27th MEETING
NATIONAL BIOETHICS ADVISORY COMMISSION
February 2–3, 1999
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Princeton University
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DAY ONE—Tuesday, February 2, 1999

WELCOME AND OVERVIEW OF AGENDA

DR. HAROLD T. SHAPIRO: Let's begin. First of all I'd like to welcome everyone to Princeton; it's good to have you all on campus. I don't know if our schedule will allow you to see other parts of the campus, but if there are other parts or people anyone is interested in visiting, please let me know. I'd also like to get a full list of when people are expecting to leave, when their planes are, so we can make arrangements for you to leave on time. As you may have noticed, Eric [Meslin], is not here this morning. He is tied up with some type of immigration procedure in Washington and will be here later on today. It's not getting out of Washington that he's interested in, it's getting naturalization proceedings underway, as I understand it. So he will be here this afternoon.

I do want to tell Commissioners that we have run into a serious conflict of interest situation on the committee having to do with the University of Wisconsin and Johns Hopkins, for obvious reasons as you learned last time or you may have learned in the paper. Both of those institutions have patent rights with respect to these new cell lines that are being developed, these human embryonic cell lines. And I don't know what those financial arrangements are, but they clearly have those, and we have two members of the Commission who have no direct conflict themselves, but they are working for institutions that have a direct financial interest in some of the things we might recommend. So to put it in its simplest, perhaps most naive way, if we should recommend that this be eligible for Federal funding and so on and so forth, that obviously would have an impact on the royalty or licensing arrangements flowing to those institutions from the Federal Government. And so it's easy to understand that there is a conflict there for the institutions and then by relationship to the individual Commissioners. I'm hoping that we can through disclosure, which has been done before this was all disclosed, perhaps get that resolved and we'll get a waiver. I'm just not sure, but you'll see later today, when, Carol [Greider] won't be here, but Alta [Charo] will be here sometime this morning—when we discuss the stem cell research, until this issue gets resolved, Alta really cannot participate in our discussions and the same would be true for Carol until this issue gets resolved one way or another. And so, just to inform the Commissioners about that and we'll deal with that as best we can.

Now, turning to our agenda for this meeting, this morning we will be dealing with the Human Biological Materials [(HBM)] Report. Public testimony, if there is any, will come later on this morning; we'll then break for lunch. The rest of our time both this afternoon and tomorrow morning will be dealing with one dimension or another of the stem cell issue, just to say that in shorthand. And as the Commissioners requested last time, we have reserved most of today's discussion, starting right after lunch, for our own discussion on this issue to try to see where we stand, where we can find some agreement, and where the disagreements arise. I found Larry's [Miike] suggestion I think helpful, and I'll say more about that this afternoon, as a way to proceed to see where we have easy agreement, where we try to identify those areas where we don't have agreement and need to think more carefully about it, and so on. And Larry's suggestion was—I don't remember if Larry made it by e-mail or at the last meeting—that there are what seem to be simpler issues, and then they get harder as you go down the chain. And I think that's a useful way to begin our discussion this afternoon, and I'll ask Larry to help us focus on that. Bernie [Lo] also had an interesting suggestion, I thought, and that was the question of whether once we get that done we might find the model that characterizes the Human Embryo Research Panel useful or not; that model, as you recall, talked about research that is fully acceptable research that needs to be regulated in some way, or research that is unacceptable. That may or may

not be a useful model, but I think that's something useful for us to discuss. We'll try to focus on those issues this afternoon.

We do have one person coming to speak to us this afternoon, Dr. [David] Blumenthal from Massachusetts General Hospital, dealing with public/private issues. We will have tomorrow morning, when we will continue our discussion of the stem cell issue through the morning, we will have Brigid Hogan from Vanderbilt come in and talk to us—that, of course, is on the science of this—and see what other issues might need to be clarified. And we also have, as you know from your agenda, some speakers dealing with some legal issues that swarm around this issue. So that's the rough order of the agenda for the next day.

We meet again in Washington roughly a month from now. As I'll indicate in a moment, my objective for the Washington meeting is to produce a brand new draft of the HBM Report. Okay. The purpose today will not, when we get to it in a few moments, be to vote up or down any particular recommendations, but to really continue the discussion we had in Washington a couple of weeks ago and refine our ideas so that we can produce enough input for the staff to generate an entirely new report. And then we'll deal with the specific recommendations, whether we like them, dislike them, approve them or not, at our Washington meeting in March. I also hope that we make enough progress on our thinking with respect to stem cells that we can draft portions of that report. Obviously, we won't have a report, but portions of it, aspects of it, by our March meeting. So hopefully we'll arrive at the March meeting with portions, at least in draft form, of what will eventually be our Stem Cell Report—and with, I hope, a very good draft of the HBM Report.

So let's turn our attention right now to the HBM Report where we are spending most of this morning, or as much of this morning as necessary, but I hope we will be able to get through it. We will in a moment go at it in pretty much the same way we did in Washington. We'll look at the recommendations, which have been altered and reordered somewhat—modestly—as a result of our discussions in Washington. And just as a way of going through that, I'd like to revisit all of these recommendations, see how we feel about them, whether we like them or dislike them, how we want to combine or recombine or change them in whatever way seems appropriate. And as I say, the intention is to provide input for this final draft—not final draft, but the next draft that will come out. It may be the final draft, I don't know, that will come out in March. Regarding the rest of the report—now referring to the HBM Report, that is, all of the things that come before the recommendations and so on—it's quite clear to me, and it's quite clear I think from the comments we've gotten from Commissioners and others, that it certainly has to be refined, reordered. It's ambiguous in certain areas, and it has to be clarified. So there is a lot of work to be done, so at least as Kathi [Hanna]

and I were talking a few moments ago, some people are going to have to go underground for a few days from now and just work on this redrafting of that. But I think we are not far from where we need to be, although there is a considerable amount of work to be done to generate that draft.

DISCUSSION OF COMMISSION DRAFT REPORT, THE USE OF HUMAN BIOLOGICAL MATERIALS IN RESEARCH: ETHICAL ISSUES AND POLICY GUIDANCE

DR. SHAPIRO: So why don't we begin then our discussion regarding the recommendations of the Human Biological Materials Report? I think all of you have seen something that looks like this, that is the revised draft recommendations, post-January meeting discussions that headed that way. And there is also what I think is a useful addendum to that, so to speak, which analyzes the public comments we have received. And I think we have received quite a few actually very thoughtful comments, from the NIH and other places, that clearly point to some issues that we need to discuss further and may want to think about. As I went through all of this material, while it may have been a good idea to renumber all of our recommendations, it sometimes was a little confusing going back and forth between public comments, which were numbered one way and not all the same way, and each of our own recommendations. But I think it wasn't that hard to define the right spot.

So as just a way of beginning our discussion, I would propose that we go through these recommendations one by one. And as we go to each one, I will ask Kathi to summarize what her own view is of the public comments and what they might mean for things we need to discuss, and then we'll take the discussion from there. So if that seems satisfactory to everyone, we could just begin. Any comments, questions?

DR. HANNA: I would just add, just for your own—to avoid some confusion—on the green sheet are the old recommendations that the public comments are referring to. That should help keep things straight.

DR. SHAPIRO: All right. Why don't we go to Recommendation 1, Kathi?

DR. HANNA: As you can tell from the staff analysis, people had problems with Recommendation 1 for a variety of reasons, mostly, I would say in general, two. One is the phrase "rendered unidentifiable by someone other than the

investigator." A fair proportion of the commentors who had problems with this recommendation thought that we should drop that requirement, that it must be done by someone other than the investigator and they gave reasons that range from it's going to add to the administrative burden to it's going to add problems—potential questions in terms of coding if you have too many hands on it, to that you actually might end up getting samples mixed up, to the fact that this might be easy for large repositories to do, but it might be much more difficult for an investigator who has a small collection. And so there are a lot of concerns about that, and I would say a lot of people took this as some indication that the Commission doesn't trust the scientific community. That clearly came through in several comments that they asked for justification for that distrust: have we found any cases of abuse? Have we found any reason to believe that people were not honoring confidentiality, that people were unethically breaking codes? So that was the one set of concerns about Recommendation 1. The second has to do with the last sentence: "Coded samples are considered identifiable." You can imagine that a lot of people said that we were wrong, OPRR [Office for Protection From Research Risk] was wrong, this is not what the regulations were intended to say, and that coded samples should *not* be considered identifiable. So, that's really, in sum, the focus of the public comments regarding Recommendation 1.

DR. SHAPIRO: These are two issues that we discussed extensively. Those aren't issues that just happened to be in there, at least as I understand it. While we have found that—we were glad to find that OPRR interpreted it this way. We felt that was correct, that is, in our previous discussion, felt that that was correct. Coded samples should be considered identifiable, and we were concerned about who it is that rendered the samples unidentifiable. And in my mind it wasn't so much a question—I thought that was a good suggestion, to have some person other than the investigator do it. It had nothing to do with trusting anybody. It had to do with making sure the people who were supplying material had confidence, full confidence in the set of procedures as a sort of preventive medicine, as opposed to any scandal that I know about in this area. That was just my judgment. What's your feeling about these things? Alex?

PROF. ALEXANDER M. CAPRON: I had an introductory comment about this recommendation and several others. This is not a recommendation, and I think we need to somehow figure out how we're going to sort out the conclusions from the recommendations.

DR. SHAPIRO: The conclusion is also something that I consider observations or commentary.

PROF. CAPRON: Yes, and a lot of the commentary has now been moved out. But some of it— in some of them there are a series of conclusions, and then

a recommendation based on that conclusion. This doesn't come to any recommendation at all. We could turn it into a recommendation in the same style—conclusion, conclusion, recommendation—if we wanted to say that OPRR should issue clarifying commentary or regulations to make certain that everyone understood this. We are actually advisors to the President or to the Science Council. And so I think we need to turn this into a recommendation or separate it out. If we did that, the only comment that I have is that I think we need to change the language of "someone other than the investigator" to say "someone independent from the investigator." Now this may, in the view of the scientist, reflect a distrust. I think it could be presented in the commentary more clearly that it is simply a recognition of the fact that, either intentionally or unintentionally, coded samples can become identified, and that it is more or less not a statement of belief that people are malefactors out to do ill to people—but, simply, we've set up a situation in which that characterization leads to the conclusion that if something is going to qualify as exempt it has to be truly anonymous, and things that are not anonymous are coded and linkable and not unidentifiable. So I believe we should modify the language to say "rendered unidentified by someone independent from the investigator." We don't have to say it has to be the repository; I think in most of our thinking we assumed it would be the repository. There may be some intermediary institution that handles samples from a number of repositories and sends them out and becomes a clearinghouse. I don't think we can imagine every arrangement, but I would stick with this recommendation as to its substance.

I also wanted to ask Kathi, since I wasn't at the meeting the last few hours when it was discussed, was the sentence about "coded" dropped from here intentionally? Because it's not on the version that you gave us. It was on the December version, and it seemed to me that it was an important sentence.

DR. SHAPIRO: It's certainly clear to me that that is the intention of the Commission.

PROF. CAPRON: Yes.

DR. SHAPIRO: That "coded" is considered "unidentifiable."

DR. HANNA: It's actually that—what happened was that the discussion about "coded" equals "unidentifiable" was moved down into Recommendation 2 in the new recommendations, because it used to show up in two places, I think—

PROF. CAPRON: I see.

DR. HANNA: In the old Recommendation 1 and the old Recommendation 11, so they kind of got merged as a separate point to be made. At the discussion at the last meeting, people wanted to say two things and say them separately—the first having to do with what research is exempt, and the second having to do with what we consider to be "coded," or "unidentifiable." So they've been split into two, essentially, so that "coded" equals "unidentifiable" now is discussed in Recommendation 2.

PROF. CAPRON: I can see that, except that the advantage of the earlier sentence was it was just *clear*. Here the thought is—it's a subsidiary thought that's assumed in number 2. In a way, it's still linked with number 1, because it says what isn't identifiable. And if it's going to remain as a sentence maybe it belongs in 2, but I think it belongs there as a sentence: "Coded samples are considered identifiable; therefore, the current Federal policy is applicable to research conducted by linked samples."

DR. SHAPIRO: In Recommendation 2, as it currently stands—we'll get to that in a minute. But it's also an example of what you mentioned before: it's not quite a recommendation.

PROF. CAPRON: Yes. Right.

DR. SHAPIRO: It's an observation.

PROF. CAPRON: That's correct. And it's also what you said: The last sentence is more or less a comment.

DR. SHAPIRO: That's right.

PROF. CAPRON: Which probably ought to be in there.

DR. SHAPIRO: That's right.

PROF. CAPRON: In the commentary, in the text, not in the body.

DR. SHAPIRO: Let me just ask a question. I want to make sure that we are comfortable with the idea, that we want this "rendered identifiable by someone." If I understand the comment, they would—some of the criticisms would take Alex's suggestion, which is probably a good one, that "independent of the investigator." That's even worse than what we've got here, right? Because that means it can't be their research assistant, it can't be their whoever—post-doc, or whoever.

PROF. CAPRON: And that's what we meant.

DR. SHAPIRO: Yeah.

DR. ARTURO BRITO: I think that's right.

DR. SHAPIRO: Yes, I agree, but I just want to point this out: that those people who didn't like them would like them less.

DR. DAVID R. COX: I'd like to speak to exactly this point. I think that for me the issue isn't *who* but *how*, and that what we really are talking about is that we want to have a process by which we see these things really are rendered unidentifiable. I think focusing on *who* does it is in some ways missing the point, because the IRBs [Institutional Review Boards] need to have a plan presented to them that shows that that plan in fact will be effective at rendering things unidentifiable. I think it doesn't make any difference *who* carries out that plan. What counts is that the plan is clearly laid out and deemed to be effective. This addresses the issue about whether it's a big repository or a small repository. It doesn't say that it allows for the option of there being many different plans for doing this. But I think that—and I'd like to really see more of a focus on it—the recommendation be that a plan is presented for scrutiny, rather than focusing on who does it. So that's my suggestion.

PROF. CAPRON: I didn't follow you, David. Are you saying that you *like* the language here?

DR. COX: I *don't* like the language here because I think it misses the point by simply focusing on *who's* going to do it, instead of saying what we want to see is a plan of how it's going to be rendered unidentifiable. The plan approach I think is a better approach. It's a more general approach, because what it does is it allows for a variety of different types of plans depending on the situation. But at the end of the day, we need to see people come forward with what their plan is to show that these things won't be identifiable.

PROF. CAPRON: I guess my sense is *where* and *when* is more important than *how*, as it were. They may come up with techniques to render unidentifiable in a number of different ways, but it should be something that happens *before* it comes into the hands of the investigator. Because once it's come into the investigator's hands, the potential is always there—the temptation, even under the best process used, to say, "Well, as soon as we get them we'll take the codes off."

DR. COX: Yes, so—

PROF. CAPRON: But someone, in some lab in that process, is going to say, "Well, if we ever need to figure it out, why don't we just keep the codes over here and we won't have them on them when we're doing the research on them."

DR. COX: No, Alex, I understand this.

PROF. CAPRON: And you know, I don't think that the average IRB—I mean I just don't have faith in IRBs to have thought through all of these issues at every research institution in the country. We've spent two years talking about this, and it took a long time for us to understand all of the different ways this could happen and the potential of the problem. I think we should simply very clearly say it should be someone independent of the investigator. And in the commentary we should make clear that that might happen in a number of different ways, and the IRB does want to make sure that it will happen. And if it's going to—the IRB administrator, whoever is going to sign off on the waiver, is going to look at it and say— it's not going to be the whole IRB that looks at this, it's going to be the IRB administrator or chair that gives the waiver and says that this is exempt because they are getting samples that have no identifiers linked to any person on them from the pathology lab or the XYZ Company or wherever it's coming from—and when they arrive they meet the qualifications that OPRR has put out now to explain what the present National Bioethics Advisory Commission [NBAC] meant when it said "someone independent." So I don't want to leave it up to individual IRBs to try to figure out is it okay if the method that the assistant to the investigator is using is one thing or another. It should just happen before then.

DR. COX: Alex, I have two points, quick ones that I'd like to make why I disagree with your approach, and the first one is a very practical one. Oftentimes, it's not simply going to be the situation that the identifiers are shipped off before they get into the hands of the investigators. They *start* with the investigators. In fact, these samples *come* to the investigators. And so from a purely pragmatic point of view, thinking of it in that mode, that somebody else is going to have these first before it gets to the investigators, isn't the real world. In a significant fraction of situations the samples *start* with the investigators.

PROF. CAPRON: Fine; then they're now unidentifiable. That's fine. They can just go through another process.

DR. COX: But the second point that I'd like to make is that rather than putting this in the hands of someone else, one of the main things that we've tried to do in our deliberations is—at least from what I've been interested in focusing on, and I think the rest of the Commission, too—is bringing the research community into this process of being closer, not further from the human subjects, and being more

responsible, not less responsible for doing this correctly. I think that it's not a complicated situation. If the researchers in fact have the materials and they have the codes, there is a straightforward way to make sure that there is no link forward. And I think that to have the researchers take personal responsibility for that, I think will lead to better protections for the human subjects. I really believe that.

DR. SHAPIRO: Okay. Does anyone want to comment? Larry, then Eric.

DR. LAWRENCE H. MIIKE: That's okay.

DR. SHAPIRO: Okay. Eric?

DR. ERIC J. CASSELL: I hear you, but the object is getting an investigator to understand that this is human subject research even though they may be looking at a piece of paraffin block. But the temptation to keep some samples identifiable is there. And so it makes me feel that Alex is right, that it ought to be the way we have it said here—just because knowing that they are doing human subject research doesn't mean that they are not going to try and follow the samples back to their origin. So I think "independent" is the word I would favor.

DR. SHAPIRO: Let me raise one other issue, which is—we'll come back to this issue because we'll have to resolve this issue. As I said before, we're not voting things up and down but just trying to reach a consensus so we know how to write it; we can deal with voting particular alternatives the next time. But one of the public comments that was raised had to do with the issue—maybe Kathi can help me with it. It was someone who collects large data sets under the Public Health Service Act [(PHSA)] from the Government. Was it the CDC [Centers for Disease Control]?

DR. HANNA: It was the CDC.

DR. SHAPIRO: And they pointed out that in their situation they had, as opposed to rendering something virtually unidentifiable as a way of protecting them, they followed another tack: namely, to associate penalties with breaking confidentiality provisions. Now I haven't checked the particular public law they referred to so I don't know how effective those penalties are, how large they are, whether they're trivial or nontrivial. I just don't know; I haven't checked it. But I just wanted to point out to the Commission that was one of the public comments. It is, of course, another way to afford protection, that is to associate meaningful penalties with treating material inappropriately, as opposed to just through regulation. I don't know if any of you—how many of you saw that particular comment and what, if anything, you think we ought to do in response to that comment. Bernie?

DR. BERNARD LO: First, a clarification. My understanding of the CDC comment was that they call attention not to penalties but to the use of certificates of confidentiality, which are a legal means of protecting the code from discovery in legal proceedings, which I think is fairly standard in many social science studies that deal with sensitive topics like drug abuse and HIV [human immunodeficiency virus] infection. I think it does raise an important point about research that is on biological materials that happen to be questionnaire answers as opposed to physical samples of tissue or blood. And I guess, knowing how some of these publicly available data sets are used, I think the concern is that the CDC or the National Center for Health Statistics goes through a lot of trouble to issue these data sets in ways that make it very hard for anybody to backtrack to the original source using other available means like reverse phone books and census data. And they actually will change some of the data fields to make that harder to do. I think the concern would be—that if that is a data set that even though it's coded it's very, very unlikely the code will be broken either by going back to the original code or by using external information to identify individuals—why have the investigator go through any IRB review, particularly when most IRBs probably are not as expert on the confidentiality risks of these kinds of data sets as, for example, a well-formulated committee at the CDC or the National Center for Health Statistics?

So I think we were thinking mainly of samples that were biological tissues as opposed to social survey data, and where I think the concerns are about breaking the code or identifying in other ways—you know, visual memory by a pathologist, or the slide being associated with a person, or the far-fetched cases we talked about where carrying out DNA [deoxyribonucleic acid] analysis gave you a fingerprint of an individual. It seems to me the concerns with these surveys are different, and there may in fact be adequate protections through the mechanisms that the CDC and others have worked out that achieve the objectives within a coding situation. I don't know if we want to carve out an exception for that, but it seems to me that there would be concerns about putting administrative oversight burdens on the situation where the risks simply may not warrant it.

DR. SHAPIRO: Do you think this— I'm sorry. Larry?

DR. MIIKE: Just to get it clear again: When we're talking about "someone other than the investigator," we're talking about "rendering unidentifiable." We're not talking about coding it, so I don't see what the issue is here. I mean, if we're talking about rendering it anonymous, it doesn't make sense for the investigator to do that, so that's a part. And we're not excluding the coding being done by an investigator. So. On the issue of the penalty, I would see that as a worse situation than what we're asking here. Because all we're asking here is that. Maybe just an administrative review

by an IRB to come down on the other side with a penalty for some of these things seems to be—I would think that that would be a worse solution.

DR. SHAPIRO: Yeah.

DR. LO: I don't understand where the notion of penalties came in, because I don't think I took the CDC as talking about—certificates of confidentiality are not a penalty mechanism. It's just sort of a way of keeping the code from being learned through a legal process.

DR. COX: Are those two separate comments, perhaps?

DR. LO: Yes. I'm looking at page 2.

DR. SHAPIRO: I was—it's certainly the comment I was thinking about.

PROF. CAPRON: The comments extracted at the top of page 2 are commentary. Separate respondents suggested that NBAC recommend ways to code samples and penalties for inappropriate use of codes, as opposed to considering coded samples identifiable, and then there is a separate comment from the CDC.

MR. STEVEN H. HOLTZMAN: So the CDC—on page 4 the CDC letter makes the point that data from the surveys conducted by the National Center are compiled into public-use data sets. These data sets are treated as exempt from IRB review even though they are coded because the code is protected by PHSA 308(d)'s assurance of confidentiality. But according to NBAC's recommendation, these public-use data sets would not be exempt because they're coded. And then they go on to say that perhaps NBAC is suggesting that there be a different standard to meet with biological samples that are publicly available and other types of information that is publicly available. So that's one set of comments. The recommendations about protections, and then penalties, come from a number of different sources such as the pathologists who talk in terms of—that the issue is not the collection; the issue is the misuse of information, and the locus of protection should be there.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: I think that there are a number of issues that are being smooshed together here. The assurance of confidentiality, as I understand it, is something that is provided to people and to protect their data from being subpoenaed

and used in proceedings—if, for example, the data related to drug use and then they were to be prosecuted for drug use. It is a limitation on the use of identifiable data, in other words. What we're talking about here is something that wouldn't be protected by a certificate of confidentiality, because I think we're talking about either someone maliciously—not the investigator necessarily—or someone for what they feel are very good and compelling reasons to take something, which someone didn't know was happening, with themself: an investigation is going on. "My goodness, you have the gene for XYZ. I want to get back to you and tell you about this, because it's a ticking bomb." And so it's the call that comes in saying, "You didn't know we were studying you, but we're getting back to you because you have this ticking bomb that we think is very important for you to know about."

And I thought our view was that unlike in these publicly identifiable data sets where there is the data—the numbers are there: how tall you are; what you do; how you live; what you eat; what your income is, it's all there—something about biological samples is this infinitely expandable thing. When your sample was taken, for whatever reason, you had no idea that all of these kinds of things were going to happen to you. We can establish—we do establish different procedures for situations in which a person says, "In the research I want to conduct, I want to be able to go back to the person. I want to get their data. I want to give them data." Okay, fine. That's just a different process. This is for things where you just get out from underneath all of the human-subjects regulations because you're just interested in the material, the quality of material: "How many out of a hundred samples have this gene? I don't need to know who they are; I'm not going to contact them. I'm not doing long-term followup. I just want to know what's the prevalence—or the incidence, or whatever the correct scientific term for that kind of research is—" and if I can do that, and if I can identify the gene, then I'll do a study where I find out what happens to people's lives, and I'll have to get their consent to look at their records," and so forth. So this is not the end of scientific research. This is a particular category that we were told was valuable research that people would like to go on. And I want to see it go on with as few impediments as possible. But I want to restrict it to that category of research.

DR. SHAPIRO: Does anyone want to comment? Bernie?

DR. LO: I agree with your analysis. But I think the CDC's comment is: Are the kind of public-use-questionnaire data tapes they and other Government organizations put out to be considered the same way as these repositories have biological samples, which in your language have sort of an infinitely—

PROF. CAPRON: No.

DR. LO: Or is it—okay.

PROF. CAPRON: This is a report on biological samples. It's not on -- it's not on everything else, as far as I can tell. I thought we went into this saying this stuff was different. And I don't know enough about their data sets. But I suspect that if my data is in there, somebody has come and said to me, "Will you fill out this questionnaire?" or "Can I ask you some questions?" or "Can I look at your records? We're building a repository for some public use." And I say, "Yes, it's okay to put it in there." We know that for most of the 200 million samples that are there, no one had any idea that someone would someday be doing genetic analysis on them. Most people don't even know their samples are there. And this says, "Fine, use them." They're a wonderful scientific resource, but use them in this way that doesn't link them to people.

DR. SHAPIRO: Kathi just pointed out to me that if you look down further in the CDC comment, they themselves suggest that there might be a difference between biological materials and other things. I think this is the Human Biological Materials Report that we're focusing on. Diane, did you have a comment?

MS. DIANE SCOTT-JONES: I think that maybe the CDC is responding just to the sentence out of context, that says, "Coded samples are considered identifiable." And maybe that sentence could be changed so that it could not be taken out of context, to make it clear that it's referring to human biological materials. Because their comment is inappropriate, in my view, unless you take this sentence completely out of context.

DR. SHAPIRO: Okay.

DR. MIIKE: That would fit, too.

DR. SHAPIRO: Thank you. I'm going to exercise a certain discipline here to keep on moving this morning, and I want to move on from this one right now. I do want to get just a straw vote so we'll see how people feel. There is an issue that I think has divided us here, which David brought up. And the question really is whether we want to stick with something like "rendered unidentifiable by someone independent of the investigator," a sentence or phrase like that vis-à-vis approval of a process. If I could just have a caricature of your suggestion without meaning. How many of us—let's just have a brief show of hands—would prefer to stick roughly in the neighborhood of, "rendered unidentifiable by someone independent of the investigator," or words to that effect? One, two, three, four, five, six. And how many others would prefer to try to construct something along the lines that David suggested?

DR. BRITO: Can I make a quick comment about that?

DR. SHAPIRO: Yes.

DR. BRITO: Okay. I think it's the difference, going back to Alex's very first comment, whether or not it's a recommendation or a conclusion. So I'm in favor of it as a conclusion. I'm not sure as a recommendation how to handle that yet.

DR. SHAPIRO: All right. Okay. This is a conclusion. We will -- that's very helpful. I mean, the majority of us here feel that we ought to stick with that; as we go through and try to articulate this more carefully we'll try to pick up that issue.

DR. COX: Harold, I certainly recognize this. The only plea that I would make is that for investigators, they're not going to have a clue of who that "somebody else" should be. I mean, they have the samples. They collected them. Who should they go to? So we need to give some guidance about that, because if it's not going to be them we've got to figure out and help them with who it is. But I clearly see the second part.

DR. SHAPIRO: Okay. That seems like a reasonable notion. We'll try to incorporate that and give some suggestions. Let's move on. We can circle back if we have to, but let's move on because we only have this morning to work through this. We now have what is currently under the new numbers, and let's not concern ourselves at the moment with what's a recommendation, a comment, or an observation; 2 was a good example of that. But I guess the key issue for us is really what we have just been discussing: whether coded samples are considered identifiable. We've discussed this many, many times. I'm not worried—let's not focus on the wording here. If I recall the discussion correctly at our last meeting, we had some back and forth about "impossible" versus "very difficult," and the huge majority of the Commission—I think one person on the Commission wanted "impossible" and everyone else wanted, you know, something restrictive, but not "impossible." And that's where we ended up. Are there any concerns about that—without looking at the wording itself here—the fundamental position that we took?

All right. So that will be reflected in the material that will come in the next draft. Thank you very much.

What is now Recommendation 3, previously 2. Kathi, do you have anything you want to point out in what is Recommendation 3 under the new numbering system?

DR. HANNA: I think on this one several commentors had I think a very legitimate concern about enforcement issues and recording and reporting issues. They thought that the language of the recommendation was somewhat vague. And they had questions like: What kind of documentation? From whom? Whose responsibility is it? If the IRB has approved the protocol, is that sufficient documentation of IRB approval sufficient? So the questions with this—I don't think people had real principled opposition to it. It was more, How are you going to implement it? What kind of documentation are you talking about? Make it more clear who has responsibility to do what.

PROF. CAPRON: So the suggestion is that we add the words, "from the investigator's IRB"?

DR. HANNA: In fact, yeah, there was some suggestion that there be documentation of IRB approval, and that we say clearly that if that documentation exists, that would satisfy this recommendation—or that it could be the repository's IRB, or both. Some repositories do have ethics boards or IRBs. So, there would be either IRB approval from the investigator's institution, or from the repository, or in some cases both. And they had given just the request that there be one.

PROF. CAPRON: I don't see how the repository's IRB could document that the research will be conducted in compliance with applicable Federal regulations for the protection of human subjects. I mean, the protocol describing what the research is going to be will have gone through the IRB of the investigator. And what would the IRB of the repository know about the investigator's processes? It's either duplicative, because he's going to have to have gone through his local IRB, or it was an IRB that would not necessarily know anything about this person or how he operates and they'd have to send someone to his lab to look at his procedures or something. I don't think it would make any sense.

DR. SHAPIRO: Kathi?

DR. HANNA: I think that the suggestion that it be the repository's IRB came from pathologists, who might be working as investigators in the repository.

PROF. CAPRON: Are they carrying out?

DR. HANNA: They're conducting research. They're pathologists. They are scientists associated with that particular repository.

PROF. CAPRON: But then it's in their hat as investigator that they're going to carry out the study. And so it happens that it's the same IRB because they're looked at only at one institution. But I think it would be clearest to respond by saying, Provide documentation from the investigator's IRB that research using, etc., etc.—the same way that the Federal Government won't fund something until you've gotten your IRB to sign off on it. It's pretty straightforward.

DR. SHAPIRO: David?

DR. COX: That's the mechanism, really how it's done now. And I think this is another one of those examples where we have in mind what we want but we're just not spitting it out in a clear way. And I actually am very in favor of this investigator's IRB. In some cases the investigator is the repository *and* the investigator, so that you have to keep track of what role a particular person is playing at what time. And what we're talking about is, as you pointed out, Alex, the investigator's IRB, and that the repository just has to have documented that the person has gone through that. This is a standard thing that researchers are doing now. They'll understand it, and it won't lead to confusion, I believe.

