributed in advance of the meeting and I think it is really pretty straight forward. Let me just summarize it very briefly so we will see what the work is that is ahead of us for today and tomorrow.

We will be spending really all of this morning on working towards our report dealing with human biological materials and various aspects of that. We will again today try to be working our way through what is chapter five with the perspective of trying to provide adequate input and perhaps some initial decisions so that we will have a full report to review and, hopefully, approve at our next meeting.

We, of course, have not redone the early chapters yet. At least we have not distributed to them as still they are being worked on but we will have an entire

-- the objective is, at least, to have an entire report available for our consideration and possible approval at the April meeting.

So when we begin our discussion of that report we will go immediately to chapter five, which, as you know, has been somewhat reorganized, restated and so on but there still may be issues that are missing.

For example, we certainly have to discuss something about the privacy issue. There may be other things which you think are missing or there may be recommendations which you think really ought not to be in the form of recommendations but go into something like guidance or something else, which is sort of advice IRB's as opposed to others, investigators, and so on.

So we hope to be able to spend a considerable amount of time on that chapter today and possibly tomorrow if necessary so that we really feel confident about developing the report in its entirety for the April meeting.

Quite a number of commissioners have made very important and useful contributions to the chapter as

we have distributed it to you today and I want to really express my gratitude to them and, of course, to the staff, Kathi and other members of the staff.

We also will be hearing on the privacy issue, which I mentioned a few moments ago, from John Fanning later on this morning, sort of in mid-morning. We are very grateful he has been able to spend some time with us today to look at that issue. This is a huge issue and it is getting huger every day given technological developments and there are obviously other groups working on this, in fact, with a more comprehensive view not only dealing with these particular kind of materials but with medical records more generally speaking.

So we will have to decide just how we want to take notice of it and what we want to mention being cognizant all the time that, as I say, other groups are working on this at somewhat more of a megalevel so to speak than simply with our particular problem but I do not think we can leave that issue without any mention. Of course, there is some mention in the earlier chapters and we will have decide what, if anything, we do in chapter five on that issue.

We will spend all of this morning on that, also including the privacy issue, other discussions regarding chapter five and that particular report.

This afternoon we will turn to our discussions regarding stem cells. We will hear from a number of speakers at that time, John Fletcher and Lori Knowles, and later on in the afternoon Leroy Walters but I think we have tried to schedule us so there is plenty of time for discussion so that we can kind of catch up on the work we did at Princeton at our last meeting and there has been, I think, a decent summary of what we discussed in the Princeton meeting, which was provided in your agenda.

And our first order of business is we touch base with that. Is this one an accurate representation or not of what we did because it is very important to establish that base and that will be our first item of business and then, of course, we go on from there to some of the issues which still require considerable discussion.

I expect that we will sort of begin actually putting that report together immediately after these

meetings today so that we will really have something to look at, at our next meeting, although we still might not be at the stage of approving anything by that stage because there will probably be still some outstanding discussion but it would be very helpful today if we went as far as we could at least to identify those areas where we might have serious disagreements amongst ourselves or issues that we might want -- there may be issues of fact which we want to get more clarification of that you can set the staff working on and so on.

So I would hope by the April meeting that we would have at least the skeleton, meaning a considerable amount of text, not just points of the report put together to see how that looks and see if we can bring ourselves towards conclusions on some of these issues.

We have left tomorrow a considerable amount of time for discussion. We will begin tomorrow with an update on our international project and then really from midmorning until we adjourn we will have for discussion of any issues that maybe continue to be dealt with in the stem cell area or if we want to turn to some issues regarding the HBM report we can also do that tomorrow.

We are currently scheduled to adjourn early in the afternoon tomorrow. As always, it seems, our precise time of adjournment is a flexible matter depending on our strength, interest and issues that are before us. So we will just have to see. We will adjourn no later than what is indicated on the agenda. If we adjourn early or not, I think it is a little hard to say, is depending on the nature of our discussion.

So it is a full day-and-a-half that we have in front of us so why don't we begin. Let me turn first to Eric to give a brief report from our executive director and then we will go immediately into discussion of the HBM report.

EXECUTIVE DIRECTOR'S REPORT

DR. MESLIN: Thanks, Harold.

A few items just to update you from the home office.

We are happy to have some new administrative staff joining us. You will hear a new voice when you call NBAC offices. Her name is Sherrie Senior.

An administrative tech person, Catherine Botts (?).

And we have also hired an editor to work with us in-house, Sara Davidson.

With respect to the Capacity Report follow-up, a letter has been sent to Dr. Shapiro from the President thanking him and the commission for the Capacity Report. A copy of that letter is available to everyone and the letter indicates that Dr. Neil Lane will be ensuring that all agencies who conduct research with human subjects review the report and respond to the commission's recommendations so we look forward to hearing follow-up from agencies and others.

Printed copies of the Capacity Report are winding their way to our offices and should be there today or tomorrow at the latest. We hope to be able to provide you with those printed hardbound copies. They, of course, have been available on the web for some time now but anyone in the audience who wishes to get a hard copy please call the NBAC office or preferably send an e-mail through our web site so we can ensure that you get one.

I want to give a quick update on the Comprehensive Report, which is not on our agenda today,

commissioners know that we have been prioritizing our work in such a way that we cannot get all of our reports on every agenda and for a number of other reasons we have decided that we wanted to step back from finalizing the Comprehensive Report until we had a better sense of what we wanted to say.

We are now in a position where we think we can produce a very short and concise initial statement for the commission's consideration and forwarding on probably by the next meeting. That short report would likely be limited to the survey that staff conducted over the past year.

Professor Charo has agreed to assist staff in helping to work through that document so we hope to have something for you by next meeting and then we will have a more complete plan for the presentation of the entire set of materials that make up the Comprehensive Report.

Just to remind you, we have included issues of IRB review and oversight mechanisms within the Federal Government as part and parcel of that project.

I can take questions on any of these items but let me move on.

I wanted to give you a quick update on the Global Summit of National Bioethics Commissions, which was attended both by Harold and Alex Capron, Tom Murray and Alta Charo in November. This produced the Tokyo Communique," a document in which more than 35 national bioethics commissions and international organizations pledged to work together and to develop collaborative relationships.

That document has previously been circulated but I wanted to give you a quick follow-up because one of the tasks of a small interim working group which was established shortly after that meeting was to actually make some specific plans for how bioethics commissions internationally working through this global summit process would continue to work.

There are some eight members of that interim working committee. Alex is our representative on that and we expect that probably by the end of this month the tasks, which include planning for the next meeting, a set of bylaws, educational and other communication strategies, will be in place. We hope to share that with you at that time.

I wanted to mention just very briefly not only our upcoming meetings, a copy of the timetable for which is available at the front desk, but we now have all of our meetings scheduled with places for those meetings from now until September. Later on in the meeting, I think, Jim Childress will talk about the April Belmont Conference, which we have correspondingly arranged to have an NBAC meeting nearby. We will be meeting in Chicago in May; back here in Washington in June; in Cambridge, Massachusetts, in July; and then back in the Washington area in September.

We will now start the process of asking you to clear your schedules for the remainder of the calendar year. That is not an indication that we know that we will be meeting any time after September but it would probably be better for us to anticipate the possibility of meeting for the rest of the calendar year into next year rather than to wait to find out about extensions and whatnot so be prepared to get an e-mail from staff with calendar dates for the rest of the year.

The only other thing I will say, Mr. Chairman, in the absence of Pat Norris, who is unable to

be with us today due to an illness, we regularly have a public comment session. We do so today as well. Anyone who wishes to sign up for public comment, please do so at the desk out front.

And that is my report. I am happy to take questions from the commissioners.

DR. SHAPIRO: Thank you very much.

Questions?

Alex?

PROFESSOR CAPRON: On the Comprehensive Report what do we have by way of formal written responses from the agencies which received our preliminary findings many months ago? Have we had point by point responses on that?

DR. MESLIN: We had a handful of responses from some of the agencies. A meeting was held with a good number of agency representatives in October where the preliminary materials were presented to them. We have had -- Kathi received some as well -- probably less than half a dozen from individual agencies who asked us to either put into context the survey findings because they have either updated their policies or procedures

since then.

We have taken no action on updating any document as a result of that but we have received probably less than half a dozen.

PROFESSOR CAPRON: I was particularly concerned because some of the agencies seemed quite advanced in the work they do and others seemed almost surprised to be reminded that they had responsibilities and I was wondering whether our existence and our questioning had begun to result in any attention in the latter group.

DR. MESLIN: I think it is fair to say that our survey had an effect on those agencies who may not have been as familiar with or as involved in human subjects research as some of the larger agencies.

PROFESSOR CAPRON: My general sense is in reports -- this is just a personal predilection -- I do not like reading in reports about "us" for the most part and in reports where we constantly have to say "NBAC concludes," and so forth. I would draw, however, an exception on this Comprehensive Report.

We may need to have a description and I guess

Alta has been handed this assignment. I should say hot potato but I think it would be a rather cold potato these days. And it may well be that in this field the existence of our work, we have to take account of our own activities in bringing about some change. And I say that, in part, because I think otherwise we have the embarrassing situation that three years into our existence we have not reported on the one thing that was clearly set forth in our charter.

The other question I had was while we have been attending to other matters the world has not stood still on the issue of relocation of the oversight activities and you and I had some e-mail exchange but I would like to get it on the record and I think there may have been in some of the congressional attention recently indications from the administration as to a willingness to move the oversight activities or create a new oversight mechanism.

Again I would like to know whether we are still in the loop on this. I mean, I know that we are being kept abreast of it but is it really other people's issue now or do we still have a role where people will be

looking to our recommendations?

DR. MESLIN: Alex is referring to the existence of a committee established by Dr. Varmus at NIH to provide him with recommendations regarding the appropriate location and function of the Office for Protection from Research Risks. That is a wholly owned NIH committee.

And my understanding, which is the reference Alex made to being kept abreast, is that committee has met a number of times. Staff -- NBAC staff has been aware of the existence of that committee and I have been in touch with the secretary to that committee.

I do not know if there might be someone from NIH in the room who knows more than me about when that report is going to be completed but my understanding is that it is about to be completed within the next short while. I cannot give you a day or a week.

As to whether we are either out of the loop or not able to engage in this issue, I actually do not think that is the case. The location of OPRR as an issue is only one of many that I think NBAC is prepared -- has agreed to take on with respect to federal oversight. I

think we would enjoy receiving that report, enjoy commenting on it, inviting the chair or co-chairs of Dr. Varmus' subcommittee to come and present testimony to us and tell us what they found.

We have already on the record two commissioned papers from Dr. Fletcher and Dr. McCarthy specifically about this issue and a related paper from Professor Gunsulas on the issue. So I do not think we are missing the boat by observing NIH making a recommendation about keeping OPRR where it is or moving it to some other place.

PROFESSOR CAPRON: One final comment on that.

I found Tina Gunsulas' report quite interesting but it did not, it seemed to me, fit the bill of what David Cox had originally talked about.

If there are four legs to the table, the IRB issue, the adequacy of the agency, the question of the location of OPRR, a fourth leg of the table was going to be the extension of federal protections to all subjects. And one of the issues that ties that one with the oversight question would be would this new body be in a

position to be the oversight mechanism for efforts to ensure that subjects in private research are protected?

And I thought David was raising -- and I thought it was a very good point when we were first talking about this a couple of years ago -- was what about the willingness or, as he saw it, even the interest that a lot of private sponsors of research in biotechnology area and elsewhere would have in making sure that the regulations were reasonably crafted to encompass them if they were going to be brought into it.

And so I thought that the third paper -- we were going to have papers by someone who was skeptical about a federal -- a high federal level agency and someone who was in favor of it but we ended up with two papers, both of which said move it up. And then I thought that the third paper was going to address that and that really was not what Gunsulas did.

As I say it was a good interesting paper but I did not really think she engaged, for example, the pharmaceutical industry, the biotechnology industry and other sponsors of research, particularly in the behavioral area, the whole use of research by managed

care and so forth as part of research on behaviors of physicians and patients and the like, and I thought we were going to have some idea of that by the time we were done.

Since again we have had a delay I wonder if it would be possible to look further and to get someone to give us that. It is really -- to a certain extent it is not analytic. It is really empirical information that we need about whether when confronted with this possibility of regulation these groups are, in fact, receptive or highly resistant and what special concerns they would have about being encompassed.

Senator Kennedy apparently plans to take up the mantle that Senator Glenn had been wearing as the champion of the notion of the extension of the research protections and again it would be -- I hope that we are in good touch with his office about that but that is my final suggestion.

DR. SHAPIRO: With respect to this issue those are very helpful suggestions and with respect to this issue I intend this spring, regardless of where we are formally, to send at least an interim report to the

President of where we are, what we are doing and what the status of our work is because I think -- in fact, I think that is overdue and we will do that some time in April or May.

DR. LEVINSON: A couple of quick points. One, at the risk of putting a fifth leg on your chair, what it becomes at this point I am not sure, I would encourage you also to think about not just the oversight mechanisms but what they are overseeing. It is not just implementation of the Common Rule but to look actually at the Common Rule and see whether or not that is the appropriate basis upon which to have some oversight.

The other is going back to Eric's point about the locus of OPRR. I would echo what he said and then add to it that the report that is being done at NIH, as I understand it, would still be limited to looking at OPRR within NIH or somewhere else within HHS. Your earlier discussions went beyond that. To look outside of HHS is another possibility.

DR. SHAPIRO: Yes.

Thank you.

Any other comments or questions?

Larry?

DR. MIIKE: Just a technical question. Are these things working?

(Laughter.)

DR. MIIKE: Are these mikes?

DR. SHAPIRO: They are mikes in some cases, I think. Are you having trouble hearing people?

DR. MIIKE: I do not hear any output.

DR. SHAPIRO: Thank you for raising the issue. I apologize. There seems to be enough electronics around here to have a rock concert so I hope we can repair this. I apologize.

Let me ask the commissioners in the interim at least to speak up as best as possible so that people at the back of the room can hear us as well as communicate with ourselves.

Any other questions for Eric?

Okay. Let's move on then to the first item of our agenda, which is to consider the material in the redrafted chapter five.

I think, Tom, if it is all right with you, we will just go through this, as you did last time, one by

one.

There is a cover note from Kathi about this material raising three specific issues. And I think the second one of which deals with privacy which I suggest we postpone until later on after we have heard Mr. Fanning.

The third one has to do with the FDA and we will take that up, Tom, whenever you think it is appropriate.

It may be, and I leave this to you, Tom, that the first one having to do with how we define publicly available we can either take up when it comes up or in addition to whatever you prefer.

So why don't I turn the chair over to you.

DISCUSSION OF THE COMMISSION DRAFT REPORT

DR. MURRAY: Will you let us know if you can hear us? Can you hear me right now? Good. Okay.

I guess we are back into a situation where we have to talk into the microphone to hear anything. This is the rock star. The reference to the rock star.

Kathi has a few words of introduction. Kathi Hanna has been our chief scribe and composer on this report.

So, Kathi, what is it you wanted to say?

DR. HANNA: I just wanted to --

DR. MURRAY: Kathi, you are not on.

DR. HANNA: Okay. I just wanted to point out that there is --

DR. MURRAY: The switch is on the mikes.

DR. HANNA: The chapter has been reorganized to try to reflect the conversation we had in Princeton. All of the recommendations now appear at the end of the chapter. So in addition to having your substantive comments on the text and on the recommendations, it would also be useful to know whether you think that this presentation style works or whether you would rather have recommendations scattered throughout the report. Other issues have to do with whether you like the groupings of the recommendations or do you think they should be lumped in different ways.

So any and all comments would be appreciated.

DR. MURRAY: Any questions for Kathi?

I know I have a number of comments about the text, not just the recommendations, but I am wondering what the commissioners feel. I think that five -- the

ultimate meat of this report is the recommendations. Should we begin with that? That is my inclination. Begin with the recommendations.

I think there is time available after we talk about the recommendations and the couple of other issues that Harold and Kathi mentioned. We can go back and look at some other issues in the text.

Does that seem like a reasonable game plan? Okay.

I believe Kathi is putting recommendation number one up on the overhead right now.

(Slide.)

I will solicit your comments. I have a comment in connection with involving the first three lines of the current text. Currently it begins, "When federal regulations..." et cetera "...are determined to apply in..." I don't know why we need to put it in that sentence. Why don't we just say, "Some federal regulations governing human subjects research..." et cetera "...should be interpreted by OPRR..." et cetera?

PROFESSOR CAPRON: Second.

DR. MURRAY: All right.

Well, we should adjourn the meeting. We have agreements and we have consensus.

(Laughter.)

DR. MURRAY: Other comments on number one? Why don't we go through -- since it is three separate parts, A, B and C. Are there any further comments on the text preceding the subparts? Any comments on subpart A? On subpart B?

DR. SHAPIRO: Subpart B, Tom, is where we need to fill it in.

DR. MURRAY: Yes.

DR. HANNA: Right.

DR. SHAPIRO: And I think -- I talked to Eric about this yesterday and we sort of formed some language that at least the report could start with and maybe we can take a look at that, and I do not know if Eric can get copies of that. Maybe you could also read that for those who do not have binoculars.

PROFESSOR CAPRON: Come to your commission meeting without opera glasses?

(Laughter.)

PROFESSOR CAPRON: What an oversight.

DR. SHAPIRO: While we are waiting -- while we are getting that up, I am wondering if anybody was around when the Code of Federal Regulations incorporated this phrase "publicly available." I guess I had always thought this to mean -- the group cause of inclusion of this language was things like observing crowd behavior and information that simply is publicly available.

PROFESSOR CAPRON: Phone books.

DR. SHAPIRO: Phone books or some other you or I could get a hold of or have access to relatively easily. Is there anybody who has -- who remembers that comment or what the --

PROFESSOR CAPRON: Yes, I remember that comment.

DR. SHAPIRO: And could help us understand it.

(Laughter.)

PROFESSOR CAPRON: My understanding, yes, was the same as yours. That what we were talking about were data that someone from a member of the public, a journalist, could get access to. In other words, if there was an invasion of privacy that had already

occurred when whoever put that information together put it together and there is responsibility there and awareness that that information is available. Whoever is bothered by it would already know that and know to whom they address themselves. In a way you are going back to some of that material that you have skipped over in the first 33 pages and I take strong exception to some of what is said there about the notion that the American tissue type culture ---C -- whatever it is --

PROFESSOR CAPRON: -- Center is in that sense publicly available. It does not fit the notion, it seems to me, of what was meant by that language.

DR. MURRAY: Eric?

DR. CASSELL: I agree. I think that publicly available is not what is listed up there for research. That is not publicly available. That fits any research materials they could get. I agree that publicly available means anybody in the public who wants it can have it.

PROFESSOR CAPRON: And if there is not an intrusion on someone in any fashion --

DR. CASSELL: Right.

PROFESSOR CAPRON: -- because it is already there. If someone came to a researcher and said, "Wait a second. You are doing stuff meddling around with me." He would say, "What do you mean? That was already there. It was in the newspaper last week or it is in the phone book or you can go to the library and look it up." Anybody can see that.

DR. CASSELL: Right.

PROFESSOR CAPRON: And that does not seem to be the case with tissue samples that may have been passed on by some pathologist into some collection somewhere.

DR. MURRAY: I thought I may have seen one or two other hands up.

Steve?

MR. HOLTZMAN: I just want to try to think that through. I mean, I essentially -- I have people all the time calling up ATCC and getting samples so what you were just talking about in terms of intrusions and whatnot, there is no intrusion. I just think we need to start to separate the conditions of access versus the issue of intrusion and perhaps connected maybe with

information.

PROFESSOR CAPRON: May I respond since I am the one who used the word? What I meant was once you have the tissue, as we know suddenly it is like a storehouse of information, and that information is not now in any sense publicly available and getting to it does not become publicly available simply because there is this ATCC that holds it, it seems to me.

The common sense understanding of publicly available was something which was already in the public domain, records, available as Tom says in the case of people who are doing studies of crowds to public observation and then it was recorded and someone else looked at it.

If I come to your house saying, "I am doing a study in which I intend to establish a data bank of customers of Amazon.com and how -- whatever, and then I will record that information and make it available to people who are doing marketing." And you say, "Sure, I would be glad to talk with you." And it is then on record and it is something that is sold publicly. That is publicly available, you have given it.

But if you go, it seems to me, to a doctor and some tissue is excised, and turned over, and then it ends up in a collection with your name still on it, the notion that that is publicly available because you as a researcher have been able to get to it seems to me wrong and what is so important here is the phrase "publicly available" goes along with existing as an alternative to the whole set of protections that arise from information which is anonymous.

And the whole sense it seems to me of publicly available is it is neither something which like your presence in your crowd you made publicly available even though you are not really anonymous there or it is because you have explicitly consented in this interview with someone to have them record this information and make it publicly available.

DR. MURRAY: Okay. Bernie?

PROFESSOR CAPRON:

We are talking here about what is exempt and to say that everything at ATCC is exempt seems to me to nullify the whole notion of any protections at all.

DR. MURRAY: Bernie?

DR. LO: It seems to me -- I am trying to think of where this has come under my experience of investigators asking questions. The areas that seem to come up now have to do with survey research where data tapes are made publicly available and actually many of those fit under two as well as one but they are actually available. You pay. You write your check and you get the data tape and the codes.

The second example, I think, would be that people publish genomic sequences --

DR. MURRAY: Bernie, you have to talk very close to the microphone.

DR. LO: -- literally publicly available on the internet. Again most of those, it seems to me, also fall under two except for this funny exception we talked about where you could sort of decode and identify through DNA sequences.

So I am not sure what we are gaining here by trying to make one a totally separate category so I think I am seconding the spirit of Alex's remarks but also to say that most of the things that people are claiming as publicly available in the current climate of doing

research with existing samples actually really falls under two and so one in a sense is redundant.

I agree that it does not mean that just because a researcher was able to get access means that it is publicly available. That sort of contradicts the term.

DR. GREIDER: Could I just ask a clarification, Bernie? What do you mean by "falls under two?" I was not following that.

DR. LO: Well, if you --

DR. GREIDER: Well, two --

DR. LO: I am sorry. Page 5 where it lists the CFR regulations.

DR. GREIDER: Okay.

DR. LO: That is --

DR. GREIDER: I was not sure.

DR. LO: I do not think that.

DR. GREIDER: Thank you.

DR. MURRAY: Larry, Alta, Eric?

DR. MIIKE: I think there is a simple solution, which is that when we are talking about storing biological samples it is a meaningless phrase to talk

about publicly available. There is no such thing as human biological materials that are publicly available in the sense that we are dealing with here so I think we should just dispense with that at all.

DR. MURRAY: That is a Gordian knot solution. Okay.

Alta?

PROFESSOR CHARO: I feel, though, that by dispensing with it entirely we are now eliminating the opportunity perhaps to address what we do want to have happen with large scale collections in existence.

I mean, to me part of the problem is that outside of the crowd situation, which absolutely I share with you the paradigmatic case, it is the survey data that has been the kind of secondary notion of what is publicly available and that is an example of how it is that in the past we have published certain forms of information and the biological materials are a form of information but we have not figured out what constitutes the analogy to publication.

It strikes me that there are going to be many circumstances under which you want to make it possible

for large existing, often even standardized collections, to be quickly and easily accessed and the source of our concerns are simply going to be the conditions of storage at the repository more than anything.

If materials are stored in the repository in a way that -- I am trying to figure out how to say this at 8:30 in the morning. I am never good in the morning.

If materials are stored under circumstances in which people have an expectation of privacy then it would be wrong to simply release those materials without any further third party oversight, which is the whole function of IRB review, and so in some way I think that it really comes down to questions about expectations of privacy. That is why it is that one can be observed in a crowd and have research done on them. That is why their name in a phone book would render them subject to research.

So I guess what I am trying to say is before we just say that it does not apply at all is to try to understand what the expectations are and that, in turn, is going to depend upon how they came to be in a repository and what the conditions of storage are.

DR. MURRAY: Eric, Carol and Alex?

DR. MESLIN: I only wanted to -- these are attack microphones. I only wanted to mention that the suggested language, which only is a suggestion, does not distinguish between access to materials and the public availability of materials versus the availability of the information contained in materials. So the description of whether or not the ability to obtain them is accurate, reasonable cost, compliance with regulations should not be confused with issues of privacy and protection per se.

It may be that two things can be accomplished by redefining or re-explaining the term publicly available because there are two concepts going on. One is really public access or access to the materials themselves and whether it is discriminatory or prohibitive to put a thin mechanism such as paying for it, these are raw materials so to speak, they should not be given to you for free, versus the analogies that have been described of the telephone book. Anyone can get a telephone book. You do not have to pay for it. They deliver it to your door. It is the information and privacy protections associated with that information that

is the other part of it. This may not do it but that was the meaning behind the description.

DR. MURRAY: Carol?

DR. GREIDER: I just wanted to respond to something that Larry said and that is I agree with the idea that in this context the term publicly available has very little meaning but I do not see how we can just do away with it because it comes up on page five as one of the considerations that one needs to address in determining whether or not something is exempt from review. It is already there. So if we are working in the context of the current recommendations we have to say something about it. We could say that it is --

(Simultaneous discussion.)

DR. GREIDER: But then we have to -- I am just pointing out that we need something in there because it is already in the existing regulations.

DR. MURRAY: Alex?

PROFESSOR CAPRON: I agree with Larry but it is not that we have been ignoring it. I think what we have to say is that OPRR and others should make clear to IRBs and investigators that that exemption does not apply

to research on biological materials.

And the discussion to a certain extent if I could respond to something that Kathi invited us to talk about before, I think maybe the indication that a separation of the discussion from the recommendations that grows out of it is problematic here because you have dealt on page five with that issue to a certain extent and then we come back to it.

Eric, I do not think this is a question which is answered by the question of publicly available meaning ease of access. Some of those directories which are publicly available and you may have to pay for, certainly running a tape or getting a tape you can run with data in it and you have to pay for the data, that is not really the issue.

I think Alta is mostly right about the expectations but it may well be here that there are no -- there is not a well developed set of public expectation about this the way there is about the information about you that is in the phone book. I know I do not have to list my address in the phone book if I do not want to and the phone company tells me that and everybody is aware

that if you, you know, do not want that to happen you can just list your city and not your address.

I do not think the average member of the public knows all the 200 plus million samples that are out there and it may well be that the only expectation is the one that the commission can bring to the policy making rather than looking case by case and saying, "Now, what was the expectation of people about this particular sample in this repository."

I think Larry's suggestion of how to deal with this is a better one and to just say, "This is not what we meant. When that exemption was crafted it made sense. We do not think it should be thrown out of the federal regulations. There are other kinds of research where it is applicable but it should not be applied here."

DR. MURRAY: Bette?

MS. KRAMER: That pretty much covers it. I was going to say that the very sense that biological materials might be publicly available in the manner in which a phone book is publicly available is offensive. So I would not go along with that conclusion at all.

DR. MURRAY: I have on the list Alta, Steve, Larry and Eric.

PROFESSOR CHARO: I will defer.

DR. MURRAY: Steve?

MR. HOLTZMAN: Maybe Elisa or Kathi had answered us is it not the case that the overwhelming majority of samples in places like the ATCC are stored in what we call an unidentifiable manner and, therefore, even if we say ATCC does not quality under 102(b)4 exemption it would be --

DR. MURRAY: It will be exempt.

(Simultaneous discussion.)

DR. HOLTZMAN: It would be subject to the 102(f) exemptions.

DR. MURRAY: Yes. It will still be exempt but for a different sort of reason. Mainly the identifiability.

DR. HOLTZMAN: Right.

DR. MURRAY: I think that would fit well with our sense of what people would want.

DR. MIIKE: Maybe I just learned my lesson that I should be a little bit more deliberate in my

writing. What I meant to say was that, number one, when you are dealing with issues, the issue of -- I was going to raise the issue about expectations of Congress. I cannot imagine any kind of a tissue being given without some expectation that it is not going to be made available. The other part is that by modifying the Common Rule here we really need to say something about biological materials than just to ignore it while it is still in rule making.

Of course, the other part is that we want to give reassurances that this does not set up a substantial road block for research in this area. There are other ways of accepting these types of research projects without unnecessary scrunity.

I have learned my lesson and I will give longer speeches.

DR. MURRAY: Eric?

DR. CASSELL: Well, it's something about what Bette said that she cannot imagine a biological sample being publicly available but the question is if you do the DNA analysis on a sample and you are going to publish that information from that sample and that certainly

could be publicly available and it would be the same as if the sample was in the case. The information -- I mean the sample is the only example in the sense of the information it contains. It is the information that causes the trouble and not the paraffin on a specimen.

DR. MURRAY: Carol and Bette?

DR. GREIDER: Just to respond to that, different levels of information can be gotten out of a sample so if you publish a particular set of information but you do not publish everything known about that sample so I disagree with the idea that just because a sequence is published everything is known about that sequence and it is publicly available.

(Technical difficulties.)

DR. CASSELL: Well, we could you tell the same thing about the sample. If you do not have yet a technology to do X, Y, Z then that sample cannot give that information but ultimately will. If the DNA analysis at whatever level that is out there, the information about me is out there.

DR. MURRAY: Bette?

MS. KRAMER: Eric, I think that I certainly

would feel that there was a presumption that whatever conclusions that were reached that the conclusions are appropriately publicly available but that behind the conclusions the work that was done to produce those conclusions was not from samples that were readily available to the public again in the sense that a phone book is.

DR. CASSELL: Well, I --

MS. KRAMER: I do not --

DR. CASSELL: -- beyond saying that if it were not the case that that information was that way then there would not be privacy issues about DNA testing on arrested people prior to conviction. It is not their little specimen of blood or mucus membrane that is causing the trouble, it is the information.

DR. MURRAY: I am going to try and make an analogy. I do not know if it is a good one or not but just placate me for a moment if you would.

Let's suppose someone interviews me about my family's health history. What did my relatives die of, what problems did they have, either emotional problems, psychiatric diseases, and I agree to participate in the

interview so I give this information to the researcher. And the researcher says, "Do I have your permission to, you know, further use this information in additional research?"

And suppose I say, "Yes," to that.

I do not think that should make me publicly available. I think that is providing research with certain expectations of privacy and that they all could capture that. That is a key concept here.

My inclination right now is to say, I think to agree with what Larry and Alex and the others have said, is that as a rule we should presume that the collection of specimen and tissue samples are not publicly available unless there are compelling reasons to believe otherwise. I can imagine a person collecting a set of tissues where they specifically ask people, "May we make this available for whatever purpose." I am not sure anybody would donate but I could at least imagine it.

That is my comment right and we will give Harold -- we will let Harold jump the queue, and then we have Bernie, Alta and Steve.

DR. SHAPIRO: I think that as I listen to this discussion, I think it is really pretty clear to me at least now what to do and I am concerned we spend too much time on this issue and I think it is important to recognize -- I think I can summarize what others have said.

Mainly that the purpose here is to get exemption from review. That is the purpose of this part of the regulation, whether you get exemption or not. And I think it is really a pretty neat solution to this problem to just say that it does not apply in these cases, and you go immediately asking other questions as to whether you have to get -- you know, if you strip the identifiers you can get exempt and if you do not you have to go through review, and that seems to me a very neat solution to this problem.

So if you look back on Chart 3 on page whatever it is. It is --

DR. SHAPIRO: Chart, thank you. Where it talks about are these data publicly available sort of in the top right-hand corner of that chart. In fact, this

is not a question anymore if I understand what you are saying.

Do you see that?

DR. SHAPIRO: Just sort of take that out. You just take that chart out and you go immediately into whether this is -- has got identifying information, whether you want it exempted or not and you go through the process. It just seems to me that is the implication of the suggestions I have heard around the table.

DR. MURRAY: I like this idea. Rather than simply declaring it exempt, you need to give a reason which would be a reason in line with all the suggestions about expectations of privacy that have sort of been reinforced by Bette's idea. Would that be --

DR. SHAPIRO: My own sense of this is it is just much neater to take this thing out and let the IRB's and so on deal with it.

DR. MURRAY: I agree. I understand we need to give a rationale for that. Do you agree with the expectation of the privacy rationale?

DR. SHAPIRO: I would have to hear it again.

I am not sure but I do not recall exactly what the --

DR. MURRAY: Alta is shaking -- Alta authored that. You are shaking your head. You have problems with that?

PROFESSOR CHARO: I am not sure that -- I am just not sure that it can be used that way. I mean, I think the simple common sense fact here is that it is very rare that biological materials are left in a condition in which they are publicly available and usable.

We all leave biological materials around in the public all the time. We are shedding cells all the time. We rarely leave them around in a condition that is usable. The tissues that are left in a condition that is usable are almost never being left in the public. They are being left often from waste but in the control of a single person who has some fiduciary responsibility to the patient or subject, whatever.

So I think what Harold is summing up is probably not based on expectations of privacy so much as something much simpler, which is that one can simply say it will be the very rare case in which human biological

materials that, in fact, have been left in a place or situation that is genuinely public. And if they have been, then the research on them would, in fact, be exempt but examples of that do not even really come to mind.

In thinking about beauty parlors and hair cutting settings, and even there exactly what they have -- I am trying to think of something that even comes to mind.

DR. SHAPIRO: I think, Alta, I understand that probably -- but it does not seem to me helpful actually in this context.

PROFESSOR CHARO: Exactly. Just say it.

DR. SHAPIRO: So if we just, I think, go back to the suggestions of Larry and other is very helpful and I think we can draw up easy language to get that done.

DR. MURRAY: Right. We still have three people who wish to be recognized -- who have expressed a wish to be recognized on this issue. Let's see if they have anything they still want to say and perhaps close the discussion after those three people. Larry, Bernie and Steve.

DR. MIIKE: Just to reiterate, I do believe

there is an expectation of privacy.

DR. MURRAY: Bernie?

DR. LO: I am sorry. I just think we should move on to some other issues.

DR. MURRAY: Steve?

MR. HOLTZMAN: Nothing.

DR. MURRAY: Very good. I think the commission has decided on this one.

We are still on recommendation one, however. However, we are now on part -- subpart C. Any comments? Kathi has some.

DR. HANNA: I just want to point out that we had a footnoting problem with the footnote at the end of recommendation C. The footnote actually shows up on page 32. I do not know how this happened. And it is numbered as footnote 15. So if you were looking and trying to figure out where to find that -- I cannot explain to you how it happened but that is where it is.

(Simultaneous discussion.)

PROFESSOR CAPRON: Number 15.

(Simultaneous discussion.)

DR. MURRAY: It is well disguised.

PROFESSOR CAPRON: It is well disguised. It is anonymous.

(Simultaneous discussion.)

DR. MURRAY: With that said, any comments on subpart C?

Steve?

MR. HOLTZMAN: And this may just be my density, if existing means stuff on the shelf, including stuff which in the future is on the shelf collected, for example, in the clinical context and is being summoned up for a research purpose, I am not sure I understand what the word "future" means here and how we intend it to be read. I think, I do but I think we want to be very clear.

DR. MURRAY: Alta?

PROFESSOR CHARO: Yes. In some ways I am kind of sorry that the sentence about the interpretation of existing showed up again because I think it sheds confusion rather than light.

Research that involves tissues that were collected before they are used is research on an existing piece of tissue. All right. Future collections involves

obtaining additional material. This is so straight forward that any attempt to interpret only can confuse.

(Simultaneous discussion.)

DR. MURRAY: So what do you want us to do, Alta? What do you propose? Nothing? Leave the language as it is?

