31ST MEETING

OF THE

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

RESEARCH INVOLVING HUMAN STEM CELLS

P R O C E E D I N G S

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DISCUSSION CONTINUES WITH COMMISSIONERS

DR. SHAPIRO: Let's get our meeting underway. Let me just, before we get started, turn to Eric, who has a particular comment he wants to make.

DR. MESLIN: Although we do not have a full room I wanted to let the commissioners know that today will be Randy Hull's last commission meeting with us. Randy, as most of you know, is probably the longest serving staff member on NBAC and was one of the original group that was brought in. We have been very pleased and happy to have Randy on staff and I am especially proud to let you know that he has been accepted to Syracuse law school and will be beginning in the fall.

(Applause.)

We wish you all the best and thank you very much for all your hard work on behalf of the commission staff.

DR. SHAPIRO: Also on behalf of all the commissioners. You have helped us all in many ways and

we are really very grateful to you and wish you best of luck at Syracuse. We hope you will visit once in a while if you are ever back in Washington when we are meeting there.

We have some time this morning to look over some issues from yesterday which I want to revisit. One in particular. And then -- I mean, two principal items of business this morning are to pick up any issues that anyone has from yesterday that they want to further discuss at this time and then we have two visitors.

One of which we know is late because of the late arrival of the aircraft from, I guess, Washington. I am not sure. But anyway one is local so to speak and can get here by train and we expect Lori Andrews around 9:00 o'clock and we should go directly to that when she comes.

Someone is going to speak to us -- Dr. Shapiro -- with respect to IVF clinics. It is his plane that is late coming from, I think, Washington but I am not sure. Madison. But his plane is late but we hope he will be here at 9:45. We will just have to play it by ear and see how it goes. We all know what these

estimated time of arrivals are like once things start getting backed up and so we will just have to wait and see what happens.

I wanted to return to the last issue that we discussed yesterday, which was the question of oversight, that is what level of oversight, who should carry it out, et cetera, et cetera. All those issues were just sort of swirling around in not too organized a way as might be expected in our first discussion.

There are a number of items that came up which I would like to revisit just to clarify things in my own mind as I think about it further.

One was there was a desire to have national oversight on this at some level, although we had not quite articulated what, in fact, would take place at the national level. Whether that would just be protocols for the derivation of new cells or it would be also protocols for the use of these cells and so on but we wanted to some type of national oversight as part of this process and something more than just, as the initial proposal was, accrediting local IRB, some more substantive, not more substantive but more direct kind of oversight, if

you like, at the national level.

I wanted to raise an issue which I discussed very, very briefly with Eric and Kathi this morning. I think not successfully, that is I do not think they thought it was a very good idea.

But in any case I wanted to see what others think about it and that is I began thinking about whether what we needed was a single national group that would carry out this oversight, however articulated and defined, or whether we could follow another strategy which said that any federal agency, because we are talking about federally sponsored research here, wishing to sponsor research in this area would have to mobilize at the national level an appropriate group to carry out the following type of oversight functions, whatever it is we decided they were.

That has some obvious disadvantages. One, it is not everything -- they might do it somewhat differently. All right. So it would not necessarily have a common approach, that has pluses and minuses to it. The Common Rule, after all, is a tradition that goes exactly in the opposite direction and that history has

been -- I think people have been satisfied with that aspect of the history. Other aspects may be more problematic.

So what could one say on the other side of things that might make such a proposal worth thinking about at least for two or three minutes?

On the other side of things it seems to me are -- is the avoidance of what inevitably is a cumbersome process of getting the whole thing put in place in the first place. Getting a national group put together has all the various issues that come around whenever you assemble some national group to which all agencies are going to in some sense use for their purposes. And that might take quite some time for one thing. And I am not quite sure just how it would work.

So I just was sort of fumbling around with this idea as you can tell from my rather incoherent description but I would be interested in knowing whether your reactions are that that is basically not even a path worth exploring or whether it is something worth exploring.

Does anybody have any views about that?

DR. MIIKE: Can you describe again? I am not quite clear what structure yet?

DR. SHAPIRO: The structure would be if NIH wishes to sponsor research in this area, it would have to form some kind of national review body to carry out oversight, which we will describe in our report. And if the Veteran's Administration wants to do work in this area, it would have to mobilize a group to carry out the kind of oversight which we would describe in our report.

DR. MIIKE: I think a more straight forward way would be that some lead agency such as NIH have a body like that and you have an interagency liaison from each of the departments that would feed into it. That is a common mechanism, I think, that is used all the time. Either within a particular department or across departments.

DR. SHAPIRO: And if we had such a thing as opposed to -- you would think NIH would be the appropriate lead agency.

DR. MIIKE: Or NSF or --

DR. CASSELL: It is got a slightly fox in the chicken coop quality.

DR. SHAPIRO: Yes.

DR. CASSELL: Because --

DR. SHAPIRO: All right.

DR. CASSELL: -- while they could bring together, I mean, an organization quicker than most people, it is because they are so eager to get it going.

DR. SHAPIRO: That is right. I mean, that is an issue.

David?

DR. COX: And so the potential compromise in that is -- consistent with Larry's and Eric's -- is Health and Human Services so that it is not as hard as going out de novo, you know, and getting a national body but it is having it be a governmental body organized through Health and Human Services, which has a whole variety. It has CDC. It has a whole variety of other things under it and I think would answer the fox in the chicken coop a little.

DR. MURRAY: I just want to remind everybody that the dysfunctional/nonfunctional Ethics Advisory Board was housed in HHS, which I think in those days had a different name.

DR. SHAPIRO: Bernie?

DR. LO: I wonder if we should instead of asking about the details of sort of where something is housed think sort of a little more generally about sort of what are the goals we are trying to achieve and what are sort of the dangers or problems. It seems to me we may be in a better position to sort of lay out the policy options and the pros and cons and make specific recommendations.

It seems to me if we make a list of sort of centralized versus decentralized sort of modes of administration, we are coming to, I think, a common understanding of what we are trying to achieve and what some of the pitfalls are. And I think the pitfalls are there could be inordinate delay. There could be less than candid or thorough scrutiny.

I think if we can develop a list of what some of the potential problems are, there may be other people better situated than we are to sort of make a determination as to which level within the administration this committee might best sit.

I am just a little concerned that there are

people who sort of deal with this on a day-to-day basis for playing one agency off against another, and I am not sure that we are the best group to make those decisions but we could certainly help them understand what the considerations they need to keep in mind are.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Can someone with a better memory than me remember whether the Embryo Panel recommended the formation of a body? What the charge of that body was? Where it was located?

DR. SHAPIRO: Bernie?

DR. LO: That body recommended that the Director of NIH convene a time limited commission so that he/she would be appointed and be responsible at that level as opposed to HHS. Part of it was this notion that it could be assembled fairly quickly and it would not -- it would operate in smooth conjunction with the rest of NIH review process and not hold up grants and the criticism would be some of the concerns that Eric raised that can you both supervise a program and oversee the scrutiny of it.

MR. HOLTZMAN: What about its charge, Bernie?

The specifics of what it was charged with doing.

DR. LO: It was a double charge. One was to review. It was an additional layer of protocol by protocol review on top of the ordinary peer review, which does contain some sort of ethics review. The reason for that was not just because it was thought these were new issues that deserved special scrutiny but the goal was also to, by working through a series of cases, grants, develop a set of guidelines under which there could be sort of a common understanding of what things were not problematic and what would be acceptable or unacceptable solutions to common problems.

Pat King used the analogy of sort of a common law based series of sort of precepts and the idea was that by looking at a whole bunch of cases in sequence one group could come up with a set of precepts and guidelines that could then serve local IRB's, investigators and others who had to consider these sorts of protocols.

DR. SHAPIRO: Eric, and then Trish.

DR. CASSELL: Could it be the same organization that we proposed for the human -- for the capacity report? I mean, does it have to be specialized

for this or could it be just a super ordinate organization?

DR. SHAPIRO: I mean, I think that -- my own view is that depends, in part, on what goals and tasks we give it and how busy it is going to be. If we decide, for example, this is going to be a protocol by protocol issue, that is one issue -- that is one set of tasks.

If we decide it is something different than that and it is mainly focusing -- take the other extreme -- on these broader, long range issues, some of the issues you talked about yesterday, that might lead me to think a little differently about it. In part, it depends on which task we are doing and how busy we are going to be.

Trish, and then Tom.

PROFESSOR BACKLAR: Where was the RAC housed?

DR. SHAPIRO: NIH. At least that is where I think it was housed.

Tom?

DR. MURRAY: We have focused quite appropriately on the -- I think what Eric dubbed the fox in the henhouse problem, and that is a concern.

There is another concern, which is given the political sensitivity of embryo research, and given our experience with the Ethics Advisory Board in the late 1970's and early 1980's, we should think seriously about ways in which a body would be able to operate in relative independence of, you know, immediate political waves.

I mean, you want it to be in the larger sense politically accountable, yes. I am not -- we are not talking about setting up a totally -- this is not a judicial body that is supposed to be independent of the political process. But it would be better if it would be at least somewhat insulated, I think, from -- you know, from immediate politic occurrence because it would be -- the research will be very sensitive for a period of time.

DR. SHAPIRO: If I -- I am sorry. Bernie?

DR. LO: To follow on that line of thinking, history would then suggest that housing it within HHS would put it at the mercy of the political buffeting. I mean, it is not just the Ethics Advisory Board. More recently in the current administration the Surgeon General was prevented from making recommendations on needle exchange for HIV prevention that I think were

pretty solidly endorsed by all the public health communities.

So I think that the more -- obviously NIH still serves -- is still subject to political forces in their appropriations process but it is a little bit more -- a little bit less direct than I think what the Secretary of HHS would be.

DR. SHAPIRO: Tom?

DR. MURRAY: I guess I will make this a question to Harold. If I recall correctly we are officially, although most of us are -- at least I am not very conscious of this relationship, we report to -- is it the White House as the President's Science Advisory or Science and Technology Advisory Committee?

DR. SHAPIRO: Mm-hum.

DR. MURRAY: Of which you were previously a member?

DR. SHAPIRO: I was a member of PCAST.

DR. MURRAY: PCAST.

DR. SHAPIRO: Yes.

DR. MURRAY: President's Council of Advisors on Science and Technology.

DR. SHAPIRO: Yes.

DR. MURRAY: Would it be appropriate to have this committee be reporting to that body? Would that afford it a kind of accountability but also some insulation? Really I do not know. I am really asking it as a question.

DR. SHAPIRO: My gut feeling is no but I would have to think about it more. I do not want to give a quick response.

DR. MURRAY: It just strikes me that that body is less -- somewhat less subject to the political whims than some other organizations we can imagine.

DR. SHAPIRO: You know, we already have a situation here where different rules apply to different federal agencies. Right? The ban applies to NIH. Right? It is in the NIH authorization bill. At least that is my understanding.

You know, so, in fact, current federal agencies are already operating under different restrictions, precisely on the topic we are talking about. And I am not quite sure what that means other than it is a fact but, I mean, I am not quite sure what

its implications are for what we are talking about.

But, you know, as I hear all these qualifications come up, which are all genuine concerns -- I mean, it is not -- every one of them is something I can certainly understand.

It seems to me that there might be, and I say this very conditionally, a strategy which says that an agency wishing to sponsor work in this area has to do the following. Okay. And assemble a group, the group will have these characteristics, these are the things that it will have to consider, this is what it should do, this is how it relates to local IRB's, et cetera, et cetera.

It is a difficult issue because this -- we are covering an area here which is human subjects, in part, but not human subjects in another part. I mean, there is a whole complex of issues which make this a very special case and -- well, I mean, I am very undecided on the issue myself. I have not -- Laurie?

MS. FLYNN: Just sort of an obvious question, and you have obviously thought a bit more about this, what would be the effect if we moved in that direction and over time different of these agencies dealt with and

even determined differently about essentially the same science.

DR. SHAPIRO: Yes.

MS. FLYNN: That is, I think, the one issue --

DR. SHAPIRO: No, it is a very serious --

MS. FLYNN: -- that is very hard to --

DR. SHAPIRO: -- very, very serious issue. I agree. It is a very serious and maybe fatal disadvantage to anything like this. My only response, lame as it is, to that is that if these processes are open, those issues will be available -- you will be in front of people's eyes, so to speak, to be discussed, changed, challenged and so on. But I agree. It is a very, very serious problem you raise and it mitigates against any thinking along this direction on it.

David, Bette, Bernie, Steve, and Trish?

DR. COX: So from a scientific point of view, I think what Laurie brings up is a real concern but what is really attractive about your proposal, Harold, is that we do not have to wait for 20 years for some commission to get set up that does not exist because this group can

then set what the criteria are that allows it to proceed.

Now there is no sort of audit so it is lacking the audit part of it but it is proceeding, you know, with great haste with what the substance of it needs to be. So the -- it is -- I think that is an interesting trade off between actually having the substance out there of how it needs to be evaluated but then having everybody do that in commonality.

I worry about that more than I do about people adjudicating differently about the science, oddly enough. I actually think that there is going to be very few places besides the NIH that is actually going to adjudicate about the science and people will probably defer to that group looking at it.

But if we have all sorts of different structures set up in terms of how people even analyze the problem I think we are in just for a nightmare and that is why I think overall I am supportive of your idea, Harold.

DR. SHAPIRO: Bette?