DR. SHAPIRO: I interpreted the—I think that's right, and I fully favor these last comments. There are some repositories that have their own views of what's appropriate and the IRBs have their own views, but that's their business. I mean, if they don't want to release it, they don't have to release it. That's their business. We don't have to tell them that now. They may feel they have certain protections they want to afford people who provided them with materials; that's their affair. But I think the investigator's IRB is the right way to do this, and I think that's straightforward enough and does not require anything extra from the investigator. It's a process you have to go through, so it seems quite straightforward to me. But are there other questions?

PROF. CAPRON: Could we put your statement just now into the commentary to make clear that an additional protection is certainly in place? I think the sentence also reads better if we change it from "investigators" to "an investigator." And then we can say, "the investigator's IRB" and leave "repositories" plural so that works.

DR. SHAPIRO: Yeah, and we could put this other last comment I made in the commentary—

PROF. CAPRON: Yes, exactly.

DR. SHAPIRO:—in the text somewhere. That would be fine. Would you make note of that, please?

DR. HANNA: Uh-huh.

DR. SHAPIRO: Any other comments on current number 3? I keep on having to distinguish the current from the previous number 3.

MR. HOLTZMAN: Can I have a question?

DR. SHAPIRO: Yes.

MR. HOLTZMAN: Is it within the spirit of Recommendation 3 that someone could say to the repository, "There are no applicable Federal laws for this sample, thank you"?

DR. SHAPIRO: That's what came up last time. Okay. Let's go on to what is currently here Recommendation 4. From the recommendation's point—

PROF. CAPRON: Wait a minute. Steve, I don't understand what that means. If, for example, the person says, "I'm asking you to send me unidentifiable samples; here is my waiver from my IRB, signed off that since they are unidentifiable I'm not subject to further review by the IRB." I don't understand that there would ever be a situation where you'd say there are no applicable Federal regulations when they're using human samples.

MR. HOLTZMAN: Suppose there are identifiable samples—coded. The repository has collected them. It has them in its possession.

PROF. CAPRON: Right.

MR. HOLTZMAN: Now someone wishes to conduct research on them that is not federally sponsored. You know this stuff much better than I, I think.

PROF. CAPRON: Well, if it's not federally sponsored, then they would have a statement from their IRB. Our general, or our multiproject, assurance does not require us to review non-federally sponsored research. Most of them do. The OPRR has sort of worked out this little deal where they reach most research.

MR. HOLTZMAN: Well, I'm just—

PROF. CAPRON: But if they weren't, then the statement from their IRB would say, "This is not subject to Federal regulation because it's privately sponsored, and at our institution we don't review." And Harold says if the repository says, "We

don't like that kind of stuff," they can hold back the samples. If it's okay with them, it's beyond the reach of Federal law.

MR. HOLTZMAN: I was asking a very simple question.

PROF. CAPRON: I agree.

MR. HOLTZMAN: I'm a dumb old repository. I'm sitting down reading NBAC Recommendation 3.

DR. MIIKE: What was the first adjective? What kind of repository?

PROF. CAPRON: Dumb old.

DR. MIIKE: I thought you said "Dumbo."

MR. HOLTZMAN: Dumb old, little old me, just trying to understand.

DR. COX: The technical term is—

PROF. CAPRON: It's the famous "McDumbOld's" Hamburger.

MR. HOLTZMAN: I've complied. I have my IRB. Now someone calls me up and says, "Please send me a sample." It's a coded sample, as 99.9 percent of these will be. They will be coded. They will not be anonymous.

PROF. CAPRON: And it doesn't ask you to strip them.

MR. HOLTZMAN: That's right. Well, it's coded, right? And that research is not subject to Federal regulation because it's not federally sponsored. So my question is, Will it be clear to a repository if they have fulfilled the spirit and wording of our Recommendation 3?

PROF. CAPRON: I think our commentary should say that the IRB would still be expected to produce a statement saying, "This person has come to us saying he's doing non-federally sponsored. We don't review non-federally sponsored. He can do whatever he wants with non-federally sponsored in our institution, so here is our certificate saying it's not subject to our review." If you're comfortable with that repository, give them the samples.

So I agree we should make that clear in the commentary. I think that's an unusual situation given most multiproject assurances and most research institutions, but there may be a private researcher who is not subject to it.

DR. SHAPIRO: Or it could be private but, you know, not just a solitary private researcher. It could be a group of well-financed private researchers.

PROF. CAPRON: Yes, yeah, right. I didn't mean a hermit.

DR. SHAPIRO: All right.

MR. HOLTZMAN: It could be a pathology department at a county hospital, not a major research institution. And I believe, according to Elisa [Eiseman], that's where—what percent of the samples are?

PROF. CAPRON: Yeah, it's not where the samples are, it's where the research is mostly done that's the issue. I assume that a lot of pathology labs are not subject to Federal research regulations if they're not conducting research. They're just repositories.

DR. SHAPIRO: Okay. Let's go on to Recommendation 4. First of all, Kathi, your analysis of the public comments.

DR. HANNA: Okay. By and large the public commentors have absolutely no problems with the first and second sentences. They don't like the third sentence for a variety of reasons. One is that they don't know what "mindful" means in terms of implementation. And then there are a number of commentors who had just general concerns about group considerations at all. They don't think IRBs should consider group harms. And people used language like "This is a slippery slope." On the other hand, for example, the American Society of Human Genetics made I thought a useful argument for why in some cases group identifiers are important for the kinds of research that they do. So they wanted us to comment further on how you might keep ethnic or racial identifiers on samples yet keep them unidentified for the purposes of doing research that geneticists tend to do on various populations and subpopulations.

So there are a lot of different issues there. One was just asking for greater clarification on what we meant by "mindful"; others asking for more guidance on when it is appropriate or inappropriate to keep group classifications on things, and then other people who just said IRBs shouldn't even get into this.

DR. SHAPIRO: Larry.

DR. MIIKE: Yeah, we went over this many times. And I think that the purpose of this is just to raise the consciousness of people to consider these issues. And I think there is a simple solution. Most of it revolves around the very last phrase of the last sentence. And I think it's too hard where where we say that, therefore, "design research that minimizes such risks." I think a simple way of dealing with this is to take that "researchers should be mindful" clause and move it, so that the last sentence becomes, "Some types of research," etc., "might pose potential harms to groups, so researchers when designing their research should be mindful of these issues." So that instead of saying you "should design," in order to address this you say, just "be mindful of this when designing your research." I think that that would take care of the awareness issue without leaving them in a conundrum about us recommending that they design the research the way we actually address this.

PROF. CAPRON: Comment?

DR. SHAPIRO: Yes, Alex?

PROF. CAPRON: I thought I was going to entirely agree with Larry. I partially agree. I don't think it's helpful to begin that sentence, "The researcher should be mindful...."

DR. MIIKE: Right.

PROF. CAPRON: I agree with him it should begin with "Some types," but I put a period after "individuals" and then had that last clause become a sentence. I didn't see that there was a problem with saying that as I understand our point here: since you can't identify they're individuals, they are not individually at risk. But if you're doing research that aims to say something about the group, you may be posing risks to them and you should therefore design your research to minimize those risks. You may not be able to eliminate them if you're working with Ashkenazi Jewish samples; somebody is going to be able to say, "Here is another Jewish gene," or something, I mean, whatever. And what you ought to be able to do is to design your research so as to do that with harm in a minimal way, either by the way you publish the research and explain it, or trying to use two sets of samples—a Jewish and a non-Jewish or whatever it happens to be—just to reduce that as much as possible. The phrase, "Be mindful of it" I would understand people objecting to because it doesn't tell them, "Well, now that I'm mindful, what am I supposed to do?" What we want them to do is to minimize the risks, and I think we should say so directly.

DR. SHAPIRO: Other comments about this? Trish, and then David, and then Bernie.

PROF. PATRICIA BACKLAR: I agree with what Alex said. But I also in looking at this recommendation noticed that we have a Recommendation 13 on page 4 that also deals with the issue of groups where there might be potential harm to individuals or groups. And it seems to me that this is the issue that we're looking at, and I'm wondering why we have 13 somewhere else, whereas actually the issue is the design to begin with, and then you go from the design to about how you get the information also.

DR. SHAPIRO: I think—I know David and Bernie wanted to speak, but let me just make a comment. I think this issue does come up in too many places; that is, we haven't focused our recommendation here, or whatever it is we want to say here. I think in particular, what is currently Recommendation 4, in my opinion, is one of the cases that is not a recommendation, right? It's an observation. Things are okay, but we should be mindful of this, or whatever. "Mindful" I think is the wrong word, whoever pointed that out. I like the changes that have been made. But it seems to me that, one, as we get to the next track we have to focus this concern in a more coherent way. And in particular this recommendation—what I think should remain in the report on this idea doesn't seem to me to be quite a recommendation, but it's an important observation that should be made in the appropriate place. That's my sense of this anyway. David.

DR. COX: I completely agree with what you just said, Harold. It's an effort for clarity; people have to see what it is. Whether we like it or not, a lot of the mindset right now is, What is it that I have to do in order to be in compliance? And our report isn't crystal clear about that. Instead, we need to be clear what in our recommendations are things that people have to *do* versus what are some examples and considerations that people take into account. They are two very different things. And we kind of mix them up together in what our recommendation says.

I think we need some examples of this. If you get some examples out saying what "mindful" meant, there'll be no conflict there. We have lots of examples for the one or two situations where we're describing what "mindful" means, such as the following.

DR. SHAPIRO: Kathi, whatever you want to say, then Bernie.

DR. HANNA: I just want to respond. We actually got some good examples from other sources, and I think they can be very easily put in.

DR. SHAPIRO: Bernie?

DR. LO: I just want to reinforce the point that I think we should be specific and give examples, because what's scary to a lot of people when they read this is they see the general maxim and they think the worst case when in fact we have something very different in mind. Having said that, I think it's also important that we make a distinction between minimizing risks, and in the language of Recommendation 13, to "control" or "reduce" them—and minimizing risks in this situation from harms is a very strong requirement for a risk that is poorly understood. And I would sort of favor something more along the language of "controlling" and "reducing."

DR. SHAPIRO: That's helpful; thank you. Trish?

PROF. BACKLAR: Also, as we go through I find it very confusing that we're not being very clear about what is in the recommendations for research with retrospectively collected specimens or samples, and what is going to be current.

DR. SHAPIRO: No, this—that issue came up at our meeting in Washington. It's a very important issue, because I think there are a lot of people who—the first thing they'll want to know when they look at this report is, What if I use retrospective samples? Where do I go and find out? And you can get that out of here, but it's not easy. So we're going to have to organize that somewhat differently, including the flow diagrams we have at the end and so on. I agree; it's a good point.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: It seems to me that in light of several of the comments this recommendation really flows most directly from the first recommendation because we are talking here about unidentifiable samples. And it seems to me we have two choices. If we have reached the conclusion that this is not a recommendation—with which I don't quite agree, although it's certainly not a recommendation for Federal action; it's a recommendation for investigators, actually—then the whole thing could be put into whatever format we're going to use for conclusions and tied to Recommendation 1. I mean, once we say something is unidentifiable, if it's going to remain as a separate point, it seems to me it flows most naturally after number 1. We say this is the number one category.

I would then suggest that we take that sentence that now begins, "Researchers should be mindful"—and I thought that there was sort of a consensus coming out, but maybe I was wrong, along the lines of what Larry had suggested about dropping that phrase—and beginning, "Some types of research on unidentifiable

samples, while posing no potential for harm to the sample source, might pose potential harms to groups of individuals (see Recommendation 13). To the extent possible, investigators should design their research so as to minimize such risks." That then becomes the recommendation that flows from the two or three statements of conclusion before that. So I would be comfortable with this being called a recommendation, being number 2, and ending up with that recommendatory language, and then in the commentary put in some of the examples that we have from our comments.

DR. SHAPIRO: That sounds helpful. Larry, then Diane.

DR. MIIKE: I want to get to the issue of whether we're going to have some of these as conclusions and some of these as recommendations. I would argue against that. I think these should be *all* recommendations. Obviously, some are recommendations that say it should be required by law or a change in reg[ulation]s, and some are recommendations to researchers that we implore them to do certain kinds of things. It will get confusing if we make some of these conclusions and the others are recommendations. So I would suggest we make recommendations, but it's quite clear that some are, we're giving advice and we're hoping they comply, and some others that we're seeing we should have the force of law behind.

DR. SHAPIRO: Diane, and then Alex.

DR. SCOTT-JONES: My comment is a followup to Alex's. I agree with how he's recommended moving Recommendation 4 to follow Recommendation 1 or to be associated with it. But I think that that recommendation, that last sentence, makes a point that's somewhat different from the point in Recommendation 13, which also talks about harms to groups. But Recommendation 13 is centered on dissemination of results of research, whereas in Recommendation 4, as Alex suggested, there are strategies that a researcher might use in designing the study. For example, instead of limiting the study to one socially defined group, the researcher might well include another socially defined group so that the results could be compared from one group to another. So I would not be in favor of eliminating the thought about what you would need to do in the design phase, because that's critical; 13 clearly focuses on dissemination.

PROF. CAPRON: I agree.

DR. SHAPIRO: Thank you. That's helpful and useful. Alex?

PROF. CAPRON: I agree, and one might say, "See *also* Recommendation 13," just to make it clear. One thought about—I basically agree with Larry's idea that it's confusing to have conclusions *and* recommendations. If a lot of

these statements here have two or three sentences, and the first couple are kind of the conclusion, then the recommendation—for the first recommendation, as it stands what we have now in the text, Larry, is a conclusion. We could have a final sentence along the lines of, "The Office for Protection From Research Risk should issue appropriate guidance for investigators and IRBs or, if deemed necessary, modify the language of the regulations," and that then is our recommendation. And with all of these, we can have boldface type and italicize the part that's the recommendation in boldface also. In other words, we can signal people what we're doing—that we recognize we're making two kinds of statements here. I mean, I think we can get the point across and still call them "recommendations," or call the whole thing "conclusions and recommendations" and just number them, and don't keep repeating the word "recommendation" every time.

DR. SHAPIRO: All right. Those are very useful.

PROF. CAPRON: They're almost cosmetic, but they help to avoid confusion.

DR. SHAPIRO: All right. That's very helpful. Arturo?

DR. BRITO: Something that Diane just said. I agree with the fact that Recommendation 13 focuses on dissemination and the number 3 or 4, the 4 here, and the new one focuses on the design. But I'm a little bit confused now about what in the design itself would present a risk to the groups. Can you give an example of something how—

DR. SCOTT-JONES: Okay. I'll give an example, but I don't want us to get sidetracked on this issue. It is a very serious one. In studies -- say you may define a social group as a biological group. Race in this country is social, but people consider it biological. It's a horrendous problem. It's been written about extensively by many people. When I represented the Commission at the meeting of the French Bioethics Commission in Paris, a whole series of speakers talked about how race is simply a biological fiction. We treat it as a biological reality, and it is extraordinarily harmful in this society. It has a history of harm. I could go on and on, but I won't.

DR. BRITO: No, that suffices. Thanks.

DR. SHAPIRO: Hold on. Okay, thank you very much, and thank you for those comments. Kathi, why don't we go on to what is now currently Recommendation 5?

DR. HANNA: Yes, and *was* Recommendation 5.

DR. SHAPIRO: And was Recommendation 5. Excuse me.

DR. HANNA: I think the fact that we dropped that last sentence the last time around—I mean that's disappeared—a lot of people had concerns about that. The last sentence in the green version of Recommendation 5, that's gone. So let's address some of the concerns in the public comment. By and large, as expected, the research community really likes this recommendation. There are only two things that they would add. They would say in—now we're talking about the revised recommendation language—the fourth line, "The requirement should be waived," there is a suggestion by many that we say, "The requirement *may* be waived," just to make it more clear.

The other thing that people had a question about was that we went down the list of the criteria for the waiver of consent but we didn't really say anything about the fourth one, the fourth being that "whenever appropriate, the subjects will be provided with additional pertinent information after participation." We stopped at the practicability one and didn't go the last step. And so a lot of people asked, Did the Commission have anything to say about that one? Many people suggested that the Commission should also suggest dropping that requirement as well. This is—I mean that last condition is usually, it's commonly referred to as the "deception clause" for research that has to be done deceptively with the requirement that the investigator then go back and tell people that they in fact were subjects of research. So I think that the research community would like to know whether we have anything to say about that.

DR. SHAPIRO: Okay, thank you. Questions, comments, reactions from members of the Commission?

PROF. CAPRON: Excuse me. I have found this recommendation as presently written totally opaque. I realize that there is a certain amount of lingo that's used here that's very familiar to aficionados of the Federal regulations, but I think we ought to spell this out just a little bit more and not use the shorthand of the practicability requirement and so forth. At the very least, if we're going to do that we ought to gear the section of the regulation that we're referring to and put it in English: "The requirement under blah, blah, blah, that it be impractical." Isn't that what we're saying? It's really the impracticability requirement more than the practicability requirement.

I also think it is not going to do for us to say this requires a change in Federal regulations. I think we should say what the change we believe is warranted is, in so many words. In the first part of this sentence, I also thought the phrase, "is determined to be of minimal risk with no adverse consequences for the subject's rights and welfare" was unclear. And I wondered, Kathi, if it wouldn't be clearer to say, "...is determined to present minimal risk to the subject's rights and welfare." Isn't that

what—because we'll never have a situation in which someone could say, "with no adverse consequences." Consequences are what's going to happen. You know after the fact what the consequences are—the idea of linking the risk, to present minimal risk to the subject's rights and welfare. Unless I'm suggesting language that goes against the wording of the Federal regulations, to me that would be much clearer, and be shorter and easier to read that part of the sentence. Is it clear to everyone what I'm saying? "If research using identifiable existing human biological materials is determined to present minimal risks to the subject's rights and welfare, the consent requirement...."

DR. HANNA: I think, Alex, that this has kind of been the struggle that the staff have talked about, gone back and forth. The language of the regulation treats minimal risk as one criterion and adverse effects on the rights and welfare of the subject as a second criterion. I mean, these are not "and/or's"; these are "and's." So in trying to craft language that reflects that you're going down this checklist, 1, 2, 3, 4—

PROF. CAPRON: Right, but we spent some time at an earlier meeting discussing that. And I didn't hear Gary Ellis contradict a reading of those regulations to say that the phrase "welfare"—as opposed to the phrase "rights," the phrase "welfare" refers to what most people think of in the first instance as risk, which is risk of physical harm—and that the phrase "rights" refers to protection of other interests that one has in confidentiality and so forth and so on. We are all looking around saying, "We didn't bring our regulations with us," or do you have yours?

DR. HANNA: No, no, I have them with me. I was just asking Andy Siegel if he wanted to say anything.

PROF. CAPRON: So my sense is that although those are separate, in fact a careful reading of the regulations reveals that in the end it's the risk to rights and welfare that's at issue. And as I say, if my rewording of it does an injustice to or mangles the difficult-to-read regulations, it's wrong. If it in fact clarifies what the regulations are really after, then I would prefer to use that. And I don't have my copy of the regulations with me; I probably should have them, the way Justice [Hugo] Black used to carry the Constitution in his pocket. I suppose I shouldn't leave home without my regulations.

DR. MIIKE: Just to restate what the regs say, and then just say we simply recommend dropping the practicability requirement.

DR. SHAPIRO: If I understand this regulation, this recommendation here, that is the gut issue. That is, we're dropping the practicability requirement from the existing set of requirements. I think we have to find the right language, and I think we

ought to investigate the issue that Alex raised, but I think it does need to be reworded, I believe. But that's the gut issue that we're doing. We're dropping the practicability requirement, and Kathi, who's raising the issue through the comments, says people in public comments are asking whether we want to drop an additional requirement—namely, the one that Kathi just mentioned. I don't have the words in my head right now, but it has to do with informing or keeping people up to date on what we've done. Would you want to read that one again?

DR. HANNA: "Whenever appropriate, the subjects will be provided with additional pertinent information after participation."

PROF. CAPRON: It's the debriefing.

DR. HANNA: It's the debriefing. Participation by itself is unclear in the context of using stored samples.

DR. SHAPIRO: Bernie?

DR. LO: I think the problem is that we're working from a regulation that is poorly crafted and probably doesn't make as much sense today as when it was first written, and I guess the issue is how far do we go. I think our main point is to drop number 3, which is the practicability requirement. I think once we start tinkering with the recommendation, saying we're going to change the Federal regs, then I think the issue comes up: Should we change the language of 1 and 2 along the lines Alex suggested? Because you know it kind of isn't optimal. I actually would favor number 4—at least a clarification saying our understanding of number 4 is that it really refers to deception studies and should not be literally applied to all these kinds of research on unstored tissue samples unless it really fits those sorts of situations.

I think, given that we're asking for a major change in regulations, the question is, Should we try to change the whole thing, or just one piece? I also liked one of the comments here that said while we're waiting for these regs to be changed, do we want to give some guidance to IRBs saying that until the regs change, at least treat number 3—give number 3 a lot less weight than numbers 1 and 2, which operationally may get to the same end result in terms of review during an interim period where the regs are still in place as written.

DR. SHAPIRO: If you'll help me out here, I think—I don't know what the status of the recommendation for us would be to say, "The regulations are what they are until they are changed. We suggest you interpret it this way." I don't know who we'd be making that regulation to. Someone could help me out. I don't think we could

make that regulation as a meaningful instruction to IRBs, that is because we don't have the authority to waive 3 or to make 3 less important or—

DR. LO: Does OPRR?

DR. SHAPIRO: So we'd have to include in any recommendation for them to consider; as they implement, we could say we recommend that OPRR consider giving this or something of that nature. I don't have the language. But I guess the language on number 4 deals with "as appropriate" or "as inappropriate," so it's not a requirement, because if it's appropriate you may do this. I guess as a suggestion, if I understood your words, Bernie, that we encourage OPRR, if that's the appropriate thing, to interpret "appropriate" as really referring only to deception studies. And that question is—that's what I understood you to be saying. Other people? Steve?

MR. HOLTZMAN: Maybe there is a stronger way in terms of saying what we think "appropriate" is. And I'm thinking here, I believe the driving animus behind the Commission's approach to treat "coded" as "identified" is the concern about the "go back," the inappropriate "go back." If here we're saying in the case of "identified," that is "coded," coded will be minimal risk and we're rationing—we're saying that can go forward pretty straightforwardly, and we get rid of the practicability. I think the onus comes back on us to then say we think it would be inappropriate to go back. It just seems to follow from the logic of how we've approached this whole subject.

DR. SHAPIRO: David?

DR. COX: I don't really see this so much as going back as just—maybe I'm missing the point here, but here we have a lot of retrospective stored samples that we're getting general information about. And what happens is, if we get general information about that you make some general comment about it for the public. This is basically what scientists do with this general stuff. It's not useful in the context of individuals per se, but it's generally useful information.

MR. HOLTZMAN: But David, the reg isn't trying to put a general obligation on scientists to publish useful results; it's directed to the idea that you have waived the consent requirement of that individual. You're examining whether or not the waiver of that consent has had any adverse impact on that individual, and then you're going to ameliorate any potential adverse impact, okay, via an appropriate "go back." So I don't think it goes to the general view of giving back the information.

DR. COX: Exactly, Steve, that's exactly why I made this point. Because if it's in the context of a specific individual, then I'm in favor of waiving the second part of it, too, because the—that's just my sentiment.

DR. SHAPIRO: I don't know how other members of the Commission feel. I myself would not be at all bothered by either the interpretation that this applies only to deception studies or where I think it does have a role, at least—well, Diane, you would know better than I. You may have some experience from some of your colleagues who may do that kind of research. It may be important in the so-called deception studies. I'll accept that. Is that correct?

DR. SCOTT-JONES: In deception studies it's essential to go back and explain to the participants what the study was about. Also, one of the principles in our ethical principles at the Society for Research on Child Development is that as researchers we need to be extremely careful in the information we give to individuals following research participation, because our words may carry undue weight. So when we have what are the results of participation in a study and not intensive clinical interviewing, we're to be extraordinarily careful in giving any of that information back to the individual. So I think going back to give information from research has to be done in a very careful way, because it's not the same as examining a person for other purposes.

DR. SHAPIRO: Kathi?

DR. HANNA: This is jumping ahead a little bit, but I think in the discussion here it's been clear to me that this feeds into what we say later about recontact and "appropriate"—when it is appropriate, when it is not appropriate to recontact for either getting consent or giving people research results. And we'll get to that later, but I think it's—Steve made the point that in some cases it would clearly be inappropriate to go back, and so if this were a requirement, it becomes contradictory. So I think we can address the recontact issue, which really this is, later on, and just say that in the commentary.

DR. SHAPIRO: Any other comments or questions?

PROF. CAPRON: Could someone summarize where we are then?

DR. SHAPIRO: I'll try to do that. There are a number of issues here. The thing I think we are agreed on unambiguously is that we are eliminating the so-called practicability—whatever the right way to phrase that is—requirement here. There is an issue regarding the regulations and how they are—

PROF. CAPRON: Could you just pause just long enough to—

DR. SHAPIRO: Yeah.

PROF. CAPRON: We are suggesting that it be eliminated as to this category of research.

DR. SHAPIRO: Correct, correct.

PROF. CAPRON: That is, that an exception be made from this category.

DR. SHAPIRO: Identifiable existing human—where the other things hold, there are no adverse consequences, etc. There are minimal risks but no adverse consequences. There is an issue regarding interpretation of the relationships: whether "minimal" is supposed to apply to simply risk or whether it also applies, given the interpretation, to rights and welfare—that is, minimizing any adverse impact on rights and welfare. I think we have to resolve that. It's not resolved in my mind yet just how we're going to phrase that.

PROF. CAPRON: Okay. In other words, there are two issues there: how we're going to phrase it—

DR. SHAPIRO: Right.

PROF. CAPRON:—and whether part of our recommendation is that this ambiguity in the regulations, which seems to separate the notion of risk from the notion of rights and welfare, be clarified generally. I mean those are—

DR. SHAPIRO: My view, well—

MR. HOLTZMAN: Can I ask a quick question there, if someone has the reg? I thought "minimal risk" described the research, the rights and welfare, the impact on the rights, and if that went to whether the waiver of consent resulted in an impact on the rights and welfare. Two different things are being described. Is that correct?

DR. HANNA: Well, I just handed it to Dr. Shapiro.

PROF. CAPRON: Steve, you're right.

DR. HANNA: Minimal risk comes up in two places. It comes up in the waiver of informed consent. It also comes up in expedited works that are published.

PROF. CAPRON: Yes, you are correct. It says, "The waiver or alteration will not adversely affect the rights and welfare of subjects."

MR. HOLTZMAN: Right. The waiver, not the risk but the waiver—whereas the risk—minimal risk is in the nature of the research, not the waiver.

PROF. CAPRON: And that's not actually the way it's stated here.

DR. SHAPIRO: Correct. That's right. Let's see. Diane?

DR. SCOTT-JONES: I think the way we have this sentence framed, with "no adverse consequences" following the phrase "minimal risk," it makes it appear that one could foresee, before doing research what the consequences would be. And I think we need to be very careful. I think we need to maintain the notion that risks and benefits of research are all probabilities that we cannot precisely foresee, that we cannot make the statement that a minimal risk study means there will be no adverse consequences for the subject's rights and welfare. The way the phrase is, "following minimal risk," it makes it appear that we can foresee what has not yet happened, and I think that's a mistake.

MR. HOLTZMAN: I hate to be pedantic, but I think you're asking the question with respect to potential adverse consequences with respect not to the research but with respect to the waiver of consent.

DR. SCOTT-JONES: But it needs to be worded that way.

PROF. CAPRON: It's not worded that way here.

DR. SCOTT-JONES: It's not that way here.

DR. LO: Let me offer a suggestion for wording.

DR. SCOTT-JONES: I'm not disagreeing with you.

DR. SHAPIRO: Okay. That's all right.

DR. LO: Why don't we say, "NBAC recommends that Federal regulation blah, blah, blah, be revised." Currently the regulation reads 1, 2, 3, 4, and we should state 2 the way it's stated in the regs as Steve has clarified to avoid the confusion Alex and Diane have pointed out to us. We should then say we believe number 3, the so-called impracticability requirement, should be dropped.

PROF. CAPRON: As to this category?

DR. LO: For this category of research.

PROF. CAPRON: An exception should be made for—

DR. LO. Moreover, we think that OPRR should clarify that number 4 really is meant to apply to deceptive research, and add in some language Steve said about tying this conceptually back to our notions from the previous recommendations.

MR. HOLTZMAN: And I personally wouldn't bother with whether the OPRR should clarify its deceptions, because I can imagine that we're failing to imagine other research. All right? And I would just go to what we're thinking about, which is that once we're in this fear of where we're waiving the consent and the right, we think it's inappropriate generally to be going back.

DR. COX: Exactly.

MR. HOLTZMAN: Okay?

DR. COX: Exactly. That's the message.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: This recommendation stretches to the absolute limit my willingness—and I'm not complaining about it, it's just that this is at the edge. I realize I have been reading this as a recommendation about existing tissue samples. This goes to the point that Trish made a while ago. I see no reason to waive the practicability requirement as to samples collected for research purposes in the future. I mean, the whole difficulty—the argument is, we have these 200 million samples. How can we find these people? They've all moved. Half of them are dead. Who knows what? We can presume it's impracticable. That's what we're sort of saying here—to do that. And if you're only going to expose any people who actually could be identified in this process to minimal risk, we ought to allow the researchers across the board to waive this. That's what we're saying. But I think we have to be clear, if that's what we all agree, that we're talking about as-existing samples: samples existing prior to the implementation of this new exemption. In the future, I don't see the need for that. I mean, you can plan right up front now. You're collecting the sample. Go through the methods that we talked about in the report, and that we should remind people of, for allowing recontact or for

segregating people into categories: those who you're going to keep unidentifiable or use only for minimal risk studies, and those that you're going to potentially want to recontact, use information—and you get their advance consent to allow their research to be used this way and have some way of getting back to them to find out what their health status is, etc., etc., etc. And there is no reason to waive consent as to those people.

MR. HOLTZMAN: So there will be no existing samples in the future?

PROF. CAPRON: There will be no—

MR. HOLTZMAN: In the future there will be no existing samples?

PROF. CAPRON: The people who collect samples in the future ought to be on notice that if they are going to use them for this purpose, they go through a process that avoids this "Uh-huh-huh, I don't know what to do. I don't want to waste these samples." Don't waste the samples. Collect them in an appropriate way.

MR. HOLTZMAN: So all the pathology departments in the United States will—I'm trying to play out that we provided sufficient guidance, such that in the future there will be no existing samples that would fall subject to this.

PROF. CAPRON: I see this as a time-limited exemption, yes.