PROFESSOR CHARO: Delete the explanation of "existing."

DR. _____: Where is that?

(Simultaneous discussion.)

PROFESSOR CHARO: It is in the text. It is back in the text earlier. So you were confused by -- you actually were confused by this even without the text in the --

MR. HOLTZMAN: I know what existing means. It is because I know what existing means according to the --

PROFESSOR CHARO: Right.

MR. HOLTZMAN: -- regs and according to our recommendation of how the reg ought to be interpreted, which we agreed to in Princeton, but it is the concept of future there that I think is confusing.

PROFESSOR CHARO: Well, actually --

(Simultaneous discussion.)

PROFESSOR CHARO: I am sorry.

DR. MURRAY: Take out both words, existing and future and --

PROFESSOR CHARO: And take out the word collections and that --

(Simultaneous discussion.)

PROFESSOR CHARO: It is research conducted on human biological materials that are --

(Simultaneous discussion.)

PROFESSOR CHARO: It is not research on collections.

(Simultaneous discussion.)

DR. MURRAY: I am sure that the President's commission -- this commission would be delighted to know that we are debating the meaning of existing if not existence.

(Laughter.)

DR. MURRAY: All right. Research conducted on human biological materials. Good.

Any other comments on subpart C?

Recommendation two.

While Kathy puts it up, any comments on the sentence introducing it or on subpart A?

(Slide.)

Alta?

PROFESSOR CHARO: I apologize, Tom, because I cannot discuss A without discussing B because I consider the problems to be interwoven just by way of warning.

DR. MURRAY: Fine.

PROFESSOR CHARO: I find that in our discussions as a commission that we have been struggling to imbue the phrase "rights and welfare" with some kind of meaning distinct from the meaning of minimal risk and that we have never yet been comfortable in some clear distinction between the two where each criterion addresses a specific concern the IRB should have before waiving consent. And I think our confusion has now spilled over into the text built on our discussions that precedes these recommendations and now in the recommendations themselves.

I do not have a conclusion in mind about how we should cut it but I think we should cut it somehow and

I would like to suggest places here where the overlap is obvious and there is some possible way to cut it.

If you take a look at the text of "A" in which we are trying to describe the basis of this presumption that research on existing coded samples is probably minimal risk. We have three factors that indicate probable minimal risk. And the first two are factors that go to minimizing the magnitude of realizing the probability of the risk. All right. Minimizing the probability that certain events will come to pass.

The third is really distinctly different. It is about the magnitude of the risk. It is about the nature of the harms that we are trying to prevent. All right. And the harms that are identified -- and then when you get to adversely affects rights and welfare we are once again beginning to talk about the kinds of harms.

Now if we could cut -- if we could make the difference between minimal risk and rights and welfare would be the only way we -- minimal risk refers solely to probability issues and rights and welfare refers solely to the kinds of harms that we are concerned about,

invasion of privacy as well as legalization of -- as well as concrete losses of insurability and reportability, et cetera.

Or you can say that minimal risk is something that, in fact, incorporates both probability and type of harm, which is the traditional way of looking at it, and the rights and welfare is something different in which rights and welfare might be narrowly interpreted to mean only legal rights like the legal right to privacy embodied in the Medical Record Statute or in common law ruling or something that is distinctly different.

Or it could be that rights and welfare about dignitory (?) harms and minimal risk is more concrete harm but as it is now we do not have a clear distinction between the two.

And I think we really need to make it probability versus type of harm. It has to be probability of some kinds of harms versus a distinct set of harms. Otherwise we just --

DR. MURRAY: Harold?

DR. SHAPIRO: I think, Alta, you are right to point out not only in these recommendations but in the

text it is not clear. We do not have a clear idea at least as I read the text right now regarding what status and importance minimal risk considerations have versus status and importance rights and welfare have and that is, in part, because we do not -- have never thought carefully probably about just what goes in one category and what is in the other.

I do not think it is possible to separate probabilities and harms. That is put the probability somewhere and the nature of the harm is somewhere else since in the -- whatever definition of minimal risk you have you are going to have to have a probability in there no matter what the function is or what the concern or potential harm is so that I do not think the idea of separating the two is a good one.

I do think we have -- and I think it is probably one of the most difficult problems with the text as it currently stands. We do have a problem of trying to distinguish between one of these categories and the other. And, indeed, part of this text goes on to say this thing -- maybe we should get rid of minimal risk all together and just deal with rights and welfare and all

fall in one category. One way of dealing with this is to have one category, whatever you are thinking about it goes in that category.

However, the regulations do talk about minimal risk so it is hard to, I think, to talk or to formulate one's way around it but I think you have put your finger on an important issue in the text as well as the recommendations. And if you look at the text, we -- the highlighted text currently highlights some of the difficulties of understanding just what minimal risk is in this kind of context.

And I interpret the text right now as saying, well, this is all very difficult but we always have the rights and welfare. You have got to think about that, too. So whatever is not in one happens to be in the other. It is on your mind and that is the stance right now as I interpret it.

And so I just want to say that I think you put your finger on an issue which we have not dealt with and it is very hard to think of a way to deal with it. It is not an easy issue so if we can discuss something about this it might be helpful.

DR. MURRAY: Alta, and then Larry, but I have something I want to say first. Just looking at the concepts first on minimal risk and then rights and welfare there is overlap in the very concepts. Part of what constitutes the welfare, protecting the welfare of individuals, is to not expose them to unreasonable risk. Part of what constitutes respecting the rights of individuals is not exposing them to significant risks without their consent or some such thing.

So, I think, you know, weighing the overlap as long as those two concepts exist as separate concepts which we are both -- which the regulations asks us to define. There is no way to avoid some duplication because at least -- simply -- particularly rights and welfare affects much of what falls under minimal risk.

Now practically what we should do about that now in our report I am not certain at this instant but surely we cannot be the first group to have recognized that there is this conceptual overlap and so shame on all the others that did not but anyway that is where we are.

Alta, and then Larry.

PROFESSOR CHARO: I agree. I mean, obviously

the problem lies -- the problem lies in the regulations and we are free to recommend that they be changed or interpreted into nonexistence.

I would like to suggest that there is a partial way out of the dilemma that is a little bit different than the one that appears in the text that is hinted at, although we have not yet found our way completely into the writing of it, it is hinted at in the recommendations.

That is first to keep in mind that one of the reasons we are concerned about this is that the minimal risk category is inherently relative, that is it puts into perspective kind relative degrees of risk and comparisons to daily life. Whereas the criterion about rights and welfare rings quite absolutist. It says that the research does not adversely affect the rights and welfare. It is much more constraining on IRBs that would like to find a way to waive consent. So we have to keep in mind there is some significance about where you place various concerns.

I think that most of what we are concerned about appropriately belongs in the category that is

called minimal risk, that is the concerns about possible breaches of confidentiality wielding a specific consequence, embarrassment, stigmatization, loss of insurance, loss of employment, et cetera, as well as unexpected and unwanted walk backs with information and that these are the kinds of harms that are probably the most easily incorporated in there.

I think further that the text discussion about medical records gets us 85 percent of the way there but did not make the final step which is to say, "Wow, we would not want to use the risks of inappropriate use of medical records as the measure of acceptable risk to people in the use of their biological materials."

That the risk imposed by proper use of medical records might be a very good way to measure the appropriate level of risk for people -- for use of people's biological materials and what proper medical record use constitutes is use that is in conformity with the law and that the development here about what that absolute level of risk is, well, that is a social judgment and it is being made every day as the laws are reformed. Right now it is the social judgment that more

privacy is warranted than before and so the acceptable level under absolute sense of risk is going down because people have decided so but that is not a bad measure for the minimal risk category.

And then in the rights and welfare we have something slightly different. I think the rights part is actually easy. Regardless of whether somebody can actually be harmed and regardless of whether they even know that their privacy has been violated, if a particular protocol is going to violate a specific rule based in regulation or in state law or in federal law governing, for example, access to medical records, that is considered a violation of somebody's rights. That would be a pretty straight and fairly narrow way of understanding "the does not adversely affect rights" portion and it is appropriately absolutist. All right.

Even if it is only minimal risk. You should not be able to waive consent if that actually violates somebody's legal rights. And I would expand that more clearly to include common law rights as well as even perhaps customary rights.

The term "welfare" is much more problematic

and still now lacks any significant content. It is here that I might suspect we could properly place the concerns about group harms and that is where you might not want to put that under the minimal risk category, which is really quite individualistic in its focus on its concerns about what might happen here but a person's welfare is tied to some extent by these concerns about the way in which some group with which some group they have a significant identification is being tainted by virtue of the research. And that is a way to force consideration of the group harms issue by the IRB under appropriate circumstances and in this way we kind of clearly segregate our concerns.

Almost all of them are in the minimal risk category subject to this kind of daily life notion, which I think, in turn, can be tied to medical records. Rights and welfare would be rights in a fairly narrow legalistic sense and welfare perhaps, I am suggesting, in the context of a focus on group harm, and in that way really clean this up.

DR. SHAPIRO: Larry, Bernie and then myself.

DR. MIIKE: I think this is another example

of trying to shoehorn regulations that were made in a different context into this area and so that we are not talking about clear physical harm from an experimentation on an actual living person or on tissue that may deal with issues other than physical harm.

My suggestion is not to take a sequential approach to this thing and try to define what is minimal risk and then is what is rights and welfare but to -- but I do not see anything stopping us from suggesting that both these areas be looked at in parallel so that you give people the flexibility of saying because we know the imprecision in which we are focused we go in a sequential manner.

Let us look at this collectively so we can deal with all of these kinds of individual harms or potential harms together and try and use an approach where we -- if we are going to retain a minimal risk and rights and welfare criteria that we deal with some of the things that are in parallel rather than sequentially.

DR. SHAPIRO: Bernie?

DR. LO: I agree with this whole line of discussion. These are concepts that are hard to define

and hard to sort of implement regulations and the fact that we were handed them as tools to deal with makes it even worse.

I am having trouble understanding what the intention of the original regulations was. Just as we tried to go back earlier today, can someone explain to me why these regulations were crafted in the first place? Someone must have thought it was a reasonable approach. I am just having trouble grasping this.

And then, secondly, I would like to suggest that if we come up with an example of the type of research -- an example of research on human biological materials that does not involve greater than minimal risk but does we believe adversely affect subject's rights and welfare, I think Alta started to do that.

An example, I think, would be really better because I think to make it very abstract will lose the audience.

DR. MURRAY: Diane, did you want to respond directly to that point?

DR. SCOTT-JONES: It is just about this whole general issue of minimal risk and rights and welfare.

DR. MURRAY: Well, do you mind then if we go through the list then?

DR. SCOTT-JONES: Okay.

DR. MURRAY: Bernie?

Alex?

PROFESSOR CAPRON: Bernie, I think that the language has a definite history. The minimal risk language, as you know, goes back to the article examining what had happened in a number of research studies and reaching the conclusion that for most people in research the kinds of risks they were exposed to were comparable to the risks of ordinary life.

My sense is that while there is a lot to say for Larry's parallel rather than sequential thinking the regulations were crafted with sequence in mind.

The first question was much more a question of physical harms because that was the kind of research that was being thought of. The record is quite clear, I believe, that despite the inclusion of behavioral research under the mandate of past commissions and, therefore, under the drafters that most of the focus was on direct physical harms and the kinds of things that

happened in deception studies were just kept slightly to the background and were intended to be gotten to by this waiver and consent.

The reason it is sequential is that having once decided that something is minimal risk then they say, "Okay, we are ready to waive." Now does that waiver create a risk to rights and welfare?

I think that Alta is correct in saying that the inclusion of the -- or at least I interpreted her saying that the inclusion of the word "welfare" there is puzzling because welfare sounds like physical well-being again. And it leaves us all trying to tease out now what are the other ways.

And in this context she suggested that we had in group harms, which were certainly not in the regulators' minds when this was made up. There was --I think no reason -- I cannot think of any example going back to that period when that was being written. But really the emphasis is there now that we have decided to waive would that waiver expose a person to adverse effects on their rights and welfare.

And as she says, it is much more absolutist

if you say adverse means anything at all then you could negate a prior judgment that it had minimal risk.

I would interpret adverse there to mean adverse in the sense of being serious, some serious harm, a serious impact because we have already decided that with physical welfare there really is apparently no -- we are not exposing any adverse effects on your welfare.

But maybe you are right. Maybe you are right to say this is too much an invasion of privacy. Maybe you are right to say I do not want to participate. I do not want my being somehow to be used to advance research I do not like. So the more controversial research would be the kind of thing where a person would say, "Well, I would want to be able to say yes or no to that."

My sense is that a major use of it was vis-a-vis deception studies and I would be very interested in Diane's comments about this because my sense was when a deception study was one where people did not think it was going to be very shocking, this would be someone being deceived, was there still some sense that their right to say no to that was going to be adversely affected. And that could be, as I think our report is here to say,

affected by the design of the study, the debriefing, the opportunity to have your material withdrawn afterwards.

The shoe salesman who is not really a shoe salesman but is looking at mother-child relationships in the process of buying shoes or something and is doing research then says, you know, "when I ask you a few questions, I am going to get rid of the entire data about you if you do not want to be included."

Well, the thought was it was not really very risky to start off with but the fact that a person could get their data out and not be included would be a protection of their right and so, therefore, the waiver of informed consent up front -- the waiver of informed consent up front was not to be problematic and so forth.

So it really was not sequential thought to answer Bernie's question. I do not see any reason why we should say in this one area of research as sequential should be gotten rid of.

It is difficult. In a certain way this raises the underlying question of do we want to write this whole report around the existing regulations and we made our determination a long time ago that is what we

were going to do for better or worse. We were not going to come up with a whole new approach.

DR. MURRAY: Diane?

DR. SCOTT-JONES: I would just like to comment on my understanding of the notion of minimal risk and it is as is written on the bottom of page 36 and the top of page 37, minimal risk to a subject's rights and welfare. It grows out of the idea that participation in research -- before one participates you cannot know with certainty whether there is going to be harm or benefit so you talk about risk meaning probability of a negative outcome or potential benefit meaning the probability of some good that is going to result from participation in research.

So the concept of minimal risk is used precisely because we do not know adverse effects or benefits beforehand so in my view it is appropriate to talk about minimal risk to a subject's rights and welfare because you are just making a judgment about the probability of some harm to the person. Hence the word "welfare." And you use the word "rights" when there is something that is -- either through some legal mechanism

or some commonly shared value recognized as a right.

It seems to me that we are making distinctions unnecessarily because we use the word "risk" because we do not know adverse effects ahead of time. We are just making probability statements rather than absolute statements.

DR. MURRAY: Steve, Trish and David? I really feel the need to get some settlement of this issue so let's see if we can move as quickly as we can.

MR. HOLTZMAN: Just a quick endorsement of what I think Alex's and Alta's position, as attractive as Larry's is. The subject of the two thing -- the two -- number one and number two are very different. Number one is the research is minimal risk. The second one, the question of adverse effect, it is the waiver of consent. So even if a lot of the same things come into play as you think about it if you keep those two things in mind you are being asked to evaluate two different things.

DR. MURRAY: Trish?

DR. BACKLAR: I waive my time.

DR. MURRAY: David?

DR. COX: Yes. I endorse what Steve just

said. I also endorse Alta's point. And for myself, that for any grounding on this I go back to the Belmont Report and I said what are the three components that we are talking about in terms of ethical responsibility of conducting research.

I think that the difficulty here in number two is that when the original regs were proposed people did not pay attention to the Belmont Report because there is different components there. There are three components.

(Technical difficulties.)

DR. COX: So that I think here we may be able to help clarify the situation by basically pointing that out. I mean, the Belmont Report is something I can understand because it gives three principles on which you can do stuff and base it. So I think that using that as the grounding here may be helpful is my suggestion. But in the substance of it I really agree with what Steve and Alta said.

DR. MURRAY: Alex, and I hope you provide us guidance as to specifically what we should be doing.

PROFESSOR CAPRON: Two points then. On "A" I

just wanted to draw people's attention to point number one, which I found in subpoint 1 there. I found it confusing. It says, "The study makes provision for maintaining the confidentiality of the research results," which sounds like something that a biotech company would be very happy, that is to say you are not going to publish your research, we are just going to use it for all the trade secrets that you give us.

I do not think that is what meant, that is confidentiality of personal information in the dissemination of research results. And if that language is acceptable I find point 1, therefore --

DR. _____: A biotech company would be quite happy with that.

(Laughter.)

DR. _____: I agree with that.

DR. MURRAY: Does everybody agree?

DR. LO: No.

DR. MURRAY: Bernie does not agree.

DR. LO: No, it is not just the results. It is the data. It is not just when you publish it. It is when you are sort of collecting and storing the data you

want to protect --

PROFESSOR CAPRON: Yes, fine. Fine.

(Simultaneous discussion.)

PROFESSOR CAPRON: Obtained in the course of research.

DR. LO: Right.

DR. MURRAY: All right. Confidentiality. Is that it? Okay. We have got an agreement on that.

(Simultaneous discussion.)

PROFESSOR CAPRON: Identify -- personally identifiable information, which includes -- we have already said coded is personally identifiable but you may very well be publishing a lot of that information but now in a way which is probably aggregated and so forth that it is not going to be linked to -- link-able to any person.

PROFESSOR BACKLAR: And this is the kind of keeping things in --

PROFESSOR CAPRON: Well, it is -- but yes. Yes. That is the maintaining of the data itself which is I think is what Bernie and Carol were underlining here. I was saying that research results usually implies

publication and the word "confidentiality" does not go well that without telling what it is that is being kept confidential.

In "B" what seemed to me was missing there was the notion that your rights -- by waiving your rights of consent it was not just your entitlement to privacy but there are certain categories of research. I know we have gone around this and it may be that we decided -- I cannot remember if we decided that there was no way of expressing the notion that certain categories of research are simply more sensitive and the use of biological material without your right to say take me out of accrual, I do not want to contribute to that, is more likely to be seen as a violation of someone's right in that kind of research than in other kinds.

Alta identified one area which I think is important. Research which aims to make statements about particular groups that are disadvantaged or subject to discrimination and prejudice because of history that we know. Sort of the statements about people's ethnic background or their sexual identification or whatever would be an example of research where someone would say I

do not want to contribute to that and I do not -- and you should have known that I would find that and you violated my right by waiving consent there. And it seems to me that that is not picked up here and I thought it was a useful contribution which she made but I do not object to what is here.

DR. MURRAY: We have Bernie and then Alta.

DR. LO: Just one small point back on "A". I think we could put in a modifier for a provision of appropriate or adequate or something because you can make provision and it just may not be enough.

PROFESSOR CAPRON: You mean after --

DR. LO: Right.

PROFESSOR CAPRON: -- protects the confidentiality of personal information.

DR. MURRAY: You mean like the study adequately protects the confidentiality of --

(Simultaneous discussion.)

DR. MURRAY: We will use that as a working phrase. Thank you, Bernie.

Alta?

PROFESSOR CHARO: Okay. A couple of quick

items although I think probably in the end it will be most helpful for us to just actually try to write these things and give you fresh text completely.

But on 2(A) and (B) I think in light of this discussion that sub-3 in (A), which refers to the examination for specific kinds of traits, I think that actually belongs in (B). And the last sentence of (B), which talks about revelation of information with d employable, insurability, da, da, da, that belongs back in (A). Those two should be swapped, I think, in light of this discussion here.

DR. MURRAY: Do we have an even trade here to --

PROFESSOR CHARO: There is an even trade, that is right.

Who did the Yankees get and who did they give away?

DR. SHAPIRO: They gave away --

(Laughter.)

PROFESSOR CHARO: I know it has something to do with sports.

PROFESSOR CAPRON: And there was a lot of

argument about it.

(Simultaneous discussion.)

PROFESSOR CHARO: Because the discussion so far has leaned toward the notion that the minimal risk category is about the risk of possible kinds of harm that come from the study itself and that (B), which is the explanation of a harm does not -- by the way, we need to somehow get the "does not" into that first sentence or the whole thing does not work.

The term "does not adversely affect rights and welfare" is about whether or not the waiver of consent, given that things are minimal risk, given that the study is minimal risk, does the waiver of consent in and of itself adversely affect some kind of right or some aspect of the subject's welfare.

We have already determined that there is a minimal risk of harm to insurability, harm to employability, et cetera, of a particular protocol.

And in that I would suggest that we say instead "does not violate any state or federal statute" and that we expand that to something on the order of does not violate any law or customary practice.

And, finally, I would like to make sure that in the text that follows this at the bottom of 36 and the top of 37, I have to say I just disagree with you, Diane, and I would like to get rid of the phrase "to present minimal risk to a subject's rights and welfare." It is confusing to categories. Again, it is present minimal risk of harm and separately given minimal risk of harm that the waiver does not -- and this is a very absolutist sense -- does not adversely affect rights and welfare.

MR. HOLTZMAN: Are you suggesting Alex's kinds of concerns in the community, harms or whatever going to --

PROFESSOR CHARO: Yes. In fact, that is why I was saying what is now listed as 2(A)(3), which is asking the IRB to consider whether the study involves examination of traits not commonly of political, cultural or economic significance be moved to (B).

Because what is happening is you are saying, well, there is very minimal -- there is minimal risk that you are going to lose a job, there is minimal risk that you are going to be embarrassed by this but as a matter of respect for your moral and legal rights or respect for

your welfare as a member of this larger group you are entitled to say, "No, I do not want to support research that is going to promote what I think of as being an elitist agenda, or a rightist agenda, or a leftist agenda, or whatever agenda it is."

MR. HOLTZMAN: Then I would say if that is the basis of that, all right, and we are going to put that here, we are going to have to come back and look at the case where the sample is rendered unidentifiable, which under current regs would exempt it, and whether or not whatever is impelling us to make the case you just made in terms of rights of the individual and autonomy rights are not equally compelling that it is going to be identifiable.

PROFESSOR CHARO: That is a fair point but it is hinted at in the text several times.

DR. MURRAY: Larry and Harold have the last words on this subject except for my effort to move us on.

DR. MIIKE: Aside from being totally confused from this discussion let me just say the following: I agree with Diane that if we are going to go in a sequential fashion that the minimal risk should be

applicable to the rights and welfare. It should be minimal risk to rights and welfare of the subject.

We never really asked the question about what we meant by welfare. The phrase rights and welfare covers everything we need to cover without having to define exactly what that means.

I see the risks here as not so much physical harm but the issue about rights and welfare.

So if we are going to go in a sequential fashion we need to talk about minimal risk but link it to the second part about rights and welfare and the discussion I have heard right now does not do that.

DR. SHAPIRO: I guess I have a somewhat different perspective but let me suggest we move on whatever our various perspectives are because I think you have to stipulate that there is no final way to separate these two things. There are sensible ways to go about this. There is alternative sensible ways. As long as we have one of them we will be all right in this area. And I think -- so I think we just have to accept that we have one that is sensible and appropriate but not the only one that makes sense so I think that the structure we have

will work.

There are lots of important amendments that have been made here which will certainly improve it and we have to live with the fact that there is no single way to deal with this. As long as what we have is a sensible way and is consistent with what is in the text we will be all right here because I do not think we really have any differences amongst us in a substantive way here regarding what we are trying to protect and when the protection will roll in. In fact, we all agree on this as far as I can tell.

It is just a question of how we phrase it and I think, Tom, there is more than one way and let's just take these suggestions and try to do it in a thoughtful way and move on.

DR. MURRAY: Thank you, Harold.

Larry, for what it is worth, my understanding of where -- and, Diane, where minimal risk comes from, not just in this part of the rule, the Common Rule, but in other parts was a way, in part, to -- a way to respond to a moral objection to scientific research, mainly that any research that imposes an risk on some person without

compensating benefit to that person is unjustifiable. That is the kind of argument that one might make and I think probably explicitly in some of the events.

The minimal risk idea says wait a minute, that is not morally sensible. You really need to put this in the context of what our lives are like. Our lives are not minimal risk generally. So let's say a more reasonable baseline of this notion of when the scientific research imposes risks on the subject that go beyond the minimal risk is to define a category of minimal risk and simply stipulate that that category means the risks we face in our every day lives. That is where that, I think, comes from initially. That is kind of how that came out in terms of its moral significance at least.

Clearly the concept of welfare, as I tried to say earlier, encompasses that, the minimal risks as well as well as benefit. That is what -- that is what any -- the philosopher talking about welfare, it is sort of the totality of harms and benefits accrued to an individual. So that is what I was trying to say earlier when I was saying to Alta that these things are -- even conceptually

you cannot rip them apart completely. They are just -- particularly the concept of welfare incorporates the notion of harm and the concept of rights go beyond that.

It is not just -- rights is not exhausted by harms --

(Technical difficulties.)

-- affront someone's right, you can violate their rights without causing them any discernible harm so that is a more inclusive category.

But we had a discussion. I am not certain we know exactly where everybody is on this but I think we will try with the help of -- I do not want to lay the burden on any particular people at this point, we will do it at break, try to rewrite (A) and (B). It would be very helpful to move through (C) and (D) before the break.

Can we do that? Does anyone have an objection or a question about (C)?

Alex?

PROFESSOR CAPRON: I think we come in (C) to the ambiguity in the word "existing" because in our earlier discussions we have used it in two ways. And I

know we discussed this in Princeton and I just want to say that I intend to a file a dissenting statement on this.

If existing means, as it is in the regulations, that materials existing at the time of a research project starting, fall within the series of exemptions or waivers that are allowed, I understand that as a reasoning to differentiate it from samples that have been collected in the course of the research after which consent is obviously a requirement.

The whole reason it seemed to me for point (C) and basically waiving the whole --

(Technical difficulties.)

-- of practicability was that as to these 200 and some million samples that are now stored the sense was this is a very valuable resource. It is very probable that it would be quite burdensome to contact most of the people who are in that sample because many of them go back many years. A certain percentage will be dead, many will have moved, and just be extremely burdensome. And rather than telling every IRB to force every investigator to work out a burden statement for

their research explaining why they think a particular sample they are going after it would be impracticable to get them. We will just waive them.

That logic does not, it seems to me, apply as to future in the sense of from the point at which new rules are announced because at that point everybody who is collecting these things -- and let's be clear about that -- there are going to be a lot of commercial outfits or pathology labs and nonprofits that are seeing this as a source of income and so forth to work out arrangements with biotech companies to build up samples, and that is all well and good but they all now know the uses that are going to be made.

And they ought to, therefore, develop means to notify people that these uses are in prospect and ask them the kinds of questions that we get to later under consent about do you want to know, what do you want to know, when do you want to know what uses can be made, do you want to get contacted back with results. All those kinds of questions.

And I do not think there is any reason to

apply a blanket impracticability rule so I am just telling you I am going to dissent on this point and since I seem to have lost that argument in Princeton I just wanted to let you know why I think this meaning is not a blanket existing. But as to this impracticability I think there is a reason to differentiate now from the future.

DR. MURRAY: Alta?

PROFESSOR CHARO: Well, first I have got to say I apologize. I was not at the Princeton discussion because I had difficulties with weather getting into town. I remember having a fairly lengthy conversation with Alex about this at one of our meetings. I think we were at an American Indian museum, walking through the museum looking at exhibits and talking about practicability. The classic commissioner moment.

I remember coming out of that conversation --

PROFESSOR CAPRON: That was not a commission meeting.

PROFESSOR CHARO: What was that?

PROFESSOR CAPRON: That was the Macy Foundation.

(Simultaneous discussion.)

PROFESSOR CHARO: Oh, goodness gracious. Too many hotels, too many meetings.

(Simultaneous discussion.)

PROFESSOR CHARO: I do not recall as I -- as I supported the notion of weakening of the practicability requirement -- I do not recall feeling it was necessary to weaken it into the future. It was really a grandfathering problem. It seems to me that we might be able to accomplish our goals if we were to amend this slightly in two ways.

First, rather than calling for the repeal of the practicability requirement we could take advantage again of this notion of presumptions. It allows for the fact of specific reviews of cases. And we would say the following: That where a researcher is using a sample that had been collected prior to date X, or date X is when these recommendations come out, right, that the IRB should presume that it is going to be impracticable to go back and get stuff. And that presumption can be overcome if it is obviously simple and cheap in this case to get consent and to continue to respect people and their

dignity even where there is minimal risk.

And that for samples that are collected after the date of these recommendations that that presumption does not exist because it is, in fact, part of our recommendations that for new collections the consent process ought to incorporate some notion of future use.

And that might be a way to avoid your need to dissent because it more narrowly focuses what we are suggesting.

PROFESSOR CAPRON: That is exactly what I --

DR. MURRAY: Alta has made what I think is a very fine proposal. Is there any comment, a quick comment, or any dissent from her proposal? As I understand it, let me make sure just to try to articulate it, here we are not talking -- we are not going to use the phrase identifiable. It is just really to denote samples collected or specimens collected prior to the effective date of this policy and specimens collected after the effective date. So that is the key distinction and we create a presumption in favor of impractibility prior to that date and then that presumption is over once the new rules are in effect.

Is that correct? Okay. Do we agree with that?

DR. KRAMER: Yes.

DR. MURRAY: We do. Very good.

DR. SHAPIRO: Shouting does not count.

DR. MURRAY: Larry?

DR. MIIKE: Aren't we in other areas also talking about in future collections strengthening the informed consent requirements?

DR. MURRAY: Yes.

DR. MIIKE: And then we are dealing with minimal risk categories only in this recommendation?

PROFESSOR CAPRON: No. We are dealing with waivers.

DR. MIIKE: But it says is determined to present minimal risk.

PROFESSOR CHARO: It only comes up when you are in a situation where you are asking can you waive consent and minimal risk is one of the four criteria for waiving consent.

DR. MIIKE: Impracticability is another --

PROFESSOR CHARO: The question of

impracticability is only relevant in a discussion where the question of minimal risk is also at issue. The two are linked. You never find yourself discussing practicability unless you have got a minimal risk protocol in which you waive consent.

DR. MIIKE: So what is the harm? I do not understand the big concern. If we are dealing with strengthening future consent requirements and we are dealing only with a waiver of the practicability requirements for minimal risk research, what is the harm?

PROFESSOR CHARO: What is the harm of what?

DR. MIIKE: What is the harm of dispensing with the practicability requirement for future research?

PROFESSOR CHARO: The practicability requirement is there, I think, because of concerns about respect for persons. It says the following: Even if something poses minimal risk to you and even if a waiver has not adversely affected your rights, your welfare, a violation of --

(Simultaneous discussion.)

PROFESSOR CHARO: -- that as a matter of respect. It is easy enough to ask you and we should ask

you anyway.

DR. MIIKE: I understand that but what I am saying is in the other parts of the report we are saying for future collections we are requiring some form of informed consent. We are not leaving it the way it is now.

PROFESSOR CHARO: Yes. Therefore --

DR. MIIKE: Therefore, what is the harm? What is the harm if we are in another section of the report recommending that in all future collections that some form of informed consent be done --

PROFESSOR CAPRON: Because it would not apply. People could say, "Look, they allowed it to be waived over here so we do not need to bother about it."

DR. MIIKE: But what we are saying is that in future collections of material a general consent or a specific consent be made.

PROFESSOR CHARO: Are you assuming there is going to be perfect implementation of that recommendation?

DR. MIIKE: Are we dealing with perfect worlds in our policy statements?

PROFESSOR CHARO: No, which is why you often have things that have overlapping effects.

DR. MIIKE: But there is a certain amount of redundancy that gets to be really sort of obstructive and all I am raising is the issue here is that so far the discussion is going we are not going to be doing anything to improve future collection and I am saying we are. We are requiring that informed consent be done in future collections and Alex's objection was to future collections. I am simply pointing out that we are putting in some safeguards in future collections.

PROFESSOR CAPRON: Where consent is required.

DR. MIIKE: Yes.

PROFESSOR CAPRON: This allows somebody to go in where there has been no consent because someone says, "Well, we are going to have a waiver." This will be a collection which will be used for --

DR. MIIKE: If they are going to be collecting in the future and they are going to go through an IRB for those collections they are going to have to pass muster about getting informed consent.

PROFESSOR CHARO: Right.

DR. MIIKE: They are not going to be able at that time to say, "Oh, we do not care because some time in the future we may use these samples and there is going to be minimal risk and we do not have to have informed consent."

PROFESSOR CAPRON: It is the use that you get consent form.

DR. MIIKE: Right. But aren't we making recommendations for future uses of materials collected, whether that be in a general sense or whether that be -- we are going to be -- we are offering people the choice of saying you can use my -- for whatever or I want it uses only in these particular areas or, no, you cannot use it. That is part of our package of recommendations.

PROFESSOR CHARO: Larry, I am not sure I understand one thing, which is why it riles you so much to switch from an elimination of the practicability requirement to the use of a presumption. The advantage to using presumption is that it gets us away from requiring a regulatory change before the recommendations can be implemented, which is efficient as a matter of just pragmatics.

DR. MIIKE: But your compromise came about because Alex was worried about future collections and I am simply pointing out that the future collections are not -- our package of recommendations are not to be left the way they are.

PROFESSOR CHARO: Regardless of the motivations for suggesting the compromise I gave you another advantage. Another advantage. Two for only $1.99. You could, in fact, make it easier to implement this thing without having to actually change the regs if all we did was say let's incorporate a presumption as opposed to calling for the elimination of specific regulatory language which requires notice of rule making, public comment, and another 13 year process.

DR. MURRAY: Harold?

DR. SHAPIRO: If I understand what Larry is saying it is not the issue of whether it is a presumption or not. That is not what is at stake in his comments. What is at stake is whether this presumption will cover only the existing samples -- what existing means. Existing means only as of this paper. It means just before the research started.

Well, I am just saying that is the concern. It is not the concern, as I understand what Larry says, over presumption versus assumed or something. That is, I think, not the issue.

The issue is whether in 2004 a researcher approaches this problem and says, "Well, it is some existing sample that were collected last year and they fall under this."

That is the focus of the concern here as I understand Larry and the nature of his arguments. It is really a straight forward question. It is a question about how the commission feels about....

That is for samples collected in the future under whatever regulations are going to be adopted do we want to presume under these circumstances that if minimal risk is determined that consent can be waived, whether that was collected in 2002 or 1802, can consent be waived.

And there was division on the commission the last time we met. Some said, "No, only if it us collected before the date of our report." Others said, "No, that will be too much. Given everything else that

is too much bureaucracy. It is not worth it. It is too constraining on research. Let's presume that it applies to anything before the researcher decided to proceed with the project."

It is a simple matter and we may disagree on it but I think that is where the issue is. The presumption idea I think is interesting. Maybe that is good regardless of what the answer is to this but I think we should try to settle this question again on existing versus what existing means. Does it mean before a date certain or does it mean before you started your research?

DR. MURRAY: I may hear it a little differently but let me try and say it the way I think I heard it. I do not hear a controversy about what people do -- I am going to use an acronym here -- before the implementation of the commission report, BICR, before the implementation.

Alta is saying let's have a presumption that it is not practical. Okay. I think there is general agreement about that.

What I took Larry's concern to be is what happens after our recommendations are implemented. Okay.

And here if I may paraphrase Larry's concern here we say, "We are going to shoot the sucker dead but we are going to beat it." We have sort of fixed it by requiring consent.

We are also now going to say you also have -- we are going to let you waive consent. What I am hearing from Alex and Alta is that it is not the right way to understanding the situation after implementation.

So can we just set aside before implementation and let's just talk about after.