MS. KRAMER: I am just thinking about -- I am just thinking more politically in terms of Tom's question

about it being located within the Executive Branch as opposed to the Legislative Branch and I am wondering if that does not make it more politically liable. It is -- they have to deal with the legislature anyway. They can -- they have always got the -- they have always got jurisdiction in terms of the budget. But to put it in the Executive Branch it seems to me it might make it very, very vulnerable in terms of the pressures on the particular president who is sitting at that time.

I do not know. I am just raising that as speculation.

DR. MURRAY: All the options we have been discussing are in the Executive Branch, Bette. NIH, HHS would all be in the Executive Branch.

MS. KRAMER: True.

DR. CHILDRESS: And one experience I think connected with legislative was BEAC and it was a disaster.

MS. KRAMER: I am sorry. Was what?

DR. CHILDRESS: Bioethics Advisory Committee.

MS. KRAMER: And that was in the legislature?

DR. CHILDRESS: It was a disaster. The worst

of all the commissions ever created.

DR. SHAPIRO: Some would argue with you.

(Laughter.)

MS. KRAMER: But maybe then -- maybe my pondering has relevance as opposed to -- in the President's suite as opposed to the President's, you know, structure as opposed to HHS. I do not know.

DR. MURRAY: My reasoning about with PCAST -- and thank God I have no emotional stake in this. I do not understand the hierarchies and the relationships well enough to really know.

But PCAST, it does have to -- even if it is a White House appointed group, it is accountable as well to the scientific community and these are heavyweights in the world of science and technology policy and in science and technology, and could act as a counterweight, a kind of buffer to political whims because these are very substantial individuals who are on that council and they are in relative -- at least relative independence. They are not -- they do not -- it is not a cabinet secretary.

DR. SHAPIRO: I have a lot of people on the list so let me just go down the list. That is the

fairest way to handle this.

Bernie?

DR. LO: A couple of quick comments. One, first, I think it is probably unlikely that an agency other than NIH will play a major role in this. I mean, I think they are going to attract the best scientists and they are going to have the most money so that we may be designing something if we are going to put it in different agencies that -- where NIH is really the major player.

And then secondly I think there is a trade off we have to acknowledge between independence and power that we can make some -- we can make this commission very independent and have it report to an advisory body but that advisory body does not have line authority to sort of authorize, for example, grant making.

So one of the things with placing it within NIH is that you can have this review running parallel with the other sorts of scientific review, and the peer review process, and the allocation of grants. I think we need to keep in mind that there are lots of different constituencies here. Obviously there is public and those

who are concerned about the ethics of this.

But I think the experience of the RAC is very germane that a lot of scientists thought it was baloney becasue it was just an extra bureaucratic hoop that delayed things, that people did not really know what was going on, and it did not have credibility.

I think if we design something that satisfies one constituency but is viewed with disdain by the very scientists doing the work, that is not a good thing either. So I think we need to be very careful at sort of making sure that we do not try and achieve one goal and sacrifice others.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I am not sure where it belongs but I am pretty sure it is an "it" as opposed to many when I think about what "it" will be doing. I do not see this body adjudicating scientific questions. All right. I do not see protocol by protocol review in the sense of adjudicating the quality of the science. The role of early protocol by protocol review, if at all, is to understand the limitations which we believe moral constraints place on the science.

To the extent that we have been asked to deal with the question of what, if any, of these activities should be federally funded because of moral counterweights, I think that is something which one looks to have a uniform perspective on. One thinks about the kinds of things we are heading towards and recommending in terms of the conditions that will govern the generation and derivation of the ES cells, e.g. from spare embryos if and only if those spare embryos are collected with certain consent provisions, separation, et cetera.

We are taking as a model a federal statute which is uniform for all such activities in the case of fetal tissue regardless of where they take place. So that leads me to think it is a single body.

DR. SHAPIRO: Okay. I have Trish, Tom and Larry.

DR. BACKLAR: I will pass.

DR. SHAPIRO: Tom?

DR. MURRAY: It seems to me a general problem in public policy is how to balance between on the one hand a kind of flexibility, diversity, let 1,000 flowers

bloom, the laboratory of the states in legislative matters would be an analogy, and the desire for a kind of consistency, uniformity, simplicity so that people know what the rules are and they are not different if you go from Chicago to Milwaukee or if you go from NIH to FDA or to some other agency.

And that is a trade off. And the reason it is a persistent trade off is there are virtues and disadvantages either way you go so we need to think about the virtues and disadvantages for the particular set of issues that we wish this particular body or bodies to deal with.

I have a couple of thoughts about that. If we went with the multi -- the many bodies route, what would we have? Well, researchers would face a wide variety of different rules and most researchers will not want to invest considerable portions of their time just to figure out what the rules are, and they will complain about the lack of uniformity among the different agencies, the rules are being changed in them all the time. We can hear a lot of those complaints so that is a disadvantage to the many bodies rule.

Another disadvantage to the many bodies rule is some agencies will simply not think this is very important. They will follow the letter of our recommendations, that is they will set up a body but they really will not pay attention to it. They really will not care and the body will understand that and will exercise minimal judgment and control and things will be done.

And some things will be done that may outrage segments of the American public. Other agencies will be very, you know, careful and try to make sure that things do not run off the deep end but some agencies will not be -- and things will be done. That is what we will be fixed on and so in a way the many bodies rule might create a larger political vulnerability because things will happen because of inattentive agencies that will make people angry.

DR. SHAPIRO: Larry?

DR. MIIKE: If you look at what we are going to recommend, we are going to be recommending things as a bioethics commission and what we ought to be saying is that given the more concreteness of the potential of the

benefits of this technology we feel comfortable in saying that at least the wedge opening in two areas, aborted fetuses and extra embryos from IVF's, and that we are also saying that we feel comfortable in doing that because the promise of the benefits are more tangible now and that is why -- one of the reasons why we want to track the tangibility of that.

Beyond that I do not think we should go -- and the issue becomes really more a one-time and then a follow-up kind of issue. The one-time one is, okay, if that is so, what are the concerns around the derivation process about how you get the stem cells. And then after that it is almost a mechanical kind of thing, is that how does one assess the fruits of the research of using stem cells, which is going to be the peer review process, et cetera.

So I was thinking that what could be done is that since we have the excuse of a time limited recommendation in terms of what we come up with by next month or the following month, I would say that in terms of the derivation issues this is a one-time study that something like the Institute of Medicine could do and

they could also work with the agencies to say what is the proper accountability or evaluation process by which one tracks the research, and then leave it also up to them to say five years later what is the advancement in this area.

So that I do not really think we need a commission or a large body that is continually looking at the derivation side. I do not think we need a commission for the use side of the stem cells. So I think a body such as IOM which is a different -- it will most likely have ethicists on it but it will have a heavy scientific component on it and they are outside the government and they are well-respected institutions. So that is what I would recommend.

DR. SHAPIRO: Let me go to one particular part of that recommendation, Larry, because it is something that I have also been thinking of, and that is a distinction that Steve raised yesterday but I am not claiming to summarize what he said but I remember him raising this distinction and that is that it is a distinction between use and derivation.

Let's just think about use for a moment.

What do we want to happen if there are protocols accumulating now as we speak before NIH to use existing cell lines for particular purposes? What do we want to happen in that case? Do we want this to just be judged by the scientific review, typical scientific review that goes on in peer review and so on to get NIH grants or other grants of that kind? What do we want to happen? Do we want IRB's to be involved or not? Who is going to specify, if anyone, whether these cell lines were derived from the sources that we are speaking about? What do we want to happen if we are just concerned with protocols on use? Now put aside derivation for the moment.

Where, if anywhere, should these get reviewed outside of the normal study sections and so on that go with any kind of research grant? How do people feel about that rather restricted issue? It would help me a lot to understand how we wanted to deal with those simple cases.

Eric, and then Bernie?

DR. CASSELL: Well, they are not simple questions.

DR. SHAPIRO: They are simpler than others to

describe.

DR. CASSELL: Well, actually I think that the -- my answer to that underscores what Larry said. We want to see the goal of the use. We want to know where is it going to. What kind of technology is it leading to? Is it leading to something that is an enhancement technology for just a few more or is it going to have widespread benefits for the country as a whole? Is it using resources the way we indicated that it should? In other words, there are certain social issues where judgments are made on a social rather than a purely scientific basis and that is the thing the IOM was actually set up for. In its original charter that is what it was out after doing.

DR. SHAPIRO: That would presumably -- you want to do that on a protocol by protocol basis?

DR. CASSELL: No. I think that once you get by immediate use -- I mean, derivation, the protocol by protocol basis has to meet certain tests and that is what this committee/commission should be setting up and should be deciding. These are the tests that a protocol has to meet. Whether it goes on a protocol by protocol basis to

see if the tests are met is secondary to establishing what they should be.

After all, we do not really know what is going to be with all this stuff. What is going to come down the line. And so it is sort of not saying, oh, well, this protocol says "X" will happen. It is more on a basis of if the promise is realized what social or biological or philosophical issues are raised by that that have to be resolved for its proper utilization.

DR. SHAPIRO: Bernie?

DR. LO: Yes. I guess I would echo Eric's comment. I think the studies dealing with use are simpler than the ones done with derivation but they are still not entirely straight forward. I am a little reluctant to sort of say there is scientific review and that will take care of most of the problems with this class of studies because it seems to me there are issues that are scientific but also have a real sort of value component to them.

I agree that there are a lot of studies, it seems to me, that will be very basic science having to do with identifying growth factors and protein products and

things where it could be applied to almost anything. I do not think you can say what the end use will be but would be justified as being important.

Then it seems to me there are other studies that really have to grapple with the question of whether you can do similar research with nonhuman cell lines as human cell lines. I mean, one of the things that -- I mean, if respect for embryos as being more than just clumps of tissue means something, it means that we need to be especially -- we should not use them indiscriminately. We should not use this technique when other techniques can suffice. So it seems to me there is some justification for saying the time is right to use a human cell line rather than an animal derived cell for the following reasons.

The NIH panels that do peer review do not -- they are scientists and I think that this is something that is exclusive in the domain of scientists, and I think that the chance to have sort of lay input or disinterested or less -- input from scientists who are not experts in the field is a valuable one and that is missed, it seems to me, by the current peer review

process.

The other thing I think that we need to -- I would suggest we pay attention to is this notion that this is new, this is uncharted territory. We maybe get into unanticipated ethical dilemmas that we need to be prepared to solve and I think that some of the concerns about any new -- radically new technology like this have to address the newness of it in the sense that we do not want the technology to get out of control.

And I think it would be worth paying attention to those concerns and designing systems that at least at the beginning has a sort of go slow component to it that is temporary but is -- sort of shows that we want to take an honest look and reassure everybody that when this gets started it is going to be well managed. It will be not uncovering unanticipated ethical problems.

I think to say, you know, this is straight forward and we are not going to have to worry about it without really seeing what happens may to some people seem to be short sighted and I think we need to sort of be willing to say there may be things that crop up that we cannot anticipate until the studies actually take

place. So I think that it is a balancing act.

DR. SHAPIRO: There are two classes of things here as I am trying to listen to these comments. One is issues that are sort of longer term in nature, asking ourselves, you know, where has this set of activities brought us two, three, four years from now? What are the new technologies contributing to that? How do we assess it? How do we adjust what we are doing? There is those kinds of things which are not day-to-day issues. They are issues of at some point sitting down and thinking carefully and deeply about these issues once again and recommending changes.

There is a whole series of very worthwhile issues which ought to be on our minds here.

Then there is the issue of just how do we handle the authorization of -- what we are saying is not that the federal government should spend X on this? We should say that these things if they are meritorious ought to be eligible for federal funding.

And I understand that and accept the notion, Bernie, that we agree that this is special material and, therefore, it has to be treated as special. It is not

just like any other research grant which goes through the NIH or somebody else's process and, therefore, we need something. I really -- but I think that is the reason I feel that we need something that is right there, that this -- we have decide this material is not like other material. Whatever -- we have different views of just what this material is but it is -- we agree that it is special and deserves some respect.

And the question I would then ask is if we focus just on that, if we focus just on the fact that this is new territory, it is morally contested territory, we all think it deserves some kind of special care in thinking about what to do and what one should authorize. Now if you think -- just focus on that issue, then does that lead you to say that we need protocol by protocol review at, for example, a national level? If not there, where else could it occur? It is somewhat different from the standard IRB stuff which comes out of another tradition all together.

Where, as you see it, would that occur?

DR. LO: I would actually support it occurring on a couple of levels but primarily national.

I mean, I think that a research scientist that submits a grant to the NIH on this ought to take the humble position that maybe this is very straight forward but maybe it contains some ethical dilemmas that I have not thought about, my collaborators have not thought about, and it will be good to get some fresh input from people and start at the university and have somebody at the university local level look at those issues.

But then I think I would actually favor a protocol by protocol review at least at the onset. We are assuming that the usage protocols are going to be straight forward in that they will not call into question the assumptions about the derivation but if in the first ten protocols, in eight of them serious questions were raised about the consent under which cell line was derived, a payment for the cell line, issues like that, the payment either to the person making the cell line or the payment to the woman who donated the oocyte, it seems to me that would start to raise concerns. Whereas, if they were just really embryos that were discarded or fetuses where the abortion decision was clearly insulated.

I mean, I think we are making some empirical assumptions that the decision to abort and decision to donate the fetal tissue are separate and that certain things about the donation of the oocytes were appropriate. Those turned out not to be true. I think public confidence is going to be really shaken, as well it should be.

DR. SHAPIRO: I should not be talking so much especially since I have four people on my list here but I want to just pursue one part of this and then I am going to stop and go to my list.