DR. SHAPIRO: I have thought about this back and forth in different ways myself, to see how—and obviously, this has to do with what we mean by "existing." And what worried me is—we will make some recommendations as we go along about what we should do in collecting samples in the future—what worried me somewhat about your views, Alex, is that I don't know in the future whether all samples will be collected that way and with appropriate consent and so on, and in my own mind didn't want to—if that all happens, if it all happens with the appropriate consents and so on, we're home free. If it doesn't, we're left with a problem: this particular category of research, that is minimal risk, no adverse consequences, etc. I think it's an important point that you're raising.

PROF. CAPRON: Thirty years ago a lot of researchers said, "We can't do research if we have to go through—"

DR. SHAPIRO: I understand.

PROF. CAPRON: "—all of these processes that you're telling us to go through." Those are now standard processes and people have incorporated them, for better or worse. Some do better jobs than others, but they're all there. No one doubts that you can do research. The argument, which to me was compelling, is that it is a shame to throw away 200 million samples because people didn't know that they would be used for genetic research or would even go through a process. Yes, in the future, Steve, there will probably be some samples collected by people not using processes that allow them to be put into this identifiable, coded category anymore. I don't think that spells the end of research. I think researchers will be in a position to say to pathologists, "Here is your incentive." Some of the pathologists will say, "It's going to cost me more; it will cost you more." All right. Protection of people costs something, because you have to go through some processes, you have to keep some records. I am comfortable with saying that's the price of protecting people's rights and welfare.

MR. HOLTZMAN: So I think it's very important to be respectful of someone who may take a different position from you, to accord to them the possibility that the animus is not simply "Get out of the way of research," but that the animus is that there is a fundamental difference between a human subject and interventions on the human subject versus research on tissues. And so therefore the reasoning for treating them differently is not simply "Get out of the way of research" but rather that the individual does not inhere in the subject, that they don't buy into a line of argument about "wrongs" versus "harms." I mean, if the harms are protected against, okay, there *is* nothing wrong.

PROF. CAPRON: But we all know that there is no chance of physical harm to the person in using their tissue sample.

MR. HOLTZMAN: No, I meant in *your* sense of harm. I have listened.

PROF. CAPRON: Yeah, but it seems to me that there are harms *and* wrongs, and that part of the gist of our report is that doing all of the many kinds of studies that can now be done on tissue samples, and that will done in the future, do make those samples deserving. Because when they are linked to a person, they're deserving of the kinds of protections that we usually give to the person; the only thing we've removed is that you won't be of physical harm to somebody from just looking at a cell.

MR. HOLTZMAN: Okay. And when I say I would—I understand your thoughts here. If that's the argument that we are putting together in support of our position, and I believe it is, I think we really have to go and look at this report and see if that line of argument is fully supported in this report.

DR. SHAPIRO: Okay. There's an important issue here that I want to pursue. Trish?

PROF. BACKLAR: Actually, the important issue that I think is here is the problem we have with talking about confidentiality and looking at the same issue in terms of the medical record. It seems to me that what we really want to do, or what I would like to see happen from this report, is to address that issue of the medical record and confidentiality, because this is what we're talking about; this is the harms that we're speaking about, and those harms are already out there. And this is what makes the difference about research on the intact person, where there is physical harm, and on the pieces of a person, where the same thing is obtained in terms of privacy.

DR. SHAPIRO: Let me ask—I think that's another important issue. But I want us to clarify this last issue we were talking about so that we know where we stand on it, just for purposes of presenting a recommendation that the majority of the Commission might find acceptable. And that is, in Recommendation 5, Alex suggested—I don't have his exact words, but "existing" means in his mind samples—this whole thing would apply only to samples that were collected, so to speak, before our report, just to put it that way.

PROF. CAPRON: Or before whenever the change in the regulations occurs.

DR. SHAPIRO: Right—or whenever the implementation of the changes in the regulations takes place. After that, samples collected in the future, AT plus one, will not qualify under this recommendation. I think that's the nature of it.

PROF. CAPRON: That's correct.

DR. SHAPIRO: Kathi?

DR. HANNA: This issue of "existing"—I might be wrong, but I thought that several months ago we decided that we would use the word "existing" to describe the samples that were existing on the shelf at the time that the research was being proposed.

DR. SHAPIRO: Yes, that's right.

DR. HANNA: And so we were using "existing" in that sense, not "existing in terms of NBAC's timing."

DR. SHAPIRO: That's right. But that's the issue that Alex wants us to address and I think we should address it. Yes, Larry?

DR. MIIKE: I don't see why there is so much controversy over here. Because the practicability requirement will come in if there is no consent given on a form, so that in the future when we're asking for it we're going to get it later on, where I consent to all future research as long as it's so and so, and so and so. They're going to be looking and see whether something exists in that light. If it doesn't exist, then I think this should apply. So I would apply it to "existing" as you use it, which is, count up the research time and there is a sample that's existing rather than a prospect for collection.

PROF. CAPRON: Larry, I don't mean—the gist of that would be, if they had gotten the consent of the type you talk about then you are not talking about waiving consent.

DR. MIIKE: Right.

PROF. CAPRON: But if a pathologist decides he is going to collect some samples for just diagnostic or morbidity purposes or whatever they are collected for and says, "I'm not going through this process of having someone tell me that I can share these with researchers who will be doing genetic research" and so forth, and then has them on the shelf and they are "existing" the day the researcher shows up, then there won't be any consent. And the way we would get a waiver of consent would be to say there is minimal risk, no adverse consequences from waiving consent, and it's impracticable.

And we're saying get rid of impracticability. I guess I'm saying the only reason to get rid of impracticability was that people weren't on notice back then, they've got a lot of samples, and it seems wrong to throw all those samples away as to this minimal risk research and stop all the research that's going on now. But in the future people will know that there's no reason to have to waive a requirement. I don't think waiving the requirement is nugatory. I don't think there will—there is some minimal risk of harm to people in this process. It hasn't disappeared. It's just minimal. And it's acceptable given—to me, we are engaging in a process very much like what IRBs do. We're weighing the benefit against the risks. And I'm okay about saying you don't have to prove to me you can't contact these people. It seems to me it's so likely that you aren't going to be able to contact them that we can waive that requirement for these preexisting samples because the risk is minimal—not nonexistent, but minimal.

MR. HOLTZMAN: But, but—

PROF. CAPRON: But in the future, there's no reason to waive it. But you should be on notice that you should have gotten the consent if you wanted to use it.

DR. SHAPIRO: Steve, and then we're going to move on.

MR. HOLTZMAN: Let's go with your chain of thought, Alex. Wouldn't it lead you to actually say that this way of getting around consent should just totally evaporate in the future? You see, I think an illogical consequence of where you've just come out is that for the guy who kept lousy records, making it impractical in the future to go back, he'll meet the impracticable standard. So I think your chain of argument is now that NBAC has met and brought forth, everyone should be on notice of how they should go forward in the future. There really should be this avenue for getting around what we're proposing.

PROF. CAPRON: No, but you say to the researcher, "Don't go to that repository. Use another repository that keeps better records." It's impracticable now because none of the repositories have this. You can't go to any of them, and they're vanishing into a small number.

DR. SHAPIRO: Okay. I think there is an issue here.

PROF. CAPRON: "Don't use that one. You don't have our consent to use that one."

DR. SHAPIRO: We're going to have to move on now, despite the fact that there is more to be said about this subject. But just for purposes of helping us draft this recommendation, which has to be redrafted in a number of different ways—but there is a very important point here, whether this dropping of the practicability requirement applies only to materials collected prior to the implementation of whatever new regulations there are, and would not apply to anything collected after that. So the question is—again, let's have a straw vote just for purposes of trying to formulate a recommendation once again.

DR. MIIKE: I just have a comment. Remember, we're talking about minimal risk research—

DR. SHAPIRO: I understand.

DR. MIIKE:—with no adverse consequences.

DR. SHAPIRO: Correct. And the question is whether you're satisfied with "existing" meaning just before the researcher takes it, whatever that is, now or in the future, or "existing" referring only to things collected before a certain date without trying to get around that. How many of you prefer "existing" in that context, the thought meaning *before* the researcher requests the sample? 1, 2, 3, 4, 5—

PROF. BACKLAR: Wait, wait, wait, wait.

DR. SHAPIRO: Wait, wait, wait, okay. A short question?

PROF. BACKLAR: No, I'm just—

DR. SHAPIRO: Oh, you're still thinking.

PROF. BACKLAR: Just to explain it a little bit more. In other words, we're not—this is after a certain date, after our recommendations come out.

PROF. CAPRON: That's the alternative.

DR. SHAPIRO: That's the alternative. Alex is suggesting that as of a certain date afterwards, any samples collected after that date—

PROF. BACKLAR: Yes.

DR. SHAPIRO:—this would not apply. It's exempting from the requirement.

PROF. CAPRON: The waiver—the exemption from the practicability requirement, so that even if you could in those cases contact those people, you will not be required to do so in the future. Even if the records are right there, the samples were collected yesterday, and the people are still in the hospital, you wouldn't be required to go to them and say, "May we use your samples?" There's no requirement that practicability be shown.

DR. SHAPIRO: In this category.

PROF. CAPRON: In this category.

DR. SHAPIRO: Okay. Now the question I ask is how many of us like what I'll call a "prior to the researcher" version versus "after a certain date," but I think you know what they are: Alex's view versus what I think had been the view of the

Commission, at least prior to now. How many prefer, so to speak, the view we've had, namely it's prior to the research for requesting it? Okay. 1, 2, 3, 4, 5, 6, 7. And the alternative? 1, 2, 3. Okay. So that's where we stand. We'll draft with that information in mind, and then we'll see where we come to a more formal decision on this next time. In addition, you know I think we can use the time now to exchange ideas on this regarding the e-mail and allow ourselves even to change our minds. That's a possibility. Okay. Let's go on, Kathi, to Recommendation 6, and after that we'll take a short break.

DR. HANNA: Of those people who had problems with Recommendation 6, which is basically talking about the "opt-out" approach, most of them just recommended deleting this recommendation altogether. And the reason for doing that, they said, was if the research is judged to be objectionable on moral or other grounds by the IRB then there shouldn't be a waiver of consent. So they just thought that we were confusing things unnecessarily. If there were problems—and people had concerns about the research—then you just don't waive the consent. So that was the one, I would say most common, suggestion about what to do with Recommendation 6. The other had to do with the language talking about making a "good faith effort." They said coming off of the last discussion having to do with practicability, now we talk about making a good faith effort, and there was just some confusion about how what we said about practicability now applies here.

DR. SHAPIRO: Okay. Comments? Questions? Just let me ask a question about the public comments, as I have not read all of those carefully. This recommendation, at least as it's currently phrased, talks about the fact that some individuals might find it objectionable. It doesn't talk about whether the IRB would find it objectionable. Did people distinguish that in their comments?

DR. HANNA: Yeah, there were concerns about that, and they felt that that was somewhat vague. They thought that there will always be individuals who will find certain kinds of research objectionable. They had concerns about making the consent process more cumbersome because certain individuals would have problems. In fact, a lot of people said that if you're going to place the onus on someone to make that determination, it should be the IRB. And if the IRB decides that it's problematic, then they shouldn't waive consent.

DR. SHAPIRO: So again, just asking for interpretation of public comments: They would have been happier with a recommendation that focused on the IRBs' views?

DR. HANNA: I think so, although with some caveats.

DR. SHAPIRO: Sure.

DR. HANNA: People don't entirely trust IRBs to do that in a fair or reasonable way. The other suggestion was that this kind of consideration really should be addressed in the consent recommendations when we get into the whole discussion about tiered consent and trying to get a sense from—at least for perspective collections, whether there are certain categories of research that people would find objectionable—so that the individual at that point can check off "Don't use my samples for this kind of research," or "If you are going to do this kind of research, I want you to come back and check with me." So some people would say you don't have to get rid of the notion that people should have the right to opt out of that kind of research, but you should put it into the consent discussion and not here.

PROF. BACKLAR: This is, again, the problem of the difference between retrospectively collected and currently collected.

DR. HANNA: Right.

PROF. BACKLAR: And they are two different, completely different things.

DR. HANNA: And the tricky thing here is that this recommendation really applied to existing samples, where general consent, or blanket consent, or unclear consent had been given. So, this is really—the issue that we are getting at here originally was whether there was a need to go back to individuals and re-consent them, or give them the opportunity to opt out of the research.

DR. SHAPIRO: But this is the waiver. This is where consent has been waived, right, this recommendation?

DR. HANNA: Yes. The requirement for a new consent has been waived.

DR. SHAPIRO: Okay. Comments? Larry, then Eric.

DR. MIIKE: Yeah, I guess before I can answer this question of the waiver of the practicability, are we saying the requirement may, or are we saying it will—are we recommending just waiving it altogether, getting rid of it? Because I think Alex had suggested—somebody had suggested a word change from "should" to "may." So it's important to me whether this is our recommendation that's at the discretion of the IRB to waive, or we are just sort of saying you should just waive it.

DR. SHAPIRO: The suggestion from "should" to "may" came from a public comment.

DR. MIIKE: Oh, I see.

PROF. CAPRON: It came from the NIH.

DR. SHAPIRO: The NIH, I guess.

DR. MIIKE: But I don't know where we stand on it.

PROF. CAPRON: I thought we had gone to "may."

DR. SHAPIRO: Yeah, that's what I thought.

DR. MIIKE: Okay. So if it's "may," then to me it's sort of like saying to the IRB, you know, "As an additional consideration in those individual studies, you might want to consider giving somebody carte blanche," so that way I would have a problem.

DR. SHAPIRO: Right. Eric?

DR. CASSELL: Well, that makes it even less of a recommendation, what you've said. You said "may," and you know that can do a lot of things. But in my own view looking at this, either it is a risk or it is not a risk, and moral repugnance is a source of risk. So I look at this and think, either you've got to require a consent or you don't. And I find this to be vague and allowing IRBs to make interpretations that—

DR. SHAPIRO: Are you referring to Recommendation 6, Eric, or 5?

DR. CASSELL: Yes.

DR. SHAPIRO: Six?

DR. CASSELL: The re-consent thing—I mean the opt-out provision, yes.

DR. SHAPIRO: Yeah, okay, so opt-out.

DR. CASSELL: Yeah. Either they ought to have required consent, or re-consent I guess it is, or not. And if you're not going to do it because you don't find

there to be moral risk as well as any other kind, then this is too vague to me to mean anything, but it's going to make a lot of problems. I can see it making problems.

DR. SHAPIRO: Other comments or questions? Alex?

PROF. CAPRON: Well, I gather that there is a good impulse, in a way, behind this. But it comes down to saying, "Your objection to this research is not one that most people would think has any relevance, but we recognize that there are some people out there who hold different moral views and who would be disturbed if they found out later that samples from excised cancerous breast tissue from all of the women who had gone to XYZ Hospital, whom they worked on between 1990 and 1995, were used in a research study to find a new abortifacient. And everybody knows that a few people are very sensitive about that. They would feel complicit in that in some way: They had been used for something they hate. And so we want to give those people a chance. And I agree that it doesn't make a lot of sense to say that research can go forward if we regard their upset as worthy of any respect, because then we would say, "You can't say there are no adverse effects on their welfare, if their welfare includes their happiness." So this is a cop-out in a way. It's a way of saying, "They have a concern but it's not really worthy of respect, but we'll allow them to get out anyway." Isn't that what it amounts to?

DR. CASSELL: And the work requirement on the part of the investigators is about the same as they had, because they've got to go identify every one of these people, go find them and ask them if they want to opt out.

PROF. CAPRON: Yes, good point. It's basically a back door out of the waiver.

DR. CASSELL: Yeah.

DR. SCOTT-JONES: I have a comment.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: This so-called opt-out procedure is used sometimes in research in my field. And people who use it use it because they know that some people are going to throw it away without ever looking at it, and so those people don't contact you to opt out. So you therefore can assume that they consented. People who use it in my field use it and they train their graduate students; they say, "Oh, this is the way to increase consent. You just send this type of letter. People are never going to read it, they're not going to send it back, and you can claim they've consented." When it's

used in my field, it's used inappropriately. So I guess I would agree that if you have to go through the trouble of contacting people at all you really should be asking them to consent, not asking them to take the time to write back to you to tell you they don't want to be in the study.

PROF. CAPRON: But this was very consciously chosen by us as that method, but then we protected ourselves by saying this *isn't* consent.

DR. SCOTT-JONES: No, but that's a different type—

PROF. CAPRON: That last sense is it's not consent. Consent can still be waived. You don't have to prove that they got the letter. You don't have to have a return requested. It could be addressee unknown. You've just made some effort, so that after the fact if someone says, "I was offended" you can say, "Well, I tried to get in touch with you."

PROF. BACKLAR: It's a courtesy.

DR. SHAPIRO: I don't think this. My own view is this is not an empty requirement. I think myself, from writing this, I would just take out the last sentence: "Such an approach should not be considered." I believe that.

PROF. CAPRON: That was very important, I think.

DR. SHAPIRO: I understand. I understand that because consent has been waived in these cases, right? So you're not even attempting to get consent. And clearly opting out is not consent. I completely agree with that. But there are always going to be very difficult cases, and there are always going to be cases where people are finding it hard to decide just which way to come down on. And what this does, in my view, is to say in those difficult cases you might—the IRB might feel comfortable going ahead under an opt-out circumstance, which is a very small additional effort. Maybe it's not worth it; maybe the investigator will abandon the project. But it just gives another dimension, another tool, small as it is, to help make what might be a very difficult decision, and we can't eliminate these difficult decisions.

So that's how I thought about this. It has nothing to do with consent in my view—because consent has been waived, it's not consent. I certainly understand that. It's not an important issue, but I think it's something, and yes, it is abused. I can understand that. This will enable them, however, to abuse it in a certain category of research where consent has already been waived for other reasons. That really narrows the possibility for widespread abuse. And if an investigator believes—if an IRB believes

it's one, this is what enables them to go ahead and feel all right about it. Then the investigator can decide if this is worth it or not worth it. You know, it's not up to us to decide that. Bernie?

DR. LO: I think this is one of those situations where by not having a specific example in mind, or even worse people having different examples in mind, it becomes very muddy. So the example that Alex gave, I would say that that—I would agree with Alex and Eric: That shouldn't have been allowed to be eligible for a waiver of consent. I think the waiver does adversely affect the rights and welfare of the individuals. I think we should try to say that. My recollection of where this came from was the Portland meeting, Trish, that you hosted where Mary Claire King came and said, "Look, the situation I had in mind was concerns about going back to the same group of Ashkenazi Jews to do yet another study" and being concerned that some people might say, "Look, you know I was okay with the original study, the second study, and the third study, but now this is the 18th study, and I think enough is enough."

It did not adversely—it did not rise to the level of concern that Alex had, and it was sort of more along the lines that it would have been deemed appropriate by the IRB to waive consent under our revised Recommendation 5. But the investigators still had enough moral qualms that they wanted to somehow make the courtesy effort, in Trish's language, and say, "If we can reach you and you let us know that you don't want to be in the study, we will honor that." But for precisely the reasons Diane cited, if you make a positive, affirmative consent you won't get enough numbers of people in the sample to make a dent in your qualms.

I guess this to me was what to do in the really tough cases that are really dilemmas and to give some support to investigators who were concerned enough to say, look, there is something more you can do over and beyond the regulations. These recommendations are just sort of minimal guidance that we want everybody to do. If you want to do more, which would be giving people an opt out, that's fine. And we want to encourage that rather than have people say, "Well, if they told me I didn't have to do it, it's okay." I wish that first we would just give some specific examples, and one where we clarify, as Alex said, you know, we don't consider that appropriate because you should go back and get full consent in that situation. And maybe also whether this needs to be a recommendation, or whether this is better as commentary in the text in a sort of literal way.

PROF. CAPRON: Under 5, then?

DR. LO: Right, or wherever it best fits.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I mean if you moved it into the commentary text, I would think that was okay. The problem with what you suggest, Harold, is that if you give a provision that depends on the fact that people don't read their mail—and in fact you're absolutely right—then you're not meeting your criteria. You're not really giving people the opportunity to opt out, because you give somebody an opportunity when in fact you know they will take or not take the opportunity. But if they mostly just toss the mail, like I do in my home, then—

PROF. CAPRON: You should be amazed at the studies we've been doing on you, Eric.

DR. CASSELL: I wouldn't be at all surprised. But you know I introduced a bias that I couldn't even discuss with you. So, anyway, that's my problem with it. You're either going to do it or don't do it.

DR. SHAPIRO: I really — I understand that. It's a very small thing at best. And maybe that argues for situating it somewhat differently.

DR. CASSELL: Put it in the text and show it.

DR. SHAPIRO: That's a possibility. Steve and then Trish?

MR. HOLTZMAN: Or provide more guidance about what the Commission would like IRBs to be thinking about when they think about this as a study of minimal risk, including the psychosocial harms and what are the potential wrongs or harms that come from waivers of consent in certain kinds of studies. That would be the way, because I think even in the case that Bernie cited where one more — it was the fact of the 18th study. If you describe it as the 18th study instead of viewing it in isolation, well all of a sudden maybe it's going to fall within the purview again. So that would be the way to beef it up. Because again, I think the gist of what we're trying to do with our recommendations here is, Don't call everything, wink and nod, minimal risk— no harms or wrongs, right?

DR. SHAPIRO: Trish?

PROF. BACKLAR: I thought, by the way, this came out of not just Mary Claire's comments at the Portland meeting but also out of Alan Buchanan's paper where he talked and had a very interesting little section about the issue of moral problem that certain people may not wish to have certain things done. And so I think it's not

insignificant even though it may appear in some ways insignificant. And maybe one could go back and look at the Buchanan paper and see that — if you have the paper I could show you where it is — and maybe use it in the text to talk about this.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: I wonder whether we don't need at our meeting in March someone to prepare a couple of pages in which the considerations are set out and we recognize in text that we may end up wanting to use in the report exactly this tension between on the one hand something being a true courtesy—to say to people, "You may be bothered by this. It may be too much use of you or it may be for something you don't want"—and on the other hand recognizing that if that is a very serious concern it ought to be weighed against saying that there are no adverse effects, and sort of negotiate through that, and in the writing of it almost see where we want to come out on the recommendation and have us discuss something. Just this one statement here — it's too brief and it's too hard to know whether we're talking about a recommendation or whether we're talking about something that's a commentary to number 5. I think we need that larger text before us, using Mary Claire's comments, using Alan Buchanan's comments. And I would ask that staff prepare such a couple of pages that would focus on this tension between an IRB never giving waivers wherever they have concerns, and on the other hand, once they've given a waiver or the investigator herself saying, "Wait a second; maybe I ought to let people know."

DR. SHAPIRO: We will try to do that item within a text that we produce or separately in a memo. Steve?

MR. HOLTZMAN: I just want to make sure — I have a question back on Recommendation 5, either before we go to the break or after because I'm not sure what we're recommending.

DR. SHAPIRO: Let's do it now because then we're going to take a break.

MR. HOLTZMAN: Okay. One interpretation of what I thought we might be recommending was saying to OPRR or whoever writes regs, "Go back and rewrite the reg and remove the practicability standard." The other interpretation was, "Rewrite the reg but write the practicability standard as available to you but not mandatory." Which are we saying?

PROF. CAPRON: Is there a third alternative saying that the practicability standard — would there be an exemption from that standard for existing human biological materials?

MR. HOLTZMAN: No. I'm not tackling the "existing" issue.

PROF. CAPRON: No, it's not the "existing" issue as you used it.

DR. SHAPIRO: But as Larry said today, the practicability requirement is gone as to this category.

MR. HOLTZMAN: As to this category, right.

PROF. CAPRON: So we're not asking to rewrite the regulations in the sense of crossing out number 3; we're saying that they should either amend the regulation or notify IRBs that they aren't required as to this category of research to use that section.

DR. SHAPIRO: That's right. But if you look back on Recommendation 5, there's a point where the word "may" went to "The consent requirement may be waived." Someone suggested "may" rather than "should." That's where the "may" came in. But the practicability requirement disappears in this category, etc., etc.

PROF. CAPRON: As a requirement.

DR. SHAPIRO: As a requirement.

PROF. CAPRON: An IRB can still say —

DR. SHAPIRO: An IRB can do what it likes to make it acceptable. Absolutely. And an investigator doesn't have the right to insist that the IRB do this. That's the IRB's decision.

MR. HOLTZMAN: So the IRB —

DR. SHAPIRO: Is not required to apply the practicability requirements.

MR. HOLTZMAN: But it may.

DR. SHAPIRO: And other requirements. Unstated. Long list. And it could require anything.

MR. HOLTZMAN: So that's different than saying IRBs for this category of research ought not take practicability into account.

PROF. CAPRON: That's right. That's right. It's different.

MR. HOLTZMAN: Which is what I —

DR. SHAPIRO: Okay. We are going to break now. Let's try to reassemble no later than a quarter to 11.

BREAK

DR. SHAPIRO: All right, I'd like to resume our discussion. We have about an hour and 10 minutes left this morning, and I really would like us to get as far as we can, at least through Recommendation 12. We can probably deal with 13, 14, etc. by getting your comments in in written form. Those are in a somewhat different area. But the recommendations/conclusions/however you want to characterize these for the moment, between 7 and 12—it's important that we try to get some comments on them. Again, our objective is not to make final decisions today but simply to help us see where we are so that we can write a more satisfactory draft, which will be available for the March meeting. So let's go to Recommendation 7 first, and let me turn to Kathi to see if she has any comments she would like to pass on to us on this.

DR. HANNA: The only thing I would say about the public comment here was that many people suggested that IRBs already do this routinely. They look at existing consent forms. And so we should make clear that this is not necessarily something new that we're adding, that IRBs will always review existing consent forms for applicability. Some people suggested that we might even just not call this a recommendation but put it in a commentary or as a conclusion or just a statement, a restatement of what we think is good practice. The last sentence, people thought -- let's see, I'm just going back and forth between the two versions here—I think that in the redraft of the recommendations that occurred after the January meeting we addressed another issue that came up in the public comments, and that was separating out consent from recontact to deliver clinical or interim research results, and I think we've addressed that. So the only kind of relevant comment is still whether this needs to be a recommendation or whether it should just be a comment in the text.

DR. SHAPIRO: Thank you. Comments, questions from the Commission? Any views about whether this ought to be incorporated into some kind of commentary in the text or whether it reaches the status of some kind of conclusion/recommendation?

PROF. CAPRON: I think that's going to depend upon whether we label this whole section "Conclusions and Recommendations," as some of them just do not have what I was suggesting were sort of the italicized "should" sentences in them.

DR. SHAPIRO: Yes. David?

DR. COX: This has been sort of a point of a lot of our discussion today. And I think — I've gone back and forth on it myself, but I believe that the reason these things made it to the recommendation stage is because we all felt strongly about them in one way or another. And so to just put them in the text and make them go away doesn't seem right. On the other hand, to try and clarify whose responsibility it is to do what, okay, as much as we can seems to make sense, but that to keep them up front—if we just get rid of them, then all the consensus that we've done sort of goes away.

DR. SHAPIRO: Okay. Any further comment?

DR. BRITO: It just seems that the latter part is really the recommendation, and that assuming that IRBs do this on a regular basis, maybe in the discussion—the first few sentences isn't a discussion. What we're really trying to say here is that after the IRB reviews the consent on the existing samples, if they deem them to be inappropriate then consent must be obtained. So just make it very simple.

DR. SHAPIRO: Okay.

PROF. CAPRON: I agree, but it does underline that we have different kinds of recommendations. If that's a recommendation, it is simply a recommendation that says where consent is required it must either be in the form of a prior consent document or a new consent document. And that's sort of a statement of existing rules, as Kathi said originally. Likewise, there are some "shoulds" that are kind of what good practice would be; it would make research better. And there are other "shoulds" that the IRB or OPRR should make a change in. So we really have even levels of "should."

DR. BRITO: I guess it gets confusing because these are existing samples only, right? Going back to what Trish said earlier, that it's become very difficult—we had to separate them out. So whether or not IRBs do it on a regular basis is not

necessarily the issue. What are the regulations on existing samples with the consents that exist?

PROF. CAPRON: But it's not an issue as to nonexisting — if you go out to look for samples, you can get consent on them. I mean, the way the Commission — the majority of the Commission, excuse me — is now defining, or has been defining, the word "existing," it simply means "at the moment that the research begins," right? And so it doesn't doesn't have the — I don't think it has quite the same thrust as Trish's original point, which I agreed with. And I thought we were still drawing this other line between pre-report and after-report.

DR. SHAPIRO: Eric?

DR. CASSELL: It's the same kind of problem. Either the consent is adequate or it's not adequate. And to add this business about going back and informing them about what's going on—there are a lot of research projects, questionnaire research projects for population studies that go on for a number of years in which in the course of the study you learn something that somewhat changes the direction. I know of no requirement that you go back and re-consent everybody because you're now thinking somewhat differently about that project. The desire to have investigators keep in touch with subjects I think shouldn't be a recommendation. It should — if we want it at all, I think it's body copy, it's text copy. It's a suggestion.

PROF. CAPRON: Well, what are you reading from now?

DR. CASSELL: Hmm?

DR. SHAPIRO: What's that?

PROF. CAPRON: What exactly are you commenting on? That sounds like a comment on the old Recommendation 7, not the new Recommendation 7.

DR. CASSELL: I'm commenting on the new one. The following now goes into the text, and that's the question: is there to be —

DR. SHAPIRO: Oh, that part that goes in the text. Excuse me, I was —

DR. CASSELL: I'm commenting on — I'm reinforcing that if you want it at all, it belongs in the text.

DR. SHAPIRO: Okay.

PROF. CAPRON: This is simply a statement: Where consent is required, consent must be got.

DR. SHAPIRO: Prior consent must be got is adequate. Okay. Let's go on to Recommendation 8.

DR. CASSELL: I certainly don't want anything I said to be seen as slowing this process down. {Laughter]

DR. SHAPIRO: Recommendation 8. Kathi?

DR. HANNA: There are no public comments on 8 because we splintered 8 out of the previous recommendation. The old Recommendation 8 had the language about ensuring confidentiality as well as the various options for consent, and at the last meeting it was decided that those should be separated from each other and the points made separately. That doesn't mean that Recommendation 8 now is a good stand-alone or it doesn't need more work, but we don't have any public comments on that.

MR. HOLTZMAN: Kathi, I think what we do have is—there's a whole school of thought represented in the commentary, which instead of focusing on consent focuses on harms, not wrongs, and therefore focuses on the use of the information and therefore would put the locus of our attention on the ensuring of the confidentiality and would push hard for us to beef up this whole area consistent with the kind of thinking that Trish is articulating, which is that the focus ought to be on the continuity of this issue with medical information as opposed to the continuity of this with human subjects protection. So, my reading of these was — it's a position that I'm very strongly in favor of—is that where we want to beef up and articulate, if possible, the kinds of protections we would like to see in the confidentiality.