PROFESSOR CAPRON: After implementation there are -- as we said, four requirements for waiving consent. One of them is practicability. Once our regulations are out there I do not see any reason for the language that we now see. That is what I was objecting to. We are not changing the regulations. They say one of the things the IRB must document is the research could not practically be carried out without the waiver or alteration.

Now if it has been very clear to the pathology community as it were that they ought to be following all our consent rules when they collect, which is not research at that moment when they collect the

samples, so that the samples can be usable in research then I would go to an IRB would say it is practical to carry it out and just go to one of the pathologists who followed the recommendation and collected the necessary consent in the first place or kept records that you can now contact these people to get their consent. It is now practicable.

So it really is the PI, the before implementation, that at issue. And I do not even -- presumption is fine. After that point we simply say there is a reason for saying that that practicability does not have to be investigated case by case.

IRB's may presume that it is impracticable as to those hundreds of millions of samples that are already there to get consent from them. They may presume but they may find that given a particular set of samples that were collected last week at the hospital that you could get consent from them and it is not impracticable.

DR. MURRAY: I want to narrow this down if I can. Do I hear the first point Alta's suggestion that before implementation we recommend that there be a presumption that it is impracticable that that

presumption be overcome by the facts. Does everybody agree with that?

PROFESSOR CAPRON: Yes.

DR. MURRAY: The second issue is what do we do after implementation. I do not know --

PROFESSOR CAPRON: We do not do --

DR. MURRAY: Alex Capron clarified for me but I accept Larry's objection but I want to know if you are happy about it or whether you want to --

PROFESSOR CAPRON: We are not adding --

DR. MURRAY: Okay. Bette and Alta, let's make it real brief because we are going to go to a break.

MR. KRAMER: Tom, I have for some time had two basic problems with where we are in this report because I feel as though there are two issues about which we have never made a straight forward statement. One of them comes up at this point and that is do we, as a commission, feel that the existing archives of tissue are so important and that we do not want to -- I mean, make a straight forward statement -- that we do not want to impede scientific research by putting unnecessarily difficult interpretations on the regs that it is going to

make it impossible to use these.

We keep going back and forth. It seems to me that if we had made a statement such as that that in this instance we would say that this is one of those times when to insist on a practicability requirement it would make it impossible and, therefore, because we feel this way philosophically with existing samples we suggest that it be waived and we recommend that it be waived. However, going forward it should be -- still be applied with necessary conditions.

I think that the failure is our's in not having decided that, yes, this is how we feel and we just --

DR. MURRAY: Bette, actually I have to disagree with you. I think we do say that. We say that at the beginning of this. We say that in this chapter and we say it in the end of the chapter.

Clearly, if anything, I would want us to say that research is very important. These are enormously valuable resources for research and it is our conclusion that the research ought to be allowed to proceed without undue obstruction.

PROFESSOR CAPRON: Without necessarily being burdensome.

DR. MURRAY: Without unnecessarily burdensome obstruction. That is good language. If, in fact, there is no substantial harm or infringement of the rights of subjects. I think we say --

MS. KRAMER: Well, I am going to go back and agree and reread it again but as I read it again yesterday and I still did not see it. It seems to me that it is always hedged a little bit. It is just never quite straight forward and it keeps, I think, tripping us up.

DR. MURRAY: Okay. I will keep that in mind as we go through it one more time.

Alta, did you wish to be recognized?

PROFESSOR CHARO: I think I was -- I mean, after our recommendations come out, the practicability of this is there is no presumption or even direction, it is just business as usual.

DR. MURRAY: Right. That is the way I understood it.

PROFESSOR CHARO: Fine.

DR. MURRAY:

All right. I think we need to --

(Simultaneous discussion.)

DR. MURRAY: Harold?

DR. SHAPIRO: I did not mean to interrupt, Steve, if I did. It is important to realize that we discussed this exact point and came to a different conclusion and I just want to make sure those people who felt differently, although Larry is being clear that the same thing he felt in February he feels in March. A man for all seasons.

So I just want to make sure we feel comfortable with it because this was the exact point we discussed. It is unchanged in its character. If you feel comfortable, that is fine. It is not a big issue from my perspective.

DR. MURRAY: Didn't we decide that --

(Simultaneous discussion.)

DR. MURRAY: -- could take precedence over what goes on in Princeton, New Jersey?

(Simultaneous discussion.)

DR. MURRAY: Steve, if you feel passionate

about this please go ahead and have the last word before break.

MR. HOLTZMAN: It actually goes to Harold's question. I am just trying to think through where we have just come and how it is articulated, the backing for the practicability requirement is again really based in a more targeted right and originated with the deception studies and so we understand practical as it is just not possible to do -- it is in the nature of the research you cannot ask for the consent and that is why there is this fourth criteria that follows which says if you have gone and done that you better get back to that person and say you know you were in research. All right. So that the sort of practicability in the sense of practical costs and whatnot really is not in play. All right. It has to do with again the autonomy right.

So if we want to move down this line of interpretation we need to keep thinking about again how we -- what we are saying in the area of identifiers. Per se the philosophical cases --

DR. MURRAY: We will have more to say about that, I suspect.

Carol wishes to say the last word.

DR. GREIDER: Just one point that the text previous to this where we discussed the issue of practicability it seems to me, and I may be interpreting it wrongly, but we sometimes confuse the term practicable with practical which is what Steve just said. Is it practical to actually go out and do that as opposed to is it actually possible to do it. The language means back and forth and I think we should just be aware of that.

DR. MURRAY: We are now going to take a coffee break. When we resume John Fanning will be joining us to lead the discussion of privacy issues. 10:45.

(Whereupon, a break was taken at 10:30 a.m.)

DR. SHAPIRO: All right, colleagues. Let's reassemble and I would like to welcome John Fanning, who is a Senior Policy Analyst at the Office of the Assistant Secretary for Planning and Evaluation at HHS, and he serves as the Privacy Advocate of the department.

Obviously privacy issues in various forms are a bigger topic than we are dealing with but certainly it is an aspect of some of the things that we are not

dealing with and we are very fortunate to have Mr. Fanning here today. He has as much experience or perhaps more experience in dealing with some of these issues than anyone else.

We welcome you here today and look forward to your remarks.

We have asked Dr. Fanning to speak for about 15 minutes roughly.

Is that your understanding?

MR. FANNING: That is correct.

DR. SHAPIRO: And then we will deal with questions as you think they might apply to the issues that we are dealing with.

Welcome and thank you very much for being here today.

PRIVACY ISSUES

MR. FANNING: All right. Thank you, Mr. Chairman.

I am here to talk about policy choices that have been made in privacy thinking about of the use of records for research. My comments are in no way an official HHS response or for that matter even an

unofficial or informal response to issues involving the use of human tissue as such. However, there are connections and possibly analogies and I will describe some of the thinking that has gone into the question of the use of information for research.

The most recent manifestation of policy on this are the recommendations of the Secretary of Health and Human Services which were sent to the Congress a year-and-a-half ago where she recommends that Congress enact national legislation governing the use and disclosure of health information held by health care providers and payers.

Now the Secretary came to prepare this report following a command in the Health Insurance Portability and Accountability Act that we look into this issue and make recommendations to the Congress, and that took place with the assistance of an advisory committee we have, the National Committee on Vital and Health Statistics. The conclusion was that there ought to be a national law governing the use and disclosure of health information by payers and providers.

Let me describe how it affects research. In

its basic coverage we propose that such a law cover research in which care is given. We do not propose that this particular enactment cover research in which care is not given such as survey research.

Now that set aside, the principal issue now is to what extent and under what circumstances should information be allowed to be disclosed for research from existing records and in this recommendation the Secretary advises that there be a law that permits the disclosure of identifiable information without patient consent for research under carefully specified circumstances which parallel very closely the circumstances under which IRB's are allowed to waive informed consent for research. So that is the basic stance in this recommendation.

The proposal also includes that there will be a prohibition on further use of that identifiable information except under very limited circumstance. (A) for research under the same conditions. (2) in limited public -- in public health emergencies. And (3) for oversight of the particular research, which is basically a research use.

This recommendation follows policies that are

well-established in the Department of Health and Human Services. Under the Privacy Act agencies can identify disclosures that they intend to make and they publish in the Federal Register a notice of those disclosures. Many of our record systems have notices that permit disclosure for research under very similar circumstances.

So this follows a pattern.

There was given out to the commission an outline of some of this together with the actual text of the recommendation as it affects research disclosure and you can read the conditions there in more detail.

The --

PROFESSOR CAPRON: Could you point to a page number?

MR. FANNING: It is at the back -- at the very back of the document. The top is the memo from Kathi Hanna to --

PROFESSOR CAPRON: Right. Is it page 12, 13? Where are you referring to?

MR. FANNING: Well, there are --

DR. _____: It is after 17.

MR. FANNING: -- a few documents --

PROFESSOR CAPRON: Oh, that one. Fine. Thank you.

MR. FANNING: But the last three sheets are of the content of the Secretary's recommendations with respect to disclosure for research.

PROFESSOR CAPRON: Thank you.

MR. FANNING: I should point out that in the history of government privacy thinking research has always been well treated.

Much of the basic underpinning of government privacy thinking came from a report prepared by the an advisory committee to the Secretary of Health Education and Welfare in 1973 and that did envision -- indeed, it recommended that information be allowed to be disclosed for research in identifiable form without consent under carefully controlled circumstances.

Likewise, the Privacy Protection Study Commission in 1977 made similar recommendations and then a few years ago when the administration started attending to the information infrastructure the Policy Working Group of the President's Information Infrastructure Task Force came out with a set of principles regarding the use

of information where they again understood and supported the use of information for research.

Now all of these enactments and pronouncements have as a condition of such disclosure two very basic points and one point that is equally basic but not so distinct. It is always to be assumed that the information will not be used to harm the person, that there is a clear intention, indeed, that the information will not be used to make any decision about the rights, benefits or privileges of the person once it gets into the research context, and that is a basic principle that the Privacy Commission enunciated with respect to both information that is collected initially for research and for information that is taken from existing administrative records for research.

The second point is that steps must be taken to minimize as much as possible the danger of inadvertent disclosure or misuse of the information.

The third point is the understanding that people will know in advance of this possible use. It has never been conceived as an absolute and I will give you an example in a moment but the basic principle always has

been that when information is collected from people it should not be used for other purposes unless they have some understanding of what those other purposes are and, therefore, the recommendations of these commissions and so on is that when information is gathered from people for administrative purposes, whether for health care or the administration of a public benefit program, or in any situation they should be told that possible use for research is one of those uses so they will have a clear understanding of the possible uses.

That concludes my explanation of the existing policy framework out of the privacy world and I would be happy to answer any questions.

DR. SHAPIRO: Thank you very much, both for your remarks and for the materials you supplied to the commission, which I found very helpful and I want to thank you for the effort to present those to you.

I have a question but let me turn to the commissioners first.

Alex?

PROFESSOR CAPRON: You not only have been here while we discussed certain aspects of the report

that are most relevant to the recommendations made about the records but I assume that you have had an opportunity to look at the material we were looking at or is that a false assumption? Our chapter five draft.

MR. FANNING: Well, I gather the one that I saw this morning is a brand new one. I did read the previous version.

PROFESSOR CAPRON: I just was hoping that if you were familiar with what we have been doing you could highlight for us what you see as the major differences in approach that we are taking towards human biological materials from the medical records. Obviously a good deal of the research that we are talking about would draw on both. Medical records and clinical data on the one hand and the biological materials, and it is the linkage of those two that is often of research interest but can you highlight if you see any significant differences in the approaches?

MR. FANNING: You know, I simply am not familiar enough with the text that you prepared for me to say that. There is one distinction in the history of thinking about these matters that is clear. It does

appear to me that the thinking surrounding the existing protection of human subjects regulation has assumed information to be -- this is perhaps not the way you would use the word technically but it is assumed to be identified if there is a linkage somewhere. Okay.

The researcher carries away information about 100 patients each with a code number. The original holder of the record has the key between the name of the person and the code. In the design of privacy protections by law and in the recommendations of these various commissions and so on, they have not regarded it that way. The rule and the obligation to behave applies to the person who has the information in hand and the mode in which he has that in hand governs the way the information is to be treated.

I think one of the dangers of regarding all information as identified and, therefore, subject to a fairly elaborate set of rules even if it is not overtly identified is that it makes -- it destroys the advantage of taking the identifier off. One of the basic principles of handling information, and for heaven's sakes take the identifier off, pass it around only in

unidentified form, and then (a) nothing is likely to go wrong and, therefore, we will not impose a lot of special rules on you.

So the risk of regarding it all as subject to the same rules is that there may be less motivation to strip it.

PROFESSOR CAPRON: I wondered, just to try this out on you, whether the distinction that we saw between records and samples might provide some justification for that difference in treatment in that we saw records as obviously once analyzed yielding more information than they might seem to have on their face. That is if you are looking through records on an epidemiological basis you could find a marker as it were in someone's record that is there in a common test that is done for all of us to a disease that had not previously been recognized as associated with that marker and, therefore, you would, in effect, be identifying people at risk because they have the marker.

But our sense was that that notion of an unfolding -- potential unfolding of a great variety of information was much greater with a biological sample and

the potential harm to an individual of having that information known to others or even the psychological shock of learning it about one's self was larger and that unlike -- so that is one distinction.

The other is that unlike the information that is in the medical records of many institutions and all the Medicare records and so forth where one is almost certainly going to be dealing with large masses of data, and that is the major way in which this is used, to look at patterns by looking at thousands and thousands and thousands of records that a good deal of the research on human biological materials is of a genetic sort where one is looking within cohorts. Now that is not uniformly true. One could be looking at a random population of people just to see if there is a marker for a cancer gene or something. But very often a lot of these studies are done in ways that directly implicate families.

So on both of those scores -- I should not speak for the whole commission. I was convinced that some greater sensitivity was due to these kinds of materials as opposed to the paper materials and the electronic data that you are talking about.

Might that help to explain a reason for -- that would be --

MR. FANNING: Yes. I do not know that I subscribe to any particular conclusion from those distinctions but, yes, there are differences between existing paper or computerized records and a tissue sample in the first case and in terms of scope and size and so on in the second case. Yes, I think those are valid distinctions.

DR. SHAPIRO: All right. Alta?

PROFESSOR CHARO: Two questions, please.

First, you have emphasized several times the wisdom of stripping identifiers immediately and yet one of the truisms here has been that there is value in maintaining links between the samples that are being studied and the people from whom the samples were taken so that as information evolves about the samples one can revisit the medical records of those people or those people themselves in order to kind of keep refining one's work and, indeed, you will find that in our documents there is even a suggestion that people should avoid removing identifiers and should rather maintain them but

abide by these fairly substantial confidentiality protections.

The recommendations that you have provided under II(e)4 anticipate good reasons for maintaining identifiers but the phrasing is restrictive enough that I wonder how consistent you think your phrasing is, which appears, like I said, II(e)(4) at the very bottom and then on to the top of page 2. How consistent do you think that phrasing is without general assumptions that with regard to biological materials maintaining identifiers will usually be a valuable thing to do?

MR. FANNING: I think not too much should be read into this. That is a statement of the general principle.

PROFESSOR CHARO: Okay.

MR. FANNING: It is always safer from the privacy standpoint not to have identifiers attached but just as we recommend a trade off that does permit passing records around for research for good reasons I think that trade off can be read into that perfectly well.

PROFESSOR CHARO: Okay.

MR. FANNING: I might point out that one of

the reasons we keep emphasizing it is simply as a practical security measure -- when I say strip identifiers, it does not mean necessarily throw them away but keep the link locked up so that if a lot of people are processing data they do not all have the identifiers. It is a practical security measure as much as a more basic thing.

PROFESSOR CHARO: It may turn out that at the end of the day it would be ideal if the kind of language we use and the kind of language that is used by those who are writing the recommendations and rules governing medical record privacy that the language was consistent so that removing personal identifiers was understood as being -- or to destroying personal identifiers was understood as meaning removing all linkages whereas something like making the identifiers highly difficult to obtain so that the linkages are quite secure was commonly understood as, you know -- with some similar language.

The second thing is that, again on II(E)4, these recommendations from the Secretary rehearse the language from the Federal Regulations about minimal risk

as one item and second separately adverse effects on the rights and welfare by virtue of deciding not to get consent once minimal risk has been determined.

I wonder if there has been any thinking within the people who have been drafting the new recommendations as to the meaning of these terms, rights and welfare, that would illuminate our own discussion again in the hope that we might develop something consistent that is between these interrelated areas?

MR. FANNING: I think there has not been a great deal of thinking about that. We meant to parallel the existing rules so as not to create a new separate set of rules. These are the determinations that right now before any enactment by Congress an IRB would have to make in order to waive consent and we thought it simply best to follow the same pattern. It does not represent independent new judgment that this is the only way of structuring that decision.

PROFESSOR CHARO: Was anything in the discussion this morning triggering you to think, "Oh, gee, this particular approach of understanding these terms would be better for us working on medical records

versus another," just to know what might be best again in coordination?

MR. FANNING: Well, I personally have trouble distinguishing the two. To me --

PROFESSOR CHARO: Welcome to the club.

MR. FANNING: To me --

DR. _____: Now you are a member of the commission.

(Laughter.)

MR. FANNING: -- risk to me is the disclosure of information outside of the research setting and that is -- and that is also the kind of thing that will adversely affect the rights and welfare of the subjects so I do not really have anything else to add to that.

DR. SHAPIRO: I want to give you a reflection having read these and see if it is consistent. I think it is consistent with what you have already said and then I want to ask a question about the future, which is prompted in my mind by some of the comments Mr. Capron made in which I could ask you to speculate as opposed to reflect just on the recommendations before us.

I looked at the material you provided us,

particularly as it reflected to the research use, which is, of course, of interest to us and I came away from that saying that these regulations if, in fact, enacted in this way and so on would make really very little change in how researchers operate. It may make changes elsewhere but it would make very little change because it does -- as you point it, it parallels all the protections that for the most part are already enacted.

Is that an unfair or an overly superficial interpretation of this act?

MR. FANNING: No, I do not think so. I think if this were enacted into law there would be disclosures of information that are now made not subject to rules like that that would be brought under rules like that.

DR. SHAPIRO: I think it is fair.

MR. FANNING: But, no, the existing mechanism is what we thought was the correct one to use for decisions about this matter.

DR. SHAPIRO: All right. Let me ask the question then which is maybe perhaps focused on an extravagant future and just ask on the basis of your own considerable knowledge how you would think about it.

Mr. Capron made the point that medical record may be something distinct from or different in certain characteristics from the genetic profile that someone would have, which might be available in these tissue samples. But if you imagine -- or maybe let me put it as a question.

Do you imagine before very long that there will be no such distinction? Namely that all medical records will, in fact, include in there some kind of bar code that reflects our genetic profile in any case in which case there would cease to be any distinction of this kind. Is that the kind of thing that you worry about or other people worry about as you are putting this legislation together?

MR. FANNING: I think that may occur but I am not familiar enough with the science and the meaning of -- and content of that bar code to know whether it presents some new or different risk.

DR. SHAPIRO: Yes. I mean, I did not mean the bar code to be in any way a technical term but just something which summarizes your genetic profile in maybe an electronic form that may eventually be part of

everyone's medical record is all I was thinking. Bar code I just use as a --

MR. FANNING: All right.

(Simultaneous discussion.)

MR. FANNING: Let me just say that one of the principles behind these recommendations is that information in health records ought to be treated the same without regard to the specific content of it. Now we do not propose overcoming existing laws that make distinctions based on sensitivity such as HIV or mental health or genetic information but simply from the standpoint of managing record systems a single law is really a much more practical way to do it and, hopefully, it will be written at a high enough level of protection to protect everything in there to everyone's satisfaction. That is the hope.

DR. SHAPIRO: Thank you.

Other questions?

PROFESSOR CAPRON: Two short questions. What is the status of these recommendations?

MR. FANNING: They were sent to the Congress a year-and-a-half ago and there were bills introduced in

the last Congress that did not parallel them exactly but in broad outline were very similar to this. They did not get very much attention. The Congress is now beginning to work on this again and we do expect that there will be bills introduced in the near future to establish a nationwide health record confidentiality law.

PROFESSOR CAPRON: And the second question was on page 2, the first exception for disclosure, could you say a word about what was anticipated there and the extent to which you think that parallels or goes beyond existing law?

MR. FANNING: That is a difficult one. The general principle is that information obtained for research should not be used for anything but research and should surely not be used to make any decisions affecting the rights, benefits or privileges of people.

The public health people were concerned, however, that some body of data would be seen by the researcher as identifying some public health hazard, for example, and in writing a law like this since its basic stance is absolute with a prohibition on disclosure there needs to be some kind of an escape valve to permit a

disclosure that most people would find ethically required under some circumstances.

So I think that is the point of that exception.

PROFESSOR CAPRON: If I understand it then the researcher could make uses of the data which the clinician gathering it would not be able to do?

MR. FANNING: Oh, I am not -- no, I do not think that is true. Under the ?steam here and under existing law I think the clinician gathering the information finding such a signal would be and should be free to, you know, call it to the attention of the public health authorities.

The existing law on health records confidentiality, as you know, is not a terribly strict or comprehensive one and it would be hard to imagine a situation where a public health disclosure of the type envisioned here would not be allowed out of a clinical record.

DR. SHAPIRO: Thank you.

Steve?

MR. HOLTZMAN: I just want to make sure I

understand the sense of individually identifiable that is used here. In the sense in which we use coded, coded would not be individually identifiable?

PROFESSOR CHARO: No.

MR. FANNING: I forget your scheme. I read it. Here if a researcher wants the record of every case of detached retina treated in Baltimore County in a three-year period and collects all of those and on each one is a number, hospital A, patient one, the hospital retains a record that A1 is a patient with a name. That is not a disclosure that is covered by this thing. The simple disclosure of the record of the patient without the patient's name is -- would not be a disclosure under the -- our proposal.

Now let's -- we could set aside for the moment these issues of what constitutes an identifier if you have a five digit zip code, date of birth, and so on, but let's just set that aside for the moment.

MR. HOLTZMAN: But essentially if the researcher receiving the information does not have information sufficient to identify the individual but there is a code connecting sample one somewhere back in

the repository --

MR. FANNING: That is right.

MR. HOLTZMAN: -- then it is not individually identifiable.

MR. FANNING: The privacy thinking that has come out of these reports and studies, which in many cases studies privacy on a much broader basis than simply health, uses those terms -- that thinking uses the term that way.

MR. HOLTZMAN: Okay. And, consequently, there is more attention to the protection of that confidentiality of the linkage, if you will. I mean, clearly if I could just call up the repository and said, "Hey, is number one John Doe --"

MR. FANNING: Oh, absolutely.

MR. HOLTZMAN: So that is -- so then in the record -- given that interpretation and given that we know that OPRR does not identify -- does not use the same nomenclature, OPRR has said coded, in the kind of example you just gave, equals individually identifiable. All right. When it says here, "Thus we recommend that the legislation include conditions closely modeled on the

regulation," it would not be the case that you are recommending that it be closely modeled on the regulation given OPRR's interpretation?

MR. FANNING: I do not -- we did not have that particular point in mind when we wrote this but that is certainly my reading of it and, you know, this is meant to fit into the tradition of confidentiality rules.

The other thing to be kept in mind is that this is a proposal for a federal statute with criminal penalties and all the rest. Because we read it this way does not mean necessarily mean that there might not be reasons for OPRR interpreting its rule that way in particular instances or even generally.

I, for example, would always welcome IRB review to be sure it is genuinely nonidentified when turned over. So I guess I am really not addressing how it should work out.

MR. HOLTZMAN: But I am just again coming to Alta's point that whatever we do here is taking place in the context of this legislative efforts taking place. All right. And a major point of distinction right now between various pending bills is how it is understood

what is individually identifiable and how it is understood to be.

DR. SHAPIRO: Okay.

Carol?

DR. GREIDER: I will yield to Alta.

DR. SHAPIRO: Are you ready for this, Alta?

PROFESSOR CHARO: Mr. Fanning, I am now perplexed and kind of agitated becasue on page 15 under the section, "Special issues of identifiability," of this memo that you gave us --

MR. FANNING: Yes.

PROFESSOR CHARO: -- you make the point several times -- the point is made several times. I do not know who exactly drafted it. -- that precise legislation is really not what you want. There are dangers of absolute readings and yet having identified this as a criminal statute I would guess that what you want is for people to clearly understand what is meant by various terms, that they know what is covered and what is not.

Now when I read this the Secretary's health record confidentiality recommendations reasonableness

test was compared favorably to the European Union Data Protection Directive, which says that a person's identifiable when they can be identified indirectly by reference to an identification number, which would mean patient A1 from the hospital, which would mean the Europeans would consider that example to be one of an identifiable person but you suggest that it is an example of an unidentifiable person and yet you -- yet the memo suggests that the European directive is one that is similar to what the Secretary's recommendation embodies.

And I would just think that especially against the backdrop of criminal penalties you would actually want to make it clear enough to be usable by anybody who simply is reading the rules for the first time without any additional context. I now realize that it is not clear enough for me to do that.

Whether or not your -- the Secretary's judgment about what should constitute identifiable information turns out to be identical to ours or not, I would actually like to argue now in favor of clarity and against the suggestion that clarity is dangerous.

MR. FANNING: The reason we warned against

precise legislation there is that this discussion is really -- was in the context not of this reference to an identification number but other issues of how you might identify people when overt identifiers like names were not on there.

If you could run dates of birth and other factors against other -- against publicly available records and so on. That is what this discussion was about and this warning is here because there is -- in my view at least and I think that is reflected here -- insufficient work done to permit a precise legislative definition of what constitutes identifiability.

PROFESSOR CHARO: But, you know, we -- I appreciate that because we went around this many times and if one were to take a look at our categories of identifiability one would find that there is a category that we call unidentifiable where we all acknowledge that with a great deal of work under special circumstances with small cohorts and unique medical diseases one could do a kind of demographic analysis and actually arrive at the precise name, address and phone number of the person it is and we nonetheless call that presumptively

unidentifiable for the same kinds of reasons you did.

However, we found that it was, indeed, possible to separate out the question of specific links built on codes and to treat that differently and ask de novo what is the appropriate mechanism for protecting people under those circumstances because that was far more straight forward in terms of going from an abstracted medical record or a piece of human tissue back to the individual because the links are sequential and unambiguous and the question simply was what is the appropriate set of protections there, who should exercise oversight, whether or not it should be under existing regs or not.

And I would just like to urge that there be some thought about whether or not you also could make a distinction between things that are explicitly linked to codes and things that are somewhat hazily identifiable through much more idiosyncratic means.

DR. SHAPIRO: David?

DR. COX: And to follow-up on that point, and I think that you -- at least the part where you were talking that was crystal clear to me or so it seems, you

can tell me, is that the -- how it is better not to strip stuff off, strip identifiers off irrevocably but basically to keep them on but do not give them to everybody and let some people have them.

So my question to you is who has them because in that mode, you see, then somebody, a very enlightened group or person who will take care of them appropriately will -- we can trust in those people and I think that in the context of privacy that is exactly what everybody is worried about.

So my question to you then is if we are in a mode of where we protect people by keeping the identifiers on but only letting a certain group of people have them, the conundrum is in that, how we decide who has them.

MR. FANNING: Well, I think we have not given much thought to that idea of a central place. Who I envision having the code is the person who has the whole record to begin with, the hospital in which you have been treated. They already have all the information and probably more than they have given to the researcher. So I rather think as a practical matter and as a privacy

matter that is probably the best way to manage it.

Now the future may bring different organization's data that call for or warrant some type of central place but that obviously presents very serious privacy difficulties.

DR. COX: And I guess, if I may, just to follow-up on that, that is sort of the rub right now because it is secondary parties, not the primary people who have the information even in terms of the medical records but secondary -- even in the context of medical care the secondary. It is not the primary physician but it is the hospital or the HMO. And I think that that is where this analysis of who is the primary person with the data will become problematic.

MR. FANNING: Yes, but quite apart from research disclosure all of these people have it in full anyway.

DR. COX: Indeed.

MR. FANNING: And the research disclosure it seems to me is a rather small intrusion, if you will, which presents little -- provides little more than risk than having the information in its original location.

DR. COX: But certainly that is the basis for the discussion that this commission has been wrestling with and how one defines that risk, as we said before, sort of in the context of ethical principles and it is not -- so I guess that is -- now we are at exactly what the heart of the issue is. What is the risk in the context of research?

MR. FANNING: Okay. One could envision research which assembled a very sensitive body of data that exposed people to more risk than the information was in its original location. One could certainly envision that.

DR. COX: Yes.

MR. FANNING: But, you know, the vast majority of studies will not be that way.

PROFESSOR CAPRON: But isn't that the exact characteristic of the biological materials that is different?

DR. COX: That is what I would argue.

DR. _____: I do not understand that.

PROFESSOR CAPRON: Well, because -- even for a technician in the lab until the materials have been

analyzed in a research project the information is not readily available and visible.

Whereas, I think part of our sense about the medical records, at least if I understood Mr. Fanning's last comment, was that in many contexts from the physician to the nurse to the administrator in the doctor's office who fills out the insurance forms to the person at the other end who runs the insurance tapes and cuts the checks and puts the -- all the data about what you went in for, how you were treated, what drugs you got, what surgery you got, what, you know, the outcome was is all there to start off with.

And in many hospitals it is a pretty leaky thing. You walk in. There is the grease board in the ICU with the patient's name and doctor and diagnosis and current status. It is right up there. You walk in and you see it. You walk over to the nurse's stand and pull a chart off and nobody -- you know, alarms do not go off or something.

I mean, all that stuff is lying around.

Whether or not I have a fatal heart condition that is going to strike me and my siblings because of

some genetic thing is not known until it is diagnosed but it may be right in that cell in that drop of blood.

MR. HOLTZMAN: Or right in that medical record that I have a BP of the following and I have the following cholesterol. I mean, we have been through this discussion for two years now.

PROFESSOR CAPRON: It may be but the notion that just having the drop of blood or the tissue sample stored away some place does not make that accessible to the clerk who goes and pulls it off the shelf and sends it to somebody. Whereas, when they go and get the medical record off the shelf if it falls open, "Oh, there is my next door neighbor and look at all the information about him that is right here in front of my face," and there is that slight sense that one is the diamond in the rough and the other is already the open book.

MR. HOLTZMAN: Alex, the position you are taking there is that that drop of blood absent an identifier to the individual in the presence of a confidentiality system and a linking system that that has a higher risk associated with it than the full medical record floating around complete with my name, my address,

my marital status, my blood pressure, everything about my family history, you are taking the position that it is the inherent quality of that biological sample with all of this information potential with no very straight forward way to tie it to me that makes it worthy of much more stringent protections?

PROFESSOR CAPRON: I think in the -- I would say yes and give you the following line of thought: When people now are asked to participate in genetic research one of the reasons that some of them say, "I do not want to do it," is a sense that there is a black box being unpacked and they do not know what is going to be found in it and if that black box is, in effect, passed around to a lot of people with a lot of different ways of unlocking it they feel uncomfortable if the information that is gotten out could. Not automatically would but could be linked back to them.

I suppose there are people who decline to go for medical treatment not just because they are afraid of the treatment or they are denying that they are sick or whatever but because they do not want it known that they have that. We went through that with AIDS. People --

until anonymous testing centers opened up some people would not go and get tested for the HIV condition because they were afraid it would be linked with them but they knew what was going to be tested for.

I am sure when my doctor does a routine annual check up or something stuff goes into the record that I do not think about its significance but I have a general sense of what my doctor is finding and if I go in for treatment I make the decision it is more important to get the treatment than to keep my condition a secret.

So I make -- I am able to weigh the pluses and minuses of that and the fact that there will be a record coming out of the treatment is something that I know and that record realistically is not going to be highly well-guarded. A certain amount of that information is going to be in the hands of people whom I have never heard of and some of them may have some adverse interest to me but that is a balanced decision that I make.

I have a sense that we are saying -- at least I would be saying in the present day people have not gotten to that level of understanding and comfort about

the unpacking of the black box of the biological materials and that, therefore, if it can be linked, could be linked to the person we ought to give it -- treat it as though it is identifiable because they -- and go through some of the process of either assuring ourselves there is minimal risk, et cetera, et cetera, or the person is contacted and gets consent for the study, which they do not have to under Mr. Fanning -- or the Secretary's recommendations for a medical record that has been coded where the code is in the hands of somebody other than the researcher.

DR. SHAPIRO: I think we are going to have to move on. I want to thank -- I want to make one or two comments but I also want to thank you very much for taking time to be here this morning. We very much appreciate it.

I think it is not always productive in my view to compare the protections of the medical record versus any protections like proposed for these samples. These situations are not directly comparable and I just do not think that is helpful.

I, also, do not think it is helpful to

exaggerate the regulations that we would want to put people through when they are subject to -- if they have to go to IRB or do not have to go to IRB and so on. We should not exaggerate as we tend to do in a lot of these conversations just what we are asking people to do.

At the worst of things here it is not such a major requirement so I think as we go ahead we ought to continue thinking about that.

Let me ask if there is -- we will go -- we have scheduled public comment for 11:45 but let me ask now -- we have no one signed up to my knowledge but let me ask if there is anyone sitting here today that wants to make any comment to the commission and, if not, we will just go directly on to pick up, Tom, the discussion of the recommendations but let me ask that question first.

Would anyone here like to make any comments?

Okay. Once again let's return then to looking at the materials in chapter five, Tom.

DISCUSSION OF THE COMMISSION DRAFT REPORT CONTINUES

DR. MURRAY: Thanks, Harold.

(Slide.)

I sense some frustration among the commissioners that we are not making rapid enough progress with chapter five of the Human Biological Material Report. All I can do is report that and ask you all to keep your comments to that which you think is absolutely necessary.

I am afraid a little bit -- does the expression go, "Perfect is the enemy of the good?" -- that in an effort to get this report perfect that we are delaying what could actually be something useful and I take to heart Harold's comments earlier that there might be several different ways to accomplish what we intend to accomplish here. We should decide on one and follow it through understanding that others might also be equally useful.

All right.

We are on, I believe, recommendation 2D, subpart D.

Any comments?

Let me start off. I would substitute in the last line, the last full line, for the words "is not relevant," I would substitute the phrase "should not

apply" on the grounds of, you know, well, it may be relevant but we just do not think it matters sufficiently here and since this is a recommendation rather than an ontological statement let's put "should not apply."

Any other comments on subpart D?

Alta?

PROFESSOR CHARO: Well, whether it is "should not apply" or "relevant," I would just like to add the word "usually" because there will be some occasions where it will be appropriate. It is no big deal. Just leave that open to the IRB.

DR. MURRAY: Where would you put the word?

PROFESSOR CHARO: Well, originally I had it as "usually is not relevant to research." Should usually not apply.

DR. MURRAY: Okay. All right.

Any other comments on subpart D?

All right.

PROFESSOR CAPRON: When you are doing the final draft of this let's keep in mind what the regulation said. We are, I gather here, addressing -- really addressing IRB's and indirectly addressing

researchers, and we are saying if OPRR says, "You do not have to bother with this criterion in order to give a waiver or alteration of the requirements of consent --" that is -- I mean, just write it with that in mind.

DR. MURRAY: Okay. Can we move on to 3? Good.

I just -- I would -- Kathi should be putting it up behind me at the moment.

(Slide.)

I would save a few words in the first line and just have it read "Repositories should at a minimum," and delete the phrase "that are subject to federal regulations." I do not know why we have to limit our recommendations to that unless there are objections.