There is a likely -- in my judgment, I could be totally wrong, I am not a scientist like many of you are, that a lot of the early protocols are going to be using the same cell lines. So you would not want to have some group go back and ask all the appropriate questions about every cell line about 300 times rather than once if 300 protocols are using a single cell line.

So perhaps one way to conceptualize that is at whatever group we put together, whatever group was put together nationally, in some sense they can authorize a single cell line once and anyone who wants to use that

dose not have to go through that aspect of the review and maybe other aspects of the review that are raised by particular protocols that will need to be adjusted and that, I guess, might make things a lot easier if that assumption turns out to be true. Maybe it will not be true.

DR. LO: It may just be that you draw up a set of specifications that say that a cell line that meets these specifications in terms of its derivation is ethically acceptable for use in these kinds of -- but I am just saying to draw up the list in advance without seeing actual examples sort of creates the impression that we kind of know all the problems in advance, and I am not sure we do.

DR. SHAPIRO: Okay. Steve, Eric, Larry and David?

MR. HOLTZMAN: I have written this in some stuff I gave you and Eric but to me the role of this body is along the following lines:

First with respect to the derivation, I believe we are going to be laying down what we believe to be conditions under which derivation will be eligible for

federal funding. And then one role of this body is to be reviewing those conditions and asking the question as new science arises whether those are too lax, too restrictive and whether they are resulting in abuses. So that is one role.

With respect to the use of cells which meet the conditions for appropriate derivation, it seems to me that the questions that this body would be looking at is not the scientific validity of protocol by protocol but rather the question of are there classes of protocols which are acceptable, not acceptable or not acceptable at this time or worthy of examination to think about it.

If we go back to the embryo panel, it is exactly what it did. It created three buckets, all right, and thought of a body who would be looking at those buckets and thinking about them. And so the role of protocol by protocol review, as Pat King said, is so to speak to build a body of knowledge. It is not really to review the specifics of the protocol other than to try to elicit more general kinds of knowledge.

So certainly you can come up with a scientifically valid approach to inserting growth hormone

gene into a short child. The consideration is whether that kind of protocol at this time in history is acceptable and that is the kind of thing that this body should be thinking about and looking at.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I actually hear us building a conceptual structure in these comments. We are doing something which in the past would have been considered anathema. We are holding back the development of science in one area or another area. We may say promoting but that always means alternatively holding back rather than the free expression. Wherever it goes is where it ought to go.

This says in this area that is not the case, that there are some things that are more acceptable than others, that there are now social ramifications that are essential to know about before something becomes a scientific project on line, and that does involve as I have just heard from Steve, from Bernie, that does involve both looking at the derivation and looking at the direction of the utilization. And the growth hormone one is a really excellent example because it is complicated

and the people who actually do the work are just not capable of making the decisions about their own research, and I think this is much the same thing.

DR. SHAPIRO: Larry?

DR. MIIKE: On the derivation issue I do not see a problem with it -- when a research project comes up and it has a new cell source that there is a protocol by protocol review but I agree with you in a sense that that is going to be not really frequent so it is a handle-able problem.

In terms of the uses, clearly NIH is developing a research agenda for that and it seems that the obvious way to deal with that is to have something like an IOM to take a look at that and see by the classes of research that is being contemplated which are the ones that are most sensitive and which -- they might be able to parse out areas in which more scrutiny is needed.

Then my third thought is that I assume that we are not all talking about any kind of body, whatever it is, that has to be legislated because that is just an opportunity not to do anything and that if the Congress lets this go through with the funding aspects of it all

then the oversight side should be administrative and should be flexible on that.

So that is my -- I still think that a one time review about the derivation issues and, as Steve said, we are going to be setting out the parameters through what is an acceptable derivation by consent and et cetera, and which areas in which we do that. Then whatever the body is -- if we set up the parameters of it all then I do not really think that it is a big issue whether it is one big body or within the agencies that are following that protocol for that review.

And then as far as the use goes I still think the IOM is the best mechanism. They are an outside body. They have a good reputation. They can put together a group of people that would be much more diverse than anything that we can do in this body and they can -- they are used to dealing with both the social and the scientific issues around any technology.

DR. SHAPIRO: Thank you.

Steve?

MR. HOLTZMAN: So at 4:30 this morning when I was thinking about examples of what --

DR. SHAPIRO: That was 5:30 Eastern time.

MR. HOLTZMAN: It was normal time. -- thinking about what would be examples where such a body would then say this is in the use arena, here are licit and here are illicit uses, and thinking about the Embryo Panel as the paradigm.

It struck me that the notion of respect for the embryo since in each new protocol you would be destroying embryos the question came up about whether there was enough value in that activity to justify that.

But now when you move over to ES cells, if for a moment you assume that ES cells are plentiful, they are immortalized, you can proliferate them, we have had a few derivations, now we have plentiful sources of ES cells, aside from any kind of protocol which involves the reimplantation of those ES cells say into a blastocyst and then back into a woman, what are the moral considerations that would lead one to say this research activity with ES cells is respectful versus this would not be.

In other words, how do they differ in that respect once you assume that they are there and plentiful

and you are not touching new embryos? How do they differ in that respect than questions that arise say with HeLa cells or any other human cell and how would we be thinking about that? I did not have a real good answer.

DR. SHAPIRO: Bernie?

DR. LO: I think that is a great example, Steve, because I think we need to think through whether they are different in some respect because of the way they were derived. So even though right now they are plentiful, at some point they came from a morally complicated decision, unlike the HeLa cells, and it seems to me that it could be argued that we should be more careful with the stem cells in sort of how they are used and not to waste them in some sense and use them only for high quality projects where there was not a good alternative and to use sort of a minimal number rather than a extravagant number.

I do not know if that gets wrapped up in this notion of respect from the ultimate source in which they are derived even though currently they are, as you say, plentiful. I do not think it is just a -- it may not be just a numerical sort of availability problem but the

fact that somewhere back in its origin there was a morally complicated situation that we would like to try to recognize in some way.

MR. HOLTZMAN: Just real quickly, again my memory is not good enough, I tried to go through in my head the Embryo Panel, what was okay and what was not okay, and tried to figure out the moral animus to those and whether that would affect ES cells downstream, and again partly from lack of memory I could not come up with a connection but it is worth reviewing, all of us.

DR. LO: I think to be honest that was not really the major focus of our work.

DR. SHAPIRO: David, and then Larry?

DR. COX: So, Steve, I wrestled with exactly the same question because the --

DR. SHAPIRO: He is Pacific Coastal. It is 1:30 in the morning.

DR. COX: Yes. It was like really early for me.

And the answer I came up with was the following: It comes through -- for me at least, this complicity argument is that the tie with the cells in

terms of the history is if you are complicit in something that happened early on. If you are not complicit then I do not see anything special about the cells per se and I do not think anybody would worry about them but it goes back to the derivation so to me it is all about the derivation.

Now I think anything you do with human cells you are sort of respectful for but I think we get on to exactly the wrong track if we start, you know, having different types of human cells because I mean we have got jillions of human cells and a human cell has very different things. It is a very different thing than a human being. So for me it is this complicity argument and that is why I am listening very carefully to these ethical and moral and philosophical discussions about complicity because I think that is what it all hinges to.

The other thing, though, that I would like to say is that I really agree with what -- in the earlier discussions what Steve, Bernie and Larry all said about the use. I really think that it is having categories of use and if you cannot come up with a category of use that you think morally you would not want somebody to do then,

you know, it makes the use part of it not something that we have to deal with.

But I think that unless you have an IOM or somebody going and talking about are there such categories of use that you do not want to see happen, it is not going to happen in terms of an IRB review or anything else because no one is going to know what the answer is.

So use to me -- let me summarize. The action is all in the derivation. We have to decide if we want to do anything about use. To me, if we want to do something about use it involves, you know, thoughts about complicity. That even if we decide, though, to do something about use we need a list of things that through the complicity are unacceptable to do, and I want to see what that list is and that is not going to be used because we do not have enough time to do it, so some group, and I think the IOM is a good one.

DR. SHAPIRO: Okay. There are three more people. Then we are going to have to get on to the next part of our agenda.

Larry, Tom and Bernie?

DR. MIIKE: I do not think on the use side, I do not agree with Bernie on the use side about being worried about where these cells came from. If that is a threshold question that is answered and it has been blessed that these particular types of cells are okay and they were ethically obtained, we do not need to revisit that issue every time those cells are used.

I think that the more important thing, and it is going to be anathema to the research community, is that some social policy work is going to be demanded on the types of research on the use of the cells and, you know, it is -- we are going to get into the old NIH argument about scientific opportunity versus burden of disease versus social worth, et cetera, but I think somebody has to do it.

And I think that that is the -- I think that is what we are talking about, what -- how we are going to value different classes of research uses but I think that has to be done and that I think that just the fact that it is going to cause uncomfortableness in the research community would also tell everybody that we are not letting the research community decide by themselves about

what is the value of this research.

DR. SHAPIRO: Tom?

DR. MURRAY: Yesterday I raised the question of whether it was worthwhile distinguishing between thinking about the ethics involving the derivation of these cells and the ethics involving their use, and it was argued that I should not but I think today the question has reemerged in a slightly different form. Steve just capsulized it.

Once a threshold is crossed and ES cells are used in research then I think most of the morally novel questions will, in fact, concern use or concern rather derivation by use. Some of the questions about use will be -- but they will be the kind of questions that will be familiar. Human applications, when we do -- people start the first transplant experiments with ES cells in humans that will raise ethical questions, of course, but they will be familiar questions about the ethics of human experimentation.

There will be questions raised about the sources of ES cells. If people wish to create new kinds of ES cells or ES cells by new methods or from new

materials. There will be questions raised about comodification and commercialization. I certainly anticipate those. It is an issue that touches many people. But they will be issues basically -- I am agreeing with Steve and trying to underline it -- in the derivation or creation of new embryo -- new ES cell lines rather than in their use. The use questions will probably look rather familiar to us.

DR. SHAPIRO: Thank you.

Bernie, the last comment on this.

DR. LO: I guess I would want to still think through more of the issue of -- ethical issues in the nonderivation side because I do not feel comfortable with the argument that Steve and Dave and others are really quite persuasively making but, you know, once you have sort of settled the questions and you have the cell line those issues are no longer as salient.

It just seems to me that there is a -- commodification comes up in a sense that I am not comfortable saying that a stem cell line that was obtained in the past appropriately from fetal tissue or discarded embryos is just like other cells, David. I

mean, I think that if it was really just like other cells I would not be concerned about how many of them I had to use in an experiment. So if it was one out of 1,000 attempts I had to make I would not be concerned.

It seems to me if there is something about where those cells came from that makes them more than just other cells I would personally want to see a higher threshold for success rates and not to just say, well, we have got a supply, we can just use them because the supply is unlimited. I think that in a sense treats them like interchangeable sort of commodities, which is how we use other scientific materials.

I am just not comfortable and I do not know if that is rational or what but I would want to think more about that.

MR. HOLTZMAN: I think we really do need to think. I think going back to the Embryo Panel and seeing if there is anything that carries through that post derivation would be useful. Second, if staff could look at are there any guidelines, regulations, anything pertaining to the use of fetal tissue.

I mean, if your argument holds, Bernie, it is

going to carry even more strongly for fetal tissue than it is for -- as per my experiment -- plentiful ES cells. There is a reason I said they were plentiful. All right. If you take that as a starting assumption it can change a lot of the dynamics about social justice as well as some of the issues of respect. All right. So I think it would be useful to see if there is anything along those lines currently in play.

DR. SHAPIRO: Okay. Thank you very much. I think that has been a very useful discussion and I want to thank everybody for participating. Now when we actually put this down in writing we will see if anybody recognizes anything that we struggled with late yesterday and today but we will do our best.

Professor Lori Andrews is here now. I think you all have met her.

Welcome. Why don't you just come and sit at the table here at one of these -- any one of these chairs. I think that all -- first of all, I want to thank you for coming today and thank you also for the material that you have provided the committee. It is very helpful to all of us and thank you very much for it.

I believe it is fair to say that -- I do not know if every commissioner -- many commissioners have read the materials but we certainly look forward to hearing your own perspective on these and then we could go to questions.

So thank you very much for coming and since I prefer not to take a break now since we are kind of pressed this morning you will excuse various commissioners for getting up an stretching their legs, getting coffee, and so on. It is not meant as any sign of impoliteness.

Thank you very much for coming.

STATE LAWS AND REGULATIONS

LORI ANDREWS, J.D., CHICAGO-KENT COLLEGE OF LAW

PROFESSOR ANDREWS: Well, I am quite honored to be here and have been asked to comment on this important issue.

I think that in discussing the state regulation of use of embryo and fetal tissue, it actually has application to two of your projects. The first of which is the embryo stem cell project that we are talking about today but it also has relevance to the work that

you are doing on stored tissue samples because, of course, IVF embryos are stored tissue. And I think it puts in bold relief some of the concerns that do move over to your other report.

Consider the woman who undergoes in vitro fertilization and has fertility drugs and maybe has -- I know some women who have had as many as 24 to 40 embryos frozen that they later have to make decisions about using. When they go into the process they get a little form where they check off do you want these used for research, donation to another couple or termination if you choose not to use them.

Now I think the woman who checks off research and then are potential sources for embryo stem cell research may, in fact, have in the back of their mind that these will be used for research related to infertility and if that is the only directive that they give, you know, they may have an issue. I mean, think about it.