DR. SHAPIRO: I also picked that up in the material as an important theme by some of the people who commented.

PROF. CAPRON: A question here. What does "written assurance" refer to? That's to the subject, is that right? Because if that's what it means, this seems in the category of, you'll do better getting people to consent if you assure them that you're going to be confidential with the information that you develop. That's not — that's sort of a recommendation for a useful hint to researchers. It doesn't need— it's a "should" at that level. Or does it mean that the IRB should have some written plan presented to it that assures it that appropriate measures have been established to protect confidentiality? I'm not clear what that means.

DR. HANNA: I think it probably refers to assurance — well, written assurance should be provided to the subject, I think was the original intent, because it used to be tied to the consent.

PROF. CAPRON: Then it doesn't — then it seems to me like it belongs in commentary because it's a way of saying if you're going to get consent you ought to tell people that you'll protect their confidentiality and maybe tell them how you're doing it or something.

DR. CASSELL: Isn't there —

DR. SHAPIRO: Eric, then Bernie?

DR. CASSELL: Couldn't we require that the consent form — the consent form states that confidentiality will be ensured.

PROF. CAPRON: But that's not what it says.

DR. CASSELL: I know that's not what it says. But if what you're suggesting is that you're going to provide written assurance, well, where are you going — what's that, a separate piece of paper from the consent form?

PROF. CAPRON: It's not that it's separate; it's just that what you're telling people is something to encourage them to sign up, and —

MR. HOLTZMAN: That's not the intent.

PROF. CAPRON: It's not?

MR. HOLTZMAN: No.

DR. SHAPIRO: Okay. Eric, Bernie, Trish, Larry?

DR. LO: It seems to me there are a number of issues here which somehow all got smooshed into Recommendation 8 and confidentiality. I think that there are some real recommendation things we might want to make here because confidentiality is an important issue that kind of gets alluded to here and there but we never really deal with it, and it's important. I mean, do we want to, for example, reaffirm that as with other types of protocols the IRB ought to pay attention to the plan the investigator presents for maintaining confidentiality appropriately or what plans, if any, there are for possible overrides of breaches of confidentiality and to look at the sort of

system that's in place for the actual — both the procedures of the research team and the technical safeguards they have. I mean, there's a whole — on confidentiality breaches there's a lot of discussion of not just the situations in which it's appropriate to maintain or breach confidentiality, but also more specific concerns about how you're actually going to do it, and there are some standards of care that ought to be expected. You shouldn't just have investigators say, "I'm going to keep things confidential as appropriately as I always do." You should have to specify, as many IRBS do — you know, how exactly you're going to do it, how you're going to train people, how you're going to keep the records, how you're going to protect the computers.

And I'm not saying we should specify that, but we could at least ask the IRB to look at that in their process of review if they are going to review. And if OPRR wants to make some sort of additional comments on what is good practice in maintaining confidentiality, we may want to encourage that as well. This is changing really fast because it's going to, it seems to me, be carried along perhaps in whatever confidentiality laws and regs come out of the current HIPA requirements.

DR. SHAPIRO: I know that Trish and Larry want to say something here, but my own view of this had been— my own interpretation has been that we were after two different kinds of obligations here, although it's not well stated. One was to give the prospective subject some knowledge about the confidentiality protections so that they — whether it encourages them or doesn't encourage them—it gives them some knowledge about safeguarding their information. And an IRB would be required to review these procedures, whatever they might be, and give its approval. I thought that we would — and I think this may be what Bernie was suggesting, but we probably can't and probably shouldn't go into the issue, and I do believe — let me say, first of all, it does have to be beefed up somewhat. I think we do have to say a little more about this. I completely agree with the public comments in that section. I think we have to stop short of worrying at a detailed level about systems and so on, because that's going on in other places and that's a big huge subject of its own. So I don't think we can attack it at that level of really designing systems and so on and so forth. But I think the points that we can make, or I thought we should make, are, one, that we ought to beef up this and talk about it more. I think that's a point that came across in the public comments that seemed convincing to me, and that we ought to have a recommendation that will both inform patients in some nontrivial way about these protections and ask the IRBs to approve—as Bernie, I think you used the word "system" or "process"—that's going to be in place. And those seem to be reasonable. That's how I interpret it or think what we ought to be signaling around here. But let me go to Trish and then Larry.

PROF. BACKLAR: Well, I'm actually going to agree with Bernie because the issue is that if you're doing research with intact people, you always have to

say how you're going to keep things confidential, keeping their names in a locked box and nobody has access to them and so on and so forth, and their numbers are different from their names, etc., etc. So, that's something that is common practice anyway. I think one of the things when you're talking about beefing it up and that we didn't seem to deal with in here is that we might want to have recommendations at the end of our recommendations or something that we're going to suggest to states, so that instead of each state having something different that we have some kind of issues about confidentiality and genetic research in states that would be agreeable among them, not just one state doing one thing and another state doing another.

DR. SHAPIRO: Larry, then Steve?

DR. MIIKE: Yeah, well, as written it clearly is alluding to the concept of a set process rather than assurances through the IRB, but I think that I would go — this can get to be a very large topic. If we talk about assurances in a consent process we're going to run into problems about what exactly we mean by that because we're going to be asking about clinical care samples. We're going to be asking for prospective consent, etc.—what do you put in a consent form in terms of written assurances, and what exactly does that mean when you say "written assurance"? So it seems to me that at the moment I would favor more directing this to the IRBs to provide assurance from the investigator that these confidentiality issues are being addressed as appropriate. I really do see a problem if we're going to delve in any substance in the consent process itself.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I think tracing through the interconnections of this with a couple of the other recommendations at least for me is very important, and so I'm not sure we can delve into this and for the following reasons. You go and get the consent. The nature of the protections of confidentiality will have a great impact when there's a future study with that now-existing sample when you ask whether or not it's a minimal risk study, number one. Number two, when the IRB working with it now looks at that future study with that existing sample and is asking whether or not the previous consent was adequate, we agree that if you're consenting to future unknown uses of the sample because the research wasn't contemplated, couldn't be contemplated, that conceptually you can't fully consent to the procedure unless — you could consent if you were reasonably satisfied that your rights and welfare were being protected via, for example, a confidentiality mechanism. So I think it's important to spend some time on reinforcing the importance of this.

DR. SHAPIRO: Other comments?

PROF. CAPRON: I don't know if this would capture the two parts that you suggested, Harold, but what if number 8 read something like this: "For a protocol for research on human biological materials to be approved, the investigator must provide and the IRB must approve, one, a plan to ensure confidentiality appropriate to the identifiability of the subjects and the level of risk to which they are exposed and, two, an appropriate summary of the confidentiality protections that will be included in the information provided to any subjects from whom consent is sought."

DR. SHAPIRO: Well, just speaking of the idea I was trying to suggest, that nicely captures what my idea was very effectively. Just my own question. Larry?

DR. MIIKE: But my point is that I see that as basically negating any prior consent that you got at the time of collection, because if that's a strong requirement, there is no way that at the time of — for example, just look, practically speaking, in the clinical consent form, however one would craft that. I see really great difficulty in being able to write in that document the true meaning of what confidentiality is and being able to get adequate permission from the subject so they understand the confidentiality —

PROF. CAPRON: But that doesn't —

DR. MIIKE: We always have to go back —

DR. SHAPIRO: It's the summary — I just want to make sure I understand. You object to getting the IRB to review the plan for confidentiality?

DR. MIIKE: No, no, no. What I'm saying is —

PROF. CAPRON: Just the summary.

DR. MIIKE: No. That's the part I think that is practical to handle. But to say that in obtaining consent you have to give them — that you'll be able to give them—enough meaningful information about what confidentiality in the research protocol would be, would seem to me impossible if you're talking about the next phase where you're talking about clinical samples and you're trying to get prospective consent for future research. It seems to me you always have to go back to the subject to get any kind of meaningful understanding of the confidentiality provisions' impact on any particular research.

PROF. CAPRON: As I understand it, there are still — the recommendation, whatever it was that I lost out on, there are still these notions that there are going to be some situations in which you don't go to subjects, right? Now

there may have been some prior consent in some of those situations where you do need "consent." That's the second category. In those, there may have been some statement about confidentiality. The plan that is now presented for this research in which you intend to use those samples will have to convince the IRB that the level of confidentiality protection is appropriate and that whatever information was in that consent form, since you're not going back to those people now to get consent, was a good enough statement of what confidentiality they could expect to be coincident with your present plan.

DR. MIIKE: I don't have a problem with that, but the way you rephrased that included something beyond that. You have two parts. The first part would cover all of that, and I would suggest that we cover the issue about whether in the consent process adequate confidential information was given to the subject—be part of the review of the IRB. But if you read your point two, it went directly to the issue in the consent process that the confidentiality issue had to be addressed.

PROF. CAPRON: But that was all prospective. It said, "An appropriate summary of the confidentiality protections will be included in the information provided to any subjects from whom consent is to be sought." That's a prospective statement, so that if you're using samples where you already have the sample and you either waived it by consent — you still have concerns about confidentiality, you have to explain why it's okay to do it, but you're not going to get consent — or you're using an earlier consent in which there was a statement: "Any distribution of this material will be to researchers whose plan for confidentiality meets the requirements of their IRB," and the subject said, "I consent on that basis," then the present IRB is going to look at that and say, "These people consented on the basis that you have a plan and your plan, the description there, was adequate." It's only when you're going to still go out to new people and say, "Will you consent now?" that you'd be able to provide a specific summary.

DR. MIIKE: I agree with all of that. All I'm saying is that the issue about the adequacy of the confidentiality provisions in the consent process be included in the IRB review and not put as a separate part of the recommendation.

DR. SHAPIRO: Let me make a suggestion on this one because I think we have to move along. Let's just get this recommendation reproduced. We'll pass it around and see how people want to work on it. I think that's the easiest way to deal with it since we don't have it in front of us.

PROF. CAPRON: I don't have my laptop.

DR. SHAPIRO: Well, we'll get someone at the break to get it reproduced. Let's go on, then, to Recommendation 9. Kathi?

DR. HANNA: Recommendation 9 was relatively noncontroversial. In general, people thought it was a good idea.

DR. SHAPIRO: The issue that came up — the only part of this that came up at our last meeting really had to do, I think, with the last sentence here — whether it had to be a separate document or not. I think people simply disagreed on it, although I don't think people felt flatly enthusiastic one way or the other. Larry?

DR. MIIKE: What I suggested before was that — and I guess it goes to the meaning of what we mean by two separate documents, but I really was suggesting you sign twice. You sign a clinical form, and then there's something below that about research. If that's considered two separate documents, that's fine with me.

DR. SHAPIRO: That seems reasonable to me, and we ought to just be clear that what we want is so that they acknowledge some way that there are two separate issues here, and maybe we can phrase it so that we really require — I don't know how or what the right language is — two separate acknowledgments in some sense. Whether they're on the same piece of paper or not is another matter. I don't think we ought to worry about that too much. Alex?

PROF. CAPRON: I don't understand the purpose of the first sentence here. That is to say, the improvement that we suggest is the improvement in the second and third sentences, right?

DR. SHAPIRO: That was what I was thinking about this, right. And the rest was in the next recommendation.

PROF. CAPRON: Yeah. I don't think we need anything ever saying, "NBAC believes..." or "NBAC recommends...." Obviously, our report says that. If we want to say, "In order to improve the obtaining of consent where biological materials are collected in the course of clinical care," explicitly stated, that seems to me —

DR. SHAPIRO: That sounds all right.

PROF. CAPRON: Is that fair?

DR. SHAPIRO: Yeah. No, that's fair. Okay, let's go on to Recommendation formerly 8, now 10, which deals with consent itself, directly. Kathi?

DR. HANNA: The new Recommendation 10 was a response to the discussion at the last meeting. The public comments are a little bit hard to track on this now because there's so much in here that the public comments — to simplify, people felt that the consent process should be ... we should treat them differently whether the consent is for prospective versus re-consent on existing samples, whether we're talking about tiered consent. I don't want to go into too much detail about the public comments because I think they no longer reflect this recommendation. I think we responded in some ways to the sense of the public comments with the new Recommendation 10. So I think the issue now really is whether these five categories of options are what you want to say and if this is how you want to organize it.

DR. SHAPIRO: Eric?

DR. CASSELL: The way it's stated now it's unclear to me entirely whether this is to go to consent, to get consent for a piece of research and give them a list of five possible options they can consent to. You can't mean that, can you? I mean, either they're consenting to a specific protocol — I mean, are these — each time they go to get consent to give all five options?

DR. SHAPIRO: Well, I mean, it's —

DR. CASSELL: Because if it's dissent from proposed or future research uses of the sample, all that means is you didn't get consent. So you don't have to put that as an option. They either sign consent or they don't.

DR. SHAPIRO: Well, my thought along this line is that if we think of the consent as being part of a separate process, separate from the clinical care consent, there are a number of different options of consent you could ask for. You could ask for consent for a specific protocol, if that's what you had in mind, that's the only thing you had in mind, with or without identifiers, and so on. But it's just to try —

DR. CASSELL: I see. So, it's really — what this refers to is the last sentence of the previous recommendation: It's best that separate consent forms be used, and on that consent form the person gets these options.

DR. SHAPIRO: Well, I don't know if — I did not interpret it that way. That's not the way I interpreted it.

PROF. CAPRON: No, because it could be that you're going out to do research, to gather samples for research.

DR. SHAPIRO: All right. Bernie?

DR. LO: I think it's hard to put this new Recommendation 10 in context. It seems to me what we're talking about is that you already have a specific protocol and you would like to get the consent of the patients participating, and at the same time you want to try and get — you may want to get consent for future protocols. So as I understand it, in the clinical situation you probably don't have specific protocols. I think you just need to lay out a bit more what the context is, and then if we're really talking about when you have a specific protocol but may also want to talk about future samples, then I think it would help to just lay out, sort of like a tree here, the structure a bit more clearly.

DR. HANNA: I would just add to Eric's comment about the fifth option there. The reason why that was left in is because we had decided that if you had to go back and re-consent on an existing sample, you were going to treat it as a new consent. Let's say you have the sample, you have questionable or nonexistent consent, you decide you want to go back now. In some cases you might have had consent for a previous use of that sample. Now you want to go back to this person because you're required — this is considered a new protocol that you didn't get explicit consent for. You might go back now and the person might have the option; even though they'd given a prior consent to a previous use of the tissue, they might say at this point, "No, I don't want you to use my sample for this or anything else."

DR. CASSELL: But Kathi, if you have to go back to get a consent, then the issue is do they or don't they *give* consent. The fact that they gave a previous consent is irrelevant. They are now being presented with the opportunity to give or not give consent, so you don't have to put this down.

DR. HANNA: Well, I —

DR. CASSELL: I mean I don't want to nit-pick, I just — it's not clear to me at all how you present this to the subject when my research — for example, what if my research doesn't fit in all of those categories?

PROF. CAPRON: Then we need another category.

DR. SHAPIRO: Steve and Larry?

MR. HOLTZMAN: I think that Eric's reading of this is potentially saying that the consent form should look like this, is a potential reading of this, which we need to make clear, number one. Number two, I think it is in play whenever we're in the

business of consenting. If you're in the clinical context but you're thinking about the research uses, what we're really getting at is the notion of tiered or layered consent, which will come into play any time you are getting consent. A third point is because we have lumped "coded" with "identified," right, we had — it seems to me there are three different things: There's "identified" how most people use it, "coded," and then "unlinked," or what other people would call "anonymized." And I think that's important because I don't think if you look at number 3 you can give consent to future protocols with identifiers, if by that you mean truly identified, because you can't make an assessment of the harms. So you can't give true consent. You can only give consent for unspecified future research uses if you have a measure of confidence in the protection, which would come from anonymization or through coding. So I think we're going to have to clarify that.

DR. SHAPIRO: Larry?

DR. MIIKE: I think this recommendation tries to do too much; it tries to cover every conceivable situation. So is this a prospective consent form? Or is this an actual — is this only a prospective consent, Kathi?

DR. SHAPIRO: I look at this as going forward. It's whatever's happened in the past has happened.

DR. MIIKE: No, no, no. What I mean is that this does not also apply to — I now have a specific project and I want to ask for consent. Is that situation covered, too?

DR. HANNA: Yes.

DR. MIIKE: Okay. I think that's where's my problem with this. It tries to cover every possible situation, and they're going to be different. If we are going to cover every possible situation, then we need to make it clear. Because if it gets to the issue about in a clinical situation, and I get a consent form, this is not going to work if all these choices are on the consent form.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: I think I understand what Larry is getting to, and it seems to me we do have to be clear that there's an "as appropriate"—I mean, if I have a research sample because a pathologist has given it to me and I know who the person is

and it's going to be a linked sample in some way and I have to get consent from them but I don't have to ask them about future studies if I don't want to. And so I would only go to them with a description of my study and ask for their consent to whatever the configuration of it is. At that point, if that's all I'm asking, I don't even think I have to add the final fifth category.

Conversely, if I'm the pathologist collecting the samples, it seems to me, and it's in connection with the number 9 idea that clinical care — it seems to me all five of these options are here, although I would rewrite the last option to get rid of the word "dissent," which does not belong here, and just say the fifth choice does not allow a sample to be used for proposed or future research. But if the pathologist is just collecting it, that person may say, "I don't have a specific protocol in mind now," so all I'm presenting in that case is consent for future generalized use of an unlinked nature. So it seems to me that we really need a phrase, right at the beginning, giving the following options as appropriate to take into account the different circumstances in which you may be going to someone.

DR. SHAPIRO: Yes, Diane?

DR. SCOTT-JONES: I have some concerns about how this would actually appear in a consent document that a person would be able to sign. It seems to me that unlike Alex's interpretation that he just gave, it says the subject should be given the following options, and it reads as if one would have all those options in the particular consent document for a given research project. And it seems to me that some of the options aren't particularly useful. For example, a specific researcher with a specific study also asking for authorization for all future research use, then that researcher has no way to give that consent to other people in the future who would do studies with the same material. So it seems that this doesn't really apply well to specific instances or to all the general cases in which one would want to give consent. It just seems not workable as it's written.

PROF. CAPRON: That's why I want to add "as appropriate" here, because I agree with you. I agree with you entirely.

DR. SHAPIRO: I think we have to — excuse me, I didn't want to cut anyone off. David, then Bernie, then I have a suggestion.

DR. COX: I just didn't want to lose sight of the fact of where a lot of this tiered stuff came from. I really agree with your comments, both Alex and Diane, in the context of that it has to be not more complicated than it needs to be for a particular individual. That's point number one. Point number two, though, is that as we go

forward in the future, if researchers that approach patients—and that's how it's going to happen, researchers approaching patients with particular protocols — do not think in a clear way about how this stuff may be used in the future, we will end up, as Steve pointed out, with sloppy bookkeeping and sloppy thinking about how samples will be used in the past.

It's at this consent stage that people have to think about how the samples may be used. A specific example is, I approach someone with a very specific research protocol, but my colleagues in cardiovascular research want to use those samples in an unidentified way; you can't shove that under the rug and worry about it later, you have to worry about it then. So maybe this has to be clarified a little bit more in terms of the specific uses, but there is a real need for some kind of tiered consent that, although it's complicated, the alternatives I don't think are acceptable.

DR. SHAPIRO: Bernie?

DR. LO: I want to try to build on that. I think in Recommendation 10 we're both giving very, very specific advice on what you should actually say and trying to give a bigger message, which as David expressed it was, if you're going to be talking to a potential subject about using their biological materials for your particular project, you ought to think about can you also try to talk to the subject about other uses in a way that gives you valid prospective consent. In order to do that, it seems to me we may want to make a general point like that and say we think the notion of the tiered consent that has been worked on is a very promising one.

I think for us to try and actually give the specific options is biting off a little bit too much for us. I think there's a parallel recommendation that comes with if you're somehow a potential repository collecting samples, you ought to pay a lot of attention to actually how you word this separate consent alluded to in Recommendation 9. I think we're also recommending not just sort of a general "You can use it for anything you want," but if possible to develop some tiered options that are meaningful in your context. So again, I would favor it more to get the general idea out there that you should be thinking about future uses, trying to get meaningful consent, separating out the different researches, and nothing too detailed at this point about what exactly we want to say. I mean, I have real concerns about authorization for all future use with identifiers. I'm not sure that's morally valid.

PROF. CAPRON: Exactly.

DR. SHAPIRO: I think Recommendation 10, yes, we conceptualize along a number of different dimensions here. I understand the notion of trying to

accomplish this, so to speak, "social good" by getting a valid prospective consent even though you may not need such a broad consent at any certain moment, but that cannot be captured with the language here that all consent documents should be — all people should be given the following options, which are meaningless in some cases. I think that that's right.

So, if our objective here is twofold — one, to be clear to the subject what it is they're being asked for and what the conditions are, and two, to try to achieve a secondary objective, namely—to which they may consent or not consent, of course—a second objective, namely to have some kind of valid prospective consent or project, which might go beyond. I don't think they can go completely beyond, as Bernie just said. I think that's not — we went through that with our last report, that there are certain things you just — you know, you just can't consider having valid consent for every possible project that would come along. So this needs to be reconceptualized, this set of recommendations. I think it's gotten — I think Bernie said it first — as it currently stands, it's trying to get too much into one thing and gets it wrong. So we'll have to completely rewrite that, and we will do so.

Okay. Recommendation 11. Kathi?

DR. COX: Harold, can I just add something?

DR. SHAPIRO: Yeah.

DR. COX: I do think that the issues involved with this are at the crux of getting out of the problems of stored tissues that we're in right now, so how — what we say in this recommendation is critical, and it's important that we don't say too much, that we don't try to do too much. It's also important that we don't say too little, because I think that this is where we could really be in trouble.

DR. SHAPIRO: This one here is important enough so we're going to have to have some interchange on this between now and the next meeting—so that you can expect and we hope, one, that if you have ideas you'll submit them, and two, you can expect e-mail proposals on this because this is very central and we want to try to get it right, or at least close to it before the next meeting.

Kathi?

DR. HANNA: The new Recommendation 11 was previously Recommendation 10. I think in general the comments here are that people think we need to go into greater detail here in clarifying whether the recontact concerns are different for

consent versus delivering research or clinical information and whether we have separate plans or concerns given each one of those categories. Several people, by the way, and we'll get to the recontact thing in a minute, several people say that we need to revisit the CLIA [TK] guidelines for when you recontact individuals with research results, so I just wanted to raise that as something that came up from several commentors.

MR. HOLTZMAN: Kathi, didn't we at our last meeting agree that there were two very different contexts here, and we should really be clear in separating the two? So as we look at your Recommendation 11, should we be reading this as applying to both contexts or only as the recontact for research purposes? I guess what I would suggest is why don't we do it in two bites, because I think that first bite might be easier.

DR. SHAPIRO: What about the first one?

MR. HOLTZMAN: The first bite — I think the easier one to bite on is if you're going to contact someone or effectively recontact them for participation in research. This doesn't get into the whole issue of whether a research result is a valid clinical result and its—

DR. SHAPIRO: In other words, for enrollment.

MR. HOLTZMAN: Exactly.

PROF. CAPRON: In other words, for consent, as it were.

MR. HOLTZMAN: That's why it becomes effectively, to me at least, a species of genius consenting someone into research.

DR. SHAPIRO: Right.

PROF. CAPRON: Excuse me. I think that there is a link between the discussion that you just tabled on new Recommendation 10 and this point, because certainly one of the options in that menu that would be laid out would be, "Do you want to be recontacted before your sample is used in a new study?" I would certainly agree with the implication of Bernie's comment that point number 3 is almost unethical to have on the list. The notion that, particularly in the context of clinical care, a person could be asked to sign a statement in which they would say, "For this research and for any future research we want to be able to study you without coming back to you. You're now consenting forever," the level of information that a person would have there, and the possibility that they could in an unthinking way or in a way where they recognize some risk but are afraid to decline the risk because they're in clinical

care — in an involuntary way, in other words — consent to that would be on its face unethical for anybody to, or for an IRB to approve. I don't think it should be an option. But alternatively, to have said, "I agree to be recontacted and have that intrusion and have to face a future question: 'Am I willing to?'"—that doesn't seem to me unethical, and there it would obviously be with an identifier because that's how we're able to recontact you.

MR. HOLTZMAN: Yeah, but I think, Alex, that I —

PROF. CAPRON: So I want this discussion about recontact to be part of the tabled point that Harold says we're going to have e-mail exchanges on, and that is the option to say, "Yes, I'm willing to be in future research, but you're going to need to come to me first and tell me about it before you put me in it" and no blanket consent to all identifiable future research.

MR. HOLTZMAN: Well, but I think we need to get very clear on that. That's 10.3 you're talking about, right? Because I completely agree with you that by "identifier" we mean *really* identifiers—not links, not coding—that it is not possible to give informed consent because you can't make an assessment of the risks and harms, the risks and benefits, okay? Don't conflate that with the issue of coercion, because I would submit to you that it is conceptually valid to give a true consent to all future research using my sample if I believe — if there is a coding system and I have reason to believe that the probability of harm will not occur because of the coding system. I believe, and so I want to ask you, which layer are you deeming "identified"? Are you reading it broadly between what is "identifier" and what is "code," and if that is the case, would you say the same in a conceptual analysis as well?

PROF. CAPRON: No, that would be a separate analysis. And I think that although we for various reasons are putting "coded" into "identifiable," I think that the average person not aware of all our discussions would say that there is "identifiable"—coded—and "unidentifiable"—anonymous—it's just in a tissue bank and nobody knows who I am, I'm just a number in the link—and that they could regard those as having separate levels of risk to them and be more or less willing to consent.

I'm simply saying that I think it is unethical to ask a person to go into that first category of being fully identified as to all future research, in part because I don't think it's a genuine consent because you can't really know the risks very well, but in part something affects my—it does affect my willingness to allow them to consent to the other two, "coded" or "totally unidentifiable," and that is the involuntariness. It's just that the risk of being harmed by having chosen something involuntarily is so much less when your sample is unidentifiable that I'm willing to take the calculation that a few

of the people are signing a paper because their doctor is in their mind asking them to do it, even if it's a separate person—and maybe often it wouldn't be a separate person, but if it is a separate person they still think, "Here I am at Stanford. They're giving me great care. They want me to be in research. Sure. I'll sign that." Because they don't really feel they have a choice. If they're exposing themselves to almost no risk at all by doing it, I guess I'm willing to say that risk that's not truly voluntary is acceptable. If they're exposing themselves to potentially much larger risks, that's another reason why I think it would be unconscionable to have that as a choice. I don't think it's unconscionable to say to them, "Is it all right if we come back to you and intrude upon your life to ask about the use of your identifiable sample in research where we want it to stay identifiable?" I think that's okay, even if it is also a little bit involuntary for some people. Is that clear?

MR. HOLTZMAN: Yeah. I separated it too much.

DR. MIIKE: I think we can solve this by relooking at how we're organizing the sequencing of our recommendations. Clearly, to me these choices—and I think that we should take the tiered approach and not get into very specific things—should follow naturally from what we conclude the consent process should be like. And then we give a recommendation about the types of consent, and I'm talking about cross-country consent in this area, so that when you talk about general consent it's one of the tiered approach; we can talk about appropriateness of recontact in particular situations. So it seems to me that we just have to rethink these things and say so—that once we come down to these choices it will just naturally flow from our conclusions prior to that about all the specifics, about the consent process.

DR. SHAPIRO: Yes, Kathi?

DR. HANNA: I just want to add one thing. In the text that we dropped into the commentary—it'll be reworked in the commentary, obviously—there were a number of public comments about our use of the word "incentives" offered for allowing use of the sample. I was a little surprised by those comments, because I think incentives are offered to people all the time who participate in longitudinal studies. They're told that they're going to get good health care and they're going to be participating and observed. They're given t-shirts and mugs and book bags and all kinds of things, and so I'm just curious as to whether we need to pay any greater attention to that word and maybe perhaps say we're not talking about direct financial incentives. But certainly people that sign up for long-term studies are promised a lot for the research use of their samples.

DR. LO: Is "incentive" the word that is usually used on the consent forms, or is it "compensation"? "Incentive" sort of has a ring to it, but—

PROF. CAPRON: Sounds like a salesman, essentially. "Inducement" is sometimes used. "Consideration" is the term that's used, I believe, in the Transplant Act.

DR. SHAPIRO: I think we can use any one of those words. These are things that people—the kind that people ought to be thinking about, not whether they should do something about it or not. We ought not to exaggerate what we're asking in a lot of these cases. Usually it's really very modest. It's just something you might want to think about because then the whole—the incentive to get you to participate comes into question.

DR. HANNA: Okay. Now we're on Recommendation 12, the old Recommendation 9. The concerns about this were the same as those about the "morally objectionable" for various reasons recommendations. Again, people here have concerns about what we mean by "offensive," and people suggested once again that if the protocol is considered as possibly offensive to populations being studied that consent should be sought and we should just drop this and consider it to be a risk issue, and you need to get consent.

DR. SHAPIRO: But here, as I understand it—I mean, the issue I think was once we try to grapple with this and some of the suggestions is not whether it's offensive or not—well, considered just offensive to the individuals whose material is being used—is that being focused on here? Because you have the populations mentioned in line number 3 and then the individual is recontacted here.

DR. HANNA: I think there's clearly confusion between all these recommendations.

DR. COX: Exactly. The comments are not responsive to the recommendation—I mean, they're not getting the point or else the recommendation isn't clear, but certainly there's no communication between the comments and the—

DR. SHAPIRO: So let me just ask the question: What do we intend to say here? Are we trying to say something about risks to groups who are not involved in the project, that is, it's not their material but they have a certain identity associated with other people who are here? Or are we talking about the individuals involved and protecting those people?

PROF. CAPRON: Or allowing them to protect their group?

DR. SHAPIRO: Allowing them to protect their group. Eric?

DR. CASSELL: Well, there really are two issues—one, it's pointed out that you shouldn't be able to consent to any unspecified future 'cause you can't give an informed consent.

DR. SHAPIRO: Right. Right.

PROF. CAPRON: So you eliminate this category.

DR. CASSELL: That eliminates the category. The next thing has to do with consent to research involving populations, etc., etc. I mean, if you want to pick that up and say that that's a special category, that this particular person may have given consent but in fact the IRB does not believe that—I mean in some way to handle that group. Thanks. I don't know how it would be. You belong to a population like that, somebody offers you the chance to participate, you either participate or you don't. Now, the research—it might be the case that the consent form should specify the possibility because somebody reading that consent form otherwise might not realize it.