Any comments about recommendation three?

PROFESSOR CHARO: I am sorry. Could you repeat yourself, Tom?

DR. MURRAY: Yes. Just look at the first line, Alta. It would now read, "Repositories should at a minimum require that an investigator..." and then everything else remains as written.

PROFESSOR CHARO: Yes.

DR. MURRAY: Any other comments about three?

MR. HOLTZMAN: Well, just a question.

DR. MURRAY: Yes.

MR. HOLTZMAN: So if a researcher at Millennium calls up ATCC and says, "Please send me a sample," and they say, "Do you have IRB approval?", and we say, "Well, no, it was not necessary for this research," how do I read three if I am ATCC?

DR. MURRAY: Is ATCC -- are they --

MR. CAPRON: I thought we were -- I thought we discussed this last time, which is --

MR. HOLTZMAN: Well, the document -- I agree with the last part. We could say it is applicable but as written I am supposed to provide documentation from my IRB.

PROFESSOR CHARO: With documentation for applicable federal regs. If there is no federal reg applicable --

MR. HOLTZMAN: I think it is just a rewriting mission.

DR. MURRAY: That we what?

MR. HOLTZMAN: It is a rewriting mission.

(Simultaneous discussion.)

PROFESSOR CAPRON: But I thought -- well, maybe I am wrong about this but I thought we were saying that the practice that would be expected would be the researcher would get the IRB to issue its -- yes, the statement this research is not subject to our review. That is a formal error.

PROFESSOR CHARO: So you have to go to the IRB even if you do not have to go to the IRB?

PROFESSOR CAPRON: Our point about this earlier on, I thought, was the recognition that all this is really researcher initiated and we now expect the researchers to get the statement to have the -- to say to the IRB, "This is what we are doing. You do not have to review it," and they say, "You are right." The administrator just looks at it and says -- or the chairman or whoever, "It does not have to the local IRB."

PROFESSOR CHARO: I guess I did not understand that this was where this was going and I have a couple of practical concerns about that. In a

university setting that might work well where there is a local IRB but if you were working in the private sector with private sector funding outside of any form of federal regulation there would be no local IRB to whom you ordinarily would go that would quickly sign off for you. You would have to go to some random IRB out there and say, "Please do us the favor of issuing a piece of paper."

I just think as a practical matter --

PROFESSOR CAPRON: It is not going to --

PROFESSOR CHARO: -- this is going to become more complicated than it appears at first blush. I think a statement by the investigators that they are not subject to federal regulation because X, Y or Z to the repository was what I kind of had in mind. You know, "Dear Repository: I do not have documentation because I do not have to go to the IRB because I am only going to be using unidentifiable tissues which is not equal to human subjects research," or "Dear Repository: I am not going to an IRB because I am in the private sector using private funds and I am not subject to the federal regulations --"

PROFESSOR CAPRON: Yes.

PROFESSOR CHARO: "Yet." Fair enough.

DR. GREIDER: I agree with what you are saying but I think we should then say that in here and I do not have the language --

PROFESSOR CHARO: Put that in the text maybe as opposed to spelling it all out in the recommendations.

MR. CAPRON: Well, from the IRB is what everybody is objecting to.

DR. GREIDER: Right. Documentation from the IRB. Provide documentation --

PROFESSOR CHARO: Yes, I see what you are saying.

DR. GREIDER: -- that the research --

PROFESSOR CHARO: Yes.

DR. MURRAY: Using identifiable samples is the current language.

DR. GREIDER: Get rid of “investigator's IRB” and put “IRB” down later.

DR. KRAMER: Or just add another sentence that addresses investigators who are not -- who do not need an IRB.

PROFESSOR CHARO: If I understand correctly --

(Simultaneous discussion.)

PROFESSOR CHARO: -- I think if you were to -- I understand in three what you are supposed to do is you are supposed to either submit documentation from the IRB that demonstrates compliance with applicable regs or a statement that the regs do not apply.

DR. MURRAY: I really want to do two things here. One is do we agree -- do we think we agree on the sense of what we are asking for here? I think we do. The second is we need to get the language right. I do not think we should spend our time rewriting the language here and now.

What I am inclined to do actually is for any controverted -- from here on, any controverted recommendation language that we simply pick a couple of commissioners to work with the drafters, and I would be happy to sort of be a general infielder, utility infielder here, to get the language right.

So I think if we -- does anyone feel that

they do not agree with the sense of where we are headed with three? Speak up now. It is not a forever hold your peace but it is you better have a damn good reason to speak up later if you do not speak up now.

(Laughter.)

DR. MURRAY: Okay. And then who -- which people should revise this one? Carol spoke. I would like to have Carol involved in this. And Alex. All right.

Can we make a record of this? Carol and Alex and I will work on revising three. Okay.

Are you ready to go to four? Four is up behind up on the overhead.

(Slide.)

Any changes to four?

PROFESSOR CHARO: Much editing.

DR. MURRAY: Do you want to start us on that quickly, Alta?

PROFESSOR CHARO: No. You said not to do it at the table.

DR. MURRAY: Well, the sense. I mean, is the sense correct?

PROFESSOR CHARO: The sense is correct.

DR. MURRAY: Okay. The sense. Anyone? Is there anyone here who feels that what four seems to be trying to say -- I know this is dangerous --

DR. CASSELL: Whatever that may be.

DR. MURRAY: Whatever that may be. If you do not know what that may be let's raise that question to make sure we have the sense of it correct.

Eric, did you have a substantive concern or a general?

DR. CASSELL: No.

DR. MURRAY: Okay. Who would be willing -- Bernie looks distressed.

DR. LO: Yes. Are we trying to say if the IRB thinks you need to get consent that they have to prove it, they have to prove how you are going to get it? Is that the --

DR. MURRAY: Is that the sense?

DR. LO: Is that all we are trying to say?

DR. CASSELL: IRB should approve of any plan the investigator has for acquiring consent. Is that what it means?

(Simultaneous discussion.)

MR. HOLTZMAN: No, it has to do with if there is a change in the nature of the risk that, therefore, if the risks have changed then -- that is the drive here.

DR. SCOTT-JONES: I have a question.

DR. MURRAY: Diane?

DR. SCOTT-JONES: I have a question about how that would happen. How would the IRB initiate this?

DR. LO: The shoe is on the wrong foot.

DR. SCOTT-JONES: Yes. It does not make sense given how research would be conducted.

DR. BRITO: I guess this came up from our discussion when you look at consent forms and you think they are inadequate. That is how I think about this.

DR. CHILDRESS: In this case the investigator is --

DR. BRITO: Yes, I understand that.

DR. CHILDRESS: -- initiating it and that would seem to be --

DR. BRITO: The IRB.

DR. CHILDRESS: -- the two parties --

DR. BRITO: The IRB --

DR. CHILDRESS: -- well, but it says -- presumably that is not going to come to an IRB's attention unless the investigator is submitting information about it.

DR. BRITO: Using the wrong shoe I think is right. It seems like such a -- I think that is right. The shoe is on the wrong foot.

DR. LO: We could eliminate it. How about eliminating one?

DR. CHILDRESS: Is there anything in here that if -- if the IRB determines as a result of what the investigator has resubmitted for approval that the risk has changed then the IRB presumably ordinarily would be requiring this anyhow, so what is really added by this?

MR. CAPRON: Just because of more --

(Simultaneous discussion.)

PROFESSOR CAPRON: -- commentary in other words.

DR. CHILDRESS: Does it --

DR. BRITO: Do we address somewhere else -- when I read this I thought it was emphasizing any change in the use of stored samples. So if we eliminate it, is

this addressed somewhere else? Whether -- so I do not think we can just simply eliminate it. I think somewhere we have to address how an investigator could used stored samples and I do not know if it belongs here or it belongs in the consent process or --

MR. HOLTZMAN: I always assumed this had to do with if you were in the context where consent had been waived.

PROFESSOR CAPRON: Exactly because it is minimal risk.

MR. HOLTZMAN: Because it is minimal risk and now something has changed. Either there is a finding or more likely, for example, if you have got minimal risk because you are using a coding system and there is a breakdown in the coding system and there is disclosure and in such an instance whoever finds out about it could be the IRB, could be the investigator.

DR. BRITO: Just look at five. It includes four.

DR. CASSELL: Five says the same thing.

DR. MURRAY: All right. Let's look at five and see if we are satisfied that five covers what we want

to cover in four.

PROFESSOR CAPRON: No, that is not the same thing.

DR. CASSELL: Unless you want to say -- that amplifies the first sentence or the first phrase -- for research that requires informed consent. Is that what four is meant to address?

PROFESSOR CAPRON: No. Four, I think, as Steve was just saying, is intended to address a situation in which when originally submitted the research -- the IRB will waive the requirement of consent because you are going to a pathology lab, getting a bunch of stuff, and you have said what we are going to be looking for is blah, blah, blah.

During the first year of the research some new finding came along and you said, "Oh, my God, this is very interesting and we are now pursuing something else." We are up for our annual review. Let's hope that this is an IRB that actually does annual review and you submit a brief statement of what you are doing and you have now changed the focus of your research and you are looking for the gene for some fatal neurological disease that had

not been thought of before. Suddenly, we are talking about something that is higher risk.

That is what I gather this was intended to refer to.

DR. MURRAY: Trish and Alta.

DR. BACKLAR: Shouldn't this all go under --

(Simultaneous discussion.)

DR. SHAPIRO: Why don't we wait for Tom to recognize people?

DR. MURRAY: Trish and Alta.

DR. BACKLAR: Shouldn't all these kinds of things go under the consent issue rather than be in specific to the use of stored samples?

DR. MURRAY: Alta?

PROFESSOR CHARO: Seems to me that the way four is being understood is something that is really just a particular case of the general phenomenon that is already covered under current regulations and practice on IRB's. It is a matter of common -- it is common phenomenon that risks are reevaluated during the course of research as new information develops or as societal conditions change. And that investigators are under an

obligation if there has been a material change that affects a significant part of the IRB's consideration of what is minimal risk or what is rights and welfare or what is appropriate in the consent, it is the investigators' obligation to go back to the IRB and notify them of a change.

And if the investigator does not notice it or fails to live up to that obligation at the annual, which is I think the minimum -- maximum period you can go -- the, you know, annual re-approval is an opportunity for the IRB to pick up on that change because that is the moment at which protocols are re-reviewed with fresh data submitted based on the first year's experience.

So it seems to me that part of our difficulty here is we are not recognizing that this is really just done as a matter of course. We might want to just make reference to that and make special note for investigators to keep that in mind that this is an area of research that particularly is prone to a reevaluation of risks and that they should -- or maybe not particularly but just prone to it and that they should keep it in mind and that there are existing rules to cover the situation.

DR. MURRAY: So do I understand that we are demoting this from the status of a separate recommendation? That is what I am hearing and simply remind investigators in the text that they have the same obligation here as in any other form of research that if anything materially changes they need to inform the IRB. Is that correct?

First of all, do I understand what you are proposing?

PROFESSOR CHARO: Yes. I mean, I did not say whether I thought it should stay as a recommendation that said that they should keep in mind or -- yes, you can parse it into the text, sure.

DR. MURRAY: Would you prefer that we keep -- that we have it as an express recommendation?

PROFESSOR CHARO: I will take guidance here from the researchers as to whether or not they think this is a problem that is going to crop up more frequently than it does in other medical research.

DR. MURRAY: David and Larry?

DR. COX: I prefer this is not a recommendation. I agree with Alta's analysis of it and I

think that our report is -- in the interest of clarity for the people who want to use our report, I think this obfuscates more than it provides.

DR. MURRAY: I think the general principle of less is more holds for the recommendations in reports. The fewer recommendations we have the more likely people are to actually pay attention to them.

Larry?

DR. MIIKE: I agree with Trish in the sense that this should just be our introductory statement to the section on informed consent because these are really -- we are just reiterating what should be done anyway. I do not think they are anything new. It is just introductory statements to our real recommendation that follows.

DR. MURRAY: Arturo?

DR. BRITO: The only reservation I have about eliminating this, and I am not sure, when we get to these recommendations maybe it will become more clear but, Alta, this is really a question for you and what you just said. Does this also apply, okay, our current regulations, do they also apply to a researcher that

takes information from stored samples -- and this goes to the issue of design and dissemination of information. Does it also apply to use that information for dissemination of new information? To use the knowledge gained from the research --

PROFESSOR CHARO: I am not sure I understood the question. Could you try that again?

DR. BRITO: Okay. Does an investigator have to seek consent or seek IRB approval, okay, if the information gathered from stored samples will give new knowledge about whatever topic that raises the level of risk? Not just in reusing the stored samples but in interpreting the information in a different way.

PROFESSOR CHARO: I am going to try an example and I am going to ask if it captures what you are talking about because I think I am with Bernie on this one in any case.

I am going to study the detached retina that came up with Mr. Fanning's example and I have been working with coded materials, consent was waived becasue it was considered to be minimal risk and the intrusiveness, et cetera, was not enough to require

consent.

I got this wonderful stuff on detached retina and I am about to publish it. And something about the way I am publishing it is going to reveal to the world that if you have a detached retina you are also at high risk of having a tumor of the optical nerve. I mean, this makes no medical sense but it is an example for you, right. And so these people are -- all the people in the world now with detached retinas are going to flip out because they think they are about to get brain tumors.

Is this what you are talking about?

DR. BRITO: Yes, right.

PROFESSOR CHARO: No, I do not think that is the kind of thing that would require an investigator to go back. That is the unfortunate reality of opening up the New York Times every morning and discovering what you are prone to today. I do not think that is what the current regs intend when they talk about when you have to go back.

DR. BRITO: So is that something we should be concerned about? Is that something -- because we are talking -- I mean, I still go back -- I mean, I think

there are a lot of issues with -- for lack of a better phrase -- group harms and we are still going to get to the other recommendations but --

DR. SHAPIRO: You know, Arturo, on that issue I am extremely chary about restrictions regarding publication of results. I think we have contented ourselves so far in the report with asking people to be sensitive to this and do it in ways that are, you know, sensitive to these issues but I find it hard to imagine how we would have a regulation that would deal with that kind of issue you have raised.

DR. BRITO: Well, I guess, when you are disseminating information about a group of individuals why can't that be subject to IRB approval before you disseminating that kind of information --

DR. SHAPIRO: Well, as I said --

DR. BRITO: -- when that information can potentially place groups at greater than minimal risk?

DR. SHAPIRO: Everyone can have their own balancing of rights and responsibilities here. It is just my own view that that is a very expensive way to provide protection, too expensive, in terms of the

restrictions that might apply on people to share the results of their work. That is just my view. Others may feel differently.

Carol?

Diane?

DR. SCOTT-JONES: I agree with Alta's comment that what is expressed in four is already covered that the investigator is already expected to go to the IRB when there are substantial changes. So four would serve as a reminder and not really as anything new. But you could say precisely the same about the following one, number five, because it is simply stating that when the consent document is inadequate the IRB should require investigators to submit a new one. So it is precisely the same.

It seems that all of this section is reminding the investigator to do good things, and even in the text it is stating what the investigator is already expected to provide to the IRB. So maybe we should change the whole thing and note that this is just a reminder or perhaps eliminate all of it.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Two things very quick.

First, Arturo, I think, take some comfort in the fact that your concerns about dissemination are incorporated in the original risk calculus when they approve or disapprove a protocol with waivers so it is not ignored.

Diane, the one thing that I think is new in five is some direction from us as to how the IRB's should handle the issue of general consents which has been a matter of dispute among IRB's and so whether it is now relegated to text or stays as a recommendation I would like to highlight that because uniformity on this, I think, is desirable.

DR. SCOTT-JONES: Okay. I see what you are saying but as I read number five the words "general consent" are not in there anyway.

PROFESSOR CHARO: No, no, it is still only in the text, that is right.

DR. SCOTT-JONES: Okay. As it stands it just simply states what is already the case.

PROFESSOR CAPRON: Couldn't we put Diane's concern and Alta's comment to good use by revising the

text to put the general presumption against blanket, or whatever we call them, consents as inadequate on their face as a basis for the use of examples?

PROFESSOR CHARO: You mean to have that --

PROFESSOR CAPRON: That should be the black letter --

PROFESSOR CHARO: Right.

PROFESSOR CAPRON: -- I mean, that would be a contribution to say that it should be presumed that such general releases for research executed in conjunction with clinical or surgical procedure not be --

PROFESSOR CHARO: Right.

PROFESSOR CAPRON: -- adequate --

PROFESSOR CHARO: We --

PROFESSOR CAPRON: -- be inadequate to cover research and in those cases the IRB should require investigators to submit consent forms pertinent to the research.

DR. MURRAY: So this is pertaining to five?

PROFESSOR CAPRON: This is pertaining to five and I think the language is now on the tape that -- do not ask me to repeat it in other words -- that combines

the real substance that was in the text with a blander statement in the black letter as provided today.

DR. MURRAY: Could I --

PROFESSOR CAPRON: No.

(Laughter.)

DR. MURRAY: -- ask Diane --

PROFESSOR CAPRON: Okay.

DR. MURRAY: -- to work with whoever else will volunteer to get the language of this one in a usable form. Okay. Diane will do it. Diane will work with Kathi.

DR. SCOTT-JONES: It is already in the text.

DR. MURRAY: Okay. Good.

Larry?

DR. MIIKE: I do want to remind you folks though that if you look at 17 we are recommending that for future concern we do give a general consent.

DR. MURRAY: Yes.

DR. MIIKE: So you have got to be consistent about it.

DR. MURRAY: Right. Right. And one of the things that I think we should do in the report is where

other recommendations are also relevant we should expressly mention that. We do not do that, I think, consistently.

All right. Five? Are settled on -- with four, are we demoting four and --

PROFESSOR CAPRON: Yes.

DR. MURRAY: We are demoting four and we are revising five. All right. Six?

Do you have a question?

DR. MESLIN: I just wanted to know whether they want -- Trish's comment about moving these into the informed consent section. You would now have only two recommendations under regarding protocol. I want to hear whether they want to --

DR. MURRAY: Could you hear what Eric was saying? He did not have a microphone.

DR. MESLIN: Sorry. Trish made a comment about moving these two remaining recommendations to the section on informed consent. I just did not know whether you had decided if you wanted to do that.

DR. _____: I strongly support that.

DR. SHAPIRO: I think that would be a good

idea but there are no longer two. They will be transformed.

PROFESSOR CAPRON: Aren't we suggesting that the correct title for number -- the category into which the remaining number three still falls is the responsibility of repositories? I mean, that is really what we are saying-- that they are the holders of this material and they have some responsibility so it is not about stored samples as such.

Five does belong over in the consent thing.

And four has gone to commentary. Unlike Larry, I do not think it is commentary that only belongs under the consent. It seems to me it really belongs as commentary to number two because in number two we have talked about this waiver that will go on and the whole point of what was number four was "but if circumstances change as to the annual review that waiver --"

DR. MURRAY: You need to revisit the waiver.

PROFESSOR CAPRON: "-- needs to be revisited."

DR. MURRAY: Okay. So it shall be.

On to number six. Any comments about

recommendation six, and it is being put up on the overhead as we speak.

(Slide.)

I had a minor change which was in the end of that. In number six, recommendation six, current number six, granted all the numbers will change, "To the extent possible investigators should plan their research so as to minimize such harm..." and here is where my change comes in "...and consult, where appropriate, with representatives of the relevant groups." Instead of "seek input," "consult with," and also it is not just study design. It may even be the questions we ask.

One of the lessons, I think, we learned, we learned from listening to the person who worked with AIDS clinical trials was that the consultations often created entirely -- even changed the questions that researchers were inclined to ask so I would not want to limit it to just study design.

So now it would read: "And consult, where appropriate, with representatives of the relevant group."

Is that acceptable, that recommended change?

Bette?

DR. KRAMER: Tom, the issue of groups and group consultation is another issue that has bothered me. I have never seen -- I do not think I have ever heard a direct statement in a meeting or seen in the transcript where we have actually confronted the issue of groups and how we feel about it. To what extent do we feel they should be consulted? How are they going to be -- the people -- how are the supposed leaders to be identified? How much say are they to have?

We go around and around but we keep referencing it and I do not recall that we have ever made a definitive statement about it. I do not know that we ever even polled the commission as to how various commissioners feel about it. I think there is a tremendous disparity of feeling among the commission, I think, just on the basis of individual conversation as to how much input we think groups ought to have.

DR. MURRAY: Well, this recommendation should then focus on that by whether we support this or not. So let's hear what people say about it. If you object to the recommendation why don't we just say that.

Steve?

MR. HOLTZMAN: I would not object. I was going to support it in its form.

DR. MURRAY: Okay.

MR. HOLTZMAN: Okay.

DR. MURRAY: Well, that is allowable, too.

MR. HOLTZMAN: My support for it is that in any given case it may be difficult to identify who is the leader and what we are going to have, depending on the study, depending on the group, we are going to have black, white and gray, and I feel what we have tried to do here is leave room for the role of judgment. We have said to extent possible consult with appropriate people.

If we are in a case where it is not possible and you cannot figure it out and it seems harmless you cannot eliminate judgment, Bette.

I think that is what it comes down to and I think that is what we are asking the IRB's to do.

DR. KRAMER: Okay. But, no, I am not arguing against that. I am only saying I think that we ought to -- you know, that we ought to spell it out and say -- acknowledge that we have gone around on this and make a clear cut statement such as you just made.

DR. MURRAY: Larry?

DR. MIIKE: On the contrary, Bette, I think we have talked about this a lot.

DR. KRAMER: Oh, we did?

DR. MIIKE: When we first started off -- oh, yes. Even back when Zeke was part of the commission.

DR. KRAMER: But we never resolved it.

DR. MIIKE: I think we did.

DR. KRAMER: We did?

DR. MIIKE: We started off by the issue about -- in the breast cancer study about who was the appropriate one to consult and whether they should have veto power, et cetera, and I think we came to the conclusion that the best way to deal with it is from the AIDS experience and is to engage representatives of those groups in the actual study design or issues around the research project and that -- at least that the speakers that talked to us found exactly what we just mentioned, which was that often it led to an improved research design and question. I think that is reflected in this recommendation.

DR. MURRAY: Bernie and Trish are wishing to

speak.

DR. LO: Well, I would support leaving it this way. As was pointed out, it is important to give a lot of discretion. There is actually a very nice editorial by Bill Bradley in last month's or this month's American Journal of Human Genetics right on the point where he makes -- I think the points that he was making that it is a good idea you cannot prescribe in writing how it is going to work in every case because it is going to be hard to identify who is the leader, identifying the groups but this should be animated by the spirit of trying to get some input from people most directly affected.

I am not sure we can go further than sort of exhorting people to take into account how this research is going to impact on the people that --

(Simultaneous discussion.)

DR. MURRAY: Trish?

DR. BACKLAR: It seems to me that I agree with you and I cannot remember what preceded this in the chapters that went before but I am presuming you have some section about group information and speaking with

groups because we have very good examples with AIDS and with Mary Clare's work and I am presuming you will bring that into the text.

DR. MURRAY: And I think we, also, had a very rich discussion about the dis-analogies between the situation of the prospective AIDS clinical trials and some of this sort of research and that should be reflected in the text which we do not have before us, which is in the preliminary chapters.

DR. KRAMER: Well, that was the problem that I had --

DR. HANNA: Sorry, Bette, I could not understand that.

DR. KRAMER: I said that was the problem that I had and that we do not have the revised chapters that are going to go before this to know exactly how we are going to deal with it in that language.

I am only concerned that we do not leave the recommendations as finally written subject to somebody's interpretation that they have a veto power that we did not intend them to have.

DR. SHAPIRO: I think we are going to make

that clear, I think, that we have been unanimous on that issue every time we have addressed it so I think we should go to extra efforts to make it is clear.

DR. MURRAY: So I will take that as instruction for the drafters of the preceding chapters to make that clear. Does anyone think it merits -- that concern merits some substantive change in the language of the recommendation? If so, you should speak now.

What I am hearing, unless anybody objects, is that as edited we actually like recommendation six and we will not need to revise it other than what is decided on just now this afternoon.

All right.

PROFESSOR CAPRON: But we are saying that we are going to have a little bit of textual commentary.

DR. MURRAY: You want text under it.

PROFESSOR CAPRON: Under it.

DR. MURRAY: Okay. We will add some text under it as well.

PROFESSOR CAPRON: In other words, not expect people to have to have read and digested our lengthier discussion but a paragraph just saying this does not mean

veto and giving citations to any examples like Riley's article where it is dealt with in a helpful way.

DR. MURRAY: Right. I think that is a very good idea and we should do that.

DR. KRAMER: And incorporate the language that Steve used.

DR. COX: Just for the record, Eric Juengst has written an article on this too. Both of those are extremely useful on this point because, Bette, they illustrate that -- they go through the logic of the issues that we may not be able to in our report but would allow anyone who actually wanted to make sure that this was done thoughtfully to recapitulate that logic.

DR. MURRAY: Hunger is often a universal human motivation.

PROFESSOR CAPRON: You are going to keep us here for --

DR. MURRAY: How about -- let's see if we can get through these brief ones.

PROFESSOR CAPRON: In Medieval times jurors were kept locked up until they issued their verdict.

DR. MURRAY: It is a real temptation but

Harold may not permit me to do that anyway but let's just see. Let's see if we can get through the next several very quickly. If we get hung up on one we may need to break.

So, six, we have made a minor editing just for clarity's sake. We are going to have some text after it which is going to refer to the relevant text and also explain, you know, what we -- we make it clear what we try to mean by that.

What about number seven? Eric?

DR. CASSELL: Well, it is such a basic recommendation --

DR. MURRAY: You are talking about seven now?

DR. CASSELL: Yes.

DR. MURRAY: Yes.

DR. CASSELL: It such a basic recommendation. I think it really belongs much further up front. It tells you almost all the things we have been discussing. It is not specifically about design but it is mainly specifically about confidentiality and since that is a central aspect of this whole thing, the whole project is really about discussing human projects, I think it

belongs further up front.

DR. MURRAY: Other comments?

So you are not arguing with the sense of it but you want to just change where it appears or how it is -- sort of how -- under which heading it is grouped? Is that right?

DR. CASSELL: Yes.

DR. MURRAY: Bette?

DR. KRAMER: Well, I would speak to keeping it where it is because I think that not only does it specify what needs to be done but it very clearly places the responsibility on the IRB as the body to make sure that it is done.

DR. MURRAY: I have a -- Kathi, I am going to ask you to speak in just a second.

I have a -- I am going to float a proposal. Namely that we may group the recommendations in two different ways. One sort of as they come up in the logic of the development of the report and number two as expressed as they apply to particular individuals or groups so at the end we may recollect them as those pertaining to investigators, those pertaining to IRB's,

those pertaining to repositories.

DR. CASSELL: Well, you will have trouble with this because this one says the investigator must set forth in the IRB --

DR. MURRAY: Well, it appears then in both you see.

DR. CASSELL: You would have it in both.

DR. MURRAY: You would have it in both and I do not have any problem with that but if an investigator wanted to see, well, what does a report tell me, they look and we have a collection there that says recommendations one, seven, fourteen, et cetera. "These impinge on you personally, pay attention."

DR. CASSELL: Yes.

DR. MURRAY: It is just a matter of sort of recollecting for ease of reference for users later on.

Kathi had a comment.

DR. HANNA: I just thought that number seven was kind of the flip side of number three so when we regroup these -- when we regroup these recommendations I think they probably might go in the same place and I was just wondering what people thought about that.

DR. CASSELL: Yes.

DR. HANNA: On one hand it is what the investigator is supposed to do in terms of telling the IRB about how they are getting the materials and number three is what the repository is requiring before they give materials out so I think that they would probably go together. We just need to think of a new subtitle.

DR. MURRAY: Alta?

PROFESSOR CHARO: I think that is fine. I mean, there are many ways that you can organize these and they are all perfectly legitimate. You may want for the sake of making the whole report hang together to have them appear in conjunction with kind of the order of concerns or events and then you can easily create information sheets and the information sheet for investigators is where you would collect all the ones that are just for investigators and that could be easily sent out to people and not have to distort the kind of natural flow of thinking in the report.

And that would allow you, Kathi, to group this with the repository requirements even if they are aimed at different audiences.

DR. MURRAY: Thank you, Alta. That is a nice refinement on the idea I was proposing. We could have them both in the report and have separate handouts to relevant parties.

Jim?

DR. CHILDRESS: This actually raises a larger question since we said that for six there will be text added and I guess I am not clear in terms of how this chapter is now being conceived whether there will be both explanatory and justificatory text added for basically all the recommendations here or whether we are going to assume that is what is present in the previous chapters will carry the recommendations except in those few cases such as six where we are saying something should be added.

It is just a question about what the plan is. I missed the Princeton meeting so I do not know what the overall plan is for this chapter.

DR. MURRAY: I also missed the Princeton meeting. If anyone can enlighten us on that. My presumption is that in at least this latter part of the chapter we are going by the latter of the two options

that you gave us, namely that it is assumed that the groundwork has already been laid and except where we feel some additional explication is essential we do not add it here.

Larry?

DR. MIIKE: I would favor having at least some expanded text following each recommendation. To leave them alone makes it hard and I am not asking for a whole lot and for it to be consistent. I mean, that is usually what is done because there will be a lot going ahead. In the previous chapters there is a lot of introduction to this chapter but to reinforce the main reasons why we make the recommendation would not take much. It would just mean going -- it is a simple matter, I think, of going back in there and just pulling out a paragraph.

DR. HANNA: We are happy to do that. We just want you to settle on the recommendation and then we will do the interpretive text.

DR. MURRAY: Arturo?

DR. BRITO: I do not know if I can enlighten you on the Princeton meeting but I can tell you what my

interpretation was and I think this is much improved because we decided to eliminate or at least minimize how many comments.

I mean, I understand extra comments but I would caution against trying to overdo it and we are going to go back to where we were before so I like the way it is being grouped and I like the fact that the recommendations are a little more -- it is clear where the recommendations start and where they end. I am just worried that we are going to start once again saying, well, six needs some comments and eight needs some comments and nine does too, et cetera, et cetera.

DR. MURRAY: Okay. If I heard Larry correctly you two may be asking us to do two different things. Larry wants some text and you do not want some text.

DR. BRITO: I am just saying that at the Princeton meeting I thought it was decided that we wanted to minimize the amount of text. That is all I am saying.

DR. MURRAY: I just want to know what our marching orders are in the preparation of this.

DR. BRITO: Because otherwise what is going

to happen is --

DR. MURRAY: Which is it going to be?

PROFESSOR CAPRON: Minimally necessary textual explanation.

DR. BRITO: That is fine with me.

DR. MURRAY: Is that okay?

DR. BRITO: That is fine.

DR. MURRAY: Larry, the standard is minimally necessary?

DR. MIIKE: All I am saying is the minimum because we are inconsistent. There are some where there are one or two paragraphs and there is a whole bunch of them without any.

DR. SHAPIRO: I think the minimally necessary category is very operational and we can easily do it. We do not want to rewrite the report every time we put down a recommendation. No one is suggesting that. So it is just a judgment. Let's not worry and let's give a specific recommendation and one of these is let's not worry, that is the problem for writing and editing the report.

DR. MURRAY: Okay. Minimally necessary.

That is going to be the criteria we are using and we are binding ourselves to live by that criteria. Okay.

But I did not hear any dissent about number seven being important or that the language being effective and essentially correct.

Eric, did you want to add anything?

DR. CASSELL: Correct.

DR. MURRAY: Okay. Number eight?

MR. HOLTZMAN: Could I make a suggestion?

DR. MURRAY: Yes.

MR. HOLTZMAN: Instead of going to number eight, cast your eyes to number nine, which seems to be a two sentence summary of six and seven.

PROFESSOR CAPRON: Comment? Number nine -- the first sentence of number nine, I agree with Steve, looks like it is out of order. It seems to be a global statement that IRB's should get from investigators this thorough justification. The second sentence goes back to Bette's complaint that we seem to have said a lot of different things about groups but have never been exactly clear.

This notion of exercising heightened scrutiny

-- heightened beyond what?

In other words, they should greet statements from investigators with more skepticism that they are accurate representations and require more creativity on the part of the IRB? I do not know what that means.

DR. MURRAY: I thought it meant lie detector test myself.

PROFESSOR CAPRON: It seems to me it is not only problematic but it is problematic as joined with the first statement which is a blander global statement.

DR. MURRAY: David?

DR. COX: So the reason why there were originally two things is there was one dealing with groups and then dealing with issues that expanded to more immediate families and that has now sort of been changed. Not surprisingly based on all the different discussions we have had. So that now, I think, Steve is quite accurate to correctly point out that they read the same. So if they really are going to be sort of for the same issue then it is redundant. If we are going to consider -- want to make the distinction between groups broadly and more specific immediate relatives then right now the

recommendations do not do it.

DR. MURRAY: Harold?

DR. SHAPIRO: I agree with, I think, what Alex is suggesting. The last sentence in nine is either unnecessary or not comprehensible quite. The IRB's have responsibilities. We have to assume they are going to carry them out effectively and we do not need that last sentence. It is an unnecessary exhortation it seems to me. It is already in some of the other recommendations.

DR. MURRAY: What if the “for example” was not about groups but about family members?

DR. COX: But it works if you follow what Harold just said because if you get rid of that last sentence and risk to subjects, it deals with it. It does not have to make the distinction but it is just there as a general -- so it works out fine if you get rid of that last sentence.

DR. MURRAY: Arturo?

DR. BRITO: This issue, I think, is already addressed in six and then going on with seven except it is missing the term that is used in recommendation number nineteen where it says, "For harms to individuals or

groups who are related to sample source." Would it change by eliminating number nine and just adding that phrase "where investigators --" third line on number six, "Where potential harm...and individual or group related to the sample source," and then you take care of both. Understand? And then heightened scrutiny by IRB is already addressed in number seven.

DR. MURRAY: Well, I think so. I am a little worried that by lumping together, you know, first order, first and second degree biological relatives about whom we have concerns and descriptive groups that may be scattered, you know, worldwide into the same -- whether we, in fact, want exactly the same response to those two kinds of risks. I am just not sure we do.

DR. BRITO: You are concerned about lumping them together.

DR. MURRAY: Yes. Whether we want the same rules to apply to the IRB's consideration of both types of risk.

Steve?

MR. HOLTZMAN: If we believe -- let's take a clear case of potential harm to persons other than the

subject. I think in such a case we are saying that there should be solicitation or consultation from a group. Do we believe it is the case similarly if it is a family member? Do we? Because if we do, I think, the same principle is going to hold with groups whether by kinship or social association.

DR. MURRAY: That puts the question well, Steve.

DR. MIIKE: Except I remember a discussion where research subjects may object to revealing to family members the research that is going on.

DR. MURRAY: Bette?

DR. KRAMER: I was not at the Princeton meeting but I did read the transcript and if I remember correctly -- if I remember correctly you did not want family members to have the opportunity to veto the research.

(Simultaneous discussion.)

DR. MURRAY: Veto is different from consultation.

DR. KRAMER: Okay. Right. But I also thought that it extended even to consultation. It is

strange -- it is hard to figure out why you would consider -- why you would be willing to consult with a broader more disbursed -- more disseminated group than you would a more -- a group that is more immediately affected but the family --

DR. MURRAY: Except as --

PROFESSOR CAPRON: "Seek where appropriate."

DR. MURRAY: Yes.