If someone -- the research project was to make a clone, you know, one of those women may not feel right about her clone being out there but another one of

those women may say, "I was fine with having research done on my excess embryos for infertility purposes but I am not so comfortable having it made into a line of heart cells or attempt to grow a kidney out of what would have been my potential child."

So people do have strong feelings about what is done, in this case, with their reproductive material but it is just an example about how people may have interest in what happens to what you might otherwise think of as abandoned tissue.

I see that all the time. You know, for example, one New York researcher said to me he was shocked there were these embryo research laws in the states and he said, "Well, that is totally inappropriate. It is just tissue." But, you know, for some people, embryos and fetuses are not just tissue. And it echoes things going on in other areas where people have beliefs about how their tissue will be used.

For example, in Orthodox Judaism where the idea is the body should buried whole and actual -- rabbis are actually lobbying the pathologists who kept Einstein's brain without his consent to rebury the brain.

To bury the brain. There are concerns with among the Navajo about how a placenta is being used since they have other beliefs. I have just come yesterday from a meeting on newborn screening in Washington where Jane Lin Phu gave a sort of impassioned plea about what African Americans and Asian Americans think about what should be done with excess tissue in newborn screening.

So this does tie into work you are doing across the board and it becomes important.

Immediately after the embryo stem cell research was done I got a call from a clinic that said, "Hey, we look like -- we think we are sitting on a treasure trove now. You know, we have got couples who seem to have abandoned their embryos. We do not know where they live anymore. Can we just go out and sell them?" I thought that might be at the least -- at the very least a big public relations nightmare if they did that and then some of the couples did show back up.

And, interestingly, the law is beginning to recognize more and more these interests that people have in tissue outside their body. Things like Magpra (?) which has to do with returning Native American remains to

descendants.

We are all probably familiar with the John Moore case saying that a person's tissue outside their body was not property in the California Supreme Court case where a doctor made a patented cell line but that was 1990. And since then I am seeing an increasing number of cases, for example, dealing with a couple's embryo, dealing with corneas, dealing even with use that an artist made of human tissue outside the body saying, "This is property."

And so in some sense it relates to the discussion you just had about derivation and use and so forth. There is also getting to be an increasing number of cases that say you have to apply the justification that you had for first taking tissue to all subsequent uses. There is a case being litigated in Massachusetts now with respect to forensic DNA samples which said, you know, if you got it by the Fourth Amendment and had probable cause at the first taking you cannot then just do whatever you want going on. So there may be areas in which, you know, use and derivation are connected.

And I think in large measure some of the

concern has to be about what sort of trust this all generates in the research enterprise and what people's expectations are. So it is important, I think -- and you will think this strange coming from a lawyer -- not just to look for loopholes in these laws as justification. You know, I mean, just because you can do something in a certain state you might want to have the kind of level of moral discussion that was taking place as I came in today.

On the state laws themselves an important thing to recognize is that they apply no matter what the source of funding is. They do not just apply to federal funding and they do not just apply to state funding. They apply even if Geron Corporation is in that state. They apply also no matter what the institution is and, you know, whether I have opened a tissue bank in my basement or whether I am at the University of Chicago here, they apply there.

And they really came out -- these 26 states that have fetal research laws were adopted over 25 years ago in the wake of the decision legalizing abortion and the whole idea was before when abortions were done in

back alleys or women spontaneously miscarried, we did not have a collection some place of tissue that might be of great interest to scientists but once we moved abortion legally into health care facilities there was more fetal tissue available.

There was some evidence of abuses. Of research being done on late stage fetuses, some which showed certain signs of life, that the community at large did not approve of and so 26 states did adopt these laws to restrict the type of research that you could do on fetuses.

I think it is important to keep the abuses in mind because, you know, we often get so caught up in our own context of what might be beneficial research because when we look back at some of the earlier studies done, you know, peeling off the skull of, you know, fetuses, late stage fetuses to do certain research. Or around the contraception research, women were actually told to have sex with their husband before they underwent hysterectomies and so forth and not told that their embryos were being collected. And we look back on that and say, "Well, that is, you know, inappropriate now."

I just want to get us thinking, you know, at the question of how we are going to look historically with what we do at this point.

The language of these laws varies dramatically from state to state and, you know, in part because the immediate problem on the table was really research on later stage fetuses but some states defined fetus as any product of conception from fertilization. So that when other things came along, in vitro and so forth, the coverage of the laws applied as well.

Very few states actually have adopted new laws to deal with the new technologies. In Louisiana there is a law which was adopted in the wake of in vitro fertilization that said, you know, the only legitimate use of IVF embryos is for implantation. You cannot terminate them. You cannot culture them, farm them for research purposes, no research on IVF embryos.

New Hampshire in the wake of in vitro fertilization adopted a law that said, you know, that comports more with international guidelines in the area and says, "Research is fine for the first 14 days after fertilization but do not implant that embryo." We do not

want the sort of thing that then, you know, obviously had relevance with when human cloning came along. You know, we are worried about the risk to the offspring.

But those are rarities in that they had new laws to deal with the new technology.

What usually comes up is you have new technologies and then you go back to each of these state laws, all of which had different, you know, dimensions to them, many of which require referring to other statutes to see actually how did they define a fetus in that state, you know, some actually define a fetus in ways that include some signs of life and would not apply to early embryos.

In doing that what I found is that there are nine states that would ban the embryo stem cell research involving in vitro fertilization embryos and those are in a chart that I provided for you. There are other -- another set of laws then that would apply to fetuses, later stage fetuses.

And while medically fetus is defined as after the eighth-week of pregnancy, in a lot of these state laws it includes earlier stage fetuses that medically and

technically would be considered embryos through the first eight weeks so when you look at Dr. Gearhardt's work and it suggests that the fetuses used were between six and nine weeks it does not mean that if I go to one side or the other I can escape the laws because they often define fetuses as the entire -- from the moment of fertilization.

The laws are less restrictive on research on spontaneously aborted fetuses as you might imagine, given their derivation, their concern post Roe v. Wade. But that is -- that does not give us very much leeway because most researchers do not want to do research on spontaneously aborted fetuses. They are, you know, not only likely to have themselves some genetic anomalies but they are not available in the places where you need them.

So six states have laws that would cover the sort of work Dr. Gearhardt is doing where six states require mother's consent and then research can go forward. Another six states prohibit it entirely. And part of the issue, you know, on the table for you all with respect to that ban is that some prohibit the use of any part of the fetus and that may cause difficulty even

if you are talking about, you know, derived cells.

You can make a good argument in some states that the newly created cell line is something different but in other states, Arizona and North Dakota, the language is broad enough to include, you know, the cells. And these are criminal laws. You know, these are not just like federal human research regulations. We think it is a great idea if you use informed consent. We might not give you money if you do not. But it is like you go to jail and the woman goes to jail and so they cannot be taken lightly.

I did not actually address it in my paper so let me elaborate that the cloning issue, the technique used by Jose Cibelli, cheek scraping into cow egg, and part of the reason that I did not is that even though California, Michigan and Rhode Island have adopted laws to ban human cloning they only apply when you create a child through it. So we really do not have statutes that technically would apply to that procedure itself. However, you know, once you create an embryo through that means the nine states bans on embryo research would apply even if there is some cow DNA, you know, in there.

There are also issues around commercialization and there are broader -- there is a broader sweep of laws that include bans about payment. There are 13 states that ban payment for IVF embryos. Ten that ban payment for aborted conceptuses and some of these states do apply to parts, you know, and so it is not just that, you know, we do not want to have a kind of market in fetal oddities when you think about how in the turn of the century circuses they would display, you know, a two-headed fetus or we do not just want to prohibit sale at that level but also, you know, sale of tissue as well in some states.

And some of these laws apply to procurement, payment to anyone to help you procure fetal cells, and so obviously we do not want to get NIH into difficulty aiding and abetting in these criminal laws if you pay someone in a state where that very job of being an intermediary for distribution of fetal cells is illegal.

Apart from these laws, which came up very much in the context of abortion and fetal research, there is the separate set and we have a separate chart that we sent you on payment in connection with organ

transplantation. Again you have got some definitional variation but certainly not as much as with the fetal research laws. It is -- if decedent is defined to, for example, only include stillborn fetuses and not aborted fetuses then those payment applications are not going to apply. So in a state like Arizona that is the issue.

But there are other situations in which this might not apply. The dominant regulation is for payment of organs and organs is defined broadly enough to include tissue of any kind in most states but primarily in transplantation and therapy. I mean, that is where the monetary abuses were. That is where people were flying in from other countries and saying, "I will give you $50,000 for your kidney." And so the regulation responded to that abuse just like a fetal research law responded to abortion.

And so -- I mean, I think arguably in states you could say, "Well, this is in transplantation and therapy. If I am doing basic research, you know, then we would click in these bans once I tried to sell it. I mean, if I came up with some snazzy heart cell out of this and went to market it, those would apply."

And in some instances, though, a subset of those laws, about 16 of them, do allow payment for removal and storage, et cetera, and so would allow NIH then to -- even if the broad laws did apply -- would allow payment to intermediaries there.

So, you know, that is the lay of the land. There is such widespread social, moral, legal dispute over the status of the embryo and fetus. It has come to the fore in different ways in different states in terms of what they are trying to, you know, protect. Ironically, North Dakota is the only state that would ban both forms of embryo stem cell creation whether through research on the embryo or research on the fetus.

So I will open it up for questions if you all are interested.

DR. SHAPIRO: Thank you very much and thank you very much for your presentation.

Steve?

MR. HOLTZMAN: Well, first of all, thank you for this and a belated thank you for the incredible work you did in support of the cloning report on a very, very short time frame. That paper just was a blow away. It

was incredible. It is a privilege to meet you finally.

Two questions because I want to make sure I heard you right. First, do you take any of the state laws in this chart, I assume, as prohibiting research using ES cells, not the derivation, the use?

And then the second, and it may talk to that, you made the statement with respect to the sale prohibitions, I think you said would apply to a fancy heart cell line but then by implication you are saying the downstream cell line would be considered a part and, therefore, not -- I am not sure that -- is that -- did you mean to say that? So those are my two questions.

PROFESSOR ANDREWS: On the latter question first. In Minnesota, I believe it is, for example, they specifically say that the cell lines are something different and so sale of the cell lines would be permissible. Other states, though, do not make that distinction and may, in fact, consider cell lines to be part -- you know, if the progenitor cells would be covered by the ban, these downstream cells would as well.

MR. HOLTZMAN: Do they currently --

PROFESSOR ANDREWS: So there is more of an

open question about it. They were not developed with that in mind certainly but the whole problem with all these laws and the reason, in fact, some have been held unconstitutional is that they have this broad reach. They were developed for other things but they apply, you know.

MR. HOLTZMAN: But they do not currently apply to biological products derived from parts, correct, e.g. serum derived factors and whatnot?

PROFESSOR ANDREWS: I think that you still have to be careful when your source is the fetus. I mean, obviously they do not apply -- those that are in the context of fetal and abortion laws are much broader and many things that I could do with the consenting adult volunteer, I could not do with an embryo.

I mean, I point out some ways in which, for example, just embryo fetal, you know, tissue is viewed differently. For example, there are states that give funding to encourage people to give tissue and say but you cannot use any of these funds to encourage people to give fetal tissue. It is just, you know, scientifically it may have, you know, some of the same characteristics

and so forth but on a policy vein it is just -- it is looked at differently.

As to, you know, the first question, even the embryo research laws in some states do talk about parts, talk about research involving organ or tissues of fetuses, you know. So it is hard, you know, to use -- just an example of language, in Arizona you cannot use a fetus or embryo, living or dead, or any parts, organs, fluids of such fetus or embryo if it came from an induced abortion.

DR. SHAPIRO: Larry, and then Tom.

DR. MIIKE: A follow-up question and then a separate question. In some of these states if we look down the road and there are livers being able to be produced, tendons, muscles, et cetera, from these stem cells, those sales would be illegal also?

PROFESSOR ANDREWS: I think at least in some states where they talk about any part they would view, you know -- they -- the legislative intent would say, well, I am not so keen on you selling, say, eggs from abortuses, you know, which has been proposed in Great Britain and/or a kidney from an abortus.

So why should I feel any more comfortable if you change things around and happen to make it so it is more compatible to me and create out of that same abortus many, many kidneys or many cells and so forth. So in some states that will be a problem. Very few. You can obviously do it in other states.

DR. MIIKE: Right. And there would not be a federal-state issue here if we are dealing with interstate commerce once it becomes -- suppose it becomes a commodity that Eli Lily has, you know, the detail man going out and saying we have tendons, we have muscles.

PROFESSOR ANDREWS: You know, in that sense it only -- states can also regulate unless the Federal Government preempts them and in many instances, for example, the federal regulations on research with dead fetuses, specifically say in them you also have to comply with state laws.

So there are then a variety of questions. Could -- do I think the Federal Government could come in and say we will permit this under X, Y, Z circumstances or we will forbid it, I have a broader notion than many lawyers about what the Federal Government can

permissively do and the fact that patients do travel to other states to get medical services that they bill insurers in other states, I would say it is an interstate commerce issue. The Federal Government can act. When they have not, though, these state laws would apply.

When they have and they have not totally covered the field and thought of everything, you know -- in many instances we have state laws that are more restrictive and that is thought to be permissible, you know, discrimination laws, you know.

DR. MIIKE: That was just a speculative question because if the fruits of this research do come about then that is going to be an issue.