DR. COX: But you see, you don't know that situation at the time. Here's a person that basically says they can do general research—let me give a specific example: that somebody asked me, do I want to, you know, give this for general research, without my identifiers on but let's say my ethnic background. We've talked about these before, and so if someone's doing studies of psychiatric illness and I decide that well, you know, I didn't really know that was going to be done, but I'd rather that that specific study not be done. How do you figure this out ahead of time in your consent? You can't. But the IRB, given the cultural situation, can say, This is a hot ticket item, a hot button item right now, which some people may be really pissed off about, so that we suggest—IRBs suggest that the researcher should go back and give people an opportunity not to have this done then.

PROF. CAPRON: But if it's unidentifiable they won't be able to.

DR. CASSELL: But, that—see, there you're talking about unidentified.

DR. COX: Yes.

DR. CASSELL: And this specifically talks about identified. If we eliminate this thing in general terms because you can't consent in the future, then we have that other problem, and isn't that picked up by an earlier recommendation?

DR. SHAPIRO: I know this is not—I hope this is helpful as opposed to more confusing. As I look at this now, I think what this is attempting to say is that if there is a study as described here as proposed research that might be considered offensive to populations, I think what this says is that you should re-consent. I think that's what this is attempting to say. It doesn't say it very well, I'm afraid, that you might—if you have a study or protocol that comes along that the IRB believes might in some way offend a particular group that's being studied, then re-consent is required. So the individuals—not the group, but the individuals—can either choose to say yes, despite that I gave my consent—that's what this says. Whether it's a good or bad recommendation, that's what this attempts to say.

DR. CASSELL: So, if I gave my consent I could specify that this was going to be a tissue examination for the sources of schizophrenia and now has turned out—I gave a consent, they did the work, and look what's turned out. All those Ashkenazi Jews have this gene. Wait a minute, now, that isn't what I said "yes" to. I said yes to something else. Is that what you mean?

DR. COX: That's what I mean.

DR. CASSELL: Oh-la-la.

DR. HOLTZMAN: Well, I think we need to, you know, think about our thoughts on Recommendation 6 where we decided that opt-out was an issue, number 1. Number 2, again, I would point to the issue of an identifiable sample. Do we mean truly identified, or do we mean coded? Because, again, I agree there is no such thing as blanket consent to future research.

DR. SHAPIRO: We all agree with that.

DR. CASSELL: We got rid of that.

DR. HOLTZMAN: But with the coded—so now, also it is the case that we want to make sure if we're going to make a Recommendation here that it's not empty. So assume we're dealing with a coded sample for the moment. We don't want a situation in which you can get around the recommendation being made in here by simply anonymizing the sample, but leaving intact sufficient information so as to cause the potential damage. Right? I don't know who it is anymore. I'm no longer linked. But

I do know that they are of a specific racial group or that are they are Finnish, etc. I'm thinking of a specific study we're doing.

DR. CASSELL: But this is a way of saying, "If I don't like—if it looks like the research is going to come out in an offensive way"—the research is being done; it was good research; it's coming out with this finding which might be offensive to groups, I think you've got to go back to me so I can say, "Oh, I didn't know it was going to come out bad like that; I remove my consent."

DR. SHAPIRO: That's not how I interpret this at all. It's a question of using—and this is all prospective before we know what you're going to find out, but we have reason to believe it might be sensitive to a particular population. I'm not trying to defend it; I'm just trying to clarify. This is not after you've done this research; it's before you do it. And the question is whether the consent documents—whether you need to re-consent or not. This is specifically a sample that's been used before. If it's not been used before, then you go and get consent in a normal way if it's consent before and the consent documents might otherwise be considered adequate. But for this fact that the problem now being addressed is a sensitive one, you may want to get re-consent.

DR. CASSELL: Which is another way of saying, "A new risk has arisen that was not covered...."

DR. SHAPIRO: A new risk.

DR. CASSELL: Well, then it doesn't have to be offensive; it can be any new risk.

DR. SHAPIRO: Could be any new risk.

DR. BRITO: But is that up to the individual, or is that up to the IRB? I'm confused here, because when I read this I thought it meant like Recommendation 6 where we're worried about the populations of consulted groups that—I think part of the problem here is that the phrase "considered offensive" is kind of subjective, and based on what Diane said earlier I think maybe if we changed the wording to something on the order of "where it places a group of people at greater than minimal risk," or something in that nature instead of saying "offensive," because it raises a lot of subjectivity.

DR. SHAPIRO: Okay. Let me make a comment, then we're going to see if there's any public comment here before we break for lunch. But the issue, Eric, here is—what this attempts to get at again; if we want to deal with this subject at all is

another issue—is not simply a new risk that might apply to an individual. If there's a new risk, presuming the old consents are not valuable, you have to get a new consent. But this attempts to ask the question whether anyone ought to concern themselves ever with the fact that the new risk might be sort of to a group or population—might make a difficult risk here imposing on a whole population—and the question is under those situations do you want to get new consent from an individual when the individual's background applies?

DR. CASSELL: Have we asked—have we specified previously that harm to a group—if that is a possibility, it has to be included in the consent form? Have we already stated that? Well, you understand what the problem is.

DR. SHAPIRO: I do.

DR. CASSELL: If we have that in the first place, then we have—when you go get consent, if your research may reveal something that isn't good, that should be included in the consent form.

DR. SHAPIRO: Trish.

PROF. BACKLAR: I also—I'm sorry. Are we—we're talking here about retrospectively existing—

DR. SHAPIRO: Existing samples - ways of using existing samples.

PROF. BACKLAR: That are identifiable. And it seems to me that this should go wherever we have some rules about what is retrospective, as opposed to 10, which looks like it is current and prospective, right? Recommendation 10 appears to be directed toward that which we are getting currently.

DR. SHAPIRO: There is an issue of just how we organize the whole chapters in the report, whether in some sense it needs some organization around existing versus new samples and so forth.

PROF. BACKLAR: But that also seems that what we're getting currently must in some way reflect what you're talking about in 12, that there must be some consistency.

DR. SHAPIRO: Let me just ask a question. This issue obviously has plagued us every time we've tried to articulate anything on it, of group harm and what role that plays in IRB approval and/or individual consents that we might achieve. That

comes up again and again in the public comments, I think it's fair to say. Now, what do we think about that? We've struggled with that all along and so far most of the discussions we've had said, you know, this is something we should somehow be taking account of, that there is something real out there.

PROF. CAPRON: We should.

DR. SHAPIRO: We should. There is a risk out there; there is a harm out there, even though it's not anyone involved in the consent process—not even anyone involved in providing any materials. And so then the question is, well, if we continue to feel that way, where should that be recognized? I don't believe—every time we have any way of articulating it, we stumble over it. And so let's see how people feel. Eric, then Larry, Diane, and Alex.

DR. CASSELL: Well, I think that you put your finger on it. If we think it's a risk, it's a risk in original consent and we should specify that among considerations of risk is the possibility that a group will be harmed, or material offensive to a group will be discovered, and so forth. Now the wording of that is not that easy to do, but that should go way up forward. That's part of the original issue: that a special kind of risk is exposed in this kind of material. Then when we're talking about it later on we can re-refer and so forth and we don't have to bring it up here. If we bring it up here, we really have to put it in earlier on also, I think.

DR. SHAPIRO: And of course the issue may come up, not the first time you use the sample but some subsequent time, depending on the protocol.

DR. CASSELL: Yeah.

DR. SHAPIRO: And so one would have to allow for the fact that when some subsequent protocol comes along trying to use this material, how would one then deal with it? But that's—Okay. Larry.

DR. MIIKE: I think we should have it as a stand-alone subject and address the three areas of if there is a potential for group harm, because we're trying to get at this in all kinds of different ways, so that should be part of the information given in the consent process so the individual who consents is aware of that. We should also include in there that investigators should be aware of it in whatever language we have decided about how they should approach that in their design. And then for the IRB as one of the hot button issues that they should see about how the consent process is addressed then, how the research designers address that. If we try to parse it out among these different parts, we're going to still end up in this position where we're not—you

know, we're going to get confused, and I think it's an important enough subject that we should just directly look at it head on.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I think that what Larry is saying is a good strategy. I think there's a basic underlying problem that I don't know if we can comment on in our draft, and that is that there's not only an ethical issue but there's a scientific issue as well having to do with how we define groups when we decide to do studies and how we divide groups for comparison purposes so that, say, a group that we consider an ethnic or racial group might also be characterized by a certain income level, by living in a segregated part of a city where there are environmental toxins and all sorts of other things. So a large part of the problem that leads to group harms is a lapse of logic in the science in how we divide groups for comparisons, and there's currently a fair amount of writing about it and that's a large part of the problem. Some of the ethical issues would disappear if there were more logical ways to divide and organize and represent people as individuals in groups.

DR. SHAPIRO: I think that's correct. It's not clear, however, there's even a solution to the problem. But it's a real one. I agree. Steve?

MR. HOLTZMAN: I'm not sure that getting at it in the consent is going to do because as Harold pointed out, in the future there will be existing samples and you'll want to go back to them. So you're going to be—if you're facing original consent forms in which you're providing for consent to unspecified future research either because the sample is subject to a coding and confidentiality system or is anonymized, that sample will still have information associated with it which could still then go to a group or be associated with a group.

DR. MIIKE: Steve, I wasn't talking about prospective consent. I was talking about consent when that issue arises in individual projects.

MR. HOLTZMAN: Well, in the individual projects you can describe the project and the person will then make a decision about whether or not there's an issue. But again, you know if we pass this thing tomorrow, the day after there's still collections going on and there will be the issue of what is the prospective consent, and the reuse of the sample for a different kind of study is going to come up. So I agree with you. You should be talking about the prospective harm for groups if you're recognizing it up front in your study. That's just part of disclosure. But it doesn't address what I think is the real—the hard problem.

DR. SHAPIRO: Alex?

PROF. CAPRON: I think that actually there's a lot of consensus, or at least there was in the comments of Eric, Larry, and Diane. I think I agree with that. I would say that there are three strategies, or whatever, that we should talk about on this group thing. The first is that if a project is going to involve any group issue, the IRB can legitimately ask whether that is scientifically valid, and it may be in some situations rather than others. They may be looking at a gene, like the Tay-Sachs gene, that isn't associated with being Jewish or even Ashkenazi Jewish, but from particular areas in the Russian or Polish vale where there was some kind of founder effect or something that led to a higher prevalence of a particular gene. And there may be reasons there for studying that group because the gene is found at higher rates there.

But the IRB has something to say about, Is this an unnecessary or even unscientifically based study that identifies a group when they shouldn't? If there's some reason to identify the group, that should be in any prospective consent document. We have to recognize that some members of the group will say, "Yes, go ahead and do a study that's going to end up labeling my group as, you know, a group with high rates of schizophrenia or something. I'm comfortable with that; I don't mind. I think it's important research. And if you tell me it's scientifically valid to look at this group, I'll sign on." And so the only real problem, it seems to me, is what do we do with existing samples where it's met the first criterion and the IRB says that there's a scientifically valid reason to do a study of that sort, and what you have is no identifiers except a group identifier and maybe age or sex. That's one of the identifiers, but no personal identifiers. And it would seem to me there that we obviously can't go back to the person. We don't want to eliminate all such research.

Something we talked about a long time ago, and that had some correlate in something that some of the breast cancer people were doing, I thought was some method of going to a surrogate body and having the IRB test out—not that they were going to be the consenters but just what level of sensitivity and how to deal with that sensitivity would you feel if these were your samples, because in effect they are your samples because the reason we've gone to your group is that. And the biggest argument against that originally was, "Well, we're all members of so many groups; how would you ever know what group?" But here the researcher is saying, "I'm looking at middle-aged Jewish women, and I'm asking some questions about their risk for breast cancer because I think there is some gene that's in that population." It's not because they're Jewish; it's because they come from a particular area or whatever, so it's not a racial idea. They may be Polish in half their makeup. But anyway, they want to go to some group that's—like we got all these samples when we were looking for Tay-Sachs from Temple Beth Israel. We want to go back to Temple Beth Israel and say, "We're now

going to do this study. Can we use these samples? These aren't yours necessarily, but people like you gave them 30 years ago. Can we do it?" And get some consideration as part of that process, that the IRB would say the investigator has to make that extra effort. That's all I can think of to add to this so that the IRB would have more material to work with.

DR. SHAPIRO: The last two comments before we break. Bernie first, then Eric, then Trish.

DR. LO: A couple of comments to try and keep on this line of discussion, which I think is very important, and it's a tough issue and we haven't solved it and we keep coming back to it. We just need to keep working on it.

It seems to me—following the line of what Alex said, one of the things that we I think are intending to say here is that in the situation where you have an existing sample to which the patient gave some sort of blanket consent, general consent, to use it in a coded way, notwithstanding that consent the IRB may in certain protocols that raise issues of group risk or offense say that that may not be enough and that you may have to do more. Now, how much more and how to do more I'm not sure we have the answer. I think Alex gave a suggestion, which I'm actually very sympathetic to, but the critics come back and say, "Well, you know, can you really speak that way?" I think that should be all part of the discussion, but isn't the crucial issue that just because you've got a piece of paper that literally says, "You can use my sample," the IRB may say, "Oh, no, no. I'm not sure that's going to be valid because of the special circumstances."

And second; I think we need to try to think through and give some guidance on what level of concern we're talking about. The studies I have in mind are the horrendous studies that invoke these sort of historical genetic disasters. It's not that—you know, some of the critics of genetic research say, "Look, anybody can say, `Look, I'm a member of that group. I might be offended. Other people might be offended. I want to stop it.' " So I think we need to maybe give some examples of the kinds of studies where we think an IRB might seriously want to challenge the prior consent and to, I think, have the presumption be that we're not talking about sort of little, minor things. We're talking about fairly significant things that have gotten a fair amount of discussion or that invoke historical echoes. I think one of the things that's important to me here is the sense that genetic research has been misused in the past and the closer we get to those sorts of things the more cautious IRBs and society are going to be. I think some of the respondents, the public commentors are saying, "Well, but, you know, this could be for a trivial reason, not cancer research. That's not what we're

talking about." So some specific examples might sort of calibrate the types of concerns we're talking about.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I think all of us come to the "this is important" and then we get on to the details and then we get into trouble [LAUGHTER]. But Bernie is absolutely right, except the size of the cinder depends on whose eye it's in. So I think this might be an issue where we would do well to commission somebody working through this problem, because we've been around it now a number of times. There are lots of issues here. I can see—it has that quality of political correctness about it, and I can see studies that show, once again, increased prevalence among the disadvantaged of certain diseases being ruled out of court because we can't do that. And we have to be very careful about it. On the other hand, the concern is real, so maybe that's what we ought to do, is get somebody who'll think about it for more than—

DR. SHAPIRO: Trish?

PROF. BACKLAR: No, I agree.

DR. SHAPIRO: We're going to have to adjourn in a moment. I think our discussion—we've had quite a lot of discussion over time over the issue of well, you've got the subject, you've got the consents, but still there are others to whom harms might accrue who are part of a group somehow defined or self-defined in some way, and what do you do? And it is always true that if you make anything a very specific suggestion, like you consult this group back with the other group, someone's always got a reason why they're not the right group, and my recollection of all that discussion was that we nevertheless thought it would be advisable to consult in some way with a group we could reasonably identify, if not exclusively identify, both because we thought it might actually improve the research project itself and therefore give the investigators some notions about research design that might actually mitigate some of these harms, not eliminate them, but not provide these groups with any kind of veto over the work. It's not up to them to decide whether it goes ahead or not, but just a question of trying to enhance the research design in a way that did not undermine the research objectives. That's where we want to avoid the—so that if there's any political correctness here, to avoid that but might in fact enhance everybody's situation, both the researchers and the group however defined. And it seems to me that's about the level we can deal with, and we'll try to formulate something along those lines. I think it may or may not be a good idea to commission a study, but I don't really want to commission one now that's going to impact on our own report. That'd just take us too long to get to it.

Trish, just because you came so far, I'm willing to recognize you once more.

PROF. BACKLAR: But in other words, some sort of the suggestions that Mary Claire was making to us.

DR. SHAPIRO: She had some of those ideas, right.

PROF. BACKLAR: Which would be an example. But also another example was, Bernie, many, many months ago you came with the example of working with people with AIDS in San Francisco. So that we have some real examples, and Alex's Tay-Sachs example of how people were asked and how further research went on and some of the problems that actually came out of that. It would be interesting to show the different—

DR. SHAPIRO: But if you remember the breast cancer case that we didn't deal with but heard about—perfectly reasonably identified groups had different views of these matters altogether and one group was no better than the other group. They were both reasonably—but they just chose to have it—well, that can inform the researcher and maybe help minimize, but they can't determine whether to go ahead or not. And I think that's what I learned from that example, and I think that sounds reasonable.

Well, look, we're going to have to adjourn in just a moment, not just yet—but is there anybody, incidentally, in the audience here today that wants to address the Commission? If not, then we will adjourn. We will reassemble no later than 1 o'clock. For the Commissioners and staff, lunch is right over where we had breakfast today. If you weren't there for breakfast, just follow someone who was. Thank you.

DISCUSSION OF DRAFT OUTLINE ON RESEARCH INVOLVING HUMAN STEM CELLS, PLANS FOR FUTURE ACTIVITIES AND MEETINGS

DR. SHAPIRO: We want to now turn our attention to human stem cell research and the issues that revolve around that, again with the objective of trying to move ourselves systematically toward a report that we would like to have written on or about June 1, and as I've thought about the issues so far and watched some of the discussion and e-mail traffic, I think that there's every possibility that we can do this by then. As I said earlier this morning, we hope to get some parts of the report, maybe even

it might just be some of the descriptive parts or even some of the introductory parts, done by March, or at least in draft form by March, but what we want to do today is begin a discussion amongst ourselves regarding where these issues are. One way it was expressed at our last meeting is, "Let's get through our conclusions, then figure out the rest of it." I don't think we can quite do that but at least—I think no one meant that in that literal way, but it was to try to see where we are on these issues.

I think all of us now have a really pretty good understanding of the science that exists today. There are some, of course, unresolved issues, but I think on the basic issues we have a pretty good understanding of it. We have a number of other commissions who have dealt with related issues, whether it's the Human Embryo Research Panel or the Fetal Tissue Panel or a number of other commissions whose work we reviewed, say, in addition to our own work on cloning and so on, which have, in part, some relation to this. So we start from a pretty good situation. So what we're going to try to do today, what I would like to do this afternoon, and we have from now until 4 o'clock—we'll take a break somewhere in here, but at 4 o'clock we'll have Dr. Blumenthal here to address us on some of the public/private issues, and that should take us to 5 o'clock, which is our rough area for adjournment and I think we'll try to stick to a 5 o'clock adjournment for everybody's benefit. So I'd like to just get us started.

I want to apologize to some of you who have been active in e-mail exchanges this last week. I was traveling all this last week. I'm somewhat sobered even to open up my e-mail for fear of seeing something like 270 messages unread in there, so I haven't done so. That's tomorrow afternoon's work. I know some interesting exchanges have taken place just because I've heard others comment on them, and so I apologize if I am unaware of some of those issues. I thought I'd begin by turning to Larry, since Larry had some thoughtful suggestions about how we may proceed, and have him outline his thinking on this and then proceed with the discussion. Larry?

DR. MIIKE: Thank you, Harold. Also, Alex had done something similar to what I did, expressing his points of view. First I want to start off by saying I hope one day we have a meeting where we're in my time zone so I can be witty and bright. [Laughter.]

DR. SHAPIRO: You guarantee that, if we do that? You guarantee that, right?

DR. MIIKE: I can promise you a nice venue too.

PROF. CAPRON: Since you're witty and bright in this time zone.

DR. SHAPIRO: We might not be able to take that much. [Laughter.]

DR. MIIKE: As those of you who have read my e-mail know, I think we can parse out and I think come to a quick agreement on some of the areas where I think that most if not all of us would agree that we've come to on the harder issues. Let me frame it in the following way. Clearly, there are about three broad areas of embryonic stem cell research that we have to address: embryonic stem cells derived from fetal tissue; from embryos that were created for the purposes of childmaking in the IVF area, and then creating embryos expressly for research purposes, which will be the issues that we'll have to face.

I think the context nowadays is a little different from before in the sense that there are some concrete possibilities about the fruits of the research on stem cells, and it's my opinion at the current time that some form of stem cell research has to be funded by the NIH and Federal Government. And it's not just for the promise of the research, but I think that, and the scientists can correct me if I'm wrong, but I think that this area has such a big promise that if the NIH is not able to fund in this area, they are going to be a defective organization in terms of research as the years go by. They will be shut off from an area of research that is going to be so fundamental to the mission of the NIH, that it's going to be a defect to their mission. Anyway, that's my assessment of the scientific side currently.

The issue is not so much stem cell research but how the materials are derived. So that while we may want to talk about the science of stem cells from adults in the various lines like, you know, long or etc., I think that those do not rise to the level that we're talking about in terms of what we're facing. So we're really talking about embryonic origins. In the fetal research area there is established, accepted policy, and I think the issues in that area are that the current research would even allow the extraction of the embryonic stem cells from the fetal tissues. The issue around this one seems more around whether one is talking about whether we should limit it to spontaneous and therapeutic-use abortions or whether induced abortions should also be included. I think that's one of the issues in that area.

I think that if one follows the current laws that you can both do the extraction as well as the research on the stem cells. As Alex has pointed out, one other issue in this area may be what we mean by the current law on transplantation in terms of its uses. My spin on that is that the research that we're talking about is part of transplantation research, broadly speaking. Even though it may have been an original law referring to, really, the transplantation of the actual fetal tissue, I would say that I want to make a good argument the law covers it as it is.

The second area that we're talking about is that of derived from IVF excess embryos or embryos that are going to be destroyed or that the sperm and oocyte donor agree to allow it for research. Now as we all know, that currently is prohibited because of the prohibition on embryo research, but as the DHHS [Department of Health and Human Services] general counsel has interpreted, the stem cells derived from that are not organisms per se and not embryos per se, and that's allowable. Now the peculiar situation, if we just leave it as it is, is that stem cells derived from those sources would not be subject to the restrictions and guidelines that are applied in the fetal area, and it would seem that if we agree that this type of research should go on, it should at least be subject to the same oversight and guidelines as in the fetal-derived area.

The third area, in terms of creation for research purposes, my personal opinion is that I don't have any ethical qualms about that, but I do have policy qualms about that. Let me put it this way. If it's accepted policy in this country for couples to intentionally have more eggs or more fertilized oocytes than they know will create children and that it's okay for them to say, "It's okay to discard or destroy those oocytes," I see a parallel to that as saying that they are doing that for procreation purposes. They're doing it for a personal benefit purpose. They're doing it for what is accepted as a morally accepted behavior in this country. I would say that in my mind to create embryos for research purposes for public-good purposes under appropriate restrictions and guidelines, I wouldn't have any problems with that.

I do have problems, though, from a public policy perspective, and one is that if we go down that path it will so color the other areas in which I think there can be a general consensus that we'll be lost in the shuffle in terms of what we can do in embryonic stem cell research. And I think that the two current sources, which I hope we'll agree on as being acceptable, the first two being IVF and from fetal research, I think provides enough of a resource for the research establishment to do what they need to do over the next few years within a decade or so. So that from that perspective, and given what I'm sure we all understand about people's queasiness or adamant opposition to creating embryos for research—not just in this country but internationally; you see that a lot in the other writings in other countries—I think that would so overwhelm us, because of the emotions involved in there, that we would not get anywhere.

But I think that I also have a technical consideration, and again I want the scientists to tell me if I'm right or wrong, that one can never predict in terms of the future about what you think today is in terms of inventions and medical progress, but what we hear mainly for the somatic cell nuclear transfer creation of embryos research is the customization process where you can customize the tissues to the individual so you can get rid, you can avoid the issues about rejection, incompatibility, etc. I look at that from two points of view. One is that, and I'm going to have a little trouble describing

this, but in terms of accessibility to the therapeutic benefits of this research, I think that down the road the benefits will be much more accessible if one creates a large resource of tissues rather than having to customize for the individual. To put it in sort of a superficial manner, it's like saying I can go to Sears and buy something versus going to Christian Dior and having to buy a very customized kind of a thing. I think it would be much more accessible if down the road we can have either tissues stripped of their antigenic properties so that they would be universally accepted by all people who need the transplants, or we develop enough cell lines that there is a make and model for your body that can be fitted on there.

And so from the scientific perspective, I think there's enough of an opportunity in the stem cell research area that stem cells from the first two sources would be ample for the research enterprise and that if one wants to address the incompatibility issue, then the Federal funds could fund not the customization process but the areas in which one might talk about stripping off the histocompatibility or developing multiple cell lines. And I think that would be seen as an earnest and legitimate attempt to avoid, if possible, creating embryos for research and using public funds for that, to provide a reasonable alternative to that method.

Now I'm in a conundrum in terms of what to do about creating embryos for research. As I said, I don't have any ethical qualms about that within certain restrictions, which we can talk about later when we get to that area. But I would not want to prohibit it in the private sector. Now having said that, one also would like to have some guidelines for the private sector, but if one does that then one is also sort of saying it's okay, and we want to impose some ethical guidelines on that. So I'm in a conundrum about benign neglect in terms of that side in the private sector versus being a little bit more assertive about saying, if they're going to do it, what they should be doing in that area. So with that, I have many other things that we can talk about, but in a nutshell that's where I would stand: It would be acceptable for me, obviously under safeguards and guidelines, for stem cell research from fetal tissue and from excess embryos created for procreation purposes but not in the direct funding of creating embryos for research, but strongly suggesting that research be also conducted so that we would minimize or perhaps even avoid having to create embryos for research directly because of the customization versus the more universality of available resources approach.

DR. SHAPIRO: Thank you very much, Larry. I'd just like to ask one or two clarifying questions. I found the structure you presented it in being very helpful and very informative and I thank you for it, but I want to ask just one or two questions. I wasn't sure about what you said, just to clarify in my own mind. One was, I think you

said you were either undecided or uncertain on the fetal tissue issue regarding whether this came from elective abortions or other sources. Is that fair, or—?

DR. MIIKE: No. I would permit elective. I'm saying, though, that it is an issue for other people.

DR. SHAPIRO: I see. Okay. Now you also made a comment, which I think I understood—again, I'm just asking for clarification regarding whether this comes under the transplantation issue—and that has to do with whether this law actually applies. Is that correct? Is your judgment, as you look at it in a broad sense, that it does apply?

DR. MIIKE: Yes, because one is, the uses that are being contemplated in stem cell research is really transplantation into human beings.

DR. SHAPIRO: And so you think it does apply. Okay; I just wanted to clarify. Alex, since Larry referred to you in that e-mail exchange that I haven't got to yet, maybe, I don't know if you have any comments or would like to make any suggestions at this stage.

PROF. CAPTRON: Yeah. In a certain way, what I would really like to do is, say, second and move Larry's description. I took it that the central thing that Larry said at the last meeting, which he followed up on and I followed up on the e-mail, was to say we should write this report although you a little bit said we couldn't really mean this, but we should write this report by coming to conclusions in each of these three areas and then fill in as much justification as is necessary for people to understand what we've come to. So I almost want to say that rather than having a general discussion, we ought to talk about topic one, which is the Gearhart approach, and decide where we come out on that, topic two, topic three.

My own bottom line is, other than clarifying the transplantation issue, where I think we might urge that there's modification to the law, and other than dealing as I did in the e-mail—and I have copies of everybody's e-mail but my own—but I talked in there under the existing embryo thing that we do face a small problem in simply adopting the rules that exist for fetuses, because we have to say that it's fetal tissue, it's existing embryos for which there's no added payment for the donation because there usually is payment, unlike in fetuses, there is payment for the original gametes.

And I basically agree with Larry on the point about embryos created for research and the difference between not having a prohibition for private activities but not

at this point using Federal funds. I'm not sure I'm convinced on the issue that a cell bank is automatically going to be better for all people as a policy thing than having an autologous creation, in part because a lot of people who go for transplants, particularly in the kidney area, are already highly sensitized because they've been through dialysis, and it's particularly important to avoid rejection in them as I understand it. But I would just add, the only thing that I would add to what Larry said, was it seems to me that what this would lead to as a conclusion is for all of these areas, but particularly the issue of embryos created for research, we ought to urge the director of the NIH to take the largely administrative oversight body that he was going to set up and instead see this as a topic that ought to be dealt with by a more broadly based advisory body, á là the RAC [Recombinant DNA Advisory Committee] where we can start off as did the RAC, within an agreed-upon area. In that case, it was somatic cell therapy.

And the question that lay in the future was well, what about germ line gene therapy? You're going to have a body that was being useful on present protocols and answering questions as they arose but then would get to other issues as the science directed. And if it turns out that either the route of turning specialized stem cells back to pluripotent stem cells that could do everything, if that turns out to work well, then we avoid the embryo question and everybody can be happy and you can get autologous transplants by that route. Or if what Larry suggests turns out to be the case, that you can with 100 or 1,000 different cell lines blanket 99.9 percent of the population and reduce the surface antigens so that they don't cause rejection, then we don't have to go that way, in other words. But that would be something we can't resolve now, and we ought to say to the Secretary and to the director of the NIH: Establish an ongoing panel that will be in a position to give you advice a year, five years, whatever from now, as the science develops. So, I would hope that after whatever advisory comments, we begin with topic one, the fetus, and then move on to existing embryos and then move on to embryos created for research, reach our conclusions, and then the staff can fill in the background material around those conclusions instead of reading a lot of background stuff and then trying to have the conclusions flow from them.

DR. SHAPIRO: I am certainly ready to go, I want to take other comments that other people might have. I'm certainly ready to go to dealing with, go down this ladder or go down the slide, whatever you want to say.

PROF. CAPRON: Whether it's "a" doctor or "the" doctor. [Laughter.]

DR. SHAPIRO: Steve, then Eric?

MR. HOLTZMAN: It was just a quick question to Alex: In thinking about a RAC-like mechanism, is the thought that it would be approval of specific

protocols, which is one of the RAC's functions early on that I think [Dr. Harold] Varmus was tending against, or is it to more generally follow the progress of the research to be able to report on such matters as whether autologous transfer is going to be necessary, or looks like it will be the most likely route, and therefore one needs to examine the question of research embryos.

PROF. CAPRON: My thought was more the latter.

MR. HOLTZMAN: Okay.

DR. SHAPIRO: Eric?

DR. CASSELL: I just want to start off by triple-seconding and then some.

PROF. CAPRON: Raise us.

DR. CASSELL: Yeah. But I want to ask also, does the production of a blastocyst by somatic cell transfer resolve the problem of transplantation, and if we don't go to babies, do we permit that?

PROF. CAPRON: That's the third category. If it's done for research purposes, whether IVF or somatic cell transfer—

DR. CASSELL: This falls under that?

PROF. CAPRON: It's one of the two ways of doing the third thing.

DR. Shapiro: That's right.