PROFESSOR CAPRON: I mean it is not appropriate if the person says, "You may not contact my siblings about this. I do not want them to know I am going in for X, Y, Z test in your research protocol. I have no interest in their knowing that." And it is not appropriate to do it because it is confidential medical information.

I mean, I hate to put too much on those qualifiers but sometimes they are important.

DR. MURRAY: Alta?

PROFESSOR CHARO: First, because I suspect that this will only be worked out when we are actually trying to redraft I would like to volunteer to help on that.

It seems like part of what may have happened here is that we have tried to deconstruct the process of IRB review too much and that what we want is something a little bit simpler. It is simply that as always when investigators go before an IRB with a proposal they are expected to explain what the study is intending to accomplish and how they are planning to do that with a minimum of risk to the subjects and to others.

And we explain that the minimalization of risk to subjects is going to focus a great deal on things having to do with methods for maintaining confidentiality and anticipating the possibility of the need to go back to the subjects and planning for how one can do that responsibly without unduly alarming people.

And that the minimalization of risk to third parties will vary depending upon the nature of the third parties so that in some cases it may be making sure that they are kept unaware of the research and that they are not unduly alarmed by knowledge about their family but they did not have and do not ask to have.

Whereas, with more diffuse groups it may be that the minimization of harms is by some form of

informal consultation that allows them to have some input in providing insights into ways in which the research can raise public concerns and might be restructured to avoid questions or designs that enhance that risk.

In this way, by putting stuff back together, I think, we avoid the problem of trying to tie the design of a protocol to a risk to a particular party, to a particular technique that is getting us all bulloxed (sic) up in the details.

DR. MURRAY: So what should we do?

PROFESSOR CHARO: Well, at the risk of sounding like I do not have any consistency from one moment to the next, I think here excessive precision and clarity may be dangerous.

(Simultaneous discussion.)

DR. MURRAY: Let's go quickly then. We have a number --

DR. CHILDRESS: Can I throw one thing in?

DR. MURRAY: Go ahead.

DR. CHILDRESS: One way we can handle some of this actually is to make some of these recommendations subsets of others and that there would be ways to group

them.

PROFESSOR CHARO: Yes.

DR. CHILDRESS: But that is going to require more thought than I can give it right now but this is certainly one area where I think we can bring together some of the group harms under the larger category.

PROFESSOR CHARO: Yes.

DR. MURRAY: Harold?

DR. SHAPIRO: Yes. I cannot -- I have been trying to think how I can articulate what is bothering me right now but I will put it out there in an inarticulate form, therefore, and that is there is something which seems very -- to raise a level of concern and apprehension in my mind regarding the contact with, consulting with or any otherwise talking with family members of a human subject. It does not -- I have to articulate it more carefully. It sounds like a very bad thing to do to me if you are talking about adults and so on. Children, of course, are separate.

And I will have to think about that more carefully but I just want to say it sounds to me like a very bad idea. Whereas, I do not feel that way, despite

what Bette said, with respect to what has been characterized here as more diffuse groups. I think the harms are different. I think the whole calculation is different and I would resist lumping them in there unless there were qualifiers that were quite clear. I mean, I understand that appropriately could be interpreted in various ways which would satisfy me, I suppose.

So I just want -- I do not have a recommendation regarding these recommendations here but I really do not want to lump these things together unless someone could present a convincing argument for it.

DR. MURRAY: We have four people who wish to be recognized. Trish, Bernie, Diane and Bette. Those are the four that I have seen. It is about -- it is getting on to 12:30 now. We should break for lunch. I hate to do that without reaching some kind of closure. That may or may not be possible. If the people on the list could make their comments brief we would all be grateful.

Bette or Trish rather.

DR. BACKLAR: I just wanted to remind us that we had a very interesting paper about family issues from

Barta Nauffers (?) and I think it would be very useful perhaps for Kathi and some of us to go back and look at that and use some of that language in terms of when we refer to families.

DR. MURRAY: Bernie?

DR. LO: I think we need to clarify at what point in the research process we are planning to have these consultations. I think when you are designing a study and thinking about submitting to the IRB's it is fine to talk to a lot of people to get ideas on how to do it in the best way possible and that may include potential subjects, family members of potential subjects, and group representatives. I think that may avoid the issue of going to a family member or a person who is already enrolled in your trial and getting consultation at that point.

I think, I would envision this as sort of in the planning sort of design stage of the trial rather than the data gathering or publishing stage but I fully share Harold's concern.

DR. MURRAY: Diane?

DR. SCOTT-JONES: I like the way Harold

described the difference between the harms that are to groups versus a concern about family members of participants in studies and I would like to just add a comment.

It seems to me that some of the harms have to do with the -- to family members have to do with the protection of the confidentiality of the information and in that regard it is not unlike say research on marital relations where you ask one person enrolled in the study about marital relations. You are also gathering information about others who have not agreed to be in that study.

Or if you are studying family relationships from the perspectives of the child you are asking the child about parents and you are getting information about people who have not themselves agreed to be in the study and it seems to me that in that case there are similarities that should be commented on in some way that the IRB and the researchers should be -- should have some sort of heightened awareness of the possibility of gathering information about people indirectly who have not consented to be in the research.

DR. MURRAY: Bette?

DR. KRAMER: I was just going to pick up on what Bernie said and I think that if we could move that 19 into -- 19 needs to -- that does deal with families. Move it over under research design and actually let it follow on six and we will be able to draw the parallels and contrasts with groups versus families, however, we end up drawing them but that would be a logical place to do it.

DR. MURRAY: That may be one of the difficulties because that really has to do with publication and dissemination of results rather than going into the research or obtaining samples.

Harold, you are on the list both as participant and as chair of the commission.

DR. SHAPIRO: Well, as chair of the commission I might be induced to talk about lunch or something.

I mean, I think the point Bernie made is important. We have to keep in mind when this is taking place in the research design stage versus some other stage, makes a huge difference. In the research design

stage you do not know who your human subjects are. You do not know who their relatives are. You have not chosen them yet.

You may be able to identify groups in some of them but you are not into kind of family relationships at that stage and so you really cannot -- not knowing your subjects you could not know their families. And so I think it is -- you know, when we write this we should be careful about what comes in the research design stage versus what comes in some other stage, maybe at publication which is what 19 deals with.

PROFESSOR CAPRON: The points to consider used by the Recombinant DNA Advisory Committee for human subjects with gene transfer and gene therapy protocols require a statement of the plan for the dissemination of results and the protection of the privacy of the subjects. It is a slightly different set of concerns but it is right there at the initial phase a requirement that the individual and the institution have thought through how they are going to -- some of this, I agree with Bette, could be part of a research plan.

DR. MURRAY: Arturo, I will give you

basically the last word before lunch.

DR. BRITO: Okay. This is going to be food for thought. No pun intended here. But the phrase in number six -- Harold, what you are saying, I am not in disagreement with what you and, I think, Diane were saying. What makes me uncomfortable is that phrase "may potentially harm."

Sometimes -- how can you -- how can you separate an individual from a group -- an individual is not the sample source -- from a group if you know that you could cause harm to that individual in the design of the research? I think that is -- in other words, how can you -- it does not matter if it is one person, if it is a family, if it is a group of individuals, an entire population, how can you separate the two is what I am having difficulty with.

DR. MURRAY: That would be food for thought over lunch.

DR. BRITO: Yes.

DR. SHAPIRO: These are unidentifiable samples in six. You do not know who the individuals are.

DR. MURRAY: In six they are unidentified,

that is right.

Harold, I think, you know, fatigue and hunger are going to -- are overtaking our ability to make progress on these recommendations.

As much as I would like to have closed on this set I do not think we are going to do that before lunch. What I would like is some assurance that we could get back to these recommendations before we split tomorrow afternoon.

DR. SHAPIRO: All right. Let me propose our schedule calls for us to reassemble at 1:15. We had some discussion scheduled then and I think what we will try to do is reassemble at 1:30 and beginning our discussion.

We have -- we are going to go to stem cell research this afternoon but we will have a considerable amount of time tomorrow and this item really has precedence over other kinds of things we might so we really have to move along through this and may, indeed, get some time later in the afternoon depending on our discussion on other issues.

So let's adjourn now and reassemble at approximately 1:30.

(Whereupon, a luncheon recess was taken at 12:35 p.m.)

* * * * *

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

DR. SHAPIRO: Okay. I would like to reassemble now.

I would propose to the commission that we make a very modest change in our agenda. The agenda had us beginning with some discussion of the material that was an outgrowth of our discussions at Princeton and then hearing from our guests, John Fletcher and Lori Knowles.

I propose that we go after just a brief announcement from our Executive Director that we go immediately to the presentation of our guests so as not to keep them here longer than their schedule would allow and then go to discussion and then we can return to the issues as we discussed them at Princeton and review what I think is a very helpful summary.

We will want to make sure as I said before that summary is correct and not misleading in any way and then go on to discussion from there.

So, Eric, let me turn it to you to make a brief announcement and then we will turn to our guests.

DR. MESLIN: Just very quickly with respect to Professor Charo. She has to recuse herself from

discussions about the commission's report on stem cells regarding a perceived conflict of interest that may be present. That is the announcement that I have.

PROFESSOR CAPRON: At the last meeting --

DR. MESLIN: For the record, Dr. Greider has been granted a waiver for such discussions and is not in conflict.

DR. SHAPIRO: I think the commission is all very well acquainted with both our guests. Both of them have been of help to us in a number of ways in the past as you all know and it is a great pleasure to welcome you both here today. Lori Knowles of the Hastings Center and John Fletcher from the University of Virginia.

Lori, I understand that you are going to first, is that right?

Thank you very much for being here. It is a great pleasure to have you.

DISCUSSION OF COMMISSIONED PAPERS

LORI KNOWLES, LL.M., THE HASTINGS CENTER

"INTERNATIONAL PERSPECTIVES ON HUMAN EMBRYO AND FETAL TISSUE RESEARCH"

MS. KNOWLES: Can you hear me? Is this on?

DR. SHAPIRO: Get closer.

MS. KNOWLES: Can you hear me now? Thank you.

Thank you for inviting me to speak to you today. I am wondering if I can get my overheads available.

I am going to speak to you today about the "International Perspectives on Human Embryo Research and Fetal Tissue" to give you some idea of where to put this idea of primordial stem cell research and some of the guidance that you can get from the international policies that have looked at embryo research which is clearly implicated by creating cell lines from embryos.

There is a greater controversy with respect to embryo research than there is with respect to fetal tissue research so I will be concentrating on the embryo research issue primarily in my presentation.

I have examined the policies from Canada, the United Kingdom, Australia, France and the European Union for a number of reasons. I am just going to tell you why I have chosen those particular countries.

Canada, Australia and the United Kingdom

share the same legal tradition as the United States so that is an obvious connection.

The United Kingdom produced the first international policy statement of any European country, The Warnock Report.

You can put that overhead up. You can put that first one up.

(Slide.)

And that led to the drafting of the Human Fertilization and Embryology Act of 1990, which has been the blueprint of successful legislation in assisted reproductive technology also covering embryo research for a number of other countries that have then drafted embryo research policies.

France represents a totally different perspective. It is a predominantly Catholic country. It is considered a little more conservative. It has a civil law tradition but also a long history of thoughtful and pressured leadership in the area of bioethics.

The policies of the European Union obviously represent and reflect the diversity of opinion within and among the member states of the European Union.

Despite the great cultural, social and religious differences between these various regions and countries it is possible to find commonalities between the policies that they have adopted and this is useful for your task, looking at these commonalities.

Each country has found that the topics characterized between this tension between the hope for the potential of embryo research, the benefits, and also concerns about limits on embryo research, and in addition there are similarities between the recommendation strategy, the guiding principles, the appropriate limits, and the areas requiring prohibition.

Can you put up the first overhead, please, or the second?

(Slide.)

This overhead simply shows you the context within which regulation of embryo research takes place. We have assisted reproductive technology on the left-hand side, human subjects research, and then specific legislation designed only to cover embryo research on the right-hand side.

You can see that the vast majority of

regulation takes place within the context of assisted reproductive technology and it is, therefore, that context which limits and describes the embryo research legislation.

Now most of the laws were proceeded by national commissioned reports and most commissions took a period of between two to four years to come out with their final reports and this period was punctuated with public consultation, scientific consultation, and a number of reports before the final report.

Also, in discussing embryo research the reports examined the uses of embryos, the sources of embryos, including the creation of embryos, and prohibitions and limitations to regulate that research.

Most commissions stated that they would not offer definitive answers to contentious ethical issues, which is interesting, but they would simply outline the issues and elucidate the guiding principles with a lot of emphasis on discussing and elucidating guiding principles and in some cases the application of those principles in particularly contentious contexts.

Now, obviously NBAC does not have the luxury

of two to four years in this particular time but that may indicate that the best strategy is a partial response in June to be followed by a more thorough examination of the issues surrounding embryo research particularly reflecting the updated scientific information, including the creation of embryos through cell nucleus transfer.

The rapidly changing technology and resulting public concern, as well as the diversity of firmly held beliefs, makes thoughtful and intelligent assisted reproductive technology policy very difficult but one further difficulty in developing domestic policy and in understanding the international policy stems from a lack of precise or consistent use of terminology.

Many countries do not actually define what an embryo is in their embryo research legislation and those countries that do vary greatly between their definitions of an embryo. So, for example, in the Victorian Australian legislation embryos actually do not come into existence until syngamy, until the chromosomes align on the myotic spindle about 24 hours after fertilization. And so the legislation is geared to regulating embryo research. Therefore, you can fertilize eggs and you have

a 24 hour period within which you can research on those eggs.

The U.K. has a completely different definition focusing on a live human embryo where fertilization is complete but then they want to say in the legislation that includes an egg in the process of being fertilized as well.

So, you know, there is a lot of inconsistency in the definitions.

Clearly how a commission decides how to define embryo impacts greatly the resulting interpretation of the legislation and the recommendations.

One of the dangers of manipulating the terminology is an appearance of skirting the issue by an appeal to mechanistic or legalistic interpretations because whether embryos are viable or not viable, hybrid or human, whether they are the fertilized human egg or developing human form -- excuse me, whether they exist at fertilization or some time thereafter, it is the fertilized human egg and the developing human form which is the locus of ethical concern for most people

discussing this. Maybe not the scientist but that is certainly the understanding that most people will have.

The last sentence is crucial. It is whether the embryo is viable or nonviable, hybrid or human. Whether it exists at fertilization, 24 hours later, 14 days later is actually not the issue. Most people are concerned with the fertilized egg, the developing human form from the moment of the fertilized egg. That is when their concerns arise, not some time later on.

So having a mechanistic approach to defining the embryo does not actually solve your problem. That is my point.

PROFESSOR CAPRON: Is that an empirical statement?

MS. KNOWLES: I beg your pardon.

PROFESSOR CAPRON: Is your statement an empirical statement, most people?

MS. KNOWLES: Actually that is what the Canadian Royal Commission says as well. That is, in fact, one of their statements in the Canadian Royal Commission that most people are referring to the embryo as an understood term.

PROFESSOR CAPRON: I am just asking is that an empirical statement? One that is backed up by data or --

MS. KNOWLES: I do not have the statistics to tell you that most people think that. That is intuition and it also comes from the Royal Commission.

DR. CASSELL: Does the Royal Commission have the statistics?

MS. KNOWLES: I do not know the answer to that. That is what they decided in their definition of embryo. That is how they based their decision. I can certainly find out whether it is empirical or not for you very easily.

A similar problem exists with respect to the definition of research. Many countries do not define research and a few draw a distinction between therapeutic and nontherapeutic research.

For example, the Australian Federal Research Guidelines define therapeutic research on embryos as research which is aimed at benefitting the well-being of the embryo and not therapeutic research clearly as research not aimed at benefitting the well-being of the

embryo and which may also be destructive.

Now this distinction results, in fact, from the fact that the field of ART, assisted reproductive technology, there is considerable overlap in that field between innovative technologies and between research and, in fact, innovations with respect to cryopreservation and fertilization are used in therapy all the time.

For that reason both the Canadians and the Australians have recommended that innovative techniques be included under the definition of research in this particular area so that they can, in fact, be regulated. They can, in fact, be subject to regulation.

Also, with respect to this distinction between therapeutic and nontherapeutic, the European Group on Ethics and the Canadian Royal Commission have suggested that this distinction is both unhelpful, unworkable, as well as unethical because if there exists the possibility that procedures might damage the embryo which must then be implanted you are really talking about experimentation on the fetus or baby and/or mother and that clearly is unethical.

The Canadian Commission says, "The only way

to develop therapeutic embryo research is to allow for some nontherapeutic embryo research because allowing the one without the other would be unworkable and unethical because of the risks it creates for women and children."

Now the search for the appropriate limits in developing embryo research regulation can also be seen in the regulation of the scientific uses which are -- the scientific ends or uses which are approved for the research.

Many countries sanction embryo research which is aimed at improvement of infertility techniques, development of contraceptive technologies, detection of genetic chromosomal anomalies before implantation in embryos, and the advancement of knowledge with respect to congenital diseases and human development.

As most of the policies, as you can see, are directed at regulating ART, the closer the relationship is to the human infertility and reproduction the more acceptable the research is likely to be and conversely the more attenuated the relationship the more controversial the research is likely to be.

So, for example, with respect to embryonic

stem cell research where research is aimed at therapeutic approaches to disease or to tissue damage many acts and policies make no provision for these types of uses. This is a function not only of the context of regulation, assisted reproduction technologies, but it is also a function of the fact that many of the acts did not envisage these possible therapeutic uses at the time when the acts were drafted.

The British Act, for example, which is arguably the most liberal of the acts, makes no explicit provision for this particular type of research and they have just recently issued a statement, the Human Genetics Advisory Commission with the fertilization authority, which says that, "when the act was passed the beneficial therapeutic consequences which could result from human embryo research were not envisaged. We, therefore, recommend that the Secretary of State consider specifying in regulation two further purposes to be added to the act and those are: Developing methods of therapy for mitochondrial disease and developing methods of therapy for disease or damaged tissues or organs."

They are clearly actually pointing to the

stem cell research when they say that. That is within the context of their statement.

So it becomes clear that how a country determines the uses for which embryo research may be approved, it is crucial when determining the implications for embryonic stem cell research.

Also how a country anticipates change is crucial. The British provided a mechanism so that uses that were not approved could be added at the time when the science and the attitudes changed later.

As the Canadian Commission states, "Given the rapid innovations in this field the goal is to build a framework which anticipates rather than reacts."

Would you put up the next overhead, please?

(Slide.)

Now guidance on framing these issues in human embryo research can be found by examining the commonalities in guiding principles and recommendation strategy among the countries.

And common principles, which you find in these various national reports, include the respect for human life and dignity, the quality and safety of medical

treatment, respect for free and informed consent, also non-commercialization of reproduction, which leads to prohibition on sales, and minimizing harm and maximizing benefit.

And in developing policy in this area most commissions adopted a very long-term vision for policy formulation, which means that recommendations have to be general and allow for flexibility and have some adaptability in the case of future developments.

For example, the British Commission adopted a recommendation strategy which explicitly said, "Frame recommendations in general terms and leave the matters of detail to be worked out by the government. Indicate what should be matters of good practice. Indicate what recommendations, if accepted, would require legislation and likely prohibitions. And any proposed changes should apply equally throughout the United Kingdom."

The next overhead, please.

These are other examples coming up now of other common mandates so this describes their tasks.

(Slide.)

Identification of issues of concern, future

developments. The second is particularly important; outlining guiding principles and practice standards. Of course, encouragement of continued reflection and thought and the advancement of knowledge.

One of the central findings from the public consultation about embryo research in these countries is the existence, of course, of a great diversity of opinion on the acceptability due to the differences of opinion on the moral status of embryo.

The two general positions are the same as those described in this country's reports as well, that the human embryo has the same moral status as human beings and, consequently, it is worthy of the same protection or that it is not considered a human being and, consequently, is not worthy of the same protection.

Now the most common response is an explicit statement by the commissions that they will have no definitive answer to give to the question of whether a human embryo is a person. No definitive answer based on the lack of scientific knowledge that can point them to a definitive answer at this point in time. That is a very common answer amongst all these commissions.

But then what they choose to do is they choose a pragmatic approach, which is a compromised position between these two positions and seeks to balance the scientific and medical costs of not pursuing this research with the moral costs of permitting the research. There is consensus that if research is permissible limits are necessary although there is less consensus on what those limits are -- what limits are required.

Would you put the next overhead up, please?

(Slide.)

Now the limits include informed consent of the gamete donors, time limits within which research must be concluded. These are common links that you find amongst many of the countries. Including -- the time limits, by the way, reflect the developmental protection -- development of the embryo and the protection that it needs as it develops further. The most common line that is drawn is that 14 day line after fertilization which represents the point beyond which twinning is not supposed to occur anymore and is the time about just before the appearance of the primitive streak.

The Warnoff Commission says explicitly that

any time line drawn is to some extent arbitrary but this time line has these two particular reasons why it is a proper choice and, in fact, it is a very common choice among the many countries.

The embryos must be necessary. This really points to the scientific validity of the protocols that they need to use human embryos. There are no other available animal models. That is definitely one of the limits. And that the research be of significant import to require the use of human embryos.

All countries require protocol review either on an institutional local or national level. And many of the countries also called for national regulatory oversight so in addition to the protocol review they recommended the establishment of a national regulatory board, commission or authority to license and regulate this assisted reproductive technology and embryo research.

Many of the countries noted that the use of law in this area would be inappropriate given the rapid development in technologies. National commissions with subcommittees responsible for the various areas of ART,

one of which, of course, is embryo research can provide needed adaptability and can relieve the need to campaign to remove legislative bans and prohibitions as technologies and attitudes change.

They also provide more transparency in the process and more consistent application of safeguards.

The last one is particularly important. This is the use of spare IVF embryos only, which of course goes to the question of the creation of embryos. There is no consensus on this issue but the U.K. permits it.

The Canadian Royal Commission suggested it should be permitted. As you probably are aware, there is not actually a law in place in Canada right now.

And some argue on the one side that the creation of embryos without the intention of implanting them instrumentalizes them which is disrespectful but others argue that given the outer limits, the necessity for the use of embryos, the time limits, that these actually provide enough respect for the special status of the human embryo.

DR. MIIKE: Excuse me.

MS. KNOWLES: Yes.

DR. MIIKE: Can you repeat that last part again? You talked about creation of embryos for research. I do not see this use of spare IVF embryos as necessarily an issue about creation of embryos for research.

MS. KNOWLES: It is the use only of spare IVF embryos. That is the limit. You can only use those that are spare embryos.

DR. MIIKE: I thought I heard use --

MS. KNOWLES: No, I do not believe so. Use only of spare embryos or creation as well. That is the distinction I make. Or creation of embryos for research purposes only.

DR. MIIKE: There is no distinction in these countries?

PROFESSOR CAPRON: There is a distinction.

MS. KNOWLES: I am saying yes. They make a distinction. And I am saying the U.K. says you can actually also create for research purposes only and the Canadians suggest that that is appropriate in the Royal Commission. That was my point. And that other countries say that, no, you must only use spare IVF embryos. You

cannot create them for research only.

But there are actually two important issues to keep in mind when we are talking about creation. The first is that the creation of embryos provides the only way to conduct certain research, research into the fertilization process, for example, and also, this is quite important, as techniques for IVF improve it is possible that the need to create surplus embryos will be eliminated because one of the approved uses of embryo research is, in fact, itself the improvement of IVF techniques. So some legislation even explicitly directs fertility experts to try and reduce the surplus number of embryos.

So it is possible to look down the road and say if this happens and it is a desirable end in some of this legislation then embryo research, which is dependent on the existence of spare embryos, will lose its supply. If that is the only supply you have it is possible that you will not be able to do embryo research if those embryos disappear. And then, of course, you would have to revisit the issue again if you wanted to have embryo research.

It would make a great deal of sense to endorse the use of spare embryos where possible and to permit the creation of embryos where the specific research requires that the embryo be created as my previous example of fertilization or where access to spare embryos is not possible.

Well, in fact, the British have actually suggested that it would be unwise to rule out absolutely research which uses the cell nucleus replacement, as they call it, for creating embryos which might have therapeutic value. They have explicitly stated that that is something they do not want to rule out right away.

Could you put up the next overhead, please?

(Slide.)

One of the most important things that can be gleaned from this examination of national policies is that consensus does exist with respect to practices which should be prohibited and these practices are practices that are widely seen to be offensive to human dignity.

I would like to make a comment about the second on this list which is the creation of hybrid chimeras. There is ambiguity over whether this actually

talks about creation of individuals which are chimeric or hybrid in nature or creation of embryos. It is not clear. In some legislation it is clear that it is actually the creation of individuals that is being prohibited, not the embryo creation that is being prohibited.

And, in fact, several of the countries actually talk about the fertilization of hamster eggs with human sperms which is a common test to test the motility of human sperm and say that this is clearly not what this prohibition is talking about so that is an ambiguity that we need to keep in mind in the context of what I am presenting to you.

The last one on the list, the use of fetal eggs, also in many countries the use of cadavers, eggs from cadavers, female cadavers, has been prohibited.

It is likely that this last prohibition would be unacceptable to many, the majority of Americans, who already have trouble with embryo research and some also with creation of embryos, and then to use fetal eggs is probably one step very far down the line of acceptable practices.

I would also add to that list sex selection for purposes unrelated to hereditary genetic disease. That is one of the common prohibitions that you see as well.

The next overhead.

(Slide.)

DR. LO: Excuse me.

MS. KNOWLES: Yes.

DR. _____: Use the microphone.

DR. LO: (Not at microphone.) What is meant by prohibition of the fertilizations? That does that go back --

DR. SHAPIRO: Microphone, please.

DR. LO: -- does that also go back to the payment of egg donors and sperm donors?

MS. KNOWLES: In fact, it changes from country to country but there are prohibitions on -- numerous prohibitions on paying people to donate beyond reasonable expenses so, in fact, the sale of gametes has been prohibited as well as the sale of embryos and in some countries it goes further and says that embryo research cannot be conducted for financial gain so it

goes beyond on both ends actually depending on where you are but it is a common thread that runs through a great deal of this regulation.

I am moving quickly on to fetal tissue research. I actually -- these, I believe, are relatively self-explanatory, the guiding principles which you see which are common, the limits and the prohibitions. Perhaps directed donation I need to explain, which is there was a fear that woman would get pregnant and have abortions so that they could actually donate the tissue to particular relatives. That is what that prohibition is about.

I would just say that the use of fetal tissue to isolate the human germ cells is less problematic than the similar use of human embryos for three reasons. The one is that the removal of the germ cells does not occasion the destruction of a live fetus.

The second is there is no question of creating the fetal tissue for research. That question is obviously not on the table.

The third is that the use of fetal tissue in therapies unrelated to reproduction has already been

raised in the context of fetal tissue transplantation for diseases like Parkinson's and there is relatively -- there is consensus that this is acceptable for these specific uses, therapeutic uses.

Now I just have a few more comments to make on the primordial stem cell research and some of the comments that have been made specifically on that issue. There are very few which is why this inquiry is actually necessary as well.

The Australians simply say that they prohibit the use of stem cells, embryonic stem cells, to create genetically identical individuals. That is clear.

The European Group on Ethics says that what has happened here in the States requires urgent debate and opens up ethical questions. That is the limit of their statement.

The U.K. says in light of the U.S. isolation of these stem cells they recommend approving the use of embryos for therapy. I have mentioned that before. Therapy of disease tissues. And they recommend not banning the creation of embryos by cell nucleus replacement for therapeutic research.

But the most interesting is the French statement because they have a situation that is most similar, in fact, to the United States right now. They have a ban on nontherapeutic research which effectively bans all embryo research. Since the construction of embryos is not possible, creation of embryonic stem cell lines is not possible.

The French National Commission says the following: "We are approaching a paradoxical situation as a result of legislation. Experimentation or therapeutic research on stem cells from embryos are banned but it is possible to import cells from collections established without any observance of specific ethical laws applicable in France to embryonic cells."

The French Commission has suggested that taking into account prospects for therapeutic research the ban be modified this year when that law comes up for review to permit embryonic stem cell research for fundamental research for therapeutic ends.

Now the situation is obviously similar to the paradox existing in the U.S. Here we have a ban on

federal funding for research which would destroy an embryo which, therefore, bans funding for creation of embryonic stem cells but permits the uses of stem cells created without reference to national protections and oversight.

NBAC should take steps towards eliminating this paradoxical situation, outline a consistent set of protections with national application. There is clearly room for leadership in this area and other countries are watching.

This is just my last overhead of some points to remember.

(Slide.)

Long-term vision in this area. That is clear it is needed to anticipate unforeseeable changes.

The articulation of guiding principles is what is absolutely needed.

The distinction between regulatory bodies and law is to provide discretion and flexibility and to be able to articulate high standards of behavior, not the lowest common denominator acceptable behavior which is, of course, what law does.

The fact is that the IVF supply may decline.

And then lastly NBAC can and will influence ART regulations in this country if it decides to deal with this embryonic stem cell research.

Thank you for your attention. It was a great deal to go over.

DR. SHAPIRO: Well, thank you very much. It is extremely helpful.

I think the way we will try to organize the discussions this afternoon is now to hear Professor Fletcher and then we will go to questions.

Lori, I hope you can stay so we can go to questions afterwards.

John, let me turn to you.

JOHN FLETCHER, Ph.D., UNIVERSITY OF VIRGINIA

STRENGTHS AND WEAKNESSES OF AN INCREMENTAL APPROACH

DR. FLETCHER: Thank you, Mr. Chairman. I appreciate the opportunity to go over a summary of my comments. I believe the commission should have a draft of my paper. Eric and Kathi called me about three weeks ago and asked me to get to work on the question of an incremental approach.

DR. SHAPIRO: One has to talk close to this microphone to make it effective. I apologize.

DR. FLETCHER: Thank you. They asked me to get to work on a paper discussing the strengths and weaknesses of an incremental approach to the commission's task of deliberating on this topic and actually I made some overheads. There was a glitch in transmitting them so it is probably a good thing since I will be briefer. I tried to capture my whole paper in overheads but I think the summary will be quicker.

The first strength of an incremental approach is that it is familiar. That is the approach is familiar to those who work in science and ethics and law. That is when a group like this is presented with a set of cases which on their face seem similar or to belong in the same family of cases, one can proceed incrementally first trying to locate the most settled case, that is the most settled case morally speaking and ethically, and then working out from that beginning to the less settled cases and looking for similarities and differences in the moral sense between the cases.

The task as one does this is to search, as

Ms. Knowles said, and she has happily introduced many of the thoughts that my paper tries to address. The task is to search for moral judgments and the principles that guide these judgments that hold from case to case as well as for features of the cases that make them so dissimilar that one would say they do not belong to that family or line of cases.

In ethics this approach is known as case based or casuistic (sic) reasoning.

Well, the commission is faced with a group of cases of situations in which pluripotential stem cells can be derived and used in research. How should the commission deliberate about these cases? If you work incrementally I think it is fairly clear that what I call case one, that is deriving stem cells from fetal tissue, is the most settled case. It certainly has received the most debate and the ethical aspects of the consensus that was arrived at after many years of debate and conflict have been imbedded in a public law that is the Research Freedom Act.

I understand my reading of the consensus would go like this: That the first principle involved in

case one is that society should not forego the therapeutic benefits to persons of transplant uses of fetal tissue obtained after legal elective abortion because of the benefits to those persons and to science and society even though abortion is morally controversial in our society.

Second is respect for the autonomy of the donors of the tissue. That is that society should respect the altruism of donating fetal tissue for research expressed by women who have made legal abortion decisions.

The third is based on reducing or minimizing the harm that can be done by encouraging the social practice, that is to prevent the effects of fetal tissue transplant research from widening the social practice of elective abortion. Certain rules are required and Ms. Knowles went over these rules and they are quite familiar and imbedded in the law.

There are other prudential concerns about permitting payments to transport, process, preserve or implant fetal tissue or for quality control and storage of the tissue. However, the consent process about

abortion decisions must precede and be conducted separately from the consent process to donation of fetal tissue. Donation, a designated donation of fetal tissue is prohibited. Monetary inducements to women undergoing abortion as well as buying or selling fetal tissue.

Now this -- the consensus behind the law is certainly still open to challenge and one does still find challenges to this practice by those who are convinced that abortion is unfair to the fetus and that researchers are morally complacent with abortions that kill the fetus.

If you move from case one, I believe that it is defensible that the most similar case is case two, that is deriving stem cells from embryos that are donated by couples in infertility treatment when there are an excess number of embryos that are not needed for therapy. This practice has been widely permitted in the private sector but as we know it is forbidden to fund research with embryos that would cause their destruction in the federal sector.

However, the legal opinion of the General Counsel of the Department of Health and Human Services

permits or would permit the NIH to fund research downstream from the derivation of stem cells that is supported by private funds.

Cases one and two are quite similar morally in the concerns based in benefits to persons and benefits to science and society as well as respect for the autonomy of the parental donors.

Society and science benefit in many ways by permitting research with excess embryos. To derive stem cells from blastocysts for research only adds to the benefits of this research activity so this principle of benefit is consistent with case one. Although morally controversial with some I think it is quite offensible that society should not forego, put it in that framework, that is society should not forego the opportunity for research and clinical benefit because research with even donated embryos is morally controversial in our society.

I believe that it is arguable that research with donated embryos is far less controversial than the fourth case, that is research with embryos that are created for the sake of research because the original intent for the fertilization of the egg was to procreate

and was to reproduce the parents who donated the embryo for research.

Also embryo donation for research is widely practiced in the fertility clinics and in the private sector.

As Ms. Knowles reminded us, these two cases are very different in one respect. The fetus in case one as a source is dead. The embryo in case two is living and will die in the process of research although its stem cells will live on and will differentiate into other somatic cells.

The research activities cause the demise of the embryo, which is a very different feature in case two than in case one.

So there is no way for the commission to avoid taking the position on the moral standing or the moral status, if you will, of human embryos in research. If you go beyond case one, and that is your first big moral challenge, if you go beyond case one you must address the question of the moral standing of donated embryos in research.

I think there is one possible argument that

case one is more morally problematic than case two because the loss of a fetus in this perspective even at eight or nine weeks gestation occurs in the context of greater value to parents and to society than the loss of a preimplantation embryo, especially one that is donated for research.

This perspective would view abortion as a more serious moral issue than selection among three or four embryos for possible implantation or for research but there are other moral perspectives that would challenge that view.

Case three, that is deriving stem cells, pluripotential stem cells from human or hybrid embryos generated asexually by cloning, by somatic cell nuclear transfer, is in my view arguably a different case than case one or two.

To begin with, we know practically nothing scientifically about case three. It is a different type of reproduction that involves asexual reproduction and since it involves the subject of cloning which you are very familiar with as you have been down that road once, I think that it is inadvisable to take on the case three

exhaustively without -- apart from the context of cloning and the future of cloning but to do a good job in discussing case three would involve revisiting the cloning issue again.

The therapeutic potential, however, of stem cells derived from cloning technology are theoretically quite impressive and I think in terms of the quotient of moral and social controversy that would be associated with this case in my paper I put it above case four because I think that the promise -- it is maybe a little too early to talk about promise but the prospect in theory of autologous cell directed therapy for patients affected with a host of diseases, I think, is so riveting that society is going to insist, if you will, that this avenue be explored with very careful guidance and safeguards against abuses especially from one abuse that the commission has already discussed, that is creating a child by this route.

Case four, as Ms. Knowles' comments suggested, is the most controversial case of all, that is creating embryos for the sake of research. However, the case is different from case two in terms of the intent.