My other question is early on you said that in the IVF clinics there is a little checklist. You can discard my embryo, et cetera. To us that would be in terms of a human biological report a general consent that any kind of review would say if that was not what was contemplated then a better consent process would have to be -- and I would guess that you would agree that --

PROFESSOR ANDREWS: Yes. I mean, I think that people should be told that this is going to be a

proposed use and I also think we need to be -- when we get further down the line and have therapeutics -- be telling the recipient as well because some people may not want fetal tissue or fetal derived products implanted in them much as Jehovah's Witnesses do not want blood products. So I would be for disclosure on both ends.

DR. SHAPIRO: Tom?

DR. MURRAY: Thank you very much, Lori.

I have a comment to try to -- well, to thank you for reminding us that many of these laws were passed not with a single purpose in mind but really with a number of moral purposes in mind and I am going to just mention three, which I think are consistent with the ones you have described.

Namely sometimes it was because of a concern that seems to be related to the notion of the very special moral character of a particular kind of human tissue, that is tissue derived from embryos or fetuses. That was concern number one.

Concern number two was to deter kind of possible abuses like, you know, outrageous experimentation.

And number three was particularly with the organ transplantation law to embody in -- it is probably the wrong metaphor here -- but to embody a set of moral concerns about the special character of human tissue more generally or at least a tissue that was of significance in gifts relationships. You and I have had some agreements and disagreements over what that means.

PROFESSOR ANDREWS: A fourth is a potential risk to the mother because there was concern that women undergoing abortions would be subject to procedures that were riskier, they might be given drugs in advance, and I think that is another something we have to have in mind here if we are going to encourage say sale of excess embryos for research. There might be a tendency to give women more fertility drugs to create more excess embryos or it may turn out that if you treated the woman a certain way you had a better chance or you delayed the abortion you could get more of the kind of tissue that you wanted from aborted fetuses and their gonadal tissue.

Sorry, that was a fourth one.

DR. MURRAY: Not sorry at all. Thanks because that is important -- an important addition.

Two questions. One is do any states at this point have laws that prohibit not the sale of -- not the commercialization of embryos but the sale of gametes and/or -- and ova, of course, are --

PROFESSOR ANDREWS: Louisiana prohibits the sale of eggs, of human eggs. The -- you know, if you look from state to state on their definition of what an organ or a body part is there are some that are broad enough to include sperm or eggs even though that was not the intention. I mean, for example, some apply -- have exceptions for replenishable body tissue so you can sell your blood and arguably then you could sell your sperm.

Well, if I am born with all the eggs I will have for my lifetime, even though there may be a lot of them, your argument, it is not necessarily replenishable so those states might, in fact, ban the sale of eggs as well.

DR. MURRAY: The last question. Do the states that permit the use of tissue derived either from embryos or fetuses or both or that do not expressly ban it but that prohibit sale, would they -- how would they understand the way sort of we respond towards the

prohibitions and the sale of organs, which, in fact, as you point out, usually permit compensation for the costs of removal, storage, et cetera, recognizing that, you know, to get them in a usable form you have to -- there are expenses incurred but that try to prohibit any profit in going back.

PROFESSOR ANDREWS: There are some states that do allow research on aborted fetuses with maternal consent. I thought, in fact, you were going to ask me another one, do they have any rules, you know, that would help guide it, you know.

DR. MURRAY: That is a good one so you can answer that one.

PROFESSOR ANDREWS: I will just ask myself questions and answer them. You know, so beyond maternal consent very few have rules if you are not dealing with say a living fetus that is, you know -- that happens to be then aborted. You know, some have the type of information. You have to tell the woman the fact that a different person has to ask for consent, it has to be divorced from the abortion decision itself.

Those states, though, that do allow it and

ban payment tend to ban everything, any consideration, any -- you know, any nice thing you do for that other person. I mean, they just do not want any form of commercialization anywhere near the fetal and abortion decisions.

DR. MURRAY: But the cost of storing the embryo for two years?

PROFESSOR ANDREWS: Too bad. You know, they would not -- you know, they -- and they have tried to think of everything. They have tried to think of -- you know, you cannot give the woman her abortion free, you know. You cannot -- you know, anything that -- and it is not just money. It is other -- any other consideration.

DR. MURRAY: Would the same apply to the -- the analogy here would be to the hospital who is treating the person who is now dead who then brings in the organ recovery team and then -- you know, you know how these things work. Generally the -- you know, the organ procurement organization, the OPA, will come in and figure out, you know, what charges were actually attributable to the care of the patient and what charges were attributable to the effort to preserve and recover

the organ. They will pay the latter but not the former.

PROFESSOR ANDREWS: Their definition of valuable consideration is so broad. I mean, I think -- I mean, there is such a -- there is such a tendency of judges to look the other way when it is physicians involved in research in cases that I do not think that, you know, they are going to really prosecute those things.

Should they desire to, should a prosecutor be trying to get elected to higher office by doing it, I mean this valuable consideration idea could apply to that but I do not think it will practically be applied.

DR. SHAPIRO: Bernie?

DR. LO: Could I follow up on a question you were going to ask yourself and encourage you to answer it? Is there any case law on what level of consent or what specifics the women need to be informed about before donating embryos for research that will go into an embryonic stem cell line and if there are no cases how strong an argument do you think a plaintiff would have saying, well, when I checked that little box that you could use my embryos for research now that I am done with

my infertility treatment, I never thought that it would end up as a stem cell line that is going to be turned into tissue part sales that would be given to other patients.

PROFESSOR ANDREWS: Well, I mean since -- I mean, informed consent is getting increasingly detailed in its legal requirements. I mean, it used to just be the risk of a proposed procedure and now it has gone into alternatives and the nature of your condition and so forth. I mean, I would be happy to take that to a jury, you know.

I mean, I just think it is a losing case for the health care institution to say that, you know, in turning someone's future child in their mind into a product, you know, is going to play -- a commercial product no less and there may be, you know, did you know this big, bad biotech company was buying up these embryos and da, da, da.

You know, so I think that in this area more than other areas of fetal tissue that those concerns will come into play and even the John Moore case saying the patient did not have a property right did say they had a

right to know if this was going to be used for research and for commercialization.

So I think that that will be seen as relevant. I mean, the -- I mean, the general informed consent laws have, in part, the standard of is it material to the person's decision. And, you know, I can think of many, many areas in which it would be material to a woman's decision what the research is going to be, you know, if the person is opposed to patenting. You know, if the person -- you know, as I said, the human clone example.

I mean, you have that -- you know, University of California -- I mean, you were a part of, you know, all of that review. I mean, where the embryos were given to other couples. Now, you know, the doctor could say I engaged in a beneficial treatment. These were just -- you know, if the couples did not want these embryos why not make other pregnancies. But I mean they are about to litigate that issue of was it appropriate without the couple's consent to turn those embryos over to the research. So I mean we will know better soon.

DR. SHAPIRO: Bernie?

DR. LO: If I could ask one follow up question. Has the Moore holding on the importance of disclosing to the patient, the investigator's pecuniary interest in the research, has that been picked up by other courts elsewhere or is that sort of anomalous ruling?

PROFESSOR ANDREWS: Well, there has not been much litigated in the research area and I actually just last week went through like all the cases that I have cited John Moore.

But I think what is more important more and more is that if you look at all of the guidelines coming out from places like the American Society of Human Genetics and what they all assume now is that you have to tell financial interests, and I think that courts in looking at other areas where physicians have to disclose their monetary interest in a nursing home or a lab to which they are referring the patient, those, you know, financial disclosures have become much more common throughout -- you know, throughout medicine.

Some states, like California, have laws that say, you know, you have to disclose the -- like the name

of the pharmaceutical company that is sponsoring the research, you know. So people can make decisions about how they feel about Pfizer or Merck or Smith Kline or whatever.

DR. SHAPIRO: Are there any barriers, constitutional or otherwise, that would prevent the Federal Government, if it wanted to act in any of these areas that we are speaking about, from simply preempting state law? Are there certain characteristics of this area that would prohibit the Federal Government from doing something like that just trying to establish sort of a national framework for all this?

PROFESSOR ANDREWS: I personally do not think so although it is a matter of -- I mean, I think I could get you an argument that would get you there but it is a matter of debate because think of the Food and Drug Administration and their powers. You know, they cannot regulate physician services and so, you know, they cannot tell doctors you should only put in four embryos, you know, in the in vitro situation. They cannot, you know, tell surgeons what they can or cannot do.

So, I mean the strongest case would be, you

know, someone in a state using, you know, dealing only with patients for that state that does a procedure to benefit the health of that individual patient, you know, saying I am not, you know, concerned with interstate commerce. I think, though, I can make you an interstate commerce argument that is okay, you know, billing to insurers, you know, all these things.

So, no, I think you are, you know, free to go ahead and I would urge you to, you know, come up with those sort of guidelines.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: In discussing what happens when a woman goes to the IVF clinic, we focused a little bit on the lack of the robustness of the consent. Let's assume it was a robust consent for the moment so let's put that issue aside. It is a striking fact that it represents the antithesis of what we mandated in the case of the fetal donations, this rigid separation between the decision to abort and then the research use. So I am wondering about your thoughts whether we can take that as a model in the case of the embryos.

PROFESSOR ANDREWS: Well, I do think there is

some difficulty particularly asking for this in advance before you -- you know, the woman has achieved a pregnancy, you know, will she really, you know, refuse her doctor, you know, so that is -- I think that is a problem and that there might be -- before research is done you might want to have some reconsideration, some recontact.

I mean, the reason it is done in advance is if, you know, the couple die, divorce, lose interest, move to, you know, some remote part of the world, you know. It is useful to know what they wanted done and, in fact, there is at least one legal decision that enforced the contract donation of embryos to research.

But perhaps -- you know, I have talked to at least one clinic that now is doing that, will not actually do any research without recontact. You know, Richard Mars, an in vitro practitioner in Southern California, you know, says, you know, "I am going to go back with the specifics of the research. I am not going to use based on that." So that may be one approach.

I do have concerns about the people wanting these -- you know, it is more -- it is less of an issue

for embryo stem cells than in vitro research in general, you know, because there are no federal funds. So there is a big impetus for IVF practitioners to get couples to check off for research. And I actually sat in on one thing where, you know, they told the woman it is illegal to donate embryos in this state, which was totally untrue. And so, you know, give them to us for research purposes, the incentives are very high. You might want to disentangle that.

DR. MESLIN: Are there any other questions for Professor Andrews?

Harold has just taken a quick call and given that our next speaker is on his way from the airport we will take a very short break now and reconvene.

I want to thank Lori for coming and helping us out very much.

Take a ten minute break.

(Whereupon, a break was taken from 9:55 a.m. until 10:22 a.m.)

PERSPECTIVE OF AN IVF SPECIALIST

DR. SHAPIRO: Okay. Colleagues, let me just indicate how we can complete our work this morning.

Obviously our guest has been delayed through no fault of his own. It is the weather that is in the area. We really do not know when and if he will be here, although we do expect him any moment. That has been true for the last 45 minutes, however, and so I do not know. I know that our schedule is such that a number of you have to leave, some at 10:30. I, myself, have to leave about then. And some at 11:00 and et cetera.

So what I would like to take a few minutes to do is to just see if there are questions that you have that we would like to put to our guest because at the very least there is probably a couple of commissioners and some staff who will sit down with him and have a very serious discussion with him if the delay goes much longer than now. So we just want to make sure we can accommodate and we make the trip worthwhile for our guest and, also, of course, for us.

So Eric will take notes because Eric will lead that discussion if it turns out it cannot be made in this context and then, of course, report to us all as we go ahead.

So let's just -- Bernie?

DR. LO: Yes. I would want to ask him -- I am sorry I am not going to be able to ask Dr. Shapiro a number of questions dealing with the derivation of embryonic stem cell lines from donated embryos. And it really gets to the issue of the nature of the informed consent process to donate embryos for research, both how it is commonly done and, secondly, what the best practices are.

So are there individual researchers or institutions that really have a good procedure in place for obtaining really robust consent, in Steve's term, so that the woman is not just asked to sort of pick one off a checklist but really is explained specifically that one of the research uses could be the derivation of an ESC line and actually what that means to her.

I think that it would be important to try and make that consent process as good as possible and sort of to learn how it is done well now would be useful. Parenthetically -- and I guess I also wanted to say that comment that Lori Andrews made about how now a lot of this is done in advance because the feeling is in IVF programs that you want the couple and the IVF doctor to

have thought through what to do with these embryos before you go around -- go about producing them and whether there is recontact after the completion of the IVF treatment to say let's now talk again about this notion of donating for research.

I just think that one thing that may make it easier here is that these couples if they have embryos in storage are sent a bill every year for the storage fee so there is continually recontact from the program back to the woman so it is not as if you cannot really go back to them over time and make sure they understand the options before obtaining their consent.

DR. SHAPIRO: Thank you.

DR. LO: Just one final thing --

DR. SHAPIRO: Oh, I am sorry.

DR. LO: -- not for him but just if we could maybe ask RESOLVE or other patient advocacy groups whether they have ideas about what a model consent procedure should be like. That could be helpful as well.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: I would like to hear a concrete

description of what they do with an embryo once they are not implanted and what happens to the embryo, what the time course of what happens is, and so forth.

DR. SHAPIRO: Thank you.

Tom?

DR. MURRAY: I just wanted to know in what context we were inviting this guest that would enable me to frame my questions more usefully. What is his particular expertise and interests?

DR. HANNA: Well, first of all, we thought it would be interesting to hear from an IVF specialist who might be making these embryos available to researchers. Secondly, Dr. Shapiro supplied some of the embryos to Jamie Thomson for his work so it was also to try and find out what process was used there. And, third, he was local and we thought it would be easy to get him here.