PROF. CAPRON: It's the way it's involved in the autologous transplant issue.

DR. CASSELL: Right.

DR. SHAPIRO: Unless it's a serious objection, let's actually go through this hierarchy and talk about the use of—let me make it clear. We're all clear about it, but just to make sure those are who may be listening. What we're talking about here when we deal with the source being fetal tissue is whether the Federal Government ought to sponsor such research. This is not against the law. That's really the focus of the issue. Most of these things are quite open to private people not using Federal funds as it

stands right now. So what we're talking about, and we may extend any observations we may have into the private sector if we like when we come to that, but let's just talk about the first of Larry's propositions, which was, as he stated, that's he's quite comfortable, for reasons I won't repeat, that fetal tissue, which is what Gearhart used if I remember correctly, is quite an appropriate type of research for the Federal Government, the NIH in particular, to be funding—that we don't have any, or at least on balance we don't have any, reservations about that as a proposition. How do people feel about that? Do we all agree on that? Is there any serious objection to this or even modest objection to this?

DR. CASSELL: What we have is two sources of evidence, so we have to distinguish those two sorts of embryo.

DR. SHAPIRO: I'm dealing just with the fetal tissue source right now.

PROF. CAPRON: You forgot the germ cells. The EG [embryonic germ] cells.

DR. SHAPIRO: Right.

DR. CAPRON: Primordial germ plasma.

DR. SHAPIRO: What were you referring to, Eric?

DR. CASSELL: Well, whether that embryo is gotten by abortion.

DR. SHAPIRO: Well, that's right. I'm just asking for fetal tissue irrespective of where it was, whether it came from spontaneous abortion or elective or any other way.

DR. CASSELL: I see. If you object to it in general, it doesn't matter where it comes from.

DR. SHAPIRO: That's right. Anybody have any objection to that? The issue—Excuse me. Bernie?

DR. LO: Let me raise an issue, which has to do with the distinction between spontaneous abortions and induced abortions. As I understand it, there are a certain number of people who would object to the latter and not the former in the sense that there's this concern about are you somehow influencing the woman's decision to terminate a pregnancy despite whatever guidelines we have. I don't know scientifically

whether the nature of spontaneous abortions makes them undesirable or substandard for doing this type of research in a sense that there may be chromosomal defects, infections of one sort or another that were the cause, the root cause of the miscarriage and therefore would not give the optimal source of embryonic stem cell research. I mean, if David or anyone else could help us with that, that would be good, because I think if we're looking for kind of trying to establish where the most public support or opposition may be, I think the difference between spontaneous miscarriage versus induced abortion may be important for some people.

DR. SHAPIRO: David?

DR. COX: I have a factual comment on that, and actually it's not what John Gearhart did in keeping with his testimony last time. He put it out in something that I wasn't aware of, a relatively small time of gestation window for obtaining these cells, and unfortunately that was, you know, it was before nine weeks, in the six-to-nine-week range. Most spontaneous terminations aren't then, so that, or even if they do occur then, most people aren't very aware of them, so obtaining this material by that route is exceedingly unlikely.

PROF. CAPRON: The present Federal policy under the statute does not differentiate.

DR. SHAPIRO: Does not and it has, if I remember correctly—Alex or others could correct me because I haven't read it in recent weeks—it also has certain provisions, as I recall, such as you cannot designate where the material goes to try to make sure that there's some buffer mechanism between encouraging elective abortions and this research use. And it was certainly well articulated in that regulation, as I recall, and seemed—at least I felt satisfied with it. And I'd like to also pose a scientific question, if anyone remembers, that came up in the testimonies last time in Washington. And that was the question of whether these cells—Gearhart type, if I could put it that way—really were the same in every significant way as the cells that would come from what we'll discuss in a few moments, that is so-called excess embryos. Does anybody remember the comments that he made along those lines? Alex?

PROF. CAPRON: He said two things. He said they haven't done all of the tests and there were three. He said there was one difference: that his cells may not have been as imprinted, they may not be imprinted in the same way. The cells may be reverting back to an unimprinted state, which is kind of ironic because they come from more developed cells, and that there may be more of a cohesion—and I don't know how to describe this scientifically—among them. In Varmus's statement to the Congress the other day there is a statement on this on page 2 and on to page 3. He says,

and I quote, "The pluripotent stem cells derived by each of these means appear to be very similar or identical in structure, function, and potential, but it will take more research to verify this." So I think the answer is: We don't know yet.

DR. SHAPIRO: Steve, then David?

MR. HOLTZMAN: Yeah. If you go to—unfortunately,she's presenting tomorrow, I guess—but if you go to Brigid Hogan's testimony, on page 3 the top paragraph goes into specific potential differences in terms of methylation and whatnot. Basically, the answer is: It's kind of early to tell.

DR. COX: My only comment was to make a distinction between hypotheses about how they may be different and evidence that they're in fact different. And there is no evidence in the human case right now that they're different and so that's not to say that they're the same, but to start making any kind of decisions based on an assumption that they're different, I think is probably not smart.

DR. SHAPIRO: Just out of my own curiosity, is there evidence with respect to non-human animals at all?

DR. COX: There's some evidence with respect to mice, in—

DR. SHAPIRO: Which says what?

DR. COX: That they may be different in terms of this imprinting. That's where that statement comes from. But let me just say that it's not at all clear that that's a general characteristic of the cells as opposed to a situational difference due to that particular experiment. So I think that there's no evidence that I'm aware of in any species that says that these types of cells are substantively different irrespective of experimental contact.

DR. SHAPIRO: Let's go back then to the central question we're asking here. I take it from the responses that we're in broad agreement amongst us that the use of these stem cells derived from fetal tissue for research purposes should be perfectly okay for the Federal Government to finance. I put that a little awkwardly, actually, but I think you get the gist.

DR. MIIKE: Not only perfectly okay, in line with—

DR. SHAPIRO: Imperative. You would say "imperative," important that they do so.

DR. MIIKE: Not just that, but it is permissible under current law.

DR. SHAPIRO: Current law. It is permissible under current law. Arturo?

DR. BRITO: It's permissible under current law but it doesn't mean that—are we talking about the plausibility from the legal point of view, or are we doing the ethical point of view, or are we sort of collecting opinions about this? Because I personally feel a little bit uneasy about the intention if we're using tissue from intentionally aborted fetuses for this and I hadn't—I need to think it through a little bit more. But as to spontaneously aborted fetuses, I don't have difficulty from an ethical point of view. Except from a scientific point of view, for various reasons it's not the most reliable source of tissues.

DR. SHAPIRO: I think it's the judgment—we'll have to say what our judgment is—but from what I understood of that judgment it is also mine, that the current rules and regulations as set regarding fetal tissue research do not make that distinction, that is. So that for that purpose and for the purposes they had in mind when that regulation was put in place, they did not make the distinction between spontaneous and elective abortion, and it's my own view that that continues to be—you know, I'm happy, I'm quite satisfied with that. But I understand what you're saying. You want to think this through some more and want to think about how you might feel about it. That's certainly fine, because how you feel has nothing to do with the law.

DR. BRITO: No, I wouldn't disagree with that.

DR. MIIKE: One other point, though, is that the current law and regs tries to address the issue because it separates the purpose from the incentive. They're making it clear that they don't want research to be the incentive for getting an abortion, and so they've addressed that issue.

DR. SHAPIRO: And there is, as I think you may have said before, there are things built into the regulations that attempt to eliminate the incentives such as designation and so on and so forth. But, you know, that only takes you so far and so you ought to think further about that.

Well, I sense that we can go on, unless there's some other issue we want to raise at this time. We'll come back to this. There are smaller issues, but I think I'd like to go on and consider the second category, that is so-called excess embryos as a source.

MR. HOLTZMAN: Can I just ask a question?

DR. SHAPIRO: Yes.

MR. HOLTZMAN: Did we just agree that it's legal to—I think we did; I know we did—did we agree we think it's morally okay? Did we agree that we think the Federal Government ought, because we think it's valuable? What are we pushing for?

DR. SHAPIRO: When I say we've agreed, I don't want to implicate everybody in every one of those three things. What I think that we've agreed to is that on balance most of us agree to all three of those things.

MR. HOLTZMAN: Okay.

DR. SHAPIRO: Now we've come to—

PROF. CAPRON: What's the third one? I hadn't heard that until the very end.

DR. SHAPIRO: Federal funds.

MR. HOLTZMAN: Was that the third? I have to listen more for these things. Okay. So there's: Is it legal? Is it morally okay? Is Federal funding allowed? That's legal, but I think we've already answered that. Do we think that the pursuit of this research is of good, which means we therefore advocate Federal funding?

PROF. CAPRON: No.

MR. HOLTZMAN: Are we taking up that question at all?

DR. SHAPIRO: I don't understand the last.

MR. HOLTZMAN: Do we—

PROF. CAPRON: Do we want to become—

MR. HOLTZMAN: Advocates.

PROF. CAPRON: Advocates of the research as an area that deserves Federal priority. I just don't think that we're asked for our opinion on that, but I don't think we're probably qualified to give it.

DR. SHAPIRO: I think Larry expressed his view that he thought this was critical. I don't want to use words that specify the future. But my own view is that while I believe that in a way, I don't think it's our job to split up the NIH budget or to decide which is the most valuable area to pursue. That's just my view, if you want my personal opinion.

DR. MIIKE: What I meant by that is that if the NIH is not allowed to pursue this area it will be a defective institution in terms of the overall research enterprise. I'm not saying how much money they should put in, what they should be doing, etc. That's all I'm saying.

DR. SHAPIRO: I agree with that. Arturo?

DR. BRITO: Yeah, I agree with that.

DR. SHAPIRO: So, I think that although Arturo has expressed some reservations about an aspect of this that he wants to think about some more—and I think that's fine; I certainly want everybody to think about it more. I'm just trying, what we're trying to do today is trying to get a general sense of where we all are. Everybody has a capacity to change their minds once they've looked at the arguments that are made and so on. Bernie?

DR. LO: Just to clarify what we think we're agreeing to on that third point with regard to Federal funding. I would suggest that we consider something along the lines that it's appropriate for the Federal Government to fund stem cell research on these sorts of tissues. Not to recommend that they do it, but that there are no sort of moral objections to that kind of Federal funding, which is a weaker sort of policy.

DR. SHAPIRO: Let me make a comment about that, Bernie. It may not come up so much with relationship to this particular source but certainly will come up with the next source. You think of the President's letter, it has various interesting aspects to it. But one interesting aspect to me is that the letter points out that there are new opportunities or new clinical possibilities, and that changes, at least for him, the balancing of all these issues as we move ahead. And I think that's, myself, a reasonable argument and therefore in some sense, certainly when we get to the next source, we will have to deal with that as an aspect of this. It's not only that it is—maybe that is enough to say—I would consider that a minimum myself: that it's appropriate. I consider it too much to say how much someone should spend and so on. That's much too much. So just how we should phrase it, we can remain open on it. Eric, then David?

DR. CASSELL: I have nothing more.

DR. SHAPIRO: David?

DR. COX: I think that Dr. Varmus made that point to us very strongly in terms of something for consideration, not just of the downsides. Arturo's voiced, I think, a downside for a lot of people: even though legally there's not a distinction between induced and spontaneous abortions, a lot of people make that distinction. I don't know how many, but certainly some do, at least one, right? You did.

DR. SHAPIRO: Well, more than one. Several did that we heard in public testimony.

DR. COX: For me, it's that then this information about potential benefits that may actually now be on the horizon that weren't on the horizon before changes my personal view with respect to that. So I think it's that balancing, and that we bring that forward. It's not to say how much you should change it but certainly that's new information that's coming forward. Now one could say, well, don't even bring up the issue of the distinction between induced and spontaneous because the law doesn't make that distinction. I personally feel that that's a mistake because that's from an ethical point of view where a lot of people are coming from. We heard that in public testimony. So I think it's important to confront that straight ahead.

DR. SHAPIRO: Alex?

PROF. CAPRON: I want to agree with David and just make sure that we're seeing one aspect, which is that the law does differentiate. It differentiates in that it places requirements on the person using tissue from an induced abortion that the abortion not have been related to the research.

DR. COX: Yeah. Absolutely.

PROF. CAPRON: Because it seems to me that those who object, object on two grounds. One, that there will be more abortions because either women will be having incentives to get an abortion because they'll be doing some good for science, or under the transplantation view some good for their grandfather or something, giving him tissue for transplantation. Here it's giving tissue for science. The second objection is, well it's not worrying about there being more, it's simply that there's a taint to that material, and that any good that comes from it is tainted in that way. And the former view is probably much more widely held than the latter view: that there would be something wrong in encouraging an abortion that wouldn't happen otherwise. The latter view says, unlike other dead bodies that have come to be dead through any different means—through a homicide, through a negligent accident, through an injury that's not

negligent, or through illness—these bodies should not be used for research. They shouldn't be like other cadavers. And I think that position is distinct and is less widely held. It is a view that was overridden when this statute was passed by the prospect that tissue transplants largely for neurological diseases would be so beneficial as to justify that taint.

It seems to me placing our conclusion into that context is to say there is every prospect that research in the area of stem cells also holds out at least as much promise as the promise that induced the Congress to make this exception here. And that it's a matter of weighing that relative taint against the benefit that could come as long as we have the protections against the incentive version of the wrong. So I think it's important to say they're not treated exactly identically there, because with the stillbirth there's none of these testing requirements and no separation of the woman's decisionmaking process.

DR. COX: Write that down, Kathi.

DR. SHAPIRO: Those distinctions are quite critical, and we're going to have to confront those arguments in the text that we use to support these decisions, which may or may not change some people's minds here as we go through them. And of course in other areas of the law there are also distinctions, quite aside from this law, that is this fetal tissue law. So that's very much, very appropriate. If you're ready to go on to the second—Kathi?

DR. HANNA: I just want to add one clarification, because I think we tend to slip into saying the NIH all the time, and we're trying to find out from some of the other agencies, the VA [Veterans Administration], EPA [Environmental Protection Agency], DoD [Department of Defense], whether in fact they also have an interest in this type of research, because obviously the DHHS ruling is relevant to them but not necessarily applicable. So we're going to try and find out more there, so when we talk about Federal funding we're really trying to cast the net very broadly to all the agencies that might have an interest.

PROF. CAPRON: And that did not come up vis-à-vis vi the tissue transplant because the language we're referring to is part of the NIH Revitalization Act and refers to the Secretary of HHS, right?

DR. HANNA: That's correct. Although the VA apparently does have an interest in this work because of spinal cord injury research.

PROF. CAPRON: But ironically, the statute didn't reach them. On a technical matter, I think at some point, Harold, if we have a conclusion on this point we have to decide if we're going to recommend a clarification of the law. And what Kathi just said underlines the notion that we may need to suggest that a statute is necessary both to address the departments and to address the fact that, Larry notwithstanding, I don't think that most people would regard this as transplantation research. It's really laboratory research on stem cells with a number of possible uses, only one of which is the transplant use.

DR. SHAPIRO: I think that we are going to have to, as we go through this in the next weeks, there will be a number of legal issues of that type that are going to come up that we'll—

PROF. CAPRON: It's not a central question.

DR. SHAPIRO: No, not central, but important to deal with, and we'll have to fill that in as we go along. All right. Let's move on. We can come back as the discussion warrants, but let's move on to the second source, which one could characterize as excess embryos coming from IVF clinics typically and so on, and see what comments, views people have on that. Larry, it's your, I think it's Alex's view also if I understood him correctly, that while guidelines would be needed, as they already exist in the fetal tissue area, that we should have no objections to the Federal Government spending money on the research on human embryonic cells coming from this particular source. I haven't misstated it, I hope, Larry.

DR. MIIKE: No. Except it would have to be in two parts because right now the general counsel for DHHS says it's okay to use stem cells derived from them.

DR. SHAPIRO: Yeah.

DR. MIIKE: What I'm saying is that the second part of that is whether the part about getting the stem cells from the embryos themselves should also be allowable.

DR. SHAPIRO: Okay. Let's deal with, well, we could deal with either part. First let's just see how people view, feel about this. Eric?

DR. CASSELL: I certainly have no objection to research involving the stem cells derived from that source. They are stem cells; they're not an organism. I also have no objection to excess embryos with some guidelines, and we have to know that this is indeed an excess embryo, that they weren't harvested with this in mind and so

forth and so on, but the alternative to that is the destruction of the embryo. Is that correct? So these are embryos that would otherwise be destroyed. If that's correct, I have no objection to that.

DR. SHAPIRO: I think this to be, if I understood what was told to us last time, would otherwise be destroyed and/or stored in some ways, indefinitely.

DR. CASSELL: That changes something. That changes things a little bit.

DR. SHAPIRO: Right.

DR. CASSELL: It's not so much my own objection to it, because I don't mind even if they were going to be stored, but it depends on who is deciding on making that decision. But at least in the first step or the second step, the first one is stem cells coming from that we don't have any source, we don't have control of the source, the second one that would otherwise be destroyed, I have no objection to that. And I also have no objection that they would otherwise be stored.

DR. SHAPIRO: Bernie?

DR. LO: Again, I think that as we're trying to do, it's very important to try and distinguish what we personally believe as Commissioners and what we would recommend as the recommendations to the committee. I think we all need to, as we're all trying to do, pay very close attention to how other people would react to this. And I certainly think Eric's on the right track when he says that if you think about how the public is going to react, it is very different to say this is an embryo that the parents were planning on destroying, and if that decision has been made independently of the opportunity to donate it for research, we said, "Okay, the scientist says you've given permission, you've asked us to destroy by not paying your storage fee for the freezer for the next year. Instead of destroying it, would you consider donating it for this particular type of research or other types of research, I guess?" That has a different level of acceptability to some than to say, "Well, you're storing them now, but rather than storing them how about we use them in research?" So I think that if we're going to preserve, if we're going to keep a hierarchy, I would suggest making that distinction.

DR. MIIKE: If I may, Harold?

DR. SHAPIRO: Yes, Larry?

DR. MIIKE: I've thought about the hierarchy because the way in which one disengages in the decision to create stem cells is precisely that. Do we disengage at

the point at which you say to the guardians of the oocytes, or whatever one calls the IVF people, do you want to donate this—do you want to donate your excess embryos for research? That's one level. The other level, which would make, I believe, Eric more comfortable, is to say that once having made a decision to destroy the embryos, then you offer them the alternative of instead of just simply destroying you make them available for research. And so, it would be important about at what level you give them the choice.

DR. SHAPIRO: Okay. Diane and then Steve?

DR. SCOTT-JONES: I agree that it's important for us to think about these issues, not only for ourselves but as we think other people might see them. And it seems that if it's acceptable to use these cells for research, that one can't then close one's eyes to the manner in which the cells are derived. So I think it's important for us to make a statement about that, and I recall when we were doing the report on human cloning, one of the religious scholars who spoke to us made the statement that he would have gotten off the assisted-reproduction train long before it got to human cloning, and so I know that it will open up a lot of questions that people have about the whole enterprise of assisted reproduction. As far as my own view as it's shaping up now, it seems to me that given some sort of oversight it should be acceptable to use the products that are left over from efforts at assisted reproduction. It should be acceptable to derive cells for research purposes given that those entities would be either destroyed or stored for later use. But I think we have to consider those issues. We can't just leave that issue aside and attend to whether the cells themselves can be used. I think we have to consider the implications of how those cells are derived and what led up to having access to those cells.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I haven't fully thought this one out.

DR. SHAPIRO: That's the purpose of this discussion.

MR. HOLTZMAN: But we're proceeding now, as I perceive it, proceeding down a logic chain, which is looking for an example of the transplant, I'm sorry, the fetal transplant paradigm. And say you need to be separating the act that produces the source from then the intention to use the source in certain kinds of ways. I certainly understand that, from a policy as well as a more general perspective, we want to separate the decision to abort from then the use of the fetus. But it starts to lead us in the case of the embryonic cells to a very similar view. And what concerns me is as we go down that path, if I take as my paradigm directed transplantation—forget fetuses

now—if my daughter needs a kidney, I have the right to give her a kidney. If I take that as my paradigm, it is very unclear to me why I do not have the right to donate a sperm and my wife an egg to make a cell line to transplant to my daughter.

DR. CASSELL: You do not have the right to give your life for her.

MR. HOLTZMAN: What?

DR. CASSELL: I mean remember, it's just not how you feel about it. You do not have the right to give your life in order to give your daughter a kidney. You are not allowed to commit suicide to do that.

MR. HOLTZMAN: I recognize that, but I'm just, I didn't say I'd thought this all the way through—

DR. SHAPIRO: Because your kidney is not an organism.

MR. HOLTZMAN: That's my question; I'm asking us to think. By going down a certain kind of justification path, taking the fetus as the paradigm and then applying it to the embryonic cells, we're going to reach that kind of conclusion and I'm not sure—I'm just asking us to think. Is there another paradigm here, and why is one—you said because it's not an organism.

DR. SHAPIRO: Okay. Bernie, and then Diane?

DR. LO: Inevitably, we're going to get dragged into metaphysics here.

MR. HOLTZMAN: That's not metaphysics.

DR. LO: I mean look, in the 1994 NIH Human Embryo Research Panel, one of the issues that the panel grappled with was some sense that the human embryo was deserving of special respect, moreso than other tissue, not necessarily the respect due to a full person in the moral sense but that it was somehow different dealing with an embryo. That was different than dealing with egg and sperm and certainly different than dealing with kidney or other tissues. Now how that plays out, I think, can be controversial. But I guess the distinction that one might make with the transplantation case is that the only considerations are your own well-being and the recipient's—daughter in your case, this would be—and that the sort of moral status of the kidney really doesn't enter into that, whereas there are people who believe to various degrees that the moral status of the embryo makes a big difference.

So I think just as people have their concerns again, there seem to be two types of concerns about using "spare" embryos. One is that somehow the prospect of using this for a benefit to either science or an individual person will tip the balance to decisions to not either store or donate that embryo for implantation into another couple but to use it to donate for research. So those who believe that's an unfortunate decision, any kind of inducement to do that may be problematic, which is why we might want to think about separating the decision to donate for research and the decision to thaw or continue to store the embryo.

And I think it's the other argument that Alex, what you call taint, but to those people who think that is a moral wrong to use an embryo for any other purpose than implantation. It's not the inducement part, it's that there was something wrong in that decision not to implant and if anything comes of that, is complicit in that, you know, in their view of morals.

MR. HOLTZMAN: But Bernie, and maybe it came across that I was making an argument, but I'm not making an argument yet.

DR. LO: I didn't mean that.

MR. HOLTZMAN: All I'm saying, because I'm ultimately familiar with all the arguments and this is not easy stuff, but if you look forward to the time at which in fact autologous transplant using somatic cell nuclear transfer is a real potential, right? Which by definition is going to involve the creation of embryos, all right, and effectively direct the transplant. What I'm asking us to think about is if that's a prospect out there, what is the set of reasoning we're going to use to come to a set of conclusions today, and what is the corner it will or won't paint ourselves into? Now to say, "Well, the science will change and therefore we'll change," you can't change your basic reasoning. Your reasoning has to be consistent with the facts today and the facts tomorrow. That's all I'm asking us to think about: how we're thinking about it.

DR. SHAPIRO: Okay. There are a number of people who want to speak. Diane, you're next.

DR. SCOTT-JONES: My comments are in response to Steve, and maybe Steve didn't mean his comments as strongly as they sounded in the context of this group. But I think we have to maintain a position of respect for people in our country who believe that life begins at the moment of conception and that the entity that then begins through its developmental trajectory has a right to be respected from that point. And you know, I can reflect on how I've taught lifespan development over many, many years now, and years ago in the beginning of that course we taught that the beginning of

life was at the moment of conception with the union of sperm and ovum and that an individual's genetic endowment came from the parents: mother and father. Now we teach about various methods of in vitro fertilization. We've changed very much what we teach about the beginning of life and I would just urge all of us to keep in mind respect for people for whom it's a great emotional issue that the union of sperm and ovum creates a process that's different from ordinary science.

DR. SHAPIRO: Okay. Trish?

PROF. BACKLAR: That's all right. I'm going to let Arturo go first.

DR. BRITO: I think this is critical here. With this second category, in general I don't have any problem with it, okay, with the use of excess oocytes, and I might sound contradictory or hypocritical of what I just said to aborted fetuses. I think the key here is the time, and yes, in the past we have looked at life at the beginning of fertilization, but in the reading I've done and as science has progressed, I'm not sure if that definition hasn't changed at what human life, the beginning of human life truly is—not unlike the United Kingdom, where they've passed allowing research up to 14 days, etc., where now they're really defining life in a different way. Science is defining life in a different way where you become an individual, an individual human being, because before that time you still have the potential to become a twin. You still have the potential to become very different, where the only thing that's important is your genome whereas environment plays a bigger role, etc., later on.

So I think we have to be real careful. Of course we have to consider these collective opinions and consider what's there, but as science has progressed, maybe definitions have changed somewhat. So my understanding—I want to make sure this is right—with excess oocytes and in IVF, they are never beyond, and I just—David, just try to clarify this for me—they're never beyond 14 days or beyond blastocyst stage. So I don't have a problem with that. I would have a problem with doing research where they would take an oocyte, a blastocyst, and try to progress it beyond fourteen days, where then you define someone as an individual.

DR. SHAPIRO: Let me get clear on that.

DR. BRITO: But the point, from what I'm hearing, the timing is a critical issue here for me, personally.

DR. SHAPIRO: No, I understand that.

DR. BRITO: I think for others, not just for me personally, but some of the scientific community.

DR. SHAPIRO: Okay. Trish?

PROF. BACKLAR: So I think one wants to look at this, not simply using the word "individual" but where there is some identity involved. This is where Warnock comes out on this. And that after you get to the—when the primitive streak is evinced and they use the 14-day marker, which isn't precise, that was news because after that identity, there may be an individual's identity may be involved. The other thing that the Warnock committee made quite clear is that this is a process, not an event.

DR. CASSELL: Those are my favorite words.

PROF. BACKLAR: And so what Diane was talking about before, trying to identify an event that occurred as opposed to a process, because the germ cells are human, so it's not as though they are not human and human stuff was not there before they got together. And I think that's important for us to be able to spell out.

DR. SHAPIRO: Incidentally, I think everybody has at their place something that was passed out just before lunch, courtesy of Trish, who Xeroxed an article she wanted, that describes the reasoning we had for that conclusion. I don't know what the date of that article was. It was a little while ago now.

PROF. BACKLAR: No, actually it was published in 1980, believe it or not. But its—

DR. SHAPIRO: Thank you. Let me see who I've got on the list here. Kathi?

DR. HANNA: I just wanted to add that some of you probably have seen the e-mail exchange that Alex and I had over the weekend, but for those who haven't caught up with their e-mail yet, I'm in the process of collecting some data and talking to IVF facilities. I think we need to learn a little bit about what they do if we're going to really look carefully at this issue of whether in fact these resources should be available or not. Just for the benefit of those who didn't see the e-mail, I've talked now to three IVF facilities. They all have very similar practices in terms of when the issue is even raised about donating an excess cryopreserved embryo to research purposes: it is generally not raised at all until the storage issue becomes an issue. Either they've successfully achieved pregnancy or they've given up or for whatever reason and they do pay a monthly fee to maintain the embryos in storage, and so at that point it becomes an issue.

Not until then is it raised. And interestingly, I think almost consistently now among the, across the three that I've talked to, most couples do not elect to donate to research—probably only around 10 to 15 percent, and the IVF providers told me that that doesn't surprise them at all because of the intense intentions of the individuals who are in that facility. And so research is not something that they are there to work toward, so when they privately, with private funds, form embryos for their own research purposes, they almost always use—or when they need to have embryos for research purposes they almost always use-unrelated sources of donor gametes who have agreed to that use of their gametes but they don't know each other, because they feel that there is a real distinction between the intent of people who give gametes or embryos for different purposes. So I think we probably just need to get more information from the people, from the providers, about what their practices are, and we'll just keep trying to do that.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, there we have another category. We've just gotten another category of embryo, and those are the embryos that are created from the gametes, from random gametes.

PROF. CAPRON: For research purposes.

DR. CASSELL: For research purposes.

PROF. BACKLAR: That's another category.

DR. CASSELL: But that's a different, that's another category. Steve, I think—

DR. SHAPIRO: I think that, if I could suggest, I think that comes up under the next step that Larry went to, that is the creation of embryos for research purposes.

DR. CASSELL: Right.

DR. SHAPIRO: We have to get to that but we're not at that stage yet and that comes up in that category, I think. Let me see who I've got on the list here. I know David—

DR. CASSELL: Excuse me. I was actually going to comment on Steve's quandary that he put forward. First of all, it is metaphysics because, I mean, we're

talking about definitions like identity and so forth, which are otherwise—[Ludwig] Wittgenstein, you know, your idol, he'd think it was metaphysics. But Steve, the issue isn't so much if you can give a kidney, why can't you give this, you and your wife make this donation. The issue for us is, How is it seen? We are not speaking for ourselves alone. We are trying to speak in a way that will be found acceptable enough so that the research can proceed and what other people, not only us, consider human values are protected. So from my point of view, I have no objection to you doing what you wanted to do, but as a generalizable proposition, can it be generalized is the issue. Should we generalize what you think you can do? That's really the issue.

MR. HOLTZMAN: I was using metaphors myself speaking. I could have phrased it generally, which is, Should we conceive of this act as one where individuals have a choice in the matter?

DR. CASSELL: Well, I wasn't thinking about you individually either.

MR. HOLTZMAN: Right. And all I'm making is the point that if it does move it on to the third category, will we all agree positively about the second category? That is, excess embryos may be used and we start to articulate the conditions under which they may be used and we put in a specification, for example, that there may not be directed use of them—which is where it's going to come out, right?

DR. CASSELL: Directed use.

MR. HOLTZMAN: Right? That's where we will logically come out on this paradigm following what comes from the fetuses.

DR. MIIKE: Okay, we're not saying anything about if they want to do it in private. We're talking about—

DR. CASSELL: We're talking about—

DR. SHAPIRO: Let's play it out. We will get back to that. We will get back to that. All right. David, you had the floor.

DR. COX: I want to play it out, but I'd like to say some ground rules first before it's played out. It's interesting, and I think this is really a very good and interesting discussion, but I'd like to make a couple points about it. First of all, as was stated in previous testimony, it's great what each of us thinks about when life starts. But what we individually think about when life starts doesn't matter, because basically there's no scientific—however much we may wish this is the case—there is no scientific

data that is going to answer that question. So I'd like to put that on the table and in as strong terms as I can. It is not a scientific question now, despite the fact that people try to make it such. So second, then, given that's the case, given that people have very different views about when life starts, that we have to take that as a given. So with that as a given, that's going to inform people's feelings about using spare embryos.