It is different from case three in terms of the scientific beginnings of it.

I think unanswered, although she spoke to it, is the question about need and that is the need for embryos to derive stem cells for research. My reading to date suggests, and my discussions with Dr. Bridget Hogan, who testified last time, in her view it would be enough to be allowed to derive stem cells from the first two sources to be able to study the differences between those cells, which in her view could be very important, different properties that could have implications for therapy down the line but to understand the different biochemical and physical properties of those cells, how they behave as the first step in large scale research in this area.

So my reflection on this to date suggests that there are enough differences between cases one and two and three and four, especially in view of the commission's time line -- I read somewhere that you wanted to have a first draft of the report by June 1st -- that pragmatically speaking there is so much work to be done being in case one and two that if you took one three

and four you would simply be swamped and unable to do an adequate job of ethical analysis and guidance for cases three and four.

And I must say when I read Dr. Paren's comments in the transcripts about challenging you to do the big picture, that is to go all the way towards the goal line, that is the whole 100 yards, to explore the way that stem cell research converges into germ line gene therapy that that would, indeed, swamp your efforts in my view.

There are also other groups that are discussing germ line gene therapy, both inadvertent and intentional. There is a AAAS task force discussing the latter and the FDA and the RAC are discussing the former so that it is not like no one else would be working on these issues.

Before I close I would like to recommend to the commission to consider, if you decide to take on case two, to recommend that the congressional ban on embryonic research be partially lifted to permit this research because there is in addition to the moral concerns about the sources of stem cell research and the uses of that

research -- there is a legitimate moral concern about the effects of the congressional ban on U.S. federal policy and science and whether or not that is the soundest policy, public policy, that we could take.

The ban has effectively kept the NIH's extramural and intramural research interests out of embryo research. There is a long backlog of projects that could have been funded but have not been funded because of the ban in cancer research and fertility research and other areas that the Embryo Research Panel reviewed several years of ago.

If the NIH were able to enter this and fund research deriving stem cells from embryos it would, I think, possibly reduce the projected timetable or time line that Dr. Hogan, Dr. Thompson and others have said is about five years of basic work to the point of where trials with stem cells could be feasible.

I think that it would be -- that is a worthy goal to reduce that time line as well as to ensure the best quality of science in the research that would be done and peer review if the NIH were involved.

I think that it is a political and a moral

paradox and a contradiction that our Congress funds the Human Genome Project liberally in the past with one hand and on the other hand prohibits promising research that could lead to therapy. The greatest problem with the Genome Project, as we all know, is the gap between diagnosis and therapy. In effect, we can diagnose almost everything but as a practical matter we can treat very, very little.

Stem cell research, the reports that have come out and the work that is being done, has truly changed the scientific landscape and I think that fact and the therapeutic direction in which it could move would be a powerful moral and political argument with Congress to take the risk of debating lifting the ban and your recommendation, I think, would be important in that respect.

So, in conclusion, I recommend that you devote a majority of your official tasks to a careful, ethical and public policy analysis of cases one and two, look over the edge at cases three and four, pick out the most important contours and features of those problems but do not try to do an exhaustive ethical and public

policy analysis of cases three and four. Leave that to other groups who will certainly be coming in to succeed you. And if you think it wise, recommend that the ban be partially lifted to permit research with embryos in case two.

Thank you very much, Mr. Chairman.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much. Thank you, both, very much. I have too many questions almost to list in my head but let me turn to the members of the commission first.

Larry?

DR. MIIKE: I may have trouble articulating this but I want to address the scenarios three and four. You have stated that nuclear transfer to create an embryo is of lesser, if I use the right word, lesser concern than using gametes for the express purposes for research. I am unclear about why you distinguish between the two.

Is that because that we do not need to address the moral status of the embryo created or is it because the supposed benefits are so unsure at the current time for somatic cell nuclear transfer that that

puts that in a lower category, or is it because we are not sure whether somatic cell nuclear transfer works? Can you tell me sort of tell me in more detail why you sort of distinguish between those two cases?

DR. FLETCHER: Between embryos created by cloning technology --

DR. MIIKE: Versus --

DR. FLETCHER: -- versus case four that is creating embryos for the sake of research only using human gametes?

Well, my basic reason for distinguishing the cases rests on the asexual versus the sexual route of reproduction. The result is the same presumably, that is morally speaking -- I read the discussion that Alex Capron had with Dr. Varmus about the moral worth of the embryos. I do not think I would argue that embryos produced by cloning were of less moral worth than those produced by sexual reproduction.

It seems to me that an embryo is an embryo and that if it is -- it would be right in my view to do research with embryos derived from cloning technology especially to see if the promise of -- especially if you

had as a gaol autologous cell directed therapy but also to see whether or not stem cells derived from that source behave in the same way and grew the same way as stem cells derived from case two.

DR. MIIKE: So let me get it clear. You are making the distinction because of the exciting research issues around the creation through cloning technology versus traditional fusion of sperm and egg?

DR. FLETCHER: No.

DR. MIIKE: Because you told me -- you just told me that --

DR. FLETCHER: No, because of the asexual origin of it and the fact that the case would involve the future of cloning technology and the future of cloning in science and society. We would have to have that discussion along side of --

DR. MIIKE: So that would fit the balance even though the moral status of the embryo created by either of those two paths would be identical?

DR. FLETCHER: That is right, in my view.

DR. SHAPIRO: Alex, and Steve?

PROFESSOR CAPRON: I have a question for each

of you and then one question for both of you about our process.

The question for Lori was in your presentation of the materials so far I was not entirely clear when you were being descriptive and when you were being analytical and normative. You commented that, if I understood you and I may be wrong on just what you have said, that a number of the commissions in other countries that have looked at the issues have observed that there are different views on the moral status of the embryos and have decided not to resolve that issue as to whether an embryo is equivalent to a human being, a person, or is not and enjoys only a lesser set of interests and a lesser degree of protection.

It seemed to me that if you then go on to say that these commissions all ended up allowing research with embryos --

MS. KNOWLES: They do not all allow it.

PROFESSOR CAPRON: Those that do allow it, are they in the same we are not deciding the issue camp?

MS. KNOWLES: Yes, it is very interesting.

PROFESSOR CAPRON: Yes. Now -- and as to

that group then, those that would allow the research, analytically whatever their own claim of not deciding the issue, isn't there quite -- if there is something more than implicit it is not -- self-evidently the case that they must be saying that the embryo has a different human status unless they are willing to depart from the basic norms of Neuremberg and thereafter?

MS. KNOWLES: Okay. Your question is exactly what they, in fact, say. They say one thing, "We will not be able to make a definitive judgment on this. We cannot give you a definitive answer." And, yes, then they go on and essentially reject one of the possible positions, which is that human embryos are human beings by choosing a middle course but that is not the descriptive process that they use but recognizing that is still a compromise position between those that believe that human embryos are like toenails and those that believe that human embryos are people.

PROFESSOR CAPRON: Right. Okay.

MS. KNOWLES: Yes.

PROFESSOR CAPRON: It would be helpful in the report you write for us, because I have a sense that we

would like to situate our own deliberations and conclusions not only in the context of past U.S. study commissions but what is happening around the world, to be clear about that, that whether or not they acknowledge it and whether they say they can explain in detail exactly what all those interests are or how broad the protections that result from those interests need to be that they are at least rejecting, implicitly rejecting, the equivalent to human beings rationale.

John, one of the things that Lori mentioned about the French situation and the parallel with our own made me want to know where you come out on that issue, the issue of use being really equivalent to the activity that creates the pluripotent stem cells themselves. As I gather, the French were saying by prohibiting the research that would create the cells we are in the on position of allowing research with them which may not be conducted up to French standards elsewhere and in importing this we have basically the same issue we have not looked at as importing because, of course, it is American researchers that have developed the technologies.

DR. FLETCHER: Well, you are referring to the general counsel's opinion.

PROFESSOR CAPRON: Yes.

DR. FLETCHER: I understood the definitional approach that took place in that opinion as one that side stepped the question about the relation between the source and the use. In other words -- and I read the letters from -- the letter from the 70 members of Congress very carefully the other day because my own member of Congress in Virginia signed it, which I was surprised about but he did sign it.

But I think they have a good point, that is that morally speaking it is -- in my view it is not wise to separate use from source and that this is one of the problems for moral reflections or ethical reflection in the distinction between public and private -- the public and private sphere. In other words, we seem to be creating two universes in our country where we have two universes of science and two universes of ethical reflection about federal and private scientific activities.

I think in the long run you get into

collisions just like the one that the NIH was in. I think that politically speaking, you know, to change the context from ethical reflection to political possibility, politically speaking, there are probably enough votes in Congress to uphold the legal opinion and to permit the NIH to do the research downstream but that still avoids the moral issue, which will keep coming back and coming back and coming back so it has got to be addressed at the source.

So the -- I think the French got themselves into this problem because their tradition and their culture is to deal with bioethics issues by law and when you write law on bioethics issues you have to elude some of the subtleties of moral experience.

PROFESSOR CAPRON: And my question for both of you is did you get a chance to look at our points to consider draft that was in the materials? Did either of you?

DR. FLETCHER: No.

MS. KNOWLES: No.

PROFESSOR CAPRON: Then you cannot answer the question. Thank you.

DR. SHAPIRO: But we will get you a draft before you leave because we would like any reflections you have on it.

I have a number of people who want to speak.

Steve?

MR. HOLTZMAN: I think this is a question to Lori though it takes off a little bit from Dr. Fletcher's distinctions. There is a great divide we see in all of these regulations and if we take Dr. Fletcher's analysis as buckets one and two where you have got aborted fetuses and surplus embryos, that is the one bucket, and to the extent I understand motivation that says it is okay, the notion is these things are going to get destroyed anyway so you might as well use them for a good purpose as long as we have separated the motivation for their use in that way from -- I am sorry, you are looking at me, Lori.

MS. KNOWLES: Well, excuse me, not necessarily --

MR. HOLTZMAN: Okay.

MS. KNOWLES: -- the destruction of the surplus embryos. They can be donated. They can be donated for implantation. They need not be destroyed.

That is just --

DR. HOLTZMAN: Okay. That is --

MS. KNOWLES: -- I do not know if that changes --

MR. HOLTZMAN: No, actually I do not think it does. But then when we move on into buckets three and four and Dr. Fletcher was trying, I think, to articulate his intuition that there seems something more okay about three, and you found yourself pointing to the fact that it was through asexual reproduction. I am not sure that really got at it and so the other question goes to Lori.

Where people have said it is okay to have the creation of embryos for the purposes of research, the way I think of that is that the embryo was never intended in any way to become a child, all right, and then do they point to -- and then they also say that science will not tell us about the person-hood status so, therefore, we have to look to other issues in society. I am asking if they think along these lines.

We have to look to other issues such as will a certain kind of social practice inure us to what we think are important human values about reproduction, its

role in society, and that line of thinking can then lead you to say that certain kinds of activities, including the creation of research purpose, embryos are valid. You have changed the calculus. You have gotten outside of the question of person-hood.

And that might point us to the kinds of intuitions you are articulating, Dr. Fletcher, of there may seem something different at stake in the social practices not in terms of the embryo but in the social practices of creating some via nuclear transfer where there was never an intent or even childhood was never possibly in plan.

MS. KNOWLES: Well, in fact, I have not seen that played out because, of course, there is very little that is actually articulated on the creation of embryos by the transfer of nucleus from other eggs.

MR. HOLTZMAN: But if you look at the basis for -- take like the U.K., for example, and you look at the basis of justification there --

MS. KNOWLES: They actually --

MR. HOLTZMAN: -- does it provide the kind of rationale for making the kind of distinctions that Dr.

Fletcher has intuitively?

MS. KNOWLES: Not if I am understanding you because, in fact, what they say is it is much more explicitly a balancing between what will be lost in possible therapy with respect to what is lost in moral costs. So scientific and medical costs versus moral costs is what is being weighed in these --

MR. HOLTZMAN: Are those moral costs, the locus of those moral costs, intrinsically in the embryo?

MS. KNOWLES: Yes.

MR. HOLTZMAN: They are?

MS. KNOWLES: Yes.

MR. HOLTZMAN: Even though they say --

MS. KNOWLES: Yes.

MR. HOLTZMAN: Okay.

MS. KNOWLES: And its connection to the human community. That is phrase. And its connection to the human community. That is where I have seen it.

MR. HOLTZMAN: Okay.

MS. KNOWLES: Does that answer your question?

MR. HOLTZMAN: In which case it would not provide the basis.

MS. KNOWLES: That is right, although I think your last point is very interesting because the embryos created by cell nucleus transfer are not, of course, within the realm of reproductive technologies. That is not what they are created for so --

DR. _____: At the moment.

MS. KNOWLES: At the moment. Well, yes, and actually internationally that is banned widely.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Thank you both very much. This question is for John but part of it will connect with some of Lori's presentation.

The question has come up a few times about how you are distinguishing the categories two and three and it seemed to me, in part, though this was certainly not explicit in your presentation, that there perhaps was something about your focus on how we might move incrementally in societal discourse and public policy, sort of a view about what the society might be ready to accept, and that there might be something like that at work here --

DR. FLETCHER: Right.

DR. CHILDRESS: -- and not simply several of the reasons that you laid out. That would be my first question and could you respond to that one and then I have a second one if I could?

DR. FLETCHER: Yes. That is -- the level of controversy and readiness to discuss the ideas as well as an information base from which to discuss three especially is very much at work. I do not think we have any experience with cloning human embryos. We have a lot with cloning animal embryos but without that information base the discussion is less well informed.

So also the idea about the degree of controversy that a particular social debate causes being proportionate to the benefits that you could gain from engaging in that debate, that is picking your fights wisely, all right, and picking the right debate to get involved in. So there is also at work in my mind a kind of proportionality given your resources, your time line, and your staff of how much you could do successfully. That is also at work.

DR. CHILDRESS: My second part of that was in connection with Lori. In your discussion of the way in

which we might move forward, especially in one and two, I am assuming, John, though, and you did not state here in your paper, that several of the kinds of limits and prohibitions that Lori identified on the international level you would want to argue would be important to maintain in our context, too.

DR. FLETCHER: Yes.

DR. CHILDRESS: But that is not something you are arguing for in this context?

DR. FLETCHER: Yes, very much so.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: They are both wonderful presentations.

John, if I understand you --

DR. SHAPIRO: Do you want to move closer to the microphone?

DR. CASSELL: -- at least part of the problem is supposing we step aside from the political, you are calling it the social debate, but the political debate which has so trapped us that it is hard to look at other ethical frameworks from which to examine this and that

supposing we look at this as though the embryo is a person and that, in fact, it would be such a benefit, suppose we could specify that benefit and that, in fact, it had happened that something that came along that would save children from this kind of research, we would be in a different ethical field, wouldn't we? It would be the loss of this living thing for the gain of life in this set of living things.

We have a number of frameworks in which we have done that and life boat ethics may be stretching a point but at least it is a similar point where a life is given up in order to gain another life because it seems to me that this is the first time in the whole embryo research debate that the possibility of benefit is so great that it allows a shift in the ethical basis for discussion. Is that what you were trying to --

DR. FLETCHER: Yes. Yes, that is -- if you go back to the Human Embryo Panel's report one of the criticisms of it was where are the benefits that prompt your recommendation that it is the right thing to do to create embryos for the sake of research.

Dan Callahan wrote about this.

I think that the stem cell reports changed the landscape importantly in that respect and that for that reason the benefits issue or the beneficence issue is more compelling. I thought it was compelling in 1990, that is the -- let's see, I would just like to make my own moral view clear about the standing or status of an embryo in terms of research, that is the -- I would agree with the position that the Human Embryo Research Panel took that as a being the human embryo does not have the properties particularly at the preimplantation stage that would lead to conclusions that it deserved the same degree of protection by society.

Although it has enough properties both at the time and potentially to deserve that the activity of research with embryos should be carefully limited and regulated in order to show the difference between research with human embryos and any other type of tissue because of a desire not to demean respect for human life.

So it is considered a moderate view, as Ms. Knowles was saying, between two other views. One that would view an embryo has having no moral status deserving respect whatsoever and the other that would equate an

embryo with the respect that the living human being or a fetus at a later stage of development would deserve.

So my qualifications about cases three and four have to do more with scientific, political and pragmatic considerations than they do basic moral considerations about the embryo.

DR. CASSELL: But aren't those -- I mean, if they benefit population, or following your argument, though, aren't they moral arguments? I mean, Dan Callahan's argument against because there is no benefit is really an argument for. Aren't you saying the argument against it is as you can show this benefit then you are implying that if, in fact, you could show the benefit there is an argument for it just as he does the same thing at the other end of life.

DR. FLETCHER: Right.

DR. CASSELL: If it is not right to waste or use societal resources to maintain a life that is of no value when it could be going somewhere else and do value then in the same moral argument can be used -- I am not saying how well it will work out when you start really going with it but I think that you were allowed to start

going in that direction and see where it leads you, and I take that to be the central method of what you are talking about.

It is switch the focus and start trying to work out a different moral basis for looking at that. It will not get you out of -- what you have just pointed out. That will not get you out of the question of is it a person or isn't it a person.

I share your view of it. That will not get you out of that but it will point you in a direction where you can begin to see this more clearly and not be trapped by that same old politics that has trapped us now for a generation.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I first would like to thank both of you for coming and giving very lucid and thoughtful presentations.

With the indulgence of the chair I am going to try and ask one of these famous double barreled questions to try and get the maximum thought from the two of you.

My questions really have to do with the problems of trying to make recommendations about public policy on very controversial moral and ethical issues.

The first question, I guess, is particularly to you, Lori. It has to do with the connection between very passionate and very divisive views on abortion and how it shapes our views on embryo research. As you surveyed other societies that have grappled with these issues are there other countries in which there is such a profound split in the population among those who believe abortion is a very grave, moral affront versus those who feel that it is tolerable in some situations. And if there are any such societies, how have they resolved the issue of human embryo research? Because it seems to me what sets us apart in many ways from societies that are not -- where the controversy over abortion is not as sort of deep and as polarizing of that.

MS. KNOWLES: Well, I am not sure I can answer your question directly but the best example that comes to mind is -- well, there are two things. The first is that countries like Ireland where abortion is absolutely not acceptable with very, very limited

exceptions, they do not permit embryo research, period.

The other thing I would note is that there is very little explicit connection made between references to abortion and embryo research. That is not a connection that is drawn. It is drawn between abortion and, of course, fetal tissue research so that is where the debates actually link up but not between embryo research and abortion.

One thing that was very interesting was to look at the European Union policies on embryo research, which do not make a mention of abortion with respect to embryo research, but they, of course, are dealing with a situation in which there is absolutely no agreement between countries on what is acceptable and what is not acceptable because they are talking about different countries, and they have said that it is not appropriate in that circumstance for the European Union speaking as a body to impose one moral code and so that they will have to allow each of the nations within a regulatory scope, a strict regulatory scope, to make decisions about embryo research.

That does not answer your question explicitly

but that is the only situation where I can see an analogy where there is a division that can be breached and it is not with respect to abortion.

DR. LO: My second question has to do with timing. Both of you pointed out that one of the things that has changed since certainly the 1994 Human Embryo Panel Report is the prospect of therapeutic benefit through stem cell research that would inevitably involve embryo research as a sort of technique and as I understand the sort of inherent tension between allowing such benefit to -- allowing people with diseases to gain such benefit and society as a whole as well, these get balanced against giving the embryo an appropriate moral respect.

If we accept that argument that there is a balance would it be fair to conclude that the more likely the more sort of short-term prospects those benefits are, the stronger the argument is for allowing this kind of research to proceed at the extent that things are still more speculative and long-term, and that there would be less of a compelling philosophical argument and perhaps less public support for sort of shifting the balance

towards allowing more types of embryo research to proceed with a view towards therapeutic benefit?

DR. FLETCHER: Well, public opinion and political opinion is not the source of ethics but in doing public policy it would be very unwise to misread where public opinion is.

In the United Kingdom the proponents of the Embryo Research Act did not introduce the act into Parliament until Dr. Handesides' first paper about preimplantation embryo diagnosis was published and the opposition to the act was there. Not to the degree in my view that it would be politically in the United States but the benefit of preimplantation genetic diagnosis that he showed by avoiding leukodystrophy and other things in his first study was a factor in the debate.

So -- and it gelled the discussion around concrete benefits so that it was harder to defeat.

So I think that, you know, the Human Genome Project was in -- the persuasion for Congress to fund the Human Genome Project, which I have been back over the legislative history of it, focused as much on the prospect of gene therapy as it did on gene discovery so

here we are today with gene therapy being in significant technical difficulty because of the difficulty of vectors carrying genes to their target when stem cell therapy may be an alternative.

I think Congress voted for the Genome Project funding as much for biological discovery, as much for therapeutic hopes as it did for biological discovery, and this would bring the two together.

The morality of embryo research in my view -- let me start that over again. I think that it is a major step in moral evolution to create embryos for the sake of research or to use embryos in research because of the sole purpose heretofore of making embryos having been for reproduction.

So that to take a society through the moral education and the political ramifications of changing such a deeply imbedded belief that there is one purpose for creating embryos to two purposes for creating embryos -- remember that our President had a lot of trouble with the second purpose. Even though he said he could accept case two, he could not accept four.

The Washington Post published an editorial

excoriating the -- you well remember -- Human Embryo Research Panel for breaching this -- they did not say this but you could read into it -- sacred barrier for the -- our one purpose embryo world.

So it takes a long time to make moral change and the best argument for making moral change in this respect is the great good that could be done for human beings as well as other species by this technology.

So I think that in the process of moral evolution since 1990 in my view the most important thing that has happened has been Dr. Gearhart and Dr. Thompson's reports. I think it immediately changed the moral landscape and I believe that you will see that it will change the tone of the political debate as well in a more benefits oriented direction.

DR. SHAPIRO: Thank you.

Go ahead, Lori.

MS. KNOWLES: I just wanted to say I do not think -- I think in this particular area the fact that there is going to be a time lag actually does not work in favor of pulling back from embryo research. I do not believe that.

I think what is likely to happen is that we will discover additional therapeutic uses for these stem cells that we cannot now envisage. That is not to say that protocol by protocol they should not be reviewed with, you know, strict scrutiny to see whether, in fact, embryos are needed and whether we can limit the number of human embryos but I think, in fact, in this area we will find further applications than perhaps what we can imagine now.

I just also want to point out that it is not necessary to recommend that embryos be created by a particular method, by cell nucleus transfer, you can do also what the British did, which was to say that they thought it would be unwise to absolutely ban this particular technique now, which was not the same thing, so that is something else to keep in mind.

DR. SHAPIRO: Okay. David wanted to speak and then I have just one or two small questions, and then we are going to have to the next item on our agenda.

David?

DR. COX: Well, Ms. Knowles, there was one point that you brought up that I found particularly

interesting that I would like to explore. It is along these same lines in terms of the potential good of therapeutic -- good therapy that could come from doing this for society, potential therapy, but I would be interested in both you and Dr. Fletcher's comments on this.

It was the point that you cannot do therapeutic embryo research without nontherapeutic embryo research. I never heard it stated so clearly and I think so much to the point. It falls under sort of the same issue of if you actually want to have good come out for society then by not allowing nontherapeutic research you preclude it.

So it strikes me that even without the potential for the stem cells it is an extremely powerful argument but yet it is one that either was not brought up or did not win the day so I am very interested in what the past history of that sort of line of thinking has been, if at all, if there has been any.

DR. FLETCHER: I wrote a paper with a pediatric oncologist from UVA, Peter Waldron, for the Embryo Research Panel. It did not get published because

Dr. Hogan thought it was too far ahead of science but it discussed retinoblastoma and genomic imprinting and if we were ever going to do therapy embryonicly for retinoblastoma we had to understand genomic imprinting.

So you would have to recruit to do that nontherapeutic research to understand genomic imprinting. You would have to recruit embryos from couples who had already had a child with retinoblastoma to understand how the imprinting factor worked and what happened in the gene expression that came from that before you ever designed any therapeutic experiments. That is what you are referring to.

She objected to the paper because it was so far ahead of research with mice that she thought it was scientifically unsupportable, that is the argument was unsupportable.

But I do think that there is a strong argument there for recruiting embryos for research when you have a particular -- when you want to understand the pathophysiology of a disease in order to do effective therapy later and to understand gene expression and that in the -- you know, today still and in the future that --

those ideas were what were behind the Embryo Panel's recommendations for those exceptions -- right, Dr. Lo? -- for that exceptionally meritorious research that led to the endorsement of using federal funds to create embryos for research. It is that kind of a scenario.

DR. COX: But yet it did not carry the day at all. In fact, in the --

DR. FLETCHER: No, and there was not even a reference in the report to the paper.

DR. COX: To it?

DR. FLETCHER: Right.

DR. COX: Ms. Knowles, it sounds like from your presentation that it was a consideration in a variety of the debates in these different countries.

MS. KNOWLES: Yes. And actually I think the most interesting is that the European Group on Ethics, which is a European Union body which represents some countries that have adopted this distinction itself, they say that despite the fact that some of these countries have adopted -- some of its member states have adopted this distinction, they consider it unethical and

unworkable. And that is a statement actually from this past year, 1998.

DR. COX: Well, and I would just like to make a personal comment. I think that it is -- as a working scientist, I mean I am as optimistic as the next guy but knowing how many years it is going to be before the breakthrough I think, you know, is anybody's guess. But one thing for sure, if you have actually have to do the embryo work before you can have breakthrough you can be sure you are not going to have a breakthrough if you do not do it.

So I find that just a compelling argument.

DR. SHAPIRO: Can I ask a question, Dr. Fletcher, with respect to your suggestion that we might want to consider recommending relaxing the embryo research ban and this refer (sic) in your mind as you were suggesting that to just making it clearer that case two, for example, is a kind of perfectly plausible area for us to be proceeding in.

DR. FLETCHER: Yes.

DR. SHAPIRO: And just not wanting to rely on the technicality of the legal opinion, is that where you came to that suggestion?

DR. FLETCHER: Yes.

DR. SHAPIRO: Thank you very much.

Let me ask just one other question of either of you. I think it was you, Professor Fletcher, who said that we are sort of operating in two moral universes where the -- here in this country where the moral permissibility of doing some of this work is contested. It is perfectly legal but whether it is eligible for federal funds is yet another matter and we have -- that creates these two different universes. Is there any other country you know of which has quite this kind of separation? And maybe, Lori, asking you or -- I do not know who --

MS. KNOWLES: A separation between public and private funding?

DR. SHAPIRO: Yes. Here you have private nonregulated and then we have public ban so to speak just

to caricature the situation.

MS. KNOWLES: Well, the only -- off the top of my head, the only thing I can think of are that the Canadian system has put out a tri-council -- three councils of report -- research councils -- which has its own lists of prohibitions and limits on embryo research and that is tied to funding, and that of course is government funding so that is only for that particular sector of funding. They are actually in the wake of some of the -- what has happened at the University of Toronto with -- or excuse me, the Sick Children's hospital researchers, they are actually trying to get that expanded to cover the private sector as well.

The second example I can think of is the Australian National Health Medical Research Council, the federal funding body as well, has a draft statement, which is supposed to be finalized this year, which affects funding from that national health council which has its own requirements as well, which are different than, of course, we in the private sector do.

Does that answer your question?

DR. SHAPIRO: Yes. Thank you. Thank you very much. Okay.

Well, thank you, both, very much for the materials that you sent to us and for being here today. It is really extremely helpful to us.

MS. KNOWLES: Thank you.

DR. SHAPIRO: Let's take a short break, that is not a 15-minute break but something like a 10-minute break and then we will resume.

(Whereupon, a brief break was taken from 3:10 p.m. until 3:24 p.m.)

DR. SHAPIRO: I want to make another small change in our agenda to take advantage of the fact that we have a guest here from the FDA who is concerned, as you will understand in a moment, with a lot of the issues we are discussing today and I think it would be just easier both for him and very advantageous for us to hear from him and his views and concerns that exist in this area, and that is Phil Noguchi, who is here from the FDA.

He is Director of Cell Based Therapies or Cell and Gene Based Therapies at the FDA.

I welcome you and thank you especially for your willingness to speak to us without much notice to put it mildly but we are eager to hear what you have to day.

FOOD AND DRUG ADMINISTRATION

PHIL NOGUCHI

DR. NOGUCHI: Dr. Shapiro, I want to thank you very much for this opportunity and I think it is very timely given especially the last portion of this discussion in terms of the status of the embryo and what we would consider source material for therapeutic purposes.

Now in 1993 FDA actually issued a policy statement which said that for cells and tissues which are what we call manipulated such that their biological characteristics are changed it would actually be regulated under both our Biologics and Food, Drug and Cosmetic Act. Since that time we have actually had a

large number of cellular therapies being conducted under investigational status.

One example is a lot of people have heard about the use of a cell line to treat victims of stroke and that perhaps some day some of these pluripotent stem cells might be able to do the same thing but in a more facile fashion. That one has actually been under FDA regulation for about four years now so we are quite aware and quite interested to see the development of this area.

I would like to go back to the issue which was raised before about therapeutic and nontherapeutic research because that really is a good way to tie in some of the federal regulatory oversight that we would have when these exciting therapies are being used in humans and the necessity for really considering the source, origin and characteristics of the embryo.

Now FDA is not going to be speaking on the ethical and moral status of the embryo but we will say such things as if you were going to be using let's say a stem cell that had been differentiated into a neuron, as

one example, certainly some of the questions we would be asking is what is the genetic make up of the source material that you have there? Have you made an analysis of the mutation rate? And we now know that the human being is a relatively poor animal in terms of mutation repair.

And so you would start to get into some of the technicalities which really relate directly to the quality of the embryo. What is the infectious disease status of that? Have you screened the donors, for example, for HIV, et cetera?

Even such trivial things that one might not think about.

At the current time all the embryonic -- human embryonic stem cells of the pluri nature that we have been talking about have been grown on a feeder layer of mouse cells. FDA, as well, has a whole policy and set of regulations for the use of animal cells, tissues and organs in humans or xenotransplantation. While the mouse cells would not obviously go into the human they are

certainly a potential source of infectious disease, aberrant genetic material and so forth, all of which are the types of questions we would be asking any sponsor who wanted to conduct an investigation with these cells.

So although I am not coming to this forum with the same viewpoint as Dr. Fletcher, I think that I echo his concern and his desire for this group as well as other public fora to really not shy away from the deliberations about embryos, how they are made and their ethical and moral status, because we will need to deal with them no matter what we do.

DR. SHAPIRO: Can I ask you a question?

DR. NOGUCHI: Yes.

DR. SHAPIRO: Very quickly. I understand you say for obvious reasons that you are interested in the source, origin, characteristics of the genetic material. In order to fulfill your own responsibilities you would have to know all about that. But I am trying to think whether that has any implication for the source and the way we are using the term here, which I do not think so.

We were using it as to whether -- take Dr. Fletcher's case -- one, two, three -- at least two, three and four. Whether it came from cloning or whether it came from donated gametes or it came from excess embryos would not be your concern. Your concern would just be what its characteristics are. That would have to be source only so you know it has a kind of code or something so you know where -- so you can trace its characteristics is really what you are interested in if I understand it correctly.

DR. NOGUCHI: Yes, that is correct but it does come back to the whole question of federal funding for such research.

DR. SHAPIRO: Yes.

DR. NOGUCHI: As an example, Dr. Fletcher mentioned the question, though, of inadvertent germ line transmission for gene therapy protocols. In fact, the available data and the science there is only slowly being shifted so that it can address those very questions that we are asking about whether or not it could possibly

happen.

Here, I think, we are at a tremendous disadvantage in that there is not the funding available either privately to begin to address those kinds of questions and so I think in the future as these potentially come to clinical trial there is going to be a big gap in the science base and we are going to have a very difficult time in assessing these in terms of safety to the future patients.

DR. SHAPIRO: I understand. Thank you very much.

Are there any questions or comments from anybody here on the panel?

DR. COX: I just had a quick comment. I can understand how many people may not be swayed by logic but they certainly are swayed by practicality and so I appreciate your comments very much.

DR. NOGUCHI: Thank you for the opportunity as well.

DR. SHAPIRO: Excuse me. Just before you

leave, I do not have a question, this is a request. If you have heard the discussion here this afternoon, you are certainly welcome to any documents that we have been producing, but if there is any materials the FDA has, members of the FDA staff have that are working on this and related issues, it would be very helpful for us to have an opportunity to review those. It would be very instructional for us.

DR. NOGUCHI: Yes.

DR. SHAPIRO: So if there are anything if you could send it to our staff that will be just great.

DR. NOGUCHI: I will be happy to do that. Thank you.

DR. SHAPIRO: Thank you very much.

All right. We will continue on our agenda now and I want to turn to the document called NBAC Staff Draft, Points to Consider in Evaluating Research Involving Human Stem Cells, and have us review that document again as a way of helping ourselves understand just how we might want to approach this topic.

So let me turn to Eric.

I think you all know Leroy Walters who is sitting right up here.

Thank you for joining us.

He and Eric are working together on generating this document and I have asked him to join in our discussion.

Eric?

DISCUSSION OF DRAFT "POINTS TO CONSIDER"

DR. MESLIN: Just as a point of introduction, the draft document that you have in your hand and in the briefing books is a first attempt to produce what could be a product for the commission's recommendation or use later on. It is a very early document that both Dr. Walters and Professor Childress had some input in as well as other members of staff.

As we noted on the cover memo, it really is an opportunity for the commission to use this to reflect on a number of issues and they may choose at their convenience down the road to adopt it or a version of it

in the report itself.

Our goal then is to have a discussion about the document. It is not necessary to come to any recommended conclusions about it per se but I would certainly leave that up to your discretion.

I thought I would turn it over to Dr. Walters, who is a consultant to the commission. He is also the Director of the Kennedy Institute of Ethics at Georgetown University.

Welcome to the commission and thanks for your input.

DR. WALTERS: Thank you, Eric.

This form of document actually goes back about 15 years. I think the Food and Drug Administration and NIH came to this form about the same time and, in fact, I feel a bit nostalgic this afternoon because in the fall of 1984 Jim Childress and Alex Capron and I had the privilege of sitting around the same table and starting to work on points to consider for human gene therapy so it is interesting to be coming back to points

to consider about a new type of biomedical research.

Clearly the draft that you have before you deals with laboratory research and preclinical research. If there is to be anything said about the recipients of human embryonic stem cells that will require additional questions and additional points to what you have before you.

I think one of the most important questions that we would have to place before you is whether we have left out anything important. We can do refinements and revisions within the questions that are there but if we have missed something that really should be there we really would like to hear that from all of you.

DISCUSSION WITH COMMISSIONERS

DR. MESLIN: Alex?

PROFESSOR CAPRON: I am afraid this is not going to be entirely responsive. I want to take half a step back and say how I was understanding this document in the context of our report.

I am glad that Leroy mentioned the process of

the RAC or actually what was then the working group on human gene therapy.

If we follow the direction which was discussed at our previous meetings, and which I think has been supported by what we heard today from Professor Fletcher and Ms. Knowles, we would be thinking about certain areas of pluripotent stem cell research and the creation of the cell lines, which in our view would be legitimate now and to the extent that barriers now exist we would be urging that they be taken down as to that area of research.

We would also be saying that there are certain types of methods of getting these cell lines which in the present context we do not believe ought to be undertaken although we do not think they have to be prohibited. And as to those, rather than just a shrug and a statement where there are a lot of issues out there, the points to consider it seems to me offers an example of the kinds of considerations that an ongoing review body would take into account and the questions

they would ask and expect answers to from investigators and IRB's before such research could be funded.