(Laughter.)

DR. SHAPIRO: Okay. Trish, and then Steve.

DR. BACKLAR: I would like to ask a question about women who are donors of eggs and what procedures they used to get women to do this and what kind of consent forms they use for women who donate eggs, and

anything else you can think of in relationship to that particular issue.

DR. SHAPIRO: Steve, and then Diane.

MR. HOLTZMAN: I am not sure these would be questions for him than so much for staff to go out and try to get answers to, which is we are making certain assumptions about the availability of spare embryos when we say there is no compelling reason and we have had some question about that. So I think we need some facts and statistics about the numbers, about diversity. All right.

There is some stuff I have written for you, Eric, that I handed you about remember there may be issues here not just about numbers of eggs but the diversity of them to be thinking about.

I think we really need to get our arms around that before we reach conclusions about whether or not there is a need for research purpose embryos.

DR. HANNA: Could I just respond to that? We have tried -- we have been trying for several months to try and find out if anyone has those data and I do not think anyone does. There are people that can give us

estimates but there is no reporting system so these IVF clinics do not have an obligation to, one, gather this data or report it to anybody.

Some of the professional societies, the Society for Reproductive Medicine and others, have some good, I would think probably fairly reliable, estimates but we will continue to try and get data but it is just not out there and it is certainly not published.

MR. HOLTZMAN: Right. But we -- there is probably an 80/20 rule here and if we could just contact them directly. I think they have a self-interest here in actually having some accurate stuff.

DR. SHAPIRO: 80/20?

MR. HOLTZMAN: 20 percent of the establishments are responsible for 80 percent of the business.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I would like to just ask questions about the views of his community, that is, the views of people who do the kind of work that he does and maybe let him say his own views about the kinds of issues that we are addressing now in working on this report.

And I would be especially interested in record keeping standards at IVF clinics. The standards that exist now and his projections for the future for what kinds of records would they expect to keep.

DR. SHAPIRO: An issue I have been thinking about for some time, and I do not know at all the answer to, and this is the status and possible existence of professional standards, which they, themselves, have adopted as a group. Are there any? If so, what they are? It is a little different than collecting records because it is, you know, are there any standards regarding important aspects of what they do that they have adopted on their own voluntary basis. I would be very interested in knowing what they are, if they are available, and if they exist.

Diane?

DR. SCOTT-JONES: I think even if there are not formal standards, if there are sort of informal norms that have evolved, if he would speak to that.

DR. SHAPIRO: Right. I agree.

DR. MESLIN: We have Mr. Tipton here from ASRM.

Do you want to respond to some of that and just describe the professional organization very briefly?

DR. SHAPIRO: You can just come and sit right over here rather than standing.

DR. MESLIN: Some of those thoughts can be put on the record.

MR. TIPTON: I am not sure what sequence to try to take some of these in. I am Sean Tipton. I am Director of Government and Media Affairs for the American Society for Reproductive Medicine.

I think one of the things I can get out of the way is that, in fact, there are not -- I would say there are not any reliable estimates of the number of embryos in freezers. We do not track that. We can track -- we could probably piece it together through some of the reporting mechanisms that we do have. But we do not -- we have quit asking the question -- I am not sure what year we quit asking the question of how many do you have in your freezers. We certainly know how many they create and how many births results from that so you could go back through and do some extrapolations, I suppose.

What else were you asking?

I think the diversity question in terms of demographics of the embryos and the egg donors, I do not think that we have data on that either. We could look through the reports. As you may know, we do a report that we have done with one of our affiliates, the Society for Assisted Reproductive Technologies, whose membership is essentially the clinics.

Since '89 they have done a success rate report, which now thanks to the Federal Fertility Clinic Success Rate Certification Act, we do with the CDC. So for '95 and '96 that data has done -- the CDC has done success rate reporting and I do not think there is demographic data in there other than age.

Now if you go back in originally -- in the original data there may be some but I sort of doubt it. For our people's purposes I do not think they saw any clinical relevance to it and, therefore, probably did not collect it.

DR. SHAPIRO: Professional standards?

MR. TIPTON: Professional standards --

DR. SHAPIRO: Formal or informal.

MR. TIPTON: -- in terms of record keeping,

there is a couple of places that may come into play. We do with the College of American Pathologists a reproductive laboratory accreditation program. As part of the standards for that there are record keeping standards in terms of the fate of -- and as part of the reporting under the Fertility Clinics Success Rate Certification Act. So they have to essentially account for the embryos they create.

The other thing that we do is we have -- and we have submitted to the commission a couple of different pieces. We have an ethics committee guideline on informed consent for the use of gametes and embryos for research. We have a couple other ethics committee pieces on embryonic research and a practice committee opinion on more general informed consent. We have stayed away from offering specific forms to our members but instead have gone with here are the pieces you need to have in place. And most of what you all have been discussing we certainly recommend to our members.

DR. CHILDRESS: Would it be possible for you to provide copies to staff?

DR. MESLIN: They have been in the briefing

books but we will remind you of the --

MR. TIPTON: Yes. Actually it is -- some of it is up on our web site, which is asrm.org and you want to go -- probably to find most of the stuff that you would be interested in, the first choice you are going to make is to hit the "for the professionals" button and you want to look under both ethics committee report and practice committee opinions. But we have supplied most of this to the NBAC and we will certainly work with them to make sure you all get copies.

DR. HANNA: Steve, all these materials should be in your February briefing book if you still know where that is.

DR. MESLIN: Were there other --

MR. TIPTON: And then finally I think in terms of -- you know, every -- I think there is going to be some variation in terms of what the individual practices and clinics are doing. I think, you know, we clearly have strong views about getting full informed -- the term of the day, I guess, is "robust informed consent" in advance. One of our concerns obviously is not having our members thrown into court in kind of

embryo custody disputes so we like to get these things taken care of up front and we strongly suggest that happen.

And most of the stuff -- certainly if they want to present it at our meetings or publish it in our journals it has to be IRB approved. You know, in this case again obviously we are hurt by the lack of federal funding and subsequent federal oversight, which we would welcome.

DR. MESLIN: Larry?

DR. MIIKE: So on the informed consent form, what Lori Andrews was saying was there is a checklist. Is that checklist used as an indication to contact them again when there is actually going to be use for research or is that -- the implication was that was just sort of a general consent and then they went ahead and did it. But you are telling me that you have a much more robust process.

MR. TIPTON: No. I think that if you are asking me do most of our members get an informed consent to do research sort of in a general way and then complete the treatment cycle for that patient, and then maybe go

back when they have a specific protocol in mind, that is probably not how it happens that often. Although it is going to depend on where they are. And obviously the folks in academic settings are going to have to -- are going to have a specific informed consent piece for the -- for every study.

So I think -- you know, the question of are they consenting for the use of these -- of their embryos to possibly be a source for embryonic stem cells -- I mean, that is so new, I think that most of them probably are not doing that.

DR. MIIKE: But you said that you did have some guidelines about what is proper informed consent. So how does that match up with what you just described?

MR. TIPTON: Yes. It is very much that the patients need to be informed as to what is going to happen with those products and they need to be informed about things like the financial arrangements.

DR. MESLIN: Were there other questions?

Sean, thanks very much, on short notice for doing that.

We are -- we have just been informed that Dr.

Shapiro is in the cab and he is on his way here so we hope people can stay.

MR. TIPTON: We will just hope he does not contradict me.

DR. MESLIN: Right.

Were there other questions that the commission had either for Sean or that you wanted to ensure we got registered to ask Dr. Shapiro when he arrives?

Diane?

DR. SCOTT-JONES: Since we have time I will ask this question of Sean, when you were asked about demographics you said that it -- that was not kept for egg donors and that the clinical relevance of that information was not obvious. Could you say a little bit more about that?

MR. TIPTON: We are probably getting well afield of my expertise. However, I think that in terms of, for instance, what we are reporting with the CDC, they have found that they report the results of IVF treatments by age because that is very relevant to its success. Other kinds of demographic data and other ways

they have tried to cut that data have not proven to be of great significance.

So I cannot -- I am not for sure what we have collected in past years. We can go back and look at that to see what kind of data we can come up with. I just am not competent there is going to be a whole lot there but we can take a look at it and see.

DR. MESLIN: Tom?

DR. MURRAY: Has there been any reaction, official or informal, at ASRM to the -- sort of the -- I do not know whether to call them excesses, but examples of comodification of gametes such as the ads offering to pay -- was it $50,000 for an egg donor?

MR. TIPTON: Speaking -- well, as long as we are on the weather problems of getting into Chicago, I actually was not present at one of our ethics committee meetings a couple of weeks ago here. They are relooking at their statement regarding that. You know, frankly, it is a tricky issue. Clearly our stance is it is appropriate to compensate for time and inconvenience and that kind of thing. For an egg donation, in particular. It is an invasive procedure.

Where you draw that line and where it becomes then inappropriate or potentially coercive is a difficult issue to say. So it is -- we will probably mostly -- we will get -- pretty fairly unanimous agreement. $50,000 goes across that line. Does it cross it at $5 or $10 is a little bit trickier. So, you know, I hope that we are not going to be in the business of having, you know, an oocyte donation inflation factor every year or something but, you know, it is a hard issue to put a bright light on. But they are clearly looking at it and I do not know what they will end up saying and it may be fairly quickly taken out of our hands,I guess, too.

DR. MESLIN: Trish?

DR. BACKLAR: I am just reiterating the question asked because I am interested to see what kind of informed consents go with those egg donations.

MR. TIPTON: Again, I think that strong informed consent for both the donor and recipient, we talk about the need for really making sure people -- we are essentially making sure people know what they are getting into, and again it is hard to know what exactly that means from place to place.

DR. MESLIN: Okay. As we continue to sort of wait a little bit, are there any other questions for Sean? Now is a good time. If there are not, let's continue to just rest for a second until Dr. Shapiro arrives.

Arturo?

DR. BRITO: Harold had to leave early and he did not talk about the next steps and obviously with the Human Biological Material Report and the stem cell report we know what we are doing.

What has happened with the International Research Project, and maybe Jim can answer this, but the Belmont Report revisited, and the whole thing. Are we going to be working on that?

DR. CHILDRESS: We sharply distinguished the Belmont conference from the work of NBAC even though NBAC was obviously heavily involved in it. And the question that Alex had raised earlier about whether we were going to -- and others about whether we were going to do a new Belmont Report on our own, that so far as I can recall has not been discussed in a number of months so I do not know what the thinking is on that.

I know that several of us have thought that, well, maybe after the conference we would have some better idea whether this was a project that NBAC itself wanted to undertake, that is to do a new Belmont or Belmont Revisited in the sense of coming up with something on our own.

But I have not been party to any conversations since then about that. I think we have all been so busy on these other projects that we really have not returned to that.

In terms of doing something with the volume, that Harold and I and others are working on, to maybe publish the papers out of that conference.

DR. MESLIN: With respect to the International Project we have had three presentations in the last two meetings from consultants to the commission. We expect that at our June meeting in Washington, which I will alert commissioners to now, we think that it will be necessary to have a full two-day meeting in Washington on June 28th and 29th, a full two days. The 28th and 29th of June. That is our next scheduled meeting. 8:30 to 5:00 both days. That is sort of an advance preparation

for you with travel plans, which I appreciate are always very difficult to arrange.

One of the reasons is that we are intending to have another set of presentations by the international consultants who are completing some of their site visit work. As you know from e-mails, Professor Ruth Macklin from the Albert Einstein College of Medicine has agreed to join the NBAC staff as a consultant for the summer months to help us pull together that report. So we expect there to be a dedicated amount of time at that meeting.

The report itself will likely be presented in draft form probably or beginning draft form at the July meeting in Cambridge and then probably a more robust draft at the September meeting. We are not meeting in August as you know.

Depending on whether or not some of those projects require further work, they may go beyond the September time period into the next fiscal year but we will have to wait for budget issues.

MS. KRAMER: Did you say it is all day Monday and Tuesday in June, the 28th and 29th?

DR. MESLIN: Yes. I am saying plan for that possibility now. If we find that the agenda changes before the 28th we will let you know but it is better to plan your travel life now for two full days at that meeting.

MS. KRAMER: With regard to questions for Dr. Shapiro, yesterday the possibility was raised of using embryos that are not deemed of sufficient quality for implantation, whether or not they could be used for the derivation of cell lines.

DR. MESLIN: Okay. So everyone can take a little break again and those who are going to be leaving and have to leave, we apologize for this but it was weather and other things. We will reconvene when Dr. Shapiro arrives for those who can remain.

(Whereupon, from 10:45 a.m. until 10:55 a.m., a break was taken.)

DR. MESLIN: For those who are here I just want to -- for the public record --

DR. CASSELL: Are we the only ones here?

DR. MESLIN: Yes.

Dr. Sander Shapiro is here and we will worry

about whether the Federal Advisory Committee Act is in play or not at this point but I wanted to welcome Dr. Shapiro here and have him provide his remarks for the public record in any event. And given that commissioners have already provided a series of questions we will be delighted to ask him those questions and have him try and provide us with some answers and then we will follow that up as a staff function.

So, Dr. Shapiro, we apologize that the group is somewhat smaller but we look forward to hearing your presentation.

SANDER SHAPIRO, M.D.

DR. S. SHAPIRO: I apologize for my lateness.

DR. MESLIN: Press the button the entire time that you speak.