So what are the key points that would be a common ground between people who have different views about when life starts that would make it acceptable or even—I won't even use the word "acceptable" but open for discussion what would allow spare embryos to be used. What are the conditions?

Now we just went through, I think Alex gave us a really articulate sort of exposé of the logic with respect to using fetuses, which is this distinction between those that were induced and those that were spontaneous and that there was a consideration of certain aspects for people that really had, that made that distinction, right? And those considerations were brought into play in terms of making the rules to allow fetuses to be used. I think the same type of logic has to be laid out in the context of the spare embryos, but in order to do that I need to hear what are the key sticking points for people—not the issue of when life begins but in terms of, are there other values that affect the things that could be done with these? The fact that the embryos are going to be destroyed anyway.

So what are the points to be considered that would make the use of such embryos, if any points, acceptable to the largest number of people? I think that's what Steve means by playing this out, but it doesn't have anything to do with when life starts and it has to do with a variety of these other issues. Now, we're going to get there on this issue, but I haven't heard us get there yet.

DR. SHAPIRO: Okay. I have on my list now Alex and then Bernie.

PROF. CAPRON: I want to follow along part of this last discussion, which is really about our function, and it seems to me that our function as a body is on the one hand not just to say what the law says—the general counsel's office does that—but more to say, and this was the question Arturo was asking earlier, what the moral view on something is. And there isn't going to be, as David just suggested vis-à-vis when life begins, one moral view that appeals to everyone.

I think our aim as a public Commission should try to be a statement of what seems a reasonable moral view about which there is a very broad consensus and then for each of us coming to that conclusion would be limited by and guided by our own moral compass, so that some of us might say, "I understand that to be a reasonable

moral view and a view that's very widely held. I personally don't agree with it and here are my reasons," that I think we may recognize on this topic when we come to that kind of a point. On the question of what is the broad moral view, it seems to me that the data that Cathy had in her e-mail, to which she just referred, tells us something. Now it may be that these people are not totally representative of everybody in the population, because these are people for whom reproduction and the achievement of fertilization in vitro is a triumph, and if they have then been successful in producing a child for themselves, they may be very committed to the notion that that is a triumph that was hard-won and if they can aid other people in that process. But it certainly does represent at least some view on their part that there is something more special about those fertilized eggs than there is about their kidney, and I think that that is something we can build into our thinking that's a reaffirmation of that view.

Two specific conclusions. One is that those views may change. That proportion may change as the value of stem cell research becomes better known to the public. The fact that people are not willing to donate for research should be taken in the context—and if we had someone here from the Annenberg School at USC [University of Southern California] or the Annenberg School at Penn [University of Pennsylvania] I bet they could back this up with real data—that the average person, when you say "research," thinks of Dr. Frankenstein or somebody else running around with dry ice. [Laughter.] We take that to be one of the most exalted stations there is in the world in pursuit of knowledge but that is not what most people think and, ergo, being told that you have a choice between giving it for other couples or even discarding it or giving it into the hands of these people who are going to do all sorts of strange things may make that third alternative less attractive—and only 10 percent like it now.

If the newspapers in the next few years are full of the wondrous things that science is doing for human health with stem cells, I bet that will change. It doesn't mean people respect the embryo less, it's just that they see that in addition to creating another child they could be giving life to many people by the creation of a stem cell line, and I think that we should recognize that. That said, I also think it's important that we recognize that the kinds of restrictions that exist for the fetal thing here are if anything more necessary here because of the fact that no one gets paid for getting pregnant. I mean, the pregnancy that leads to the abortion is usually an unwanted and unexpected event and so that the fact that an abortion follows it, people aren't paid then to abort, I suppose for the most part. Maybe sometimes a woman is induced by a man who doesn't want to father a child to have an abortion, but that's not usually part of the picture. But here, young women, and to a lesser extent young men, just because it's an easier process and pays less, are induced to give eggs, and we have to be aware that the line between "made for research purposes" and "made for fertility purposes" could easily become blurred, and sometimes made for fertility purposes" means my sperm will

be used with a "donor" egg, which is really a "vendor" egg, and that will be a fetus, which if it succeeds will be implanted in my wife and we'll have a child. Now if we have extra ones of those left over, there's been payment made to get to that point. So I think that the notion that we have to be very clear on is that that payment process cannot at the very beginning be to young women to give eggs for people who are basically researchers. But with that said, I don't see that we need much modification of present law, which allows, which would allow by analogy—it ought to be made by analogy—we do need modification in present law. Strike that. We need modification of law to bring it in line with the start of fetuses, the start of the embryos and with the start of fetuses.

DR. SHAPIRO: Bernie?

DR. LO: Let me try and continue this very important and very difficult line of thought. In terms of why we should be concerned about allowing so-called "spare" embryos to be used for ES [embryonic stem] research, there are a number of decisions that get made in the course of IVF about the number of oocytes that are harvested and the number that are implanted and so forth. And it seems to me that there could well be a number of people in the society who believe that IVF is permissible for the purposes of overcoming infertility. They don't have the idea that you need to have procreation through, you know, old-fashioned sex, but they do have very special views about the embryo and believe that if you're going to use IVF, you should create the minimal number possible to get the job done, and if all went well you would create only the number you needed to have the number of children you needed so that this whole dilemma of what to do with the spare embryos would be avoided.

To the extent that, you know, at least Kathi's preliminary data suggested, this is a very difficult decision of what we would do with the spare embryos. It's not just the decision at the time of your—you've either failed or succeeded and do you want to keep paying this monthly charge—but it really goes back to much earlier decisions as to how many oocytes are harvested, what grade embryos are stored and so forth, and to an extent this availability of the donation for ES research sort of feeds back into all those decisions. One could easily, it seems to me, have concerns that by introducing this possibility at various points in the whole series of decisions that get made at IVF treatment that you're making it easier for people to do what in total is creating more embryos than are in fact needed for reproductive purposes.That's the clinic, I mean; you separate out opponents. There are some people who just think that the whole idea of the enterprise is wrong and anything that—that it's morally wrong to try to create children outside of sexual procreation. There are other people who don't accept that but who do have qualms about what to do with so-called spare embryos, and to the extent that

there's some sort of possibility that these policies are creating more spare embryos, then it seems to me that it is similar to the abortion analogy.

To go back to a comment Steve made a couple of cycles ago and that I think is very important, I mean, I think very rightly challenges us to make sure we are consistent in the way we look at this and anticipate that there's going to be another issue coming up very soon having to do with somatic cell nuclear transfer and how can we think about that in a way that's consistent? I think that on the one hand that's true, and on the other hand I think if we try and solve everything all at once and bite off too much we also run into trouble. So I think we need to keep Steve's admonition out there, but I think we need to keep an open mind about it as well.

DR. SHAPIRO: Larry?

DR. MIIKE: You know, a couple of one-liners and then in answer to trying to define when life begins and what is a human—I don't think that's a dead-end path we shouldn't go down. Number one, on the 10 percent, I think that's a good number. Why is 10 percent a bad number?

PROF. CAPRON: It's not.

DR. MIIKE: The implication is that it's *only* 10 percent. Well, 10 percent is pretty good. It's more than enough.

DR. SHAPIRO: That's the one-liner, right?

PROF. CAPRON: Do we have a denominator, or whatever the word is?

DR. CASSELL: It's a lot. Five percent would be a lot.

DR. HANNA: Tens of thousands.

PROF. CAPRON: Ten thousand or ten ten—a hundred thousand?

DR. MIIKE: Alex, I have the floor so let me finish. I'll never get my one-liners over. On Steve's point, I think it goes back to one of the issues—around the Embryo Panel it was, "Oh, this stem cell research is so theoretical, there's no balancing here." Now there is. But your hypothesis about intentionally creating an embryo in order to harvest a kidney is too theoretical, so the issue is still, at this point, is now our research is more concrete and you can be more specific about the real possibilities of that. That's the stage we're at. Maybe one day will come that that question has to be

asked and then we'll have to look at it again. I think that's what Bernie means where we don't want to bite off more than we can chew.

But the main thing I wanted to say was that if we try to hang our hats on when life begins, we'll never get anywhere. My analogy is this way in terms of the spare embryos. Those spare embryos are destined to die. The people who have control over them are trying to do something good with that. Why is there a question about that with those embryos, those few-celled embryos, when we universally laud a British family whose child accidentally or intentionally gets murdered on the freeway and they give the heart and the eyes and the kidneys and the liver to help other people? If we see that when you have a live, a real child who had a personality, who everybody thought was a wonderful child and the parents are praised for letting that child's body parts be used in other areas—why do people have so much trouble with an embryo that's only a cell in which people debate about whether it's a human being or not?

PROF. CAPRON: The researcher didn't drive the car intentionally into the car in which the child existed to create the body parts. The embryo is *alive* when it goes through the hands of the researcher.

DR. MIIKE: No, no, no—but what I'm saying is that the embryo is destined to die because we are talking about spare embryos that were going to be discarded in the first place.

DR. SHAPIRO: I've got a list here, so let's just go. Trish, you're next.

PROF. BACKLAR: Well, I think that Steve actually brings up something that's extremely important and has to be looked at, and that is the compelling individual interest. And we already have an example of people who couldn't do this, but could—in fact creates a child so that they could save their daughter who needed a bone marrow transplant. And we looked at that ethically all over this country, certainly looked at that and examined it and one did understand the compelling interest that these people had, whether one praised this or not. I see that this will, when this research moves along, it's going to be individuals who will want to make it come about for reasons that they have a compelling interest in themselves. And that is something that we need to take into account when we're writing this up. It isn't simply the collections we're looking at; it's those individuals that are going to move the collections.

DR. SHAPIRO: Diane, then Steve.

DR. SCOTT-JONES: Again, I'm still trying to think this through and try to imagine the point of view of people in the public. It seems to me that if there's much

more public discussion of what should happen with the products that we make from efforts at assisted reproduction, that perhaps the sentiment might be that research should be directed toward making that process more efficient so that there aren't so many attempts that result in something that many people would say could possibly become a child. Why not direct the research efforts toward improving the efficiency of that process so there wouldn't be so many entities that will then be destroyed later? I'm just not sure that everyone will think about this in terms of the science of it, just because these are such emotionally charged issues for most people. And I don't want us to downplay the importance of emotional reactions to conception, whether conception in vitro or in vivo conception.

DR. SHAPIRO: Let me say something about this. I don't think there's anybody on the Commission who doesn't have a great deal of empathy for the issues you talked about both with respect to how important an event this is regardless of how this comes about for individuals and the importance of respect in that. Or for the fact that we have to be empathetic to quite different opinions, whatever our opinions are. There are a lot of opinions out there. I should say there are a lot of opinions on both sides and all sides of this question, so when we refer to public opinion I think we need to be careful. It's not one-sided. They all aren't—we're not sitting here on one side with a few other researchers and everybody else is on the other side. There are a lot of people, thoughtful people on quite a few different sides of this, and we do need to have respect for them and we should in terms of our language and in terms of how we think about it encourage everyone who will ever read our report to have empathy and understanding for alternative points of view. Nevertheless, one has to come to sometimes difficult decisions recognizing that it's not going to please everyone but having no loss of respect for those whom it may not please. And so I think we're united on that issue. I'm sort of talking to the choir here. I just wanted to make sure or stipulate that I don't think there's anyone on the Commission who would disagree with something at that general level, and that would have to be reflected in the language we use and the care we use in putting forth views that we understand will not be accepted totally, and we don't want to reject those people and don't want to denigrate in any way their points of view. Nevertheless, we'll have to come to some public policy recommendations. Steve, you're next.

MR. HOLTZMAN: Just to clarify a couple of things, and I don't pretend to be completely clear on what I'm trying to think at this point because I think this is difficult stuff. I don't think kidneys and embryos are the same or morally the same. I think there is a role of individual rights but I was not making an individual rights argument, okay? I think one has to go beyond where the technology is today, Larry, but it's more in terms not of the balancing of interests but in the conceptualizing of your position. So what I guess I'm saying is I don't think it's a metaphysical issue of what an

embryo is. An embryo is what it's always been—namely, something that given under normal circumstances, ordinary circumstances, goes on to become a kid.

What's changed is what is within the realm of the ordinary and normal in our experience now. The profound lesson to me of Dolly was what's normal. What's very normally, ordinarily, within the next few years within the realm of what could be made into a child is changing profoundly. And when you take your mind out to that fact, since we're not going to treat every cell as an embryo, all right, how are we going to treat embryos in a petri dish? Are we going to think of them as fetuses as a paradigm or are we going to think about them as these cells? And when I say think about them I'm not talking metaphysics, I'm talking about what are the social institutions we're going to adopt which will define the kind of people we are? That's what this Commission is asked to reflect about. That's what I'm trying to get at. Before we jump down one path of reasoning, we need to understand where this society—where we are today in terms of what is within the realm of the normal and potentially ordinary. That's what I'm trying to—

DR. SHAPIRO: What is the—normal, and what was the last words you said?

MR. HOLTZMAN: Potentially ordinary.

DR. SHAPIRO: Potentially ordinary. Well, those are important comments and they, I guess in my own mind, relate to a question I asked, I believe it was Dr. Varmus at our last meeting, that is when he had the cell lineage map of—what worm? Someone could tell me which one it was.

DR. HANNA: *C. elegans.*

DR. SHAPIRO: *C. elegans* out there and I asked the question: Do you think it's plausible shortly that we'll be able to move up and down this thing at will, in which Dolly then becomes just one little special case, not even so important if you actually can move up and down it. And I took his answer to mean that he believes, yes. How long? Nobody knows how long that's going to be but that's where we seem to be heading. So what would be normal in the sense that you've just talked about it or expect it or whatever is a change indeed of a kind that's in an extraordinarily fundamental way. And whether that's something that we need to reflect, and if so how, in what we're dealing with here is a hard issue to resolve. Let's see. Alex?

PROF. CAPRON: You've injected something here, which maybe we need to explore further. I did not understand him to say when we asked the question of

Gearhart we got an answer—no, excuse me, I think it was Thomson that suggested that the movement gets to a point between totipotentiality and pluripotentiality that is very important, and it's important under the definitions in the existing statute of what an organism is and that statute as it is interpreted by HHS. It's one thing to move back up the stem cell line where you can then move down anyplace else in the organism and one cell becomes another kind of cell. It could rise to another cell. The question of whether that final leap back to embryohood, as it were, is possible without beginning with an egg is really the crucial issue because if you can't go back that far, if you cannot generate an entire being, then there is a difference between Dolly and the egg modifying the transfer.

DR. SHAPIRO: That's right. You can only go back to pluripotent if that's the case.

PROF. CAPRON: And I have a sense that that would be the kind of issue that I would love to leave to a time when there's some better reason to speculate about the science there and to a body that was particularly looking at stem cell work, to an ethics advisory board on stem cells advising the director of the NIH about whether the time had come, in effect, to persuade the American public that something had to happen. That is to say, if we get to the point where we see we can't make that leap and there's great therapeutic value of having autologous transplants so the only way to get them is by creating embryos, then that board would deliberate over that.

If I can respond to the point that Bernie raised, I'm very unhappy with that point because he has pointed out that the issue is much more difficult than I wish it were. That is to say, in a certain way, just as we disposed rather readily of the fetal thing, I think we were very close to having consensus that what really needs to be done here is the removal of the second restriction in the present law that says that none of the funds may be spent for research in which an embryo or embryos are destroyed, etc., etc. And to recognize that funds could be spent for research on cells coming from an embryo that has been discarded or destroyed by someone and that would keep the same definition of organism and recognize that an embryo is that, that organism that has the potential to become a full human being. But as Bernie then says to us, it's actually much more complicated than that if you want to have a morally defensible rule because the number of such embryos that will be created in the process of science is highly manipulable—much more manipulable than the number of full-blown pregnancies probably—by scientists.

I want to add another difficulty of the same sort. Kathi said that at the moment IVF clinics don't usually cross this bridge at an early point. I'm trying to think of what happens when a couple comes in and in light of all the messy cases that have existed in the past where people didn't spell out their wishes in advance, they sit down

with someone from the IVF clinic who asks them, "What do you want to have done with these embryos, or these fertilized eggs or whatever, assuming that we're able to create them, if you die—if both of you die, if you divorce, if you become not divorced but unable to agree about the plan to create a pregnancy, or you're unable to pay our fees and we have embryos that we're not willing at our expense to keep in our deep freeze? What do you want to do with the embryos?" There are several choices, it would seem to me, that people would be told: "We can discard them; you can donate them for other couples wishing to become pregnant, or you can donate them for research." Now if what we are saying is it is important that issue be raised with couples so that we don't have the kind of messes that have come up in a number of cases, but that that third choice is illegitimate to present at that moment. I mean, it's sort of like, "Well, we could just harvest six eggs and if we get those all fertilized, that will probably be enough to give you a couple of legitimate rounds and the chances are 50–50 out of that you'll have—or we could do 12 eggs, or we could do 20, or how many you could get through superovulation. If we do the latter, you should recognize, of course, that we're very much more likely to have ones left over, if you're lucky. I mean, at what point do these issues come up either in the mind of the IVF clinic director who has a friend down the road who's doing stem cell research or in the minds of the couples being presented with it? And so I think I agree with Bernie, and I'm trying to add yet another complication of what is said and at what point the choices may legitimately be raised. I don't think we can duck those issues. I think we ought to agree in principle and I've heard a large consensus—I think—around here that the use of existing embryos *is* legitimate and that the present restrictions in clause 2 of section 511A in the NIH rider ought to be removed as to stem cell research. But then the devil is in the details here.

DR. SHAPIRO: Well, let's just test that proposition, all of us understanding that there are details that have to be filled in before any of us is going to be satisfied that we've got this right here, that we have anything close to a recommendation. But I won't restate it since Alex has just stated it. Is that where people feel comfortable right now?

DR. MIIKE: I think that can be stated in two parts. One is that it's permissible to use stem cells in research from these sources with guidelines that say what harvesting techniques and permissions, and the other one is to say that they can directly do research, or since we're on stem cells, directly derive stem cells from those sources, just like in the embryo cell. So there would be two parts. One is just the permissible use once derived and in deriving them also.

DR. SHAPIRO: I'm sorry, Larry. I'm not fully understanding.

PROF. CAPRON: Well, the first one is already legitimate according to the NIH, so we would be passing judgment on whether their reading of the legitimacy is—

DR. MIIKE: Even if we stayed with that—

PROF. CAPRON: I'm not arguing with you. I'm just saying that that's the one that Varmus has already said, or Harriet Raab has already said.

DR. MIIKE: That's right, and then we had both agreed that, but they need restrictions and guidelines sort of parallel to fetal tissues.

PROF. CAPRON: Yeah.

DR. SHAPIRO: Okay. So for us, then, as I understand where people are—as Alex said, the devil's in the details—the question is, How do we formulate those details in a way that we feel comfortable with? David?

DR. COX: I agree with that, although I did hear your admonition about when there's more science we deal with whether a cell can turn into a human being or not, and I would just say for me personally it is going to be quite a long time before we take a stem cell and by itself, without anything else—without an egg, without any other blastocyst—turn it into a human being. And that's important to me because it makes quite a distance between a stem cell and an embryo, when I think about that. So that's a personal opinion and a personal view, but I bring it up because it makes the decision easier for me, that chasm. And for other people, if it really is very close to the cell being the same thing as an embryo, I think if that were the case for me it wouldn't be such an easy decision. So again, science isn't in the position to answer this question, but I think it's misleading to imply that it's just right around the corner that we're going to take a cell and turn it into a human being.

DR. SHAPIRO: Let me make a suggestion. Why don't we take a five- or ten-minute break, and then we do have Dr. Blumenthal at 4 o'clock and I want to stick to that timing in respect to his schedule. But I suggest that when we come back we go on for the moment to see what the discussion will generate on the third category here, which is the more complicated and more difficult one in some sense, but I think we should get an initial discussion of that on the table. So let's try to get back at least no later than 10 after 3. Take a short break.

DR. SHAPIRO: Okay. Let's continue our discussion. Just so that everybody knows, and I'll introduce him more formally shortly, but Dr. Blumenthal,

who's joining us today, is back there. Thank you very much for coming. I've promised Dr. Blumenthal that we will turn to his testimony precisely at 4 regardless of where we are in mid-sentence on some of these issues.

So let's proceed. We have really gone through two steps of the hierarchy that was suggested to us and I think outlined a number of interesting issues. I think we've gotten some idea about what we agree on regarding the human stem cell issue, at least as it impacts—if its source is fetal tissue and also so-called "excess" embryos. And we'll have to, of course, return to those issues, but I think we've gotten enough to get started on this and discuss in particular the guidelines and/or regulations that might surround the research use of human embryonic stem cells in the case where the source is excess or about-to-be-discarded embryos.

But there's also the third issue, the third and fourth issue that Larry outlined originally. One had to do with the thought right now that we sort of are reaching an area of conclusion in those areas—what do we think about the creation of embryos for research use—and then we'll get—I don't know if we'll get to it this afternoon, but then there's the question of how somatic cell nuclear transfer and the creation of embryos in that venue, that type of technology, comes to bear. But the broader issue here is the creation of embryos for research purposes. I believe, Larry, that's the third of yours.

DR. COX: Do you want to treat those separately, so the somatic cell nuclear transfer we'll treat as a fourth thing?

DR. SHAPIRO: Well, we don't have to treat it, it's really one way to create it; it's a subcategory. And I think in the three-quarters of an hour we have left this afternoon for this subject we could speak to either of those. It's just a question of how we feel.

I'm trying to now paraphrase what Larry's own opinion was as opposed to what our opinion might be. I think Larry said that on the ethical front this did not for himself, as a personal issue, present any problems, but it presented very considerable problems as a matter of public policy whether Federal funds should be used for these purposes, that is, the creation of embryos, for reasons I won't try to repeat. But that was for the use of Federal funds. And he had some observations on public versus private. We'll hear more about that, I'm sure, at 4 o'clock.

So why don't we see what observations anyone might have on that third category, which is the creation of embryos for research purposes? David?

DR. COX: For myself, I'm pretty clear on this, at least in terms of what the operating principles are. The first point is that there are already lots of embryos, that is, embryos that are presently being discarded, so there has to be a real compelling reason to make more. So that's point number one.

Point number two that really again goes against, and I think is a real potential harm in making embryos, is getting the oocytes from the women in order to do it. Because that is a nontrivial procedure for the women and it is actually a real physical risk of physical harm in many situations. So that's on the negative side.

So what could be a compelling reason then to even create these embryos? Also on the negative side, the third thing on the negative side is the strong public opinion of many individuals that this isn't right, to create embryos solely for research purposes.

On the other side for me, though, comes the potential out of somatic cell nuclear transfer, because that's the new thing that's happened: the possibility about being able then to make a cell line that would have all sorts of potential for particular individuals. I don't know of any other way to find out about that research without creating such somatic cell nuclear transfers in humans.

So despite how much I dislike the potential harm to women in terms of getting the oocytes, and despite what I say about there being already plenty of embryos that are made that could be used to study for the development, we don't have to make new ones, it's that latter reason and the new potentiality from that that makes me consider the possibility of doing this even despite the political downside that Larry's talking about.

So those are the considerations. And then the question is what you end up with; the final answer is how you weigh those considerations. But to me, I'd just like to say that without the possibilities of somatic cell nuclear transfer and what could come from that, I wouldn't even consider making new embryos for research purposes.

DR. SHAPIRO: Thank you. Alex?

PROF. CAPRON: Well, on the possibility that being out of the room for a few moments for those comments I've missed their entire point, it seems to me that the situation when one talks about autologous transplants is something where one would first want to know whether it's possible to get stem cells in the directed way to grow the tissues that you want to grow, and that these tissues once grown are useful for transplantation. And the data from such experiments really ought to be in hand before

one would say that it is then justified to say, "Now we have to be able to do it without the problems of rejection that may attend nonautologous tissue."

Furthermore, the research that might be going on during that same period, either to turn back the clock on differentiated stem cells and make them go back to pluripotentiality and then redifferentiate into the desired tissue, or the research that Larry was mentioning to remove the antigens from the cell surface and make universal donors or something, all indicates to me that what you're talking about as a justification for creating embryos for research purposes is something that is not urgently needed, and where the very clinical justification that you would rely on is in part dependent on research that hasn't yet been done.

And so that's why I suggested in my first comment that what we would urge the director to do is to broaden the advisory committee he's talking about and leave to them an evaluation of whether, in light of whatever developments come out through the kinds of research I just mentioned, the justification is now present to ask for a lifting of the ban on the creation of human embryos for stem cell purposes, stem cell transplant, autologous transplant purposes. And I think that's premature and I think it adds an unnecessary controversy to our report, because to be a really strong justification it ought to be more concrete and the reality of the benefit ought to be more evident, more palpable than it is today. So I would say we can discuss that.

I am not in favor of changing the rule on the creation of embryos with public funds. I might someday be in favor of it if I were sitting on that panel if the benefits were shown to be attainable through other research that had already been done to show the predicate.

DR. COX: And your argument is that the research that would have to come first is demonstrating that you could actually make the cell type and/or create the reagent that could be used to begin with.

PROF. CAPRON: Yes.

DR. COX: I will tell you, Alex, that as of this moment there's evidence that one could do that in the context of blood, of skin, and of bladder; there's evidence that you can do that. So that I take your argument, but you will get people that will testify before this Commission that will say, that will provide you with evidence that we're there now.

So I think that using that. I understand these arguments very well, because it makes for a nice, logical way of not having to confront the issue of making

new embryos and dealing with the embryo per se. But it ain't going to work because, unfortunately, there's science there right now that makes that argument not such a nice, logical argument, although I share your identical sentiments with respect to getting into this.

PROF. CAPRON: Well, it may be that that evidence is so convincing now that as to those lines of research the argument can be made. There are two other points that still need to be met. If you say there are strong objections from enough people that we ought not to take that step lightly, the necessity of doing it that way because other ways don't work and you save lives is the kind of thing that could move some people who take that position over into an, "All right, I draw an exception because human life would be saved." And although it's something of an affront, it's not an affront; it's more of an affront when it's just done for general research than when it's done this way.

The necessity argument depends upon showing that there isn't another feasible way. If there were no indication that there were other feasible ways, I would think that you would be able to answer, "Well, there doesn't seem to be any." There are ways that have now been suggested, several by Harold Varmus, repeated by Larry, making universal donors, removing the antigenic qualities. The other is the Italian research, the turning back of the neural stem cells into blood stem cells. Either of those ways avoid this problem.

And until those are answered, even if there is the feasibility, which is one question I was raising as to kidneys and heart tissue and so forth, even if there is the feasibility you still have the necessity argument. So I don't think that's been met. And so I would still be in favor of the same outcome, although we may have to note that we're closer to having the feasibility on the blood and bladder. I know they've constructed these artificial bladders with the two kinds of endothelial cells or whatever they are, etc.

DR. COX: I just don't think it's going to—it's not going to test—it's a scientific argument.

PROF. CAPRON: This is not permanent. The whole reason for talking about this as a process and having an organized process is I do not see the feasibility issue as a permanent postponement; I see it as a temporary one. And you're telling me as to certain categories the time is extremely brief before someone would be able to demonstrate that they can, in a controlled fashion, do this with excess embryos and they should now be able to do it on an autologous basis. And I would still say, Isn't there any

other way to get there? And the answer is, Well, maybe there is. So let's explore that first is my answer then.

DR. SHAPIRO: Okay. Eric?

DR. CASSELL: My own feeling about it is that this is an interesting thing to explore and I don't have any personal great reservations about it. But I do understand that this is an area where there are great reservations. And there's a Whitehead saying, talking about science, that there's a universal human trait: to take a successful methodology and turn it into a dogma. And in point of fact, I'm interested to see how long the prohibition against this lasts in the face of scientific progress, transplantable tissues, and so forth. Because that's really the issue, that's really what the question is.

At the present time the prohibition is very strong, and I, for one, do not think that we ought to suggest changing that. Let that, either by other bodies or other things, let that cook and see what happens to it in the face of progress.

DR. SHAPIRO: Bernie?

DR. LO: Yes, I come down to the same conclusion. I just might want to state how I get there a bit differently. I think that given the grave concerns that some people in society have against this method of producing stem cells that it should be in a sense a last resort. And to Alex's ideas about necessity, showing feasibility, I would add appropriate animal studies have to be done first.

So you really want to sort of build the ground, and it shouldn't be just a couple of scientists saying we think the time is right but really a consensus in the scientific community that the time is due. But I think that if we stated it as saying that this is the area where there are the most moral concerns and we respect those views strongly enough that we want to be particularly cautious here until we're absolutely convinced that the scientific community as well as ethics and policy reviewers think that a major change is appropriate.

DR. SHAPIRO: Larry:

DR. MIIKE: Well, I've already stated my views, but just to be consistent in the other two areas, we should also consider two parts: whether we would really support creating an embryo for research purposes, but also, once that's done, whether we would really support using stem cells derived from that for Federal funding. And for the reasons that we expressed in the last two, they don't apply to this area. They are

contradictory to that because we would try to separate the creation from the derivation and use.

So as I say, just to be consistent we should do that analysis. But I would come down and say no, on either.

DR. SHAPIRO: Let me ask a question that I'm trying to get my own mind straightened out on and I'm not straightened out on yet. That is, what we're talking about here is what the Federal Government does or sponsors. We're not talking about what people can do if they feel like it. What we're talking about is what the Federal Government is doing. That's what we're focusing on. And I understand the notion that you might have a different measure for what the Federal Government does because it implicates all kinds of people than you would have for whatever an individual does. So that's presumably the basis of the current distinction we make between publicly funded work in these areas and privately funded work in these areas.

It is interesting for me to note, however, that there are all kinds of issues on which there are disagreements in the public, which we don't pay the slightest attention to.

DR. COX: That's right.

DR. SHAPIRO: For example, some people are against war, which is easily as destructive of human life as anything we're talking about here, and we pay absolutely no attention to those views. We don't consider it legitimate to pay attention to those views. You buy a package of stuff and that's what you get, and you have to pay your taxes whether you are a pacifist or not, for the most part. And there are lots of other examples people I'm sure could give.

In this area, however, for historical and other reasons, we do pay a lot of attention to it. And I'm just trying to ask Commissioners if they have thought that issue out more carefully than I have, and how therefore the conversation is, for reasons I fully understand, is very, I would say solicitous of these views, and wants to accommodate them to the greatest extent possible. I understand that very well. But it is very striking to me that in these areas that we have, by the nature of who we are, focused on, we take this as just sort of reasonable whereas in no other area do we seem to take this as so reasonable. Eric?

DR. CASSELL: It's extremely interesting because you take the example of war, there was a time not that long ago in this country where it took care of a President's next term and totally changed the dynamics of this society because of the

largeness of the protest. At the present time, the largeness of the protest also stands in the way of other things happening. So it isn't simply that we take this idea of protest in mind, we take the actuality of it and the nature of its impact on the Government and on individual communities. So I don't think it's quite the case that there aren't other examples for that. At this time, this is the one, and we know as a Commission that we step too far into that and it will wipe us out as a Commission.