That being the case it seems to me this is not -- this is a little bit different than the recommendations we made to HHS or OPRR or whatever where we are almost wanting -- we are not quite writing the regulation but we are basically saying there ought to be an interpretation that says X or there ought to be a regulation that covers this.

Here the exercise is simply saying that this is not just a lot of hot air saying, "Oh, there are issues out there that deserve consideration. Someone ought to think about them." We are being quite concrete but I would expect that that body would take as its first order of business really drawing up in the context then existing all the considerations that have come to light and its own process a set of points to consider which would then be published in the Federal Register under its name for comment and go through a process of revision and so forth.

So I do not think we have to nail down -- I mean, I agree with Leroy. If there is something missing here we ought to address it. I do not think we have to nail down the language of this. It is simply a demonstration that we are not just talking through our hat. We are not just suggesting we -- there are some issues that somebody else should look at. Who knows what they are? Go away. Do not bother us. We are being quite specific about the process.

DR. SHAPIRO: Let me make a comment exactly about that. I quite agree with the last part of your comment that the intent is not for us to come to some document which we have to nail down all the language exactly. It is to serve as a reminder to ourselves whether there are issues here which might impact the focus of what we have to say or not. Just to remind ourselves of what these issues are as they might come up and just what place it will have in the report is not clear to me at this time.

But I quite agree that we are not looking at

this to try to pin down the exact language, whether we want to say it quite this way or quite that way.

But if there are issues that are missing from here that that will be important because it might inform how we think about own set of responsibilities.

MR. CAPRON: There is one area which in italics at the beginning -- at the end of the first paragraph it is stated that we are not addressing -- and I think it would make just as much sense to put it in here -- and Leroy alluded to it -- and that is the issues that will arise particularly vis-a-vis the nuclear transplant to -- and the creation and effect of cloned stem cells for therapeutic purposes.

And the issues are probably not that exceptional compared to other transitions from the lab to the bed side but I think there is no reason to exclude them, it seems to me, because this is -- what we have just heard from Fletcher and others is that the very thing that makes category three a little bit different than category four is the potential for creating stem and

tissue therapies which are specific to the individual which necessarily requires nuclear transfer.

Now it may be that one of the questions that we would want to see asked there is are there nonembryonic sources of stem cells that can be used? And we know that there are other avenues of research going on now to try to roll back the clock and move stem cells back up the hierarchy but that is exactly the kind of issue that we are not in the position to deal with but that we ought to identify, Mr. Chairman, when you say the things that we should think about but it would also very likely be on the points to consider of any eventual body.

So I would think that would come out here and be helpful to explaining why categories three and four are different.

DR. SHAPIRO: Carol?

DR. GREIDER: Yes. I just wanted to add to what Alex just said. One of the things that I thought -- if we are talking about what might be missing under 1(A), sources of the human stem cells, as Alex pointed out,

nuclear transfer of cells, but one of the things that came up in one of our previous commission meetings -- I do not remember whether it was Dr. Gearhart or Dr. Thompson that brought this up -- is the possibility of doing nuclear transfer into existing stem cells. So currently existing stem cells that have been derived, doing nuclear transfer into those is one area that is being pursued actively and that might be a category on here.

DR. SHAPIRO: Excuse me. I need some help on this last category. I do not remember the discussion. Could you just remind me of that?

DR. GREIDER: We were talking about stem cells which have been derived already by Gearhart and Thompson.

DR. SHAPIRO: Right.

DR. GREIDER: And the possibility of taking those cells, taking out a nucleus and putting a nucleus into those cells and then deriving autologous transplant types of tissues.

DR. SHAPIRO: Yes. Right. Thank you very much. I just did not understand. I remember that now.

Steve and Larry?

DR. HOLTZMAN: A question of clarification of when -- if I am researcher when I should be thinking about these things and maybe you answered this and I was reading it, Alex, to try to get the answer.

Imagine you are in a world a year from now and human stem cells are available from your various research suppliers. This world is going to be coming, I predict, okay. So is one going to go through this whole apparatus and are we envisaging that there is a set of approvals for basic research use of those cells where there is no proposition in play of these things going back into a person?

PROFESSOR CAPRON: I understood the primary focus of these considerations to be around the creation of stem cell lines.

MR. HOLTZMAN: Okay. Because it does not say that. That is what --

(Simultaneous discussion.)

MR. HOLTZMAN: Please, go ahead.

PROFESSOR CAPRON: Is that not --

(Simultaneous discussion.)

MR. HOLTZMAN: What?

PROFESSOR CAPRON: And, therefore, to the extent that it is not clear that is the focus.

MR. HOLTZMAN: Okay. Because -- okay. So the focus is the creation of stem cells as opposed to -- so really the focus of this is embryo research of a certain kind if you will.

You know, very clearly that -- however one feels about an embryo -- all right -- one can feel that stem cells do not have those qualities that make much that is in play with embryos in play and so are we inadvertently or whatever potentially saying, no, we think that there should be a RAC-like body or the kinds of points to consider in play for every experiment involving the use of stem cells? If the answer is no I think we have to make that very clear.

DR. WALTERS: The only case in which there is not an embryo near the time of the creation of the stem cells is when fetal tissue is used, when germ cells from fetal tissue are used. There had been an embryo earlier that developed into a fetus --

MR. HOLTZMAN: I completely recognize that but we will be in a world in which basically we will be able to order stem cells. Okay. And the question is what are expecting investigators at that time in terms -- are we saying things like if you can do that line of experimentation with mouse stem cells that is preferable to using human stem cells. I do not think so. Or are we?

DR. MESLIN: Do you want to make --

MR. HOLTZMAN: I am asking --

DR. MESLIN: I was just going to say do you want to propose that this be -- would you propose that that is an addition to the preambular justification or one of the categories, either (A) or (C), include a kind of sentence that makes it clear what the purpose of those

considerations are?

MR. HOLTZMAN: I am just trying to get clarity here.

DR. MESLIN: It is a draft.

MR. HOLTZMAN: Okay.

DR. MESLIN: Which is where we are at this point so if you would like -- if you want to help refine the utility of it that is a great way to keep going.

DR. CASSELL: It comes under (B), doesn't it?

MR. HOLTZMAN: Well, I am just -- okay. If you look in number one several of the issues arise when designing research involving human stem cells.

(Simultaneous discussion.)

MR. HOLTZMAN: Right. And then with (C), for example. All right. So I will give a personal opinion. All right. If they are already out there and I am ordering them from a commercial supplier I do not see why there is any ethical imperative that says there is something special about human stem cells such that I should be doing animal experimentation first any more

than I feel an imperative to be using a mouse cell line as opposed to a human cancer cell line which has been immortalized. Okay.

DR. SHAPIRO: David, and then Larry?

DR. COX: I think this is an extremely important point to clarify. The way it is written it is the creation and use. What Dr. Varmus has said is that we will review the use, right, not just the creation but when he spoke here he said the use.

Now we need to decide from an ethical point of view if these cells because of their source deserve special ethical consideration as opposed to other cells because all cells -- all human cells derive from a human being. It is not always from a live human being but that is one of the key points that came up from our previous testimony.

The distinction is whether the cells are coming from a live human being and whether you are actually hurting, you know -- killing that human being to get them or whether the cells come from a human being who

is deceased.

I really think that right now there is tons of scientific research done on human cells from individuals who are alive and from individuals who are deceased. But we do not have specialized ways of analyzing those research proposals based on what the status of the human being that the cells came from.

So it may be a point we should debate but there is -- and I actually have, you know, views one way on this point but we should certainly be very clear about it and if we start with our outline with it not being clear then I think we as a commission run the risk of having problems later on.

DR. SHAPIRO: Eric?

DR. CASSELL: Just to follow-up --

DR. SHAPIRO: Larry, I am sorry.

DR. CASSELL: -- could you make a case for there being -- having special moral status, the fact that there are cells that -- you know, they are just human cells. They were brought down from some biological

supply house. What gives them their special moral status?

DR. MESLIN: To whom?

DR. SHAPIRO: Anybody who wants to answer. Larry will be next. The question that Eric is asking is do human stem cells have any moral status that is different or a standing that is different from any other human cell?

DR. CASSELL: That is what you were asking, wasn't it, David?

DR. COX: That is what I am asking.

DR. CASSELL: That is the essential question. What gives them their moral standing?

DR. COX: I am actually -- I do not know of an argument that they do and if somebody has such an argument or feels that way I would really like to hear about it sooner than later.

DR. SHAPIRO: Leroy and then Carol, and then Larry.

DR. WALTERS: If we think ahead to the time

when human embryonic stem cells may be used for therapeutic purposes I think that there will be some people for whom the question of where these cells came from might be morally relevant. So at that stage some people might object to -- I mean, they might have an across the board objection --

DR. CASSELL: Like a Jehovah's witness and blood.

DR. WALTERS: -- to receiving human embryonic stem cells or they might say certain settings would be all right to me but other settings would not be all right. But that is not at the level of preclinical research.

DR. SHAPIRO: Larry first and then Carol.

DR. MIIKE: My mind has steadily been falling back so I think I am about four hours behind so I am totally confused about what you people are talking about in terms of the use of this. Are we talking about this as giving us guidance for the rest of the time that we are going to be putting this study together or are we

talking about including this specifically as a very detailed specific document in our report?

DR. SHAPIRO: The latter is not the case right now.

DR. MIIKE: But the discussion sounds to me that that is what is revolving around.

DR. SHAPIRO: Well, I do not anticipate at the current time that this is going to appear in this way or in some carefully altered way in the report. It could if it is useful but that was not its intent from my perspective. The intent from my view was to help us highlight the issues that are going to be before some people that may impact -- so it, therefore, may impact what we ourselves want. See, this is not a draft outline of the report.

DR. MIIKE: No, no, no. I am not looking at it as a draft outline of the report but I am now confused about whether -- because of the discussion I have been hearing is that this is sort of guidance for researchers and experiments in this particular area so I am totally

confused. Is this just --

DR. _____: Some of us do not agree.

DR. MIIKE: -- is this just sort of a reminder to let us know about certain things that we should be aware of by the June date which we address or what?

DR. SHAPIRO: Carol was very anxious to say something.

DR. GREIDER: Well, I am actually going to ask Eric a question because I recall at our meeting the last time we were in D.C. when Harold Varmus came and talked to us, if I am not correct, that he actually asked us to specifically discuss the issue of use of ES cells. They had already decided about whether or not there was federal funding allowable to derive them or not but then the question is how can these be used in a reasonable manner.

Can anyone else on staff --

DR. _____: Yes, that is correct.

DR. GREIDER: I believe that we were asked

specifically to address that issue about the use of these cells. Can you comment on that?

DR. MESLIN: Yes, I can confirm that Dr. Varmus made a request to NBAC. This document is not intended to be a direct response, here is our response to your request, we are preparing a report on stem cell research. The suggestion for having a document like a points to consider to try and get back to Larry's question is perhaps in the fullness of time to make it available as -- or something like this.

It does not have to be this specific format. This is a convenient format that has been used by the RAC and other bodies as advice to those who are designing, conducting and reviewing research. It collects many but perhaps not all of the ethical and legal and social issues that our report might want to address but like other points to consider documents those do not either. Those are designed for use by people.

We have not decided because this is really a preliminary draft as to whether the principle consumers

of this document would be NIH, HHS, anyone who conducts stem cell research, the professional societies or investigators.

You may find that it is a very helpful document and with appropriate modification we might recommend it. We might not. We went out of our way to not place it on your agenda as something to agree to or reject. If you think it is useful, great.

So many of the questions that you are asking we are not going to answer. So if it serves as --

DR. MIIKE: So there is a real --

DR. MESLIN: -- device --

DR. MIIKE: -- possibility that this document will say, "Here, this is the NBAC's recommendation --"

DR. MESLIN: That is your decision to make.

DR. CASSELL: Well, it is mirroring what Alex said before and it is just, you know, the peaceful uses of atomic energy, the bomb went off, now the stuff is here, you have to have some viewpoint about how it is going to be used. What is the status of these cells

which helps gives us that -- which is true -- practical understanding that something is coming out of this. This is going to move on.

And that instead of saying staying dead in the water about the same question over and over again, that this sort of lays an outside parameter to the issues that we want to answer and in that way, I gather from what Lori said, is a distinctly different move from what we hear about European and Canadian.

DR. SHAPIRO: Bernie?

DR. LO: I think this is serving a useful purpose for getting us to think about things that we otherwise would not be thinking about.

It seems to me there are some issues about the scope of the report that we need to sort of think through in terms of how much we are going to do. I was impressed as I heard John Fletcher and Lori Knowles' talk that given where we are today and where we would like to be in June it may be, it seems to me, a big step to say that, in John Fletcher's terms, categories one and two

are morally permissible for the following reasons. That would be a profound shift in U.S. public policy on a very vexing issue.

If we want to go beyond that it seems to me this is a next step. So if you agree that there are uses of these cells that are permissible for federal funding the next question is, well, what are the parameters, the guidelines, the criteria for acceptable uses, and then see if this comes into play.

If you are going to do the research how do you judge whether that research is acceptable?

PROFESSOR CAPRON: It is not mostly --

DR. LO: Well, but if you are designing a -- designing or reviewing studies -- okay. So that assumes that -- I mean, either we are going to say this is going to apply to nonfederally funded, privately funded research, we want this to go through this kind of review, thoughtful review, or we are going to say if the Federal Government is going to be funding it we want some criteria by which the review will be carried out to

ensure it is ethically appropriate and these are the kinds of considerations and points that you want to consider.

I would just like to point out that is biting off a lot and I have been through this once on a commission that tried to do a lot and got nailed for the last step. I am just raising a point. Should we try and get a couple of baby steps that actually will be quite a different shift in policy or do we say one and two are obvious to us, let's just make the argument quickly and let's go on to steps three, four, five and six?

The advantage of that is, if everyone agrees, we have gone a very, very long way. It seems to me the risk -- the down side risk is that if people do not agree they are not going to buy one and two and say we are only disagreeing with three, four, five and six. So that is one point.

The scope of how much we are going to try and do here. We -- you know, it is an important point that is -- it seems to me a tactical point that has to do with

our best guess as to where we can make a contribution.

The second very specific point about are there arguments that stem cells have some sort of special moral status that is different from cells of somatic cells I think is something we should think about because it is going to be one of the issues that is going to be thrown up by people who disagree with there being any acceptable federal funding for this type of research.

As best as I could tell culling through our briefing book the argument I could draw out from some of the documents submitted was that we really cannot tell if these are totipotent or pluripotent and, in fact -- well, this is, you know, from one of the documents. And, therefore, it would behoove us to be morally sensitive and act as if they are, in fact, totipotent because they even quoted Harold Varmus saying it would be unethical to try and find out if they were totipotent rather than just pluripotent because that would involve implantation.

It seems to me that was the line of argument that I could sort of look and find when I looked for it

because I think this argument of special moral status of these cells is going to come up and it seems to me will be a point of argument for those who do not want to see any federal funding for this.

I think we should understand very carefully the types of arguments that will be used by opponents of any federal funding of this. And I think just as the arguments in favor of federal funding have shifted, it seems to me arguments against federal funding are not going to be just the exact same argument that we have seen before. To the extent that there are points that one would want to make in response to those arguments and concerns we ought to try and do that.

DR. SHAPIRO: Trish?

DR. BACKLAR: It seemed to me that Dr. Fletcher was making a point that was relevant to what you just said, Bernie, in terms of -- am I wrong? I thought that he mentioned something that Bridget Hogan said to him in trying to see the difference between case number one and case number two between the research that would

go on with fetal tissue and the research that would go on with stem cells from embryonic sources -- from embryonic stem cells.

And that that was the whole point of looking at this in a rather simpler fashion because you cannot get the answer until you have done that research, which is sort of also what David was saying, is that if you are going to have to do the research to find out if it is really going to be worthwhile and you know what you have got. Sort of this is becoming very secular.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, just again, I -- well, Bernie -- I think Bernie has a point about biting off a lot. On the other hand, if part of the emphasis in the original report of the reason for moving ahead was stem cell research in cases one and two is the applications then, in fact, we ought to make it clear that we are aware of what it means to go into the application phase and that we are sensitive to the issues there, also, but I do believe with you that the moral status of the cell

has to be determined.

DR. SHAPIRO: David, and Steve, and Alex, and Carol.

DR. COX: To me, I mean the -- again I just look at this in a very sort of simple minded way. It is clear from Dr. Shalala's letter and from Dr. Varmus' testimony that from a legal point of view use of these cells when they are derived from fetal material under existing statutes -- it is not a question. It is legal. But whether it is legal or not there are a lot of people pretty pissed off about it. And if we do not talk about this and basically make some statement about whether we think it is okay, whether it is legal or not from an ethical point of view, then we are ducking the issue.

Now it may take us some -- a little bit of time. I do not think it has to take all of our time to deal with that but I do think this is a critical issue because we will not be able to proceed further if we do not deal with it.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: My understanding of the NIH's legal interpretation is regardless of the source federal sponsorship of research using extant stem cells is allowed. All right. I understood Dr. Varmus to say he did not expect any kind of RAC-like mechanism or points to consider to be invoked in judging research proposals to the NIH for research using stem cells. If anything, it was purely administrative. That was my understanding in talking to Harold. Okay.

Then the next step, however, is if we are going to on from there and then also recommend that the feds also sponsor the creation of stem cells, hence certain forms of embryo research, then pulling into play an apparatus like this points to consider starts to make more sense to me because that is politically a very sensitive area.

DR. SHAPIRO: If I could just make a comment on that. I think you have accurately reflected what Harold Varmus said. However, our discussions at that time -- our minds may be in a different place today --

was that we were skeptical about the kind of oversight that he was proposing. That it sounded to us -- we did not take votes or anything like that but the nature of the discussion was such that it sounded to us as sort of an inadequate oversight mechanism even for the use of extant human embryonic cells.

MR. HOLTZMAN: Okay.

DR. SHAPIRO: But you are quite right about what he said.

MR. HOLTZMAN: So then to state my view, all right, when we come forward with a recommendation that it is okay and we support federal sponsorship of research using extant cells, and I envisage my world where they are available from BRL in the catalogue, I would not be supportive of requiring a RAC-like kind of review of every research proposal involving the use of said cells.

DR. SHAPIRO: Let me see that list. Alex?

PROFESSOR CAPRON: Carol had her hand up longer.

DR. SHAPIRO: I am sorry. I did not see you,

Carol.

DR. GREIDER: This will be relatively brief. I just -- I hear several different conversations going on around the table and so I just wanted to make a proposal as a way to think about this. I think that we have kind of gotten off of the topic of the points to consider here and we are really talking a little bit more about the scope of our report and I thought it was a very nice presentation by John Fletcher earlier talking about case one and case two, and how far are we going to go. So we might consider this issue that just came out about the use of ES cells and David and Steve has brought up as a point one-half.

You start off with a point one-half as the issue about the use of the stem cells and then you go to point one and two, which have to do with their derivation, and just as a way to think about the scope of the report, and three and four would then come later.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: It seems to me that it has

-- it is very useful to employ the RAC as an example as long as we realize that the experience there does not amount to a rigid template. As Steve commented a moment ago, it is on all fours. The issues that led to the creation of the RAC and then led to the creation of the Human Gene Therapy working group and eventually that taking over the work of the RAC were issues initially of physical risk to people and the questions were more technical.

It is important to recognize that the first impulse of the then director of NIH, Don Frederickson, was to have an internal working group worry about that and he saw the value, as issues even of risk are issues of valuation of what risks are worth taking and why, of broadening that and there was an evolution in the RAC as to its membership.

There also was an evolution in the RAC as to which issues had to be considered and which ones could be considered resolved well enough that you could move on to something else and have them handled by per se rules.

Right now there are some issues that are very sensitive for Dr. Varmus and it seems to me that the reason he is talking about having this administrative body is that he faces two sets of critics, some that do not believe as the letter indicates from the senators and congressmen, that it is ever permissible under their statute that they passed to pay for uses if you cannot pay for the creation.

There is no way he can fully answer them and they are going to say you are hanging us on a legal technicality but there may be others who would be reassured -- this is my reading of what he is doing -- by his statement, "We are going to stay on top of this. This is not going to sort of get out of hand where we are funding "research" and right in the same lab they are doing the creation. You know, we are going to monitor this and we are going to make sure that whatever rules we come up with are well administered."

It may be that in time -- I know I am talking about a very long time -- that Dr. Varmus would see that

the reassurance provided by that would be greater if it were a body that were more public and were more diverse. And I think in our report we could counsel him by history as to the advantage of that.

We know that Dr. Varmus is not a fan of the RAC at least as the RAC existed when he took over so those analogies are less persuasive.

I think, in distinction to what you said, Mr. Chairman, that this document ought to be in some form in our report not as something we are saying that others have to follow but as the example of the kinds of considerations that will arise. (A) they are considerations for cases one and two as the issues arise if our arguments would seem to be our consensus given the document that is in here; that case two ought to move from the prohibited to the permissible in terms of funding and the creation of these embryonic stem cell lines. Then you are going to need mechanisms for making sure that that works and they are set forth here.

And the body would then look at proposals

from someone wanting to be funded and ask relevant questions.

In the short run it would make sense for that body to also ask some of the use questions. That does not mean that everybody doing private research using these stem cells that they bought out of a catalogue has to come before this body.

MR. HOLTZMAN: But every federally funded does --

PROFESSION CAPRON: But maybe every federally funded until you get to the point where the use concerns have reduced and, frankly, I think that if Congress, if a majority of Congress, were to accept the kind of recommendation that we seem to tending to as to case two and modify the statutes to permit funding of the creation of embryonic stem cell lines from excess embryos, if they got to that point then the use issue disappears there. I mean, use is only an issue if it were impermissible to create them in the first place.

MR. HOLTZMAN: But what is the use concern

this group is monitoring, Alex?

PROFESSOR CAPRON: Well, then I think the use concern may be more a matter of volume and sort of is the scientific community behaving in a fashion which seems to recognize that although the cell once derived is like other cells, the process of deriving that cell involves a step which ought not to be as lightly engaged in as taking tissue from a dead body or from excised tissue and from a human being that does not involve the destruction of that human being.

That if cell lines that we now have from Helen Lane were only derive-able from first killing her to get those cells I think we would still say, "Well, we got Helen Lane but we do not want a whole lot of other cell lines like that." I mean, it would be problematic.

And it might be that that -- that one of the issues would be is are the kinds of concerns about using animals when possible and so forth, which are different

than using cats versus using mice -- Steve, I respectfully, disagree with you on that -- that there is still something about these cells at least in the near future where we want to be careful.

Finally, the body would exist to look at proposals in categories three and four and offer advice to the director and eventually to the Congress as to whether the science has matured to a point where the tangible benefits to be derived are such that it makes sense to also modify the barriers that exist.

In our report, to answer Bernie's concerns, we would not be saying that those barriers as to three and four should be modified now. Taking that step would be comparable, to seems to me, to the embryo research panel's problem.

I think we are in a situation where people have recognized as to category two a strong justification that they are not ready to recognize as to categories three and four but I say again the value of a document like this is that we would not just be saying that there

are issues out there for somebody to consider. We would be quite concretely illustrating the kinds of things they would do recognizing that the final document would be in their hands and not in our hands.

DR. SHAPIRO: Okay. Just a second. Larry, you will be next. Leroy wants to say something.

DR. WALTERS: Following up on what Alex just said and going back to what Steve said, maybe the one question that you would ask about laboratory use of embryonic stem cells is would there be an alternative to using human embryonic stem cells to achieve the same results or the -- to achieve the same knowledge in an experiment of this type.

So maybe 1(C) is really the principle question given the very complicated origin of embryonic stem cells.

MR. HOLTZMAN: And all I am saying is that the commission will, therefore, have to debate and come to a consensus on whether there is a sufficient motivating moral force to even asking that question.

DR. SHAPIRO: That is obviously a key issue. I quite agree with that.

Larry?

DR. MIIKE: It is my unending frustration over the past three years that we never reach closure on things and we move on to others.

To me the meetings that we have had on this subject there has been, from what I can see, at least a majority agreement that one and two permissible, that what was brought in anew today was that let's not duck the issue about use of embryos and address that directly as some permissible for embryo research and not just the products of the embryo research.

If we can reach agreement on something on those two areas, and I think we are all saying that for our own various reasons that somatic cell nuclear transfer is not an area that we feel comfortable about supporting at this time.

If we can reach agreement on whatever we are going to conclude in the narrative, which I would like to

do first, then I can see this as saying, in the terms of Lori Knowles, but there are limitations and oversight issues that we have to have in this area. Then I can see that. But to go and jump around and around and around, never reaching any conclusions is very frustrating so I would like to see -- although have a parallel process -- I would like to see some sequential decisions made in this area right now.

DR. SHAPIRO: We will get to that shortly. Bernie?

DR. LO: I am afraid I am going to get Larry upset since I was going to talk about a --

(Laughter.)

DR. SHAPIRO: He can manage. Do not worry.

(Laughter.)

DR. SHAPIRO: He can manage.

DR. _____: Take a pill, Larry.

(Laughter.)

DR. LO: Mindful that this is -- I do not what time of the day it is for you, Larry.

DR. MIIKE: I was supposed to be waking up.

DR. LO: Okay.

(Laughter.)

DR. LO: I think that is a fair summary of where we -- I mean, I think there is -- we are working towards some shared understanding of what John Fletcher called cases one and two. It seemed to me what Carol did was raise a case zero or case one-half and Steve addressed this as well, which is not the creation of a stem cell line but the use of a stem cell line that is already in existence.

It seems to me that there are a set of issues there that I would like us to really sort of dissect out very carefully rather than just saying, "Oh, isn't it obvious that is not problematic," because I think that -- again my concern is that we can make a couple of very important concrete steps but small steps. Let's do that very carefully.

I would suggest that we at some point, not necessarily now, Larry, address Carol's issue of one-half

square on and Steve's issue as well and say, "Is there a persuasive argument for saying this type of research should or should not be given more scrutiny than any other type of research that involves human tissue." What are the arguments for that and against that?

I would just say that I think they are primarily prudential perception arguments that this is something new, the public has not seen this before the federal funding, they do not understand it, they are confused as to whether -- you know, we have a very clear distinction between use of an extant line from Steve's catalogue versus creating one. I am not sure the public understands that.

It seems to me that a lot of this is just when things are new and unknown and kind of spooky, it evokes the worst fears in people. I think part of what might be useful to do is to say even if we do not think there are purely logical reasons to subject this type of research to any special scrutiny we understand that some people have very strong concerns. A lot of the public is

not as opposed on deep seated sort of revulsion but they just have concerns about is this going to get out of hand. What are we getting into? Are we are going too fast too soon? Are we going to lose control?

It seems to me that is where some degree of additional oversight can be useful. How that oversight is done, by what mechanism and how detailed, I think are a lot of points but I think that if we really want to -- you know, Shalala's letter said, "I want to assure you we are going to do everything we can to make sure this is in accord with of ethical as well as legal standards," whatever.

If we really are going to give that some meat what is that going to mean and is it going to mean, frankly, for scientists getting federal funding -- and it is a real issue if you do it with private funding or whether -- you may just choose to do that because it is simpler. But it seems to me the price you may have to pay for federal funding is to go a little bit slower, have a little bit extra scrutiny at the beginning to gain

the public trust that this is not something that is going to get out of hand.

I -- you know, I think that you can try and say, well, just go for it without extra oversight but I think that there is an argument to be made that we do it a little bit slowly now and then in two years people say, "Oh, you know, all that special scrutiny they did, it never turned out to be anything worth looking at. The scientists were really right on target and really addressed the issues and, you know, maybe in retrospect we should not have been so careful." I would rather they say that than look back and say, "My God, how could we have funded that thing in 1999 that now in year 2002 looks horrendous."

PROFESSOR CAPRON: That is exactly what happened with the RAC.

DR. SHAPIRO: Let me make -- I would like to make some points and a suggestion about proceeding from here.

I, for one, found these points to consider

extremely useful. I am not sure just what role they will have in the final report and whether these will be detailed instructions to someone or not but I found it very useful to help catalogue in my own mind the kinds of issues I would want to think about as I thought together with our more global or mega proposals.

It helped me understand in some detail what it was that I was really thinking and trying to think through. And in that sense I found them extremely useful and I think we ought to come back to them at some time. I am not sure what kind of role they would have. They certainly will not have a role, I do not think, of giving anyone some details instructions exactly what they are going to do when faced with some particular decision or not.

But let me just suggest rather than focusing on that for a moment that we turn back to the document, which is the first one at tab four, which is a summary done by Eric and Kathi regarding what we had talked through at the Princeton meeting.

And, in particular, this is -- it is a summary and then there is a summary of the summary, which is at the end, which is on chapter -- not chapter, page five of that document, which looks at things we would like to do some time today or tomorrow.

The first of those is to review a summary of commissioner discussions in the February meeting and either confirm its accuracy, change it, comment on it, and so on and so forth.

So perhaps we could go to that now and we could -- let's look at the summary of that now. That is the first of those items.

We will then get to -- we will slowly get to the other items such as the one Bernie just raised with respect to extant cell lines, protocol case zero or case one-half, or whatever you want to think about.

DR. GREIDER: 0.5.

DR. SHAPIRO: 0.5 Carol suggested.

But I would -- let's start with just your own assessment of the summary of our meeting of last time

because it is really quite important that -- some of you have referred to it already.

Larry?

STATUS REPORT AND SUMMATION OF THE PREVIOUS DISCUSSION

DR. MIIKE: Just a minor point and it is on that labeling issue right above "ongoing staff and commission --"

PROFESSOR CAPRON: I cannot hear you.

DR. MIIKE: It is that issue about we should have a pedigree or a label. I heard an additional reason for that out of the FDA person. But our reasoning was not really based on the science but an assurance that since we are not saying this wide open we needed some kind of tracking system to making sure that there were appropriate sources as we would have recommended.

DR. SHAPIRO: Well, let's -- I take it from the silence here that there -- I am sorry, Alex.

PROFESSOR CAPRON: Well, on the first point there is a suggestion in the next to the last sentence, "The applicability of existing fetal tissue

transplantation regulations was questioned." As I -- if I were the source of that question it was that what we are doing is not -- what the researchers are doing is not fetal tissue transplantation. So the framework, the set of questions are all the right questions but I believe that our recommendations should be that the statute be modified to recognize transplantation or derivation of stem cell lines to be explicit that the same considerations apply and that no one raises that later.

DR. SHAPIRO: I very much agree with that point because I do not want us to get into a discussion regarding just what the law says and whether it applies or not. Some people have raised that issue and I do not think any of us had that in mind at the time so I quite agree with that. But let's just focus for a moment just to make sure that we all understand where we are.

It is the Fletcher's case one, if you like, is the first thing that we are talking about. I am going to presume that we are not for the moment going to rely on any particular legal interpretation but try to just

think through the issue. It may or may not turn out to be consistent with some existing legislation. That is another -- legislation laws of one kind or another but that is another matter.

But we were, I think those of us who were at the Princeton meeting, quite comfortable with what has been characterized as case one. I do not want to use quite comfortable. We were satisfied with case one.

And is anybody who wants to discuss that further because, if not, we will just assume that is the case and go on?

All right. Let's now discuss case two, which is the so-called excess embryo case and the derivation of cells from excess embryos, which as you recall was Dr. Thompson's experiment, at least as I recall.

Bernie?

DR. LO: With this category of so-called excess embryos or embryos that were created for the -- with the -- for the intention of assisted reproduction and then subsequently were -- it was decided by the

progenitors not to use them for that purpose, when the cells are actually sitting in the freezer and the woman or couple are saying, "What should we do with them? Should we continue to freeze them? Should we thaw them? Should we donate them for research? Should we donate them to another couple? Then it is clear they are excess.

My concerns are much, much further. The number of embryos that you create in an IVF setting is very variable. And there are some IVF programs that are quite aggressive in trying to harvest as many oocytes per cycle and there are good reasons to say to the woman, "You do not want to go through this cycle more times than you have to. If we can get 12 let's go for 12. We can freeze them and see about them later."

Given the very, very strong influence that the IVF physician has on the woman or couple going through an ART program -- and the 1994 commission commented on this to a great extent and I must say in my own experience with investigating the UC Irvine and the

UC system-wide ART program confirms this that it is one of those situations where the woman or couple are very dependent on the physician and suggestions as to how many oocytes will be harvested and fertilized, even if made in the context of therapy, it seems to me that is just where the doctor as physician and doctor as research team member in the role of procuring oocytes and embryos for research start to get very mixed up.

So I think that my concern is that it is a very neat distinction at the tail end. I would like to give -- have us give some attention to the pressures that occur much, much earlier on in the ART process as to how many embryos get created.

DR. SHAPIRO: Bernie, just to make sure I understand your comment. There is in the case of fetal tissue a whole set of regulations that apply in an attempt to resolve some of that -- some analogous problems, not the same problem at all but it has got certain analogies. And your concern is that if we were to recommend going ahead with case number two that it

incorporate also some appropriate number of -- I do not know -- constraints, structures --

DR. LO: Well, it would be nice to create some sort of protections. My concern is that given the clinical situation where the physician who is the ART physician also plays a very important role in the research team it may be harder to separate those roles than it is in the abortion context.

DR. SHAPIRO: But the conclusion then is that we should nevertheless try the best we can or we should --

DR. LO: We should try the best we can. I think we should be at least honest with ourselves that it is going to be a little tougher and try and get whatever help we can for crafting reasonable guidelines that are going to work.

One of my other concerns is there is no real standard of practice here as to how many oocytes per cycle to harvest is a reasonable amount. There is just really no standard of practice you can point to do a

physician in good conscience can say, "Look, my practice is to harvest 10 or 12 for the following reason." And it seems to me it is very hard to sort out is it really for the benefit of the woman and couple or is it because that way we always -- we are more likely to have two or three left over at the end of the day to use for a whole number of purposes, which may be helping another infertile couple.

DR. SHAPIRO: Also, as I understand it, you can correct me here, Bernie, there really is not quite a standard of practice either on how many get implanted.

DR. LO: Right.

DR. SHAPIRO: The physicians I have talked to have quite different views of this matter as to what is safe and appropriate and so on.

Alex?

PROFESSOR CAPRON: I agree that Bernie has stated the issue nicely. We could think of the kinds of barriers that have been erected in other areas. For example, in the transplant area the insistence that the

physician caring for a patient who is a potential donor may not be a member of the transplant team. And, likewise, here since -- as I understand it, our recommendation now would be limited to the embryonic stem cell area. We are not talking about general research with embryos and saying that federal funding should exist for all of that.

If that is the case the fact that a person running a fertility center might have his or her own interests for fertility related research to want to have excess embryos. That may exist. But they cannot get federal funding for that work so that is kind of beyond our reach.

But we could say that the centers that are -- from which the embryos come have to be ones not associated with the researcher so that you cannot go to your colleague in the next immediate lab and say, "Be sure you get some extra embryos next time because I want to get some from you."

We could also talk about the kinds of

prohibitions that are in the transplant -- the fetal area which say there should be no profit making by the suppliers of the materials, either the couples or the labs. So that we remove the economic incentive that they would have to start creating and harvesting -- vending a large number of embryos to laboratories that are going to engage in the process of trying to create stem cell lines.