DR. S. SHAPIRO: I think that my being here is essentially to give you information about IVF as a practitioner of IVF and rather than making any direct statements I think the best thing is just to go through the questions you have asked and then perhaps if the questions do not cover everything that I see in this then I can tell you some other things about this.

DR. MESLIN: Thank you. There are a number of questions about informed consent. How informed consent works in practice, whether you are aware of any best practices for obtaining informed consent, so perhaps you could say a little bit about how informed consent works in your clinic and we may be able to pursue some of that a bit.

DR. S. SHAPIRO: I think it is important to note that I am at a university as a faculty member and at a university hospital and so we are accustomed to using informed consents for a lot of things that private and individual isolated clinics might not be accustomed to.

In our case, we inform every one of our patients at the initiation of their candidacy that they will be faced with a number of decisions. Most of these decisions have to do with the number of ova that will be collected and the number of ova that will be fertilized, and the number that will be replaced. Finally then they will have a decision to make about what to do with extra ova.

All this is sort of standard and routine. What eventually happens is that the extra ova are either

left as fresh ova for a decision or frozen for a later decision. In either case the couple will decide that they want these to either be used or destroyed or if the particular time is right for it we may have a project that we will suggest to them they donate the embryos to.

The first real approach of a patient then to donate embryos to a scientific project, which is already IRB approved and has a specific IRB permit and a signed consent form that would be necessary, is at the time when they have got to decide what they are going to do with these embryos. So they do not really face this sort of problem before they are initiated into becoming an IVF patient.

I think that sort of covers it initially.

MR. HOLTZMAN: I was unclear. They are an IVF patient. They come in and they donate their ova. At that time do you explore and get consent to the use of the extra ova that may be left over at the end of their attempts at pregnancy or do you not get the consent for research uses until after they are finished and there are excess ova?

The second question is do you freeze them as

ova or as fertilized eggs?

DR. S. SHAPIRO: The second question first. All of the freezing and storage is done on embryos.

As far as when we get a permit signed -- permits are perused as they become candidates but all those permits are for standard operations, not for research projects. The only time a couple is approached for research project approvals is when they have decided that they do not want those embryos.

DR. MESLIN: In any of the arrangements with women who come in and the consent process, does it involve any specificity about the subject of this commission's deliberations, ES cell or embryonic stem cell research, is that -- the nature of that specificity included in any discussions or consent documents?

DR. S. SHAPIRO: Not at all before they decide they want to discard the embryos. At the time they decide to discard the embryos they are presented with a number of options in the way they may dispose of them and at that time if we have a particular research project, in this case the stem cell, we would approach them with information about that particular project.

MR. HOLTZMAN: So if we have a woman or a couple who are now at the point where they are finished with their reproductive goals, and there are excess embryos, but you do not have a specific research project, do you ask them for use for future research projects as yet unspecified or is it if and only if there is a research project on the burner you will get specific assent to the specific research project, and in the absence of specific research projects are the options offered to them, whatever they include, they do not include the use in research?

DR. S. SHAPIRO: The permits that are requested on them are always for a specific research project that is, as you say, on the burner. There is no way that our university IRB would approve of a blanket consent.

MR. HOLTZMAN: So the options you ask -- at that point where you are faced with excess embryos, no research project on the burner, the options you are offering them are contribution to another couple or discard or keep in the freezer?

DR. S. SHAPIRO: That is correct.

DR. MESLIN: Larry?

DR. HANNA: Dr. Shapiro, I have a question about the issue of storage. I do not know if your clinic does this or not but in talking to other centers I understand that, in some cases, the embryos are discarded before they are stored. So, I mean, those embryos that are determined to not be suitable for implantation for whatever reason, so you might have some of them in culture and you might have some decision that you make about whether this looks like a viable embryo or whether it is developed appropriately and would probably be a successful implant.

One question that has been raised is whether those embryos that would be discarded because they are not considered suitable for implantation, would they be a legitimate or viable source for research purposes or are they morphologically or genetically or anatomically unsuitable?

DR. S. SHAPIRO: Well, first, the technology is changing very rapidly and our thinking due to the problems that are given us by the technology are changing. The case of an embryo that is unfit for

transfer is basically either a deteriorating dying embryo or an embryo that has formed from several fertilizations. In other words, it is more than two pronuclear. In that case the person who up to this time owns the embryos, if you will, would not be asked if they were going to be destroyed. We have had instances where we have had on the burner research projects that involved looking at those and in those cases specific permits were required of each individual.

DR. MESLIN: Eric?

DR. CASSELL: Embryos such as the one you just described that would not be satisfactory for implantation, would they be -- would it be possible to harvest stem cells from them?

DR. S. SHAPIRO: No. The stem cell projects that we have been involved with, and that have been primarily led by Dr. James Thomson, have involved taking the central core of a blastocyst and in these cases they either have not approached that advanced state or have something fundamentally wrong which would say that they will never get to that advanced state.

DR. CASSELL: So when an embryo gets to a

blastocyst stage that is diagnostic of its utility as an implantable embryo?

DR. S. SHAPIRO: That is correct.

DR. CASSELL: And what happens -- let's suppose that the couple wants to discard the embryo. It is a blastocyst stage. That is it could be used for stem cells. What actually happens to the embryo in terms of its trajectory towards being discard, dying, whatever words you wish?

DR. S. SHAPIRO: I am now supposing that the couple has been approached for this particular type of research and said, no, they do not want that. Under those circumstances that embryo is left in an incubator and it will progress slightly further and then die.

DR. CASSELL: And for how long a period of time as it is progressing slightly further towards death will it be possible to harvest stem cells from it?

DR. S. SHAPIRO: I cannot answer that. I would imagine that there is a window of approximately three days but no more than that.

DR. CASSELL: Is it possible as far as you know that there would be a period where it is no longer

implantable but it is still possible to harvest cells from it?

DR. S. SHAPIRO: I do not think that we have had enough experience with doing this to make a clear statement about that. And I cannot give you an answer in terms of mouse research. I simply do not know that.

DR. CASSELL: And then, finally, let's suppose that it has now gone far enough and it is going to die, what do you do then? Literally? I mean, in concrete terms.

DR. S. SHAPIRO: In concrete terms it is left in a petri dish to die. Once it has died by histologic criteria then it is disposed of as all other human tissues are disposed of in a pathology lab.

DR. CASSELL: And the criteria -- you can establish the histologic criteria on gross examination?

DR. S. SHAPIRO: Yes. Under the microscope.

DR. CASSELL: Under the microscope, yes.

DR. MESLIN: Steve?

MR. HOLTZMAN: It would probably be useful to get some clarifications on timing. You do the IVF. You culture out the cell to a certain stage to determine its

viability. All right. Reimplantation if it is going to take place or transfer takes place with a how many days old embryo, number one?

Number two, if it is -- I believe you take them all out and then it is also if you do not implant you freeze. And contrast that with a how many days old embryo is used for the recovery of ICM cells to make ES cells.

DR. S. SHAPIRO: The current methodology involves growing these embryos to two degrees. One is simply to the two pronuclear stage. In other words, it is still one cell and they are frozen. Or letting them grow up to six days and that would be the time at which implantation would -- not implantation but transfer would occur.

Then if a person had a two pronuclear that was brought out of freezing and grown up to that stage and it was elected not to do the transfer, that embryo, if permission were given for this sort of thing, would then be cultured for no more essentially than 24 more hours before it was dissected out and the appropriate central cells taken for the project.

MR. HOLTZMAN: So in the paradigm case it is not -- the paradigm case will not be someone who, for whatever reason, decided not to get the transfer. It was brought out of the freezer in thinking to get the transfer, they did not get the transfer, now it is leftover and you could think about a research purpose. The paradigm case is for the person who is finished with reproduction, there are excess ones leftover, and the research to make the stem cell is on the burner.

DR. S. SHAPIRO: I am not hearing your question.

MR. HOLTZMAN: Eric was exploring this -- a paradigm of the cell was there. You can -- with the goal of transplant. All right. But then the transplant does not take place and now you have a window to think about using it for research purposes. But I do not think that is probably the paradigm case. The paradigm case is probably where there are excess embryos post the reproductive project of the individual and they are being brought out of freezing specifically to take them into a consent to a research project.

DR. S. SHAPIRO: If that were the case the

consent would be given at that time to bring them out and grow them up. That is correct.

DR. MESLIN: Arturo?

DR. BRITO: I am sorry if I missed this in the beginning. But in terms of determining the viability or potential viability, how do you go about that process?

DR. S. SHAPIRO: Viability is determined at different stages but basically there are two important stages. One is does the egg get fertilized? If it gets fertilized we have got a two pronuclear cell now and it is either going to be frozen at that stage or allowed to grow further. If it is allowed to grow further it is hoped that it will go to five to six days, which would be a blastocyst, and at that time the histology of it gives an indication of its viability.

DR. MESLIN: There were a couple of other questions that commissioners -- I am sorry, Dr. Cassell.

DR. CASSELL: Just to follow-up, see one of the things we are trying to find out or what this discussion is about is that when people talk about embryos they talk about something like an abstraction. Almost as though they were looking at something they

could literally see and it is an embryo. And we are trying to find out to move from the abstraction embryo to the actual what happens to that egg as it moves through its trajectory.

So once again one of the things which we are interested in, which I think I understood you to be not clear about, which is an appropriate answer, is that in an embryo that has gone through the blastocyst stage but histologically looks like it is not going to be an implantable embryo, could it still be used for stem cell recovery?

DR. S. SHAPIRO: The answer is in all probability no because the criteria that you were using at that time to determine its viability and implantability would be the same as the criteria you would have to decide whether it is going to have cells that could be used for that project and if there is not a good central mass of cells then it is not going to be usable under either condition or for either purpose.

DR. CASSELL: And the whole trajectory, assuming that the laboratory conditions are right and so forth, are from the two pronuclear cell to an implantable

blastocyst takes how long?

DR. S. SHAPIRO: From the time of fertilization to the time there is a blastocyst that would be transferred to an individual would be approximately four-and-a-half to five-and-a-half days, and that is because you cannot tell that there has been fertilization until approximately 18 to 24 hours after you have put the ova and sperm together. So all total from the time an egg is removed from the individual it will be five-and-a-half to six days before a transfer is made.

DR. CASSELL: What percentage, roughly, of the attempts to produce an embryo for transfer are successful?

DR. S. SHAPIRO: I think that has to have several parts to the answer. First of all, you have a variable number of mature eggs that are developed in an individual woman. Under most circumstances, essentially all, all of those mature oocytes are going to be exposed to sperm. Roughly 70 to 80 percent of those that are exposed will be fertilized. Of those that are fertilized there is a great deal of variability as to how many will

go on to develop to that six day expanded blastocyst stage and it varies from essentially none up to perhaps 60 to 80 percent.

DR. CASSELL: That means that at best you are talking about half of them -- around half. Even if everything went well we are talking about half of the ovary and sperm connections going on to something that could be transferred.

DR. S. SHAPIRO: That would be the most optimistic scenario.

DR. CASSELL: And although this is not exactly the same area, what percentage of naturally implanted embryos abort or do not continue?

DR. S. SHAPIRO: That depends on how you define abortion. Let me explain. There are studies that have been done where women have been asked to stop their barrier method of birth control and then they have been surveyed on a daily basis the women intending to get pregnant and the survey being a very sensitive method of determining that they are pregnant. Under those circumstances roughly -- well, the study I am thinking of looked at 620, approximately, cycles.

Of those 620 cycles, 153 of the cycles registered pregnancy by a serum test for pregnancy. Of the 153 that registered pregnancy, approximately 105 were recognized by the women at a slightly later date as being pregnant. In other words, symptoms of pregnancy, delayed menses, et cetera. Of those approximately 105, and this is not my work so it is off the top of my head, approximately 87 of those had babies.

So you could say that better than one-third of these pregnancies, recognized pregnancies, resulted in abortion. The traditional way of recognizing an abortion is first to recognize the pregnancy without this ultrasensitive test and under those circumstances the rate of abortion depends on age.

In an 18-year old it is about 16 to 17 percent and it goes up gradually with age but in 40 year old it is about 40 percent.

Now that does not entirely answer your question because part of the question is not pregnancy in terms of implantation and measurability. I think what you want to know is how many eggs fertilize in vivo. Okay.

And there again the answer is hard to give but there were studies back in the '50s. Drs. Hertig and Rock, for instance, who asked women to get pregnant and then flushed out their tubes looking for the early pregnancies. And their findings in a very small number -- I think it was 34 or so attempts -- was that 75 percent of these women had conceptions occur, if you define conception as the sperm and the egg getting together and a two pronuclear embryo developing.

Does that cover it?

DR. MESLIN: Larry, and then Arturo.

DR. MIIKE: Let me ask you about a series of questions relating to viability of in vitro fertilization. After you have what you think is a viable embryo and you implant it, what is the failure rate after implantation?

DR. S. SHAPIRO: The implantation -- first of all, we do not implant. Implantation is a physiologic process whereby the embryo attaches to the endometrium of the utrum.

DR. MIIKE: I understand.

DR. S. SHAPIRO: Okay. If you mean by that

how often does a transfer occur and result in a pregnancy, again these figures are very new because doing blastocyst transfer is a new procedure. It has only been going on for a very short time. But we have looked, for instance, at our rates since June of '98 and 72 percent of the women who we transferred blastocysts had recognizable pregnancies.

DR. MIIKE: I am asking the question about to term.

DR. S. SHAPIRO: To term the behavior of these pregnancies is essentially the same as the behavior of a standard pregnancy and then the rate of miscarriage in a recognized early pregnancy depends upon age, being 16 to 17 percent in the younger person.

DR. MIIKE: Then is that -- am I to assume that any miscarriage or abortion after the implantation is not related in any way to the in vitro fertilization method? The reason I am asking this is that following up on a question that Eric asked, which is we were looking to see whether you could identify embryos that were not going to go on to term but were viable enough for ES abstraction. So I am just asking the question that in in

vitro fertilization and pregnancy research, obviously what you would like to do is maximize the embryos that you do have that you know will go to term.

So I am asking the question what is the foreseeable future in terms of improving that situation to the point where in the process of improving the success rate you can differentiate between embryos that are viable for ES cell abstraction but are not viable for moving on to term pregnancy?

DR. S. SHAPIRO: At the present time I do not think that differentiation can be made.

DR. MIIKE: I understand you cannot do that now but I am asking a question about whether that is of interest to you. Not for ES cell extraction but for the improvement of fertility research and as a byproduct that might happen for the ES cell.

DR. S. SHAPIRO: Perhaps this is a roundabout answer but three to four years ago we were taking three day old embryos and transferring them. The major reason for going to blastocyst transfer was the fact that at three days no one can distinguish, if you will, the good from the bad. If you were -- a very competent

embryologist could take 100 three-day old morula and he could not pick the -- let us say 20 that would go on to blastocyst at that point. The work that has been done with stem cells originated with blastocysts that developed before the time that we were actually using blastocysts for transfer.

DR. MIIKE: But see that is exactly the line of reasoning that I want you to follow, which is that you moved to the blastocyst stage because it has improved your chances of getting a viable pregnancy versus the two and three cell separation stage. Right?

DR. S. SHAPIRO: It has improved it slightly but we have moved to it mainly because we are now able to transfer fewer embryos and maintain a high rate of pregnancy. See the major problem that we have faced over the last 15 years was that the more embryos you put back, the more likely you were to get a pregnancy. But also because you were putting multiple embryos back you were running the risk of multiple pregnancy and multiple pregnancy has very great medical problems.

So the difference is that while we were putting four embryos at our particular center back at day

three, we now will put back no more than two at day six. And so we are now limiting the frequency with which we get multiple pregnancies and we are limiting the number of multiples above twins. This has substantial effects in terms of what is seen in the neonatal nursery.

DR. MIIKE: But currently the way you judge a blastocyst as being possibly viable for pregnancy is histologically?

DR. S. SHAPIRO: Correct.

DR. MIIKE: Basically you are looking at it.

DR. S. SHAPIRO: That is right.

DR. MIIKE: So what are the research tools that people are working on to improve that fairly crude method of making that decision?

DR. S. SHAPIRO: There are people doing a number of things such as measuring individual pH of cells of an embryo. There are thoughts and attempts at staining of embryos. But all these are at a stage removed from human work. They are all being done in laboratory animals and the bovine species as far as I am aware.

DR. MESLIN: Arturo, did you have a question?

DR. BRITO: Well, actually my question -- Larry pretty much covered it and I will just make sure I understood it correctly, is that once you determine a fertilized egg to be viable histologically and then you transfer it, that is where you get 72 percent of those will go on to be a pregnancy. But then a percentage of those will -- 72 percent of those will implant. Is that correct?

DR. S. SHAPIRO: Start again.

DR. BRITO: Okay. You histologically determine an embryo to be viable. Okay.

DR. S. SHAPIRO: At the day five-and-a-half to six.

DR. BRITO: Right. At day five-and-a-half to six and then you take those embryos and those are the ones that you would transfer and 72 percent of those will go on to be a complete -- not necessarily a complete pregnancy but a pregnancy in the classic sense.

DR. S. SHAPIRO: Not 72 percent of the embryos, 72 percent of the transfers. See you may transfer two.

DR. MESLIN: You are being very generous with

your time and answering all these questions. There are a couple more that the commissioners who are not here had asked to be put on the table.

One just relates to the views, if you can relate them, of the rest of your community of IVF professionals and practices, and whether the practices and procedures that you adopt in your institution are similar to or at variance with others. Could you say a bit about that?

DR. S. SHAPIRO: My only knowledge of that is just in talking to people around the country. There are committees of our organizations that are set up to look at that. In particular, there are committees of the American Fertility Society and so forth.

I think that the association for research with a university is a given and under those circumstances the restrictions or directions that are given are primarily those that come from the IRB of that particular university or institution.

To my knowledge, I think -- I believe that most of the institutions that have embarked on any kind of research of this type have done it in much the same

way we have. That is without preauthorization from a patient for what you would consider extra embryos.

DR. MESLIN: So the procedure would use the human subjects regulations model. This was an issue that was discussed by commissioners where IRB's typically look at potential harms to human subjects. In the description of your practice is the protocol that the IRB would review one in which the woman or the couple would be seen as the human subject or is it the embryo of the developing fetus?

DR. S. SHAPIRO: I would not want to speak for our IRB. My impression is that there would be a hierarchy of representation.

DR. MESLIN: Larry?

DR. MIIKE: Can you describe a bit the storage of embryos? During the time in which a couple is actively trying to have a baby and following that. Just what the usual practices are.

DR. S. SHAPIRO: It is a relative instance in which all of the embryos are frozen. That can occur when there are other technical reasons to postpone the transfer back to the woman. Under the circumstances

where there are extra embryos, different centers will choose to freeze at different times and with different methods. Most freezing cryopreservation is done at either the 2PN stage, the two pronuclear stage, or now at the blastocyst stage.

We have done both depending on the number of 2PN embryos we had at the outset.

Our problems with this -- and I think this is where your interest will be -- is how long can we preserve these and what happens later on because if you are going to preserve for a number of years you can envision a lot of things happening both to the couple involved and to others.

Our practice since we began preserving embryos, which is about 12 years ago, was always to have a consent signed and in the consent there is a statement that says you may have these frozen and kept at our institution for up to three years.

At the end of the three years if you have not chosen to use those embryos then your options are to use them and indicate you wish them used, to take them to a cryopreservation bank for longer storage where they would

be out of our interest and control, or to allow us to have them. And the "us" being the institution.

When the institution has them then, if no indication has been given by the person because perhaps they are unreachable at that time, as to what is to be done with them, they are destroyed. If they are available then we will approach them for permission to use them in whatever research projects are on the burner at that time.

It would be a specific research project.

DR. MESLIN: Kathi?

DR. HANNA: Do you -- have you in your experience with couples or individuals who have elected to donate the excess embryos to a specific research protocol, do you -- is there any difference in people's decisions based on whether the research has to do with infertility or whether -- I mean, you obviously have one event which is the derivation of the stem cells. But do you think that it would make a difference to couples whether the -- what the research purpose was in your experience?

DR. S. SHAPIRO: I do not think it would

matter with one exception, and repeatedly we have been asked, well, are you going to grow these into babies, but aside from that I do not think most people are concerned or have the sophistication to understand the implications of the individual research projects.

DR. MESLIN: And what do you say when they express that concern?

DR. S. SHAPIRO: We say, "No, that is not a possibility and that once this inner cell mass is dissected free it is no longer capable of going on to become a viable infant.

DR. MIIKE: No concerns or relatively little concerns about the commercialization aspect?

DR. S. SHAPIRO: The only time we have had support in my memory for one of these projects directly from a company was the one you are interested in and I cannot recall any individual being concerned about the financial implications of that.

DR. MIIKE: If someone said, "Well, you can use it but I want a piece of the action," then I assume that you will say, "Well, sorry, we cannot promise that and we cannot use your embryo then."

DR. S. SHAPIRO: That is right. We are not prepared to offer any compensation whatsoever. In fact, our IRB permits have said in them that there will be no compensation.

DR. MESLIN: There was a question about record keeping. I am assuming that since the studies that you are describing take place under the auspices of IRB approval then the usual rules of federal record keeping that IRB's are expected to comply with would apply here. But does your program keep records of sufficient quality that you would consider it to be of recommended nature? We are interested in record keeping processes and how individuals are kept track of. What happens after they have completed their participation in fertility care and whether you can find them later. What is the status of your record keeping?

DR. S. SHAPIRO: We have had a lot of experience with record keeping because of something that has gone on for over 30 years and that is using cryopreserved semen for initiating pregnancies. It is always a big problem. The institution, the hospital that is, is not really prepared to keep those records

themselves and so we in the unit keep those and transfer them under lock and key to the institution at an appropriate interval after the fact. Doing that we have not really had any problems.

In the stem cell research there is one added factor and that is that the researchers have no way of finding out anything about the individual from which the tissue came. They are -- the embryologists who handle the clinical tissue prepare the tissue for the research people and give it to them and they do not have any access to the -- of the patients or their histories.

DR. MESLIN: That sort of exhausts the questions that the commissioners had had. Are there any other questions that those who are here might have?

Larry?

DR. MIIKE: Just to get back to the informed consent process. Lori Andrews mentioned that in her review they may have simply a checklist that says, "Yes, I would be interested in research or to get rid of my embryos or donate." From what I understand you are saying is that -- and I -- and my question to her was that more was like a general consent and an indication

that research would be okay but that would not be okay for the actual research use.

My understanding of your answers were that you do not engage in that but if there is a project coming along that is the time that you approach the couple for possible use in research or do you have something similar to what Lori described?

DR. S. SHAPIRO: We will only approach the couple when they have said they do not want this material for their own personal use. When they have said that they do not want it then they will be given a number of options on what will be done with it and that is disposal. It can be giving it up for what we will call adoption by another couple or it can be research. But none of those options are discussed in detail and none of them have permits signed for them before the couple has decided that they no longer have an interest personally in maintaining these embryos.

DR. MIIKE: If they say they are interested in donating to research but you do not have a particular research project on board at that time, I am understanding that if you did you would then have a very

specific discussion with them. But if there is not, what happens to those eggs?

DR. S. SHAPIRO: Let's hypothetically assume that these are now frozen because if they are fresh and if we do not have anything, they are gone. If they are frozen then we might, with their understanding that they would be willing to do that, keep them frozen until a time that we had a project. But then when we had a project we would -- by the rules of our IRB -- have to go back to them and get specific permission for that specific project.

DR. MESLIN: Kathi, and then Eric?

DR. CASSELL: About how many women a year or how many couples a year do you serve?

DR. S. SHAPIRO: Ours is a relatively small program. We did about 150 cases in the last year.

DR. CASSELL: And how many years has your program been?

DR. S. SHAPIRO: Our first babies were born in 1983.

DR. CASSELL: And about what percentage of couples donate their blastocysts for research?

DR. S. SHAPIRO: That would be conjecture on my part.

DR. CASSELL: A guess.

DR. S. SHAPIRO: But I would guess it is under -- five percent or under.

DR. CASSELL: So it is a small number. And how many give them over to another couple?

DR. S. SHAPIRO: Less than one percent.

DR. CASSELL: So the vast majority of these embryos are going to be destroyed.

DR. S. SHAPIRO: The vast majority of embryos --

DR. CASSELL: That are excess. Excess.

DR. S. SHAPIRO: -- that are excess are not going to be destroyed. I said five percent might give them to research.

DR. CASSELL: Right.

DR. S. SHAPIRO: I am speaking of five percent of the total.

DR. CASSELL: The total. And then the excess --

DR. S. SHAPIRO: Of the excess --

DR. CASSELL: Yes.

DR. S. SHAPIRO: -- where -- how does that break down?

DR. CASSELL: Yes.

DR. S. SHAPIRO: I would again guesstimate that it is 50 percent or better that will give to research.

DR. CASSELL: And to adoption?

DR. S. SHAPIRO: Very few will but I also have to tell you that there is very few -- very little request for that kind of adoption.

DR. CASSELL: I understand.

DR. MESLIN: Kathi?

DR. HANNA: I just have one quick question. I know that some clinics have when the couple -- I understand that you do not approach couples until they have made a decision to discard. But I know that some clinics have for probably some sort of legal reason, they want an early determination of what to do in the event that the couple is divorced, that they both die for some reason, and so they want an up front indication. Do you require that?

DR. S. SHAPIRO: In a slightly different way. Our concern from the initiation of our freezing program was that we could be left in limbo with an obligation to maintain embryos forever and the way we have dealt with that problem is in the cryopreservation permit, that is the permit that says, "Yes, we want them preserved," in that permit they have -- they are told of what the eventual options are and there is a deadline that is clearly stated that brings the destruction issues up front.

DR. MESLIN: Dr. Shapiro, we want to thank you for making this long trip. Not as long geographically as one would have thought but long for your time. You can be assured that the other commissioners will get a copy of the transcript so that they will be able to review your remarks and the staff will probably want to follow up with you on some other matters.

I want to thank you for coming and thank all the public who has come to observe the proceedings.

DR. MIIKE: Can I ask just one last question? You know your answer to Eric, five percent of your

couples would donate to research and less than one percent to adoption, but you said that about 50 percent of the frozen embryos are okay for research. Is that what -- the reason I ask the question is that I assume from that that freezing embryos is not a usual procedure with your couples and that very few of them go through --

DR. S. SHAPIRO: No. To the contrary. The decision for freezing will be made by 95 percent of the couples if they have excess embryos.

DR. MIIKE: I meant in the actual situation. They may say yes but I meant it in terms of the percent of your couples who actually end up with frozen embryos.

DR. S. SHAPIRO: Again it is a guess but I would say that 20 to 30 percent have frozen embryos and that is because they have excess embryos after their initial transfer.

DR. MESLIN: Thank you very much.

We are now adjourned. Thank you.

(Whereupon, the proceedings were adjourned at 11:43 a.m.)

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