MR. HOLTZMAN: How would that work there, Alex? I mean, I believe the transplant legislation implies per se not just the federally funded activities, right. It regulates the industry, does it not?

PROFESSOR CAPRON: No. I do not think so.

MR. HOLTZMAN: Isn't the case?

DR. CHILDRESS: The National Organ Transplant Act.

(Simultaneous discussion.)

DR. CHILDRESS: Steven is, I think, thinking about that.

PROFESSOR CAPRON: Oh, the transplant case.

Not the --

DR. HOLTZMAN: Yes. That is what --

MR. CAPRON: Yes, right.

DR. HOLTZMAN: So I am asking you how does that work in --

(Simultaneous discussion.)

PROFESSOR CAPRON: That is a provision of the Uniform Anatomical Gift --

(Simultaneous discussion.)

PROFESSOR CAPRON: -- state law.

(Simultaneous discussion.)

DR. SHAPIRO: National.

PROFESSOR CAPRON: The Transplant Act says no vending. A separation of doctors is an Anatomical Gift Act.

MR. HOLTZMAN: Right. So I am trying to get at what you are suggesting here. How are we going to work in the no profit when we are working here solely in the context of recommendations pertaining to federal funding? It seems to me you crossed over into how we are

going to regulate that industry. I am just trying to flush out your idea.

* * * * *

E V E N I N G S E S S I O N

PROFESSOR CAPRON: What I had in mind, Steve, was that if you get funds to do what Thompson did you could not go to a fertility clinic and offer them amounts for those embryos -- for those frozen embryos which they are about to discard, which amount to a selling for consideration of those embryos.

So that the clinic has no financial -- if I am running a clinic and I have got patients and I have any Hippocratic concern that I not expose those patients to undue risk and so forth and so on, I am not doing extra cycles, I am not getting a lot of extra eggs because I know that I have got someone who will pay me $50,000 a pop for them once I -- or whatever amount once I get them, you know, that I will develop -- I will say I am a fertility center but I am really an embryo sales center, you know. That will not happen because the profit -- we will try to take the profit out of it.

Now a privately funded person doing the embryo research will not be under those strictures, I

agree, unless there is a basis for a federal statute that prohibits that. We were, as I understood it, only addressing the present ban on federal funding of research that involves the destruction of an embryo and we would be saying that where the research involves the creation of these pluripotent stem cell lines that such research could be funded even if it involves the destruction of an embryo provided that certain requirements are met and one of those requirements is that the cell -- the embryos not be purchased but be truly donated.

I mean, at the point that the person is going to throw them away why should he charge you anything to give them to you?

MR. HOLTZMAN: Alex, I understand what you are trying to do but I was asking the question will it work? If your goal is to prevent the establishment of the for profit market in the sale of embryos your proposition is that we will take part of the buying market, namely those using federal dollars, and they will go to the sellers and say, "I will not pay you more than

X."

PROFESSOR CAPRON: I will not pay you anything.

MR. HOLTZMAN: I will not pay you --

PROFESSOR CAPRON: Transportation costs.

MR. HOLTZMAN: I will not pay you more than X and I am just asking about the practicality if there is another set of buyers out there. That is all.

PROFESSOR CAPRON: Yes, I understand.

(Simultaneous discussion.)

MR. HOLTZMAN: I understood what you were saying.

PROFESSOR CAPRON: Yes. It seems to me that the objection is not spending federal dollars for activities which are objectionable. Congress has not chosen to legislate to prevent private companies now already from doing this work. Geron did this work. It sponsored Thompson doing this work and Congress did not act to make it a federal offense to do that. If it chooses to do that, that is a separate issue.

We do not have to address that. We only have to address the need for an exception in the statute and we would justify that by saying federal funds are not going to go to someone which amounts to an inducement to that doctor to create embryos for research purposes under the guise of doing it for fertility purposes.

The way to do that is to say you cannot be a colleague of the person who is going to do the embryonic stem cell work and have the benefit come from colleagueship and you cannot get paid for it and have the benefit come to your pocketbook. And that is as much of the removal of federal funds from the process of the creation of embryos for research as is possible it seems to me. It is not perfect, Steve, and it will not stop the practice in the private sector but Congress can address that separately if it wants to.

DR. SHAPIRO: Let me suggest that I judge the stance that everyone here -- not everyone, at least the committee as a whole to be -- while we do have to take care of the issue that Bernie raised and Alex has been

just addressing, we have to find some way to take care of that and articulate this in a way that would seem convincing to people, I would like to go on and just reflect for a moment on the next section of this summary, which says that in the view of many commissioners -- I am not sure what many in this case meant but in any case at least a sum -- that they really did not want to go into what we might call as case three.

Let's call it case three just using Professor Fletcher's topology here. I just want to touch base on that before we just rush by it and say we are -- I am sorry.

DR. BACKLAR: Well, no, because I want to say something about this.

DR. SHAPIRO: Okay. Fine, you will be the first speaker I recognize.

And so that there were suggestions about various mechanisms about whether the NIH might continue to monitor this but the question is how do we feel about case three.

Trish?

DR. BACKLAR: It seems to me --

DR. SHAPIRO: Get close to the microphone.

DR. BACKLAR: -- it seems to me that we cannot get away from the fact that when we talk about the scientific community we are talking about two scientific communities and I am very concerned as we plunge into this whole issue that we still have not addressed this problem of public and private. I think we are going to get into more and more trouble as we go along unless we take a little bit of time, I am terribly sorry, to address that, which I just want to put that out on the table.

Then one more thing going back -- this is a three-part, I am sorry. The issue about fetal tissue. I was very interested in something that Ms. Knowles brought up and that was that nobody talks about using fetal eggs and I believe that if we do not put this in our points to consider that we may find some difficulty along the way. So I think that there are many issues there in terms of

the difficulty of giving a woman hormones to produce eggs and so on and so forth. At some point people may be very interested in coming back to this.

And the third point that I am going to make is that in number three, embryos produced expressly for research by somatic cell nuclear transfer and IVF, there is a line here that there should be a sufficient supply of material from other sources. But it seems to me if I --

DR. CASSELL: Could you move your microphone a little more?

DR. BACKLAR: -- that there is a line here. It says there on page two under the third -- "There should be a sufficient supply of material from other sources." Am I wrong in remembering -- and actually Alta, who is not here, was in the taxi with me with Bridgid Hogan, and it seemed to me that Bridgid said that there is a problem about these sources and that it is extremely difficult to keep these cell lines going, and that it is not going to be so easy to get enough from the

first two because also one does not know if the fetal tissue is going to turn out to be the same, have the same kind of uses and the same potential as does embryonic stem cells.

So I think we are -- there is a lot of information that have been skimmed by us and we need to address these things. I do not have any answers to the questions.

DR. SHAPIRO: Question, Bernie?

DR. LO: Well, in this paragraph we sort of collapsed down several very, very different kinds of arguments. One is we do not really need them. There is another argument that we are not as convinced that it would be morally appropriate to use them as we are for cases one and two so why don't we see if cases one and two are publicly acceptable before we venture into the more controversial contested territory and I think those are very -- I mean, if they both work the same way, fine.

But if it turns out, for example, there is a shortage or there are some scientific reason to use three

rather than one or two then we have to come back to the moral policy part in this of whether we think that is a step we want to take at this time.

So, I think, at Princeton in the way it sort of was done here we put all that together and we need to be very careful about how different those are to define.

DR. SHAPIRO: Arturo, and then Eric.

DR. BRITO: I am sorry.

DR. SHAPIRO: Arturo?

DR. BRITO: If we accept John's one and two, case one and two, and not three, the only thing I have difficulty with is that we may have to explain not from the practical point of view but from the ethical point of view how it is that we justify or from a moralistic point of view how it is we justify the use of an embryo -- this is actually case two -- that has the potential to become a human life and we say that the use of a stem cell or a human embryo that at this point does not have that potential because through somatic cell nuclear transfer we do not know about the -- it has the potential but it

has not been done yet.

And how -- I am not sure why it is that we are saying that that is going to be more controversial and why it is we are saying that it is not allowed -- we are not going to -- we are more in favor of case two than we are of case three. I am a little bit confused from an ethical point of view and I am not sure other people are not going to be questioning why that came about.

PROFESSOR CAPRON: Because both three and four involve in this setting creation for research purposes and the -- of either an IVF embryo or of a nuclear transplanted --

DR. BRITO: Well, but the nuclear transfer -- the somatic cell nuclear transfer, you know, you are creating that. You are not creating that with the intent to produce a human being and that is my point. There is something --

PROFESSOR CAPRON: But you --

DR. BRITO: Go ahead.

PROFESSOR CAPRON: But you are creating --

DR. BRITO: You are creating an embryo that does not have a --

PROFESSOR CAPRON: -- for research purposes.

DR. BRITO: Right.

PROFESSOR CAPRON: In other words, create it to destroy it. That is the --

DR. BRITO: You are creating to destroy something that as far as we know would -- only has a certain potential to keep developing. It has not been -- do you understand? And yet with IVF you know that these excess embryos do have the potential to become human beings.

PROFESSOR CAPRON: Yes. The Congress -- the congressman's letter there addresses that issue and at least the -- because I was just giving you the rationales that are given for differentiating it.

If the argument is that we ought not to -- that we ought to allow it to go forward because we are not sure whether it could survive or not, it really seems to sort of beg the issue, which is why not presume -- you

know, not that any particular embryo created through nuclear transfer would survive but if you have the experience with Dolly and now all the other animals suggesting that it is, in theory, possible that if implanted it could live. That is -- all we have is theory as to any particular IVF embryo. We know that most of the time IVF embryos go in and they do not survive. They do not turn into human beings.

DR. BRITO: But it is less theoretical.

PROFESSOR CAPRON: It is a less --

DR. BRITO: I could foresee us running into some problems with acceptance of this --

PROFESSOR CAPRON: Well, put it this way: We knew that if it did survive we would regard it as a human being. Right? The cloned one?

DR. BRITO: Right.

PROFESSOR CAPRON: And so the fact that we are not certain it is going to survive is not a reason for saying that we have not created it and destroyed it for research purposes. Whereas, the ones that are excess

were not created for that reason. It is more that instead of going into the trash can they are being used for a beneficial purpose where you have the balance of benefit versus destruction.

DR. SHAPIRO: I think in the cases -- in addition to what Alex has said, I think as Dr. Fletcher mentioned before there is a lot we do not know for case three, an awful lot we do not know.

DR. BRITO: Right.

DR. SHAPIRO: We do not know hardly anything. We know what goes on in animals and we have some hints. That is what we know. And so I think --

DR. BRITO: In a nutshell what I am saying is I think we have to be very careful about how we phrase that and provide explanation because it sounds to me like right now -- or maybe I misunderstood but it sounds to me like we are assigning a different moral status.

DR. BACKLAR: We are.

PROFESSOR CAPRON: I do not think it is a different moral status. I think it is a question of

balance of justification, isn't it?

DR. BRITO: Well, Trish just said we are.

DR. BACKLAR: I thought in the sense of creating as opposed to using what is --

PROFESSOR CAPRON: I do not think it is a different moral status of the entity.

DR. BACKLAR: Oh, yes.

PROFESSOR CAPRON: It is a different justification for treating it in a way that will lead to its destruction. The argument I took John also to be suggesting, we do not know that the reason for which -- the major reason that has been argued for, for somatic cell nuclear transfer created embryos in this context of stem cells, is the notion of stem autologous cellular and tissue transplantation, we do not know if that method is going to work with nonautologous cells. I mean, we do not know if that kind of therapy is available.

We also do not know if there are other routes of getting autologous cells. Carol mentioned one, which is taking a stem cell and doing nuclear transplant on the

stem cell instead of on the embryo when you never go -- have to go through the embryonic process again.

We do not know about the reverse engineering of existing stem cells.

So all of these -- if any of these are alternatives that avoid the embryo stage entirely I think there might be a balance where you can say if you can avoid creating embryos, cloned embryos, to destroy them and get the same beneficial therapeutic results by these other methods that would be preferable.

We are not at that stage at all scientifically so it is a premature question so that is a reason in practicality -- not for saying that they are a different moral status but we do not -- it is not appropriate yet to change the law to allow that kind of research to go on. You do not need that source --

DR. BRITO: Yes, right. You are focused on the legal. I am talking about the ethical and that is my point.

PROFESSOR CAPRON: But the ethical --

DR. BRITO: So speak of science now -- if science advances in ten years to the point -- I think -- I have put this in before, I am very -- I guess I have a lot of anxiety about assigning today a different moral status to different embryos just because it is a convenience or economical issue or because it is an ignorance issue because we all know.

So I think we are going to run into a lot of problems and I personally have a lot -- maybe I am in disagreement with a lot of members here but I personally have a lot of problems with assigning a different moral status and that is exactly what we are doing to these embryos.

DR. SHAPIRO: Okay. We have quite a few people who want to speak. Let's see. There might be some other insights on this.

Eric?

DR. CASSELL: Well, listening to this discussion, it has a certain angels on the head of a pin literally. You know, how substantial is the person when

they are one thing or another.

And it brings back to mind, John, I think, as long as we keep dancing around this argument whatever you say somebody can find a counter argument about whether -- what the status of this embryo is and in this we can sort of shift the discussion. The advantage of staying away from case number three is exactly the advantage of staying away from the unknown because that always traps you because somebody says what if and there you are.

But I think that when we hear this or read the transcript and see how we have gone around the last few minutes and we will see that this is the trap in which we -- in which everybody has fallen into that we have to try and break out of.

And I think what the advantage of the previous document was is it was a beginning edge of breaking out of that.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Case three is the research

purpose embryo that is created by somatic cell nuclear transfer. Case four is a research purpose embryo created through fertilization or IVF.

I think the position we are taking says those entities themselves have the same moral status intrinsically, number one.

Number two, from a consequentialist perspective -- no, let me -- number two, we do not see the necessity at this time for federal funding of the research that leads to the creation of those things.

Number three, and this is now turning to Dr. Fletcher's argument, one can see where research using the ones created through somatic cell nuclear transplant might be something which comes to the fore as worthy of funding because of a particular benefit only available through that line of research having to do with overcoming immunological rejection. So in other words it is a consequentialist argument. It is not making any distinction between the moral status of those different embryos.

And then the fourth argument would be that -- again harkening back to Fletcher's discussion -- was the presence or the availability to have a world of embryos created through somatic cell nuclear transfer becomes more and more potentially prevalent. All right. Our evolution of the moral thinking about the role of embryos might change when as it were embryos exist all around us but that time is not here yet.

So it does not require, Arturo, saying there is a moral distinction between the two things. That is my understanding of our thinking here.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Actually a reiteration of some of the points that Steve made. It does seem to me that the intention to create for research purposes is really what we are talking about here, distinguishing categories three and four from categories one and two.

But in saying that, that does not mean that at some later point society might come back and reconsider for various reasons, scientific and otherwise,

but at least for the purposes of our discussion we do not have to assign the embryos in these different groups to different status.

Fetal tissue, abortion decisions are made, tissue is available and someone may consent to the use. The spare embryos our society is wrestling with anyhow, we do allow the destruction and insofar as society allows that destruction is it permissible to go ahead and use it in the research context.

So it seems to me that in those two situations certain societal practices occur and then the question is whether it is permissible in that setting to use those two sources of stem cells.

I think the creation -- from my standpoint, the creation for research purposes does raise further questions that would have to be addressed at some later point and I do not think we should do anything more, as someone said earlier today, than peer over the edge into those at this point.

DR. SHAPIRO: Okay. I think -- let me ask

the question. We did have some discussion at the end of the -- or at some stage during the Princeton meeting, there was some disagreement amongst us about whether creating for research -- I think one of two commissioners expressed themselves, if I remember correctly, that for them personally it might have been ethically acceptable for federal funds to support research using stem cells derived from embryos produced for research purposes, that is -- and -- but that be as it may, and there was some -- we had some discussion about that.

I am taking the conversations around the table today to really say that one way or another the thing that we ought to really focus our efforts on articulating is really what we have known -- I want to come back to case -- point five but cases one and two. People have given different reasons for that but I have not heard much enthusiasm for pushing on into creating embryos for research purposes or for us opining on that at this time. But if I am wrong then now is the time to -- let's have the discussion.

Bernie?

DR. LO: Let me clarify. It seems to me the issue is not whether we as individuals are personally comfortable with the morality of three and four.

DR. SHAPIRO: Right.

(Simultaneous discussion.)

DR. SHAPIRO: I did mean to imply that.

DR. LO: That is public policy.

DR. SHAPIRO: Right. Public policy purpose. That is right. Excuse me. I misspoke. You are quite right. Thank you for correcting me.

DR. MIIKE: Harold, that was exactly my point.

DR. SHAPIRO: Yes. No, that is quite right. I just misspoke myself.

Okay. So we can consider that to have been -- that passes. We still have a lot to do to articulate this in a way that is effective and helpful so it is not that the issue is all passed but people are comfortable that way.

Let's return to the issue, which I think Steve or Carol raised before, and that is what is our argument or what is our reasoning we have that says that human stem cells, that embryonic stem cells have some special status as opposed to other cells?

Which I think is the question you raised. Steve, have I misspoke?

MR. HOLTZMAN: Yes. I think that is it but we just said we are not going to deal with three and that is fine but the logical organization of our report right now is according to the source how do we feel about the -- federal support of derivation and use.

DR. SHAPIRO: Right.

MR. HOLTZMAN: So I think we actually do have to nail down this last issue because do we care about the source in terms of -- if there is federal funding for the use does the source matter? Because if the source does not matter then you can reorient your point.

DR. SHAPIRO: That is right.

MR. HOLTZMAN: This point five is the first

thing.

DR. SHAPIRO: Right.

MR. HOLTZMAN: All right. So to take your question now, is there something special and is there something special in terms of their source.

DR. SHAPIRO: Yes, that is exactly right. I agree with that. How do people feel about those issues?

Alex?

PROFESSOR CAPRON: I do not want to put this in terms of feeling special about it. It is just simply that I do not believe use and derivation can be separated and I, therefore, hope that the law will be changed to allow category two because if it is not changed I find it disingenuous to be funding the use while it is prohibited to fund their creation or derivation.

MR. HOLTZMAN: And what about the contrapositive? If there is not federal funding for the research purpose for embryos does it follow there should not be federal funding for their use if they came from the research purpose? You said the case two. If we are

going to say federal support of use then we have to say federal support of derivation at least from spare.

Now if we say no federal support for research purpose, is it also following your way of thinking that no federal support for use if they came from those?

PROFESSOR CAPRON: Yes, that is my point.

MR. HOLTZMAN: Okay.

PROFESSOR CAPRON: In other words, under the present situation I understand -- I agree that in a narrow legal way Harriet Rabb is actually correct. Congress said, "You cannot fund the process in which an embryo is destroyed or created for research purposes." It is the destroyed part that is relevant to Thomson's work.

They did not say that you cannot fund the use of the products of such a process because they did not have this particular kind of product in mind, I think. I think it is disingenuous to have a federal policy that says you can, in effect, pay for it by the amount you put into the research process but you cannot directly pay the

person who does it. Those federal funds have to become University of Wisconsin funds before they can do that and I think that is disingenuous.

If there is a strong public consensus that it is wrong to take embryos -- spare embryos and get embryonic stem cells out of them I think it misdescribes what that public wish is to then say but you can just do anything you want once the cell lines get created. That is my sense of that.

I oppose that by saying, "No, we should recognize it is all right to use spare embryos in this fashion if there are legitimate and very valuable scientific and potential therapeutic reasons to move in this direction and, therefore, you should be fine." Since that does not get -- that is not true of cases three and four in mind yet, I do not think the arguments for federal funding of the derivation are there.

I would also say we better make sure that the cells that are used do not come from three and four.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I agree with Alex. I agree that it is illogical to have different rules for use and for derivation and I think having that difference will undermine public confidence because it will appear that we are playing a game with these very important decisions.

DR. SHAPIRO: Larry? Bernie?

DR. LO: I just wondered --

DR. SHAPIRO: Larry first.

DR. LO: Oh.

DR. MIIKE: I just want to make sure that the reason that we say there is -- they should be linked is that it is the harm to the embryo in the derivation process because if the situation were such -- such as that you could take a cell, it became a stem cell but the embryo was not harmed, what would our position be in that case?

PROFESSOR CAPRON: You took out a single cell.

DR. MIIKE: If, in fact, you could take out a

single stem cell --

DR. SHAPIRO: And the embryo was still viable.

PROFESSOR CAPRON: It does not -- the linkage is a slightly different one. I think what you are suggesting is that there would be -- there ought to be no moral objection at all if you can take a cell out without harming the embryo just as there is no moral objection in taking one of my cells out, or a child going and having a mucal smear.

DR. MIIKE: So the answer is because of the harm in the original one.

PROFESSOR CAPRON: But that goes to whether or not the process of deriving or creating the stem cell line is itself in some ways morally problematic. What I am saying is once the public decision has been made that it is so problematic that it should not be funded with federal funds then you should not be able to fund the use of the products because you are, in effect, funding that --

DR. MIIKE: I was only trying to make a distinction between an experiment that had some harm versus an experiment that had no harm.

PROFESSOR CAPRON: Right. I mean, if the experiment has no harm I cannot imagine that it is seen as violating present public policy. It says to destroy or --

DR. MIIKE: But is that true? I mean, are we all going to accept that? I just wanted to --

DR. SHAPIRO: You just wanted to know what our judgments are as to how we come to those decisions.

Steve?

MR. HOLTZMAN: Well, there is another basis other than the harms to the embryo and the intrinsic harm, moral wrong, damaging of the research purpose embryo, where it is more along the lines of what Alta suggested in her piece which is a public policy position about respect for others and going to a certain -- going so far where you could say in respect for that you will not have federal funding for a certain activity, namely

the creation of those things, but you will not go so far as also to prohibit federal funding of the use of the downstream products. And that is not necessarily inconsistent given that basis.

DR. SHAPIRO: Bernie?

DR. LO: I agree with this line of thinking that for one and two we should say both the derivation and use are permitted and for three and four neither are permitted.

It seems to me for three and four there is an additional argument, and that is to do with the -- sort of the variant of the complicity argument. Not only do we have moral concerns about the process in which an embryo was destroyed but using it for research may, in fact, create more demand or incentive to do that.

You could, I suppose, make an argument for cases one and two even if you thought that it was morally wrong to use the -- to destroy the -- to create the stem cell lines. Once you had them you might argue you could use them because using them more was not going to sort of

create -- cause more cases of stem cell lines being created with the moral problems that would follow.

But just to say, I think, there are even stronger reasons in three and four to say if you cannot -- if it is not permissible to derive it, it is also impermissible to use them.

DR. SHAPIRO: Tom?

DR. MURRAY: I am just trying to listen and take in the various arguments here. I am having difficulty understanding the force or appreciating the force of Alex's argument about the -- that it is disingenuous to on the one hand be willing to fund the use of these embryonic stem cells but on the other hand to decline to fund the actual obtaining of these cells via the creation and/or destruction of embryos.

It seems to me that in the realm of public policy we often make fairly subtle distinctions that have to do with, you know, trying to keep arm's length from practices that make at least a significant proportion of the American public uncomfortable. While if the

practices are, in fact, kept at arm's length we can then take as acceptable the next -- you know, a step that is clearly related but not the same.

So it may not be clean but I am not sure that just to call it -- it is not a logical inconsistency, number one. I think Steve made that point very well. Nor do I even -- nor am I even persuaded that it is somehow -- that it is necessarily disingenuous. I mean, if there is a wink and a nod that we know we are paying for it anyway and just converting it through the University of Wisconsin or some other university's funds then that does begin to look disingenuous but if it is clear separation, clearer than that then I think that it might be a reasonable approach.

DR. SHAPIRO: Other comments?

I take it then for a variety of reasons not all the same that we do want to just repeat what I have said before, people feel that for public policy purposes that we should not be recommending so to speak case three

and four for a variety of reasons that could be articulated. I will not try to summarize them again now.

But also for a variety of reasons at least the way the commission's feelings at the moment with respect to public policy in this arena is that we would favor or suggest that creating and using case one and two are perfectly appropriate for federal funding. Now whether they should be funded or not, that is another matter but at least we believe they are appropriate.

Larry?

DR. MIIKE; Except that I do not think the discussion of two is complete because of what Tom just raised.

DR. KRAMER: I am sorry, Larry. I cannot hear you. Speak up.

DR. MIIKE: The discussion is not complete on two because prior to today's discussion there were rationales given for separating the use from the creation and that is where we were at that time. I guess Dr. Fletcher has sort of influenced the thinking today to go

along the more expansive lines. Is that something that we are going to --

DR. SHAPIRO: All right. Let's just look at it explicitly. Thank you very much. Let's look at it explicitly. That is whether what we think would be appropriate public policy would be to not fund, let me put it this way, the creation. But I mean it is almost -- I do not know quite how to put it because item two is -- by definition it is in the excess area, right?

DR. MIIKE: Right.

DR. SHAPIRO: By definition at least that is how I understand two. Am I wrong, Larry?

DR. MIIKE: No, but -- that is true but what Dr. Fletcher was proposing and the way that we would have bitten the bullet following Alex's conclusions was that we would also have recommended loosening the reins on embryo research in deriving the stem cells.

DR. SHAPIRO: First of all --

PROFESSOR CAPRON: Case two, is that what you mean?

DR. MIIKE: Yes.

PROFESSOR CAPRON: Case two.

DR. MIIKE: In case two but it was that -- it was not -- in case two it was not -- from what I understood Dr. Fletcher to say and what I thought you had been saying is that we would not only endorse the use of stem cells derived from excess embryos but we would endorse the extraction of stem cells from excess embryos.

PROFESSOR CAPRON: Yes.

DR. SHAPIRO: I am going to give you my own interpretation but since Professor Fletcher is here we might better ask him becasue I think I asked that direct question at the end of his testimony. I thought that Dr. Fletcher was saying that he did not feel that the legal interpretation at NIH was a sufficient basis for going ahead with case two because perhaps he was not convinced by the legal analysis or perhaps he felt that legal analysis should not be the basis of our suggestions here but, therefore, we should, in fact, alter the legislation to make it clear that two was appropriate.

Now Dr. Fletcher is here and I do not see why I should be guessing wildly at this issue.

DR. FLETCHER: I argued that a recommendation to amend the law to permit federal funding --

DR. SHAPIRO: They cannot hear you back there.

DR. FLETCHER: I argued that amending the law to permit federal funding of embryo research with excess embryos was indicated first for the reasons that Alex is propounding that the legal opinion does not give an ethical justification for anything and it is not an ethical argument.

It is a legal opinion that the use can be separated from the whole concept of derivation for research purposes.

It is almost as if derivation is not relevant to the federal domain because it is separated in the private domain.

As a moral construct I think that is very weak and evasive.

If it is right to do research with fetal tissue that is donated after elective abortion then it follows that it is morally justified and right to do research with embryos that are donated by couples who know that those embryos could either be adopted by others or used for research. They would be given the option. And they would know that those embryos could very well be discarded.

There is not 100 percent certainty that every embryo that is an excess embryo would be discarded but it is virtually certain that most of them would so they are in the same category as case one.

So there is a moral -- there is an ethical reason for recommending that the law be changed.

There is also a pragmatic -- a more pragmatic reason that it would involve the NIH and the NIH's resources intramurally and extramurally in being able to not -- to participate not only in improving the ways in which stem cells are derived from excess embryos, which you remember that is a very important issue. In Dr.

Gearhart's Science article

he said that Thomson's methods perhaps could be improved and you could do that better but it would also involve NIH in freeing up a backlog of research involving embryos of various types that has not been done since the law has been on the books.

So it would do those following things. So, yes, I was arguing for a recommendation or for you to consider a recommendation, which I would favor, of recommending that Congress amend the law to that effect.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: I want to go along with you 100 percent but I have a little trouble on the moraly equivalence of the aborted fetus or the aborted embryo and the donated embryo. That aborted embryo cannot under any circumstances go on and become reimplanted and so forth. Whereas, the option is still there on the other one. They are somewhat different.

Now I like a lot better the argument that

they are close to morally equivalent and this is the reason why:

After all a person is donating that just as they gave permission for the abortion. I take it that is part of your argument. They gave permission for the abortion, they give permission for this use, and so it is not just the status of the embryo. It is the status of the embryo in relationship to the donor. It is not just the embryo. As long as you take the embryo and pretend it does not come from a human being then there is no way to make it morally equivalent but that is one of the problems. They are not separate. They exist in relationship to the donor.

And I take it that is part of what you are saying.

DR. FLETCHER: That is part of my moral argument that we ought to show respect for the choice of parents who want to donate excess embryos for research because they know that among other things they might be sources of stem cells that could greatly benefit other

human beings.

DR. SHAPIRO: Wait a second. Jim first.

DR. CHILDRESS: Just a quick question just to follow up on Eric's comment. It does seem to me that when we are dealing with tissue following an abortion we are dealing with some different problem than embryo, spare embryo, and it is important that we end up coming to the same conclusion about what can be done, at least recognize the difference there.

But the question I would raise in terms of your proposal for us is whether given your incremental approach -- in effect, you are not pushing too far. That is to say we can address a lot in the area of our concern with stem cell research without having to go back and address the whole area of embryo research. And I guess if we want to distinguish incrementally as you urged us to do, well, maybe this does not take us too far in terms of what we would be able to address fully and what would be feasible in getting to.

DR. FLETCHER: That is certainly a

consideration. I struggled with that kind of proviso and that thought in my paper. The main reason that I recommended it had to do with several factors. One, it is being widely done in the private sector. Embryos are not being created for research in the United States as far as I know but embryos are used. I may be wrong on that.

Dr. Hanna says I am wrong.

DR. HANNA: In my conversations with some IVF clinics they do create embryos for research purposes.

DR. FLETCHER: My discussions with --

DR. SHAPIRO: Fertility research.

DR. FLETCHER: Pardon?

DR. HANNA: Fertility research or for their own quality control.

DR. FLETCHER: For fertility research. So even the most controversial case is occurring in the private sector according to your information.

The -- it seems to me that in terms of the evolution of moral sentiments and moral ideas in our

culture since 1990 -- since the early 1990's that the stem cell events have been the most important in modifying what the public may be willing to permit and I think it is -- I think that it would be an experiment, Jim, kind of moral provocation. Might be it would provoke discussion. But I think that there would be support in the public for doing this because of the benefits question.

Now, also, there needs to be access to embryos -- stem cells derived from embryos in order to compare with the germinal cells derived of stem cells.

But I think that as a matter of -- as a matter of incremental approach the position that you are exploring is certainly one that the commission ought to entertain.

DR. SHAPIRO: I have a question but Steve is next.

MR. HOLTZMAN: In your three categories -- so we have got the source, which is fetal, excess embryo, let me call them research purpose embryos --

DR. FLETCHER: Right.

MR. HOLTZMAN: I am going to lump three and four together. I am about to do a three by three matrix. That is coming down. The question is federal funding.

DR. FLETCHER: Right.

MR. HOLTZMAN: I understand that you have said -- and now we have got two new columns, derivation, federal funding of derivation and federal funding of use. I am understanding you to say with respect to fetal as the source federal funding, yes to derivation, yes to use. With respect to excess embryos, yes to derivation, yes to use of the stem cells.

DR. FLETCHER: Right.

MR. HOLTZMAN: Research purpose embryos, no with respect to derivation or do not take it up at this time. But now with respect to use of stem cells which were derived from nonfederally funded research purpose embryos, did you have a position? Because I think that is the one place the commission is left here and we have got a split.

DR. FLETCHER: I have not thought that through.

MR. HOLTZMAN: Okay.

DR. FLETCHER: So my response to you is one of immediate thought but I am impressed by Alex's commentary on the moral weakness that underlies the legal opinion and the vulnerability of that moral weakness or invasiveness to inflame the moral views of those who could bring about a stoppage all together of stem cell research. It appears --

DR. MURRAY: Excuse me. But, John, you think that saying it is okay to create them or to use federal funds to use embryos would not inflame the same views? I do not understand the reasoning there.

DR. KRAMER: He did not say that.

DR. MESLIN: Not to create, to use.

DR. MURRAY: To use. Not to create but to use. To derive the stem cells from.

DR. FLETCHER: See, I think that morally speaking if it is morally acceptable in society to

practice embryo research that it -- I mean, if our society tolerates practices that are going on now in embryo research entirely unregulated that that is the situation that the commission ought to have its eyes on and to take an incremental step to try to bring about the very best practices that you can one step at a time with federally funded embryo research and I am -- you know, I am morally scandalized by the various universes of practice that we permit in our society in every realm. I mean just look at health care not to speak of research. All right.

So here is a chance to go ahead and take a risk and say if you want to do morally acceptable embryo research as a society here is the way to do it with this one case that where you appeal to the altruism of the donor and the assumption that most Americans would accept this altruism of an embryo donation and say here is the way it ought to be conducted and regulated.

So I think it takes a moral responsible societal view to take that step.

In thinking about it I think this is my response to you, Jim. In terms of social ethics and public policy it is more responsible to tackle case two to give the arguments of why it can be justified and show how it can be regulated than it is for the sake of permitting the NIH to be able to do what the legal opinion permits them to do, which I know they would be happy with to do that, but as a piece of moral analysis it is far better in my view to go the next step.

DR. SHAPIRO: Thank you. I apologize, I did not mean to interrupt.

Bette, and Tom.

DR. KRAMER: That is all right.

DR. SHAPIRO: Tom?

DR. MURRAY: Well, John, I just want to urge caution in the interpretation of what you describe as public tolerance to what takes place in the forms of research in the fertility clinics and the like. The public tolerance that you allude to might be based not so much on a moral tolerance of practices that are known as

public ignorance of what actually goes on. I put forth as evidence your own surprise with Kathi's report that, in fact, there are IVF -- private IVF clinics out there creating embryos for the purpose of research.

My sense is and I am pretty confident of this that the American public does not have much of a clue about what is going on in a lot of IVF clinics in the form of research with embryos and I just want to make that point.

DR. CASSELL: However, you have raised a point that can be answered empirically of what the public will tolerate and it is crucial to what you say because it is now made clear what is happening out there and rather than tolerate it, it comes down like a clamp on all things without us having known that was going to happen.

DR. MURRAY: That, I think, is a possibility.

DR. SHAPIRO: Bette?

DR. KRAMER: It was exactly that and follow-up further and that is to -- I do not think the public is

aware of it and I think there is this line of standing commitment on the part of private funded research and that this is possibly a way that we can do some education around this issue and reclaim this area and begin to reclaim this area for research in the public sector.

ADJOURNMENT

DR. SHAPIRO: All right. We are nearing our adjournment time if not overstayed our time.

I would like to make sure that when we begin our discussion in this area -- tomorrow we will begin incidently -- after we are through with the international issue we will begin to go back to the HBM report. We will then return to this as soon as we can.

I really want to focus your attention on page five of the Meslin-Hanna memo because there are a series of questions there. I think we have clarified quite a number of them here today and we will see if there are others that you feel need some further clarification and we will take our discussion from there.

So I think we will begin at 8:30. 8:00 or

8:30?

DR. KRAMER: 8:00.

DR. SHAPIRO: As for me, I can be in at any time. 8:00 o'clock.

DR. MURRAY: 8:00 is fine.

DR. SHAPIRO: Okay. 8:00 o'clock tomorrow. Thank you. 8:00 o'clock tomorrow morning.

(Whereupon, the proceedings were adjourned at 5:22 p.m., to be reconvened at 8:00 a.m., on March 3, 1999.)

* * * * *