DR. SHAPIRO: David?

DR. COX: Harold, in reflecting on this for myself, I think that there's no question that this is a situation that in part defines what the U.S. is right now. But in these issues, trying to look at them on their own principles, what I like to do is go to other countries and see what other countries do about this. And in that regard I find what England is doing extremely interesting, because it's the antithesis of what we're doing. They have absolutely no problem in terms of making this distinction. They also have a very different way of regulating assisted reproduction, too. So I'm not going to say that we should be looking at England for what we should do in the U.S., but it shows to me that this isn't a basic ethical principle per se, but it is very socially–culturally driven.

DR. SHAPIRO: I understand that. But let me ask, maybe this is an example, maybe it's not an example, I'm not sure. We've just been through in an initial sort of way the first two steps and seen roughly where we stand, and that is all fluid so I don't mean to tie anyone down, and we said that public funding of the use of cell lines developed from a couple of sources seems okay to us. And now we're talking about whether public funding of the creation of embryos, a whole different matter, I understand, I accept it as a different matter.

What would be our response to the issue of what I might call private creation and public use? That is, we've talked about—well, it's pretty obvious what we've talked about. How would we feel about that? Where would that come in your thinking? I should turn over here—here are the people that are dealing with this.

PROF. CAPRON: Well, I think we're on the same wavelength, that the issue I'd just written down here to comment on is exactly that. We've been spending so much time on the creation side, and we've said it's okay created from fetal tissue, it's okay created from excess embryos, we're not ready to deal with saying it's okay from embryos created for this purpose. But Dr. Varmus has already said, and we haven't really spent any time thinking about, well, it's okay to fund the use of stem cells once they're created. And obviously, as to the first two categories, there ought to be no problem. How in the world will people using stem cells five years from now know

where those stem cells came from, and are there going to be okay sources of stem cells and ones that cannot be used for Federal purposes?

It strikes me as very similar to the problem that the California Supreme Court faced in the Moore case, where they ended up saying that they were not going to take a property ownership view toward the cells in part because they couldn't imagine what this would mean for future researchers using some cell line derived from that; would they be in some relationship with Mr. Moore, and how were they to know where those cells came from? And instead they took sort of a doctor–patient, informed consent, full disclosure view.

I think this is a real problem here. I'd like to know from the scientists whether you think it is reasonable that the derivation of cell lines will always be so well labeled that there could be, literally, like a kosher symbol or something that goes on those that come from fetal, those that come from the excess, and those that come from created research embryos, which people in the private sector can make and can use but Federal researchers may not use those. Or if that would be an impossible-to-enforce thing and we ought to recognize that—just as Dr. Varmus has now said he couldn't pay for Thomson's work but he could pay for people to use Thomson's cells—that we ought to say, "Well, you can't pay for Geron to produce these, but once they've produced them you can use them, however they got them." I'd like to have some sense from those who do research—

DR. COX: You'll never be able to keep track of where they come from. But I just must tell you is that—

PROF. CAPRON: Why do you say that? Everybody knows HeLa—hela cells—that's a cell line and we know where that comes from.

DR. COX: You think you do. But in fact, when you work with those most of the time you find out that oftentimes they're contaminated with other cells.

PROF. CAPRON: But contamination is a separate issue. If you think you're dealing with cell line 1, 2, 3, 4, 5 from X, Y, Z source, is there any reason that source couldn't easily disclose to you whether it was created from embryonic germ cells or embryonic stem cells derived from excess embryos or research-created embryos? Is there any reason they couldn't have just like an A, B, C marking system?

DR. COX: If there was a regulation that said that had to be done, it would be done.

PROF. CAPRON: Now would it be a bad idea to make that differentiation, to insist that it be done?

DR. COX: Well, what it does is that, from my point of view, it sort of puts in concrete this distinction that we're going down in terms of making the distinction between the different types of embryos. And right now that distinction is a social and cultural and political one; it is not a scientific one. And so the more you put it in concrete, the more you're going to make it difficult to change it if the social and cultural and political factors change.

PROF. CAPRON: It's just the opposite. I would think that if in the future the value of somatic cell nuclear transfer to create cell lines for particular research or therapeutic purposes were very great, and this panel that I'm recommending said to the Secretary, "You should go and get the law changed," and the Secretary took the report to the Congress and said, "There are really compelling reasons not to allow embryos to be created for every purpose but for this purpose," and they wrote it in, then category C would lose any prohibition on it.

DR. COX: Either direction, Alex. But what it does is it polarizes the situation and it helps give validity to the fact that these embryos are of different moral status.

PROF. CAPRON: But it ought—not that they're different moral status, I don't think that's it, it's that the objections of people, and we've heard those objections and the Congress has heard those objections, to the creation of embryos for research is the strongest point of objection. I mean, there is objection to the intermediary category, but this is the strongest point.

If one could say, all right, anything that goes on in the private sector is the private sector unless there's a State law that prohibits it, there's no reason for the Federal Government to regulate it. That's the view we took on cloning, right, in part because of this very work going on in the private sector. If we now said we recognize that for many people the notion of the Federal Government funding the products is basically a way of funding the research that creates the embryos—because the companies that are going to go into that business have to sell their products; if they can sell their products, they'll do it. If what they're doing is something that the Federal Government shouldn't be funding, then they can't pay for the products or they are funding it. It just becomes a—

And if we think that that view is a view that could stand in the way of category B ever being accepted, I for one would give up the use of category C in order

to have the valuable work that could go on in the excess embryo, category B, acceptable.

DR. COX: Yes. And the logic of that argument is compelling to me because it goes back to this issue of saying, What are the points of compromise that could take place between people of different views about embryos?

PROF. CAPRON: Yes.

DR. COX: I hear that loud and clear. And so I'm very in favor of that. On the other hand, this is really a political process; it's not so much a scientific process. So I mean that's—

PROF. CAPRON: Well, we're not a scientific board.

DR. COX: No, no. I'm not saying we are, Alex. It's just keeping straight, really, what the process is about here.

DR. SHAPIRO: Okay. Steve, then Larry?

MR. HOLTZMAN: I would not be supportive of that sort of a marking system, because I think implicit in that is the suggestion that the only federally sponsored work with stem cells could be with stem cells that came from—

PROF. CAPRON: Thomson's work, and that kind of work.

MR. HOLTZMAN: Yes, you would say that that wouldn't be allowed. You'd be tainted—

PROF. CAPRON: No, no. Thomson's work is okay. He used excess embryos.

MR. HOLTZMAN: Okay. I'm sorry.

PROF. CAPRON: But you couldn't use somatic cell nuclear transfer or IVF for research purposes.

MR. HOLTZMAN: I'm sorry. Okay. Right. So, therefore, I wouldn't support that, because I think what Varmus is saying is we're not going to address where they came from.

PROF. CAPRON: I know that's what he's saying. I'm asking whether that—and he's run into a lot of headwind on that. And I can see the moral argument. I could write a paragraph that made sense that said, since we don't think it's yet right on the necessity and feasibility, etc., to overcome the prohibition on creating embryos for research purposes. We recognize that the Federal funding of the embryonic stem cells that are so created through these embryos is, in effect, Federal payment for the creation of embryos for research purposes, and we understand that if the objection is strong enough to persuade us that the creation shouldn't be funded, then the use shouldn't be funded. I could write that paragraph. I think it could sound coherent. And I'm sure it would persuade a majority of the Congress that's already taken this view. Whether it should persuade a majority is a separate issue, but that's another matter.

MR. HOLTZMAN: Right. Okay. I was actually going to try to respond to your question, or take a crack at it and look at an implication of it. There are a lot of views we pay no attention to. There are other views that we do pay attention to even though we go over them; we override them. So I think, for example, on the history of pacifism in this country, even though we override it there is a respect accorded to it because there's an important value that we recognize in that position where we want to learn its lesson even though in all instances we may not go with it.

And when I think about the debate in play here, there is a value being expressed in terms of respect for life and the implications of how we treat life and how, therefore, we will treat each other in the kind of society we will be, which we want to accord our respect. I think the implication, however, when one goes down this path of thinking is that when you accord that respect to that position, it's the acknowledgement of the position and what it means as opposed to where it might cite its reasoning, and that you need to distinguish those two.

So to give a concrete example of that, there has been criticism of the Embryo Panel's report for the language of "the embryo deserves respect." That could be a shorthand for the people who have a certain view of the embryo, who represent this broader view of the role of life and how we need to accord respect, and we need to respect that as opposed to adopting their view and saying that view, that metaphysical view, deserves respect. And the important difference there then will come to be the implications of your position.

So when you, Alex, for example, say "last resort, last resort," I find myself saying, What's powering that argument? Is it something about the thing or is it that the position and the lesson of that other group whose position you're respecting, does that level of respect drive you to say "last resort?". And I think that's when we get very clear about it. And as I was trying to motion toward earlier, again, if you're going to

set up your paradigm in terms of the fetus, right, and no directed, right, and yet when we turn to David's case and we say we all know where it may go and what will be compelling is precisely when the autologous transplant is most likely, that's exactly the case where you're going to find yourself saying directed transplant is allowed; by definition it's directed transplant. Well, therefore, what did it do to the basic foundations of our argument back in the—that's what my concern is.

PROF. CAPRON: That's the difference.

DR. SHAPIRO: I understand that concern—and Larry and Diane want to speak—but it doesn't seem to me that that concern is independent of the environment in which we are considering it. That is, that very same concern will end up balancing things one way or another. That is, it is perfectly legitimate to think differently, and I don't think you're suggesting anything different, when different prospects are before us.

MR. HOLZTMAN: Well, except I think we could think consistently now. I actually think we shouldn't suggest that—I believe we should continue the Federal prohibition.

DR. SHAPIRO: I understand.

MR. HOLTZMAN: All right?

DR. SHAPIRO: Yes, I understand that.

MR. HOLTZMAN: All right. And I can create the argument in terms of respecting that position, right? When I then go to what are the kinds of restrictions we should put on it, it's not clear to me that I would pick up all of the restrictions—

DR. SHAPIRO: Yes. That's an open issue. Right. I agree with that. Larry, and then Diane?

DR. MIIKE: Yes. You were developing a really logical system and now it's sort of coming down, because the issue about whether there are actually—I thought that one kept pedigrees of cell lines, but I guess not. So now we're faced with several practical problems. One is that even in the IVF situation Kathi's preliminary information tells us that there are instances where couples are paid to produce oocytes, fertilized oocytes that are going to be used for research. So that's already mixed in there. We don't know which ones come down through there.

Expressly in the private sector producing oocytes for research purposes, there are two types. One is the somatic cell nuclear transfer, which I would expect then would have a stream of research related to why they did that in the first place. But then there are going to be others that are just simply picked for expedient purposes, that are going to pay a couple of people to produce a fertilized oocyte. And if we don't have pedigrees, then our system will start to crumble. We won't know—well, if we say it's okay in these two areas but not in the third, but there's going to be so much leakage in there that I don't—you know.

So now I'm sort of in a conundrum about what we're supposed to be doing with that situation. The simplest, without the context of the actual real world, is to say that no matter what the current position of the NIH—which is "No matter what the source, as long as it's the stem cell, then it should be okay." But our reasoning starts to fall apart when we do that.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: The comments that I want to make are similar to Larry's and to Alex's earlier comments, and that is that it's inconsistent to allow the use of stem cells but not to allow the source of the stem cell, because you're indirectly providing funding for that work. And I think also because there is some control over the products in in vitro fertilization, our third category that we're addressing now becomes not all that different from the second one that we addressed, in which we are claiming that the embryos are produced just as byproducts of in vitro fertilization attempts. In effect, those persons can be creating embryos just for the purpose of research. They're creating an excess to have them left over for research.

So our third category really can't possibly be kept distinct from category 2. And it seems to me that the framework that we've built up really can't be justified. I think we're going to have to find different ways to answer these questions if we're going to really address what's going to happen in a year or a few years from now. I think this framework really won't hold up at all.

DR. SHAPIRO: Well, I have a comment on that, but Alex first.

PROF. CAPRON: Well, the present law on fetal tissue has several requirements for attestations in it. Obviously, people can lie in this process. And there may be unconscious lying, as Bernie kind of suggested, as to how many embryos you think you need to create to offer a couple a viable chance of having a good pregnancy outcome.

But in principle, it seems to me that both the objections that you just raised and the one Larry raised could be met by a similar system in which researchers—excuse me, in which IVF clinics would differentiate between those embryos they had created for their own research purposes or for somebody else, say a stem cell laboratory's request, and those that were created as part of an attempt to achieve pregnancy as part of a true fertility program, and that they would attest that those that were now being donated for research purposes had been created without any inducement to the couple to provide them for research purposes, and so forth and so on. It's something very parallel to what's in Public Law 103-43 in the section on research on transplantation of fetal tissue, and it ought to be possible.

If it's then possible, then I think that the kinds of concerns about keeping the cell lines separate are just ones of practicality. And if we literally had an A, B, C type requirement that if you're going to have stem cells they have to be differentiated among fetal origin, excess origin, and created origin, and that the last at the moment don't qualify for Federal funding. Unlike the situation where at present if the only method available were the EG cells and if there turns out to be any difference, then the whole area of embryonic stem cell research could be something the Federal Government could sponsor.

There's really no particular reason to think Thomson's method, if it were legitimized as something the Federal Government could fund, which would be our consensus a few minutes ago, wouldn't produce lots and lots of stem cell lines for just about all the kind of research you would want to do except nuclear transfer. And that only becomes essential if there's no other way, essential for the transplant purposes at least, if there's no other way to create the cells—and if it turns out, of course, to be feasible.

DR. MIIKE: Harold, can I just briefly follow up?

DR. SHAPIRO: Yes, briefly, because I have a comment and then I want to turn—

PROF. CAPRON: That I would leave, as I said, to the future.

DR. MIIKE: I think that I agree with Alex in the sense that even if the current situation is that there are no pedigrees, the price you pay for getting research funded by the Federal Government could be that.

PROF. CAPRON: Yes. Exactly.

DR. SHAPIRO: I think as we begin to—first of all, I've heard this statement made a number of times around here this afternoon and it may be right, I'm not sure, but it wasn't what I recalled, that Dr. Varmus thinks that the origin of these is irrelevant. Now that may be right, but I want to check that. We don't have to argue that point here, but it certainly wasn't my impression from what he said.

But in any case, I think it's very important as we go ahead and try to take some of these views and put them down in some coherent way that this issue of taint or this issue of connection—it's sort of like the issue of "impossible" when we got to the human biological materials—if any connection will do, everything is connected to everything else and we might as well give up right now. But I think we can structure it so that things can work for the most part, recognizing that they won't be foolproof and there will be a case here and there that falls through the cracks, which is something we would not necessarily approve of. But I mean, if we go to the extent of wanting to look for a scheme that really provides the country with kind of airtight assurances and all this, we are certain not to get through it.

So I hope as we go through with this we'll look for schemes that try to achieve our objectives in a reasonable way, recognizing, as Alex said a moment ago, some people lie and therefore get around things, and some people don't pay any attention to laws and they get around things, too. And so what? What we want is a scheme, I think, that reflects our views that really will stand over time in a reasonable way and be adaptive over time. And if there are some people who get away with something, that's nothing new. So that's what we ought to be aiming for as we articulate this. I want to—

PROF. CAPRON: Could I ask that we not plan as of now to have a section in the report that discusses conscientious objection to the withholding of taxes and other matters?

DR. SHAPIRO: I will write that, Alex, as a personal statement in the report. Yes, we will not have it in the report. [Laughter.]

PROF. CAPRON: I mean that's a very interesting enterprise but I have a sense that if anything could bog us down—

DR. SHAPIRO: No, no, no. I wasn't suggesting we take that on seriously. I am suggesting that this issue of—when we get to this—of the reasons why we treat publicly funded research differently is not well understood and people have a hard time, if you put them on the spot, articulating it. And we could, I think, benefit from just a short, coherent explanation of that, which I think is not that hard to give; it's

done by many people, it's just not out there in the currency very much. But I think we can. My only point in raising that was to get us to the point of saying we should think about this and provide some rationale for it in our report. But we will not deal with conscientious objectors.

Okay. Thank you very much. We will adjourn this part of our meeting.

PUBLIC/PRIVATE SECTOR INTERESTS

DR. SHAPIRO: Dr. Blumenthal, do you want to join us in a sense by sitting there? As I told Dr. Blumenthal before, he's not to consider this a hearing, even though it's set up that way, but really a discussion. We're trying to become better informed as a Commission on a whole series of issues. And I want to express our gratitude to you once again for taking I'm sure what amounts to a whole day in coming down and going back to Boston. Dr. Blumenthal is here from Massachusetts General [Hospital]. We're very grateful to you. We hope your hand is not painful even though it might be uncomfortable.

DR. DAVID BLUMENTHAL: It's an advertisement for western skiing as opposed to Eastern skiing.

[Laughter.]

DR. SHAPIRO: I see. You had this problem with the icy hills in Mount Mansfield or something of this nature?

DR. BLUMENTHAL: Killington is more like it.

DR. SHAPIRO: Killington. I know Killington well. But I'm very sorry that you fell. There's not enough snowfall this year, I guess, or something of that nature. But thank you very much for being here. We look forward to your remarks regarding public and private interests, and thank you very much for coming.

DR. BLUMENTHAL: Mr. Chairman, what I'd like to do is read a brief statement and then take questions that you all may have for me. As you all know, I'm director of the Institute for Health Policy at Massachusetts General Hospital and Partners Health System, and an associate professor of medicine and health policy at Harvard Medical School.

I'm not particularly an expert on the science of stem cell research or pluripotent stem cells in general, nor am I a bioethicist. I do know a fair amount, though, about the consequences of industrial funding of research, particularly industrial funding of research in universities, which are, after all, the source of much of our fundamental knowledge in the field of biology right now and in this field I suspect as well.

The prohibition of Federal funding for this type of research will mean, in effect, that whatever research is done in universities on this topic will be done under the auspices of industrial funding. And therefore there is some relevance, I think, to your deliberations and thinking about what a prohibition on Federal research may mean for this field and the progress of science in this field.

Over the last 15 years, I've led a series of studies on relationships between universities and industries, first in the field of biotechnology during the 1980s, and then later in the field of genetics and the life sciences generally. Right now I'm the principal investigator on an NIH-funded study of secrecy in genetics, in genetic research, which will look carefully at the relationship of industrial funding to the phenomenon of secrecy.

I also serve as executive director of the Commonwealth Fund Task Force on Academic Health Centers, which is intensively studying the effects of price competition on the manner in which universities and their medical schools produce or don't produce public goods in health care markets.

My other relevant experience includes four years as the manager responsible for technology transfer at a major Harvard teaching hospital, Brigham Women's Hospital, which had a research budget at the time in excess of about $100 million a year. So I've seen the academic–industrial relationship from both the academic and practical perspectives.

The first point I'd like to make, and this one may be obvious to you but I think it bears emphasis nonetheless, is that work in universities supported by industry is different on the whole from work in universities supported by the Federal Government and by other nonprofit sources of funding. And some of the differences are the following.

First, most of the projects supported by industry are shorter in duration, usually less than two years, and smaller in size than are research projects funded from other sources. And this strongly suggests that they are more targeted in nature and that their renewal may be conditioned more on the achievement of short-term objectives than is true of other sources of funding.

And consistent with the size and the duration of industry projects, academic researchers funded by industry are more than twice as likely to say that they have changed the direction of their research or designed their projects in order to achieve some short-term commercial objective as a condition for obtaining funding from an outside source.

Industrial sources of support commonly place or attempt to place restrictions on the communication of research results and the dissemination of research results. For example, more than half of the companies that we surveyed in a random sample of life science companies in the mid-1990s said that the research—that their agreements with universities commonly contained restrictions on the publication of the results of that research that extend beyond the time required to file a patent.

Data withholding is more common among academic scientists funded by industry than among investigators funded by other sources. Evidence of such increased prevalence of data withholding takes a number of forms. Scientists with industry support are more likely to report that trade secrets have resulted from their work. They're more likely to report that they've been asked by other university scientists to supply research results from their work and that they've refused to do so. Interestingly, scientists with industry involvement are also more likely to report that they have requested information from other academic scientists and been denied it.

Investigators who receive more than two-thirds of their research support from industry published less and published in less prestigious journals than colleagues who received lesser amounts of research support from industry.

And at least in theory, the patenting and licensing of federally funded research in universities is subject to certain conditions and guarantees that assure the dissemination of research findings. Those guarantees don't exist for industrially funded research unless the university insists on them in their agreements. These have to do with requirements in the Bayh-Dole Act and other Federal regulations as far as the use of federally funded intellectual property.

Now how are these findings relevant to your deliberations concerning the treatment of stem cell research by the Federal Government? Should the Federal Government decide that stem cell research is too ethically troublesome to fund, the effect will be to ensure that all university-based investigation will be supported by companies. And this will likely have the following effects for the development of this line of work.

Less work, of course, overall would be conducted in universities in this field. It's important to note that industry funding of research in universities is still a relatively minor part of the stream of funds that universities receive. It's on the order of 10 to 14 percent of all the funds received by universities to do research in the area of biomedicine. So that this will be an area that's relatively starved if one relies on companies exclusively to fund that research.

The work conducted in universities will be more applied in nature than is true in other fields of research. And thus, progress in fundamental investigation related to stem cells and their uses will be less rapid than it otherwise would have been.

And the results of university-based work on stem cells will be less widely, completely, and rapidly disseminated than it would have been if supported in part by other funding agencies.

Now I want to make it clear that I'm not opposed to academic–industry relationships or to the funding of stem cell research in universities or elsewhere by private companies. Indeed, such relationships between universities and companies are essential to the application of university research, including federally funded investigations. It's the only way we have practically to get the results of any investigation conducted in universities out to the marketplace and into useful applications.

My point is rather that the optimal way of supporting biomedical research in this country at the current time is to create and preserve a balance between publicly and industrially supported investigations. This balance is absolutely key in multiple ways. It assures that progress in both basic and applied research will continue. It facilitates a healthy interplay between fundamental investigation and applications of that investigation. The availability of sufficient Federal funding also provides a vital check on the ability of industry to impose restrictions on the activities of university scientists.

The best way to prevent problems associated with industry restrictions that violate academic norms is to provide individual scientists with a practical exit strategy from industrial involvement, an alternative source of support that enables them to pursue their work if they refuse industrial funding. Federal funding provides the best such alternative.

That concludes my formal remarks. I'd be happy to take any questions or hear any comments that members of the Commission may have.

DR. SHAPIRO: Thank you very much. I really appreciate it. We also would appreciate it if you would agree to give us copies of your statement.

DR. BLUMENTHAL: Sure.

DR. SHAPIRO: We'd like to distribute it to members of the Commission and keep that on file. So thank you very much.

I have a number of questions. Let me get started and we'll see. One could hardly argue that a plurality of sources of funds provides the greatest degrees of freedom, and that obviously is an optimal situation for many reasons. But when we talk about the goals of research or the structure of the scientific agenda, in your experience, is it clear and obvious to you that the structure that comes out of, let's say the peer review process, that is, the structure of the agenda that comes out of the peer review process that underlies most Federal Government research, is somehow in principle superior to the agenda that would come into play if it were funded by industrial sources?

DR. BLUMENTHAL: I think it's clearly different. I don't know—I think "superior" is a judgment that one could apply as a matter of prejudice more than information. The criteria that are applied in the peer review process are most likely—they include, clearly, some attention to practicality and application and usefulness. But they also, I think, involve a level of excitement or contribution to the field and clearly take that into account in a more direct and more heavily weighted way than would funding from the other sources, industrial sources.

Also, it's possible to fund larger projects and longer term projects more reliably from Federal sources than is true, I think, from most industrial sources. We hear publicized a lot the large, long-term relationships that have occurred between some major universities and some major companies, usually large pharmaceutical, multinational pharmaceutical companies. Those actually account for about 1 in 10 or 1 in 20 of the relationships that occur between universities and industries. The great, great majority are small grants for short periods of time, and it's the rare scientist who is privileged to do basic research with industrial funding.

DR. SHAPIRO: Thank you. Other questions? Alex?

PROF. CAPRON: David, through the years, the last 10, 15 years, you've written a lot about this general area. And I wonder whether either on the general observations or specifically on those that are related to genetics researchers you have found any particular criticisms of your conclusions or your methodology that you've

taken seriously and that you might share with us rather than our—this is not a—I hope you take this comment in the right way.

DR. BLUMENTHAL: I always take your comments in the right way, Alex.

PROF. CAPRON: Let me explain what I'm thinking. I think I, basically having read your stuff through the years, have always found it rather compelling. If I now were asked to write the section of our report in which we argue for funding of the creation of stem cells through excess embryos, one of the reasons I would give for that would be the value of having this work federally sponsored. I would like to be prepared to deal with the arguments that say either there's very little indication that having it privately sponsored is problematic, or etc.

People in science are often in a position to say, "These are what the critics say and this is my best answer to them." I'd like to know what we should look at to get the best criticism and what the best answers are.

DR. BLUMENTHAL: A lot of my conclusions are based on surveys of companies and of university scientists. And there are some people who are profoundly skeptical of surveys of this kind, particularly when you're trying to ask people about behaviors that are not socially acceptable. So when I talk about seeing pressures for redirection of research, a critique that doesn't come—that comes at a more sympathetic side is usually you've underestimated the problem. As a matter of fact, I think that if you look quantitatively at the frequency with which people engage in what are considered—report engaging in some of the violations of academic norms that we've detected—the frequency is pretty small. For example, the numbers of people who would report that they've refused another scientist's request for results of their research would be around 10 percent admitting that in a survey. And I would guess that that's an underestimate. So that's not a criticism that would help you with people who would argue the other side, but I think it's probably in some ways the most telling criticism of our work, that we've underestimated the risks rather than that we have overestimated them.

The other side, I think, is that the other side of the criticism might be that we get there anyway; that one way or another we'll muddle through. And that the relationship between industries and universities is a great strength of our biomedical system, one that is the envy of the rest of the world, and that it is a mistake to dwell on the downsides of that relationship; that the pluses way outweigh in real terms and in consequences the negatives.

PROF. CAPRON: That would be an argument as to the weight we should give to your findings as opposed to any concern that the findings in fact are not representative of reality. I can't remember whether you have ever identified through independent methods a cohort of people heavily or totally dependent upon industry and another cohort, and instead of asking them what they do, just study the number of publications that they each have, the time, the size of the projects that are funded to the extent that that information could be accessed through university records, and so forth, or is that just impossible to do?

DR. BLUMENTHAL: No, it's possible. We just haven't done it. We have in fact, though, asked them to report on their publication records and then validated those against Medline searches and found them to be reasonably accurate, and therefore have used those to compare publication records among researchers who were industrially funded and those who aren't and have varying levels of industrial funding. And that's why, in fact, we find that people who have small or moderate amounts of industrial funding are more academically productive than those who have no industrial funding. But those who have a lot are less academically productive than either, than any other group. So I mean you could argue the fact. That's why I emphasize balance in this rather than either/or.

MR. HOLTZMAN: Did you say "lots" in the sense of total, absolute industrial funding to—

DR. BLUMENTHAL: More than of a relative—more than two-thirds of their—

MR. HOLTZMAN: So, relative?

DR. BLUMENTHAL: Right. Relative to smaller amounts.

MR. HOLTZMAN: There's a very important point there.

DR. SHAPIRO: Okay. I missed the question.

MR. HOLTZMAN: The best researchers have the most NIH funding, therefore proportionally the industrials will be less and those will be the heaviest publishers. So, such that, for example, my firm puts $1 million a year into this Pfizer lab at Brigham and Women's—it's also the largest funded NIH lab in Brigham and Women's, great publication record—we put a million dollars a year into Lander's lab, but he gets $8 million a year from Collins, right? In your survey, they will come out as paradigms of academically sponsored, Government-sponsored with great publication

records, but in fact, in absolute terms they may have most of the industrial money as well.

DR. BLUMENTHAL: We chose to measure dependence in terms of proportion of total funding rather than absolute—

MR. HOLTZMAN: So that would be an example of the critics' criticism of the methodology.

DR. SHAPIRO: Eric?

DR. CASSELL: What I want to get at is a little hard to frame in a simple question. But what you're describing in part is a change in the mores of science in this country over the last how many years, 15 years, something like that?

DR. BLUMENTHAL: The mores of biomedical science. I think that chemistry and engineering have long been much more integrated with industry.

DR. CASSELL: And what do you think that does in the long term to the productivity at the NIH or to scientists in general or to aspirations to go into science? Are there impacts in that area also because of, in part, the longer term consequences of this that count as much as the immediate, whether it's stem cells are produced in this lab or not?

DR. BLUMENTHAL: Well, it's a hard question to answer. I think that my view is that it would be undesirable for more than a certain fraction of university funding to be derived generally or in a particular field from one source, and perhaps more undesirable to have it derived from industry than from other types of areas. That's not to say that we wouldn't make progress, or that we wouldn't achieve breakthroughs, or that we wouldn't help people through that work.

My guess, and I can't document it, is that the preservation of academic norms has value and that industrial funding makes it more difficult to adhere to those norms than federally funded research. Now I can't give you a figure. I sort of, when I'm asked and pressed I say, "20 percent seems like a reasonable amount of industrial funding as a portion of the total portfolio." And I could give you reasons why I think it's that but I wouldn't feel that they're strongly grounded in science.

But I do think that if we were to leave a field, an important field, exclusively to industry in this country, that we would look back 20 years from now and regret that we had done so, if we could do the thought experiment that would allow us

to think of what would have happened if we hadn't done so, and there's always that limitation, you don't know what would have happened if you hadn't done it the way you did it.

DR. SHAPIRO: Well, would you think it's at all relevant—Diane, I know, I'll call on you in just a second—would you think it's at all relevant, or perhaps you have thought about this over time, there are other kinds of research that was pursued from time to time which had qualitatively the kinds of restrictions you talk about with respect to industry-sponsored research only perhaps much moreso—for example, classified research. And I'd just ask the question whether in your own research and thinking in this area, whether you find those examples useful in trying to think this problem through at all? Just trying to ask a question here.

DR. BLUMENTHAL: The issue of classified research is one that I'm familiar with, if nothing else from having been a student on a university campus in the 1960s.

DR. SHAPIRO: That was a fiery experience.

DR. BLUMENTHAL: That's right. I recall well the discussions that occurred at that time and the stands that were taken against it often, and I guess maybe I can't quite escape that molding experience. I think that many universities, mine included, will not do classified research. And I feel reasonably comfortable with that position, though I could imagine exceptions, making exceptions to that rule when there was a very strong social need—in wartime, for example, or for some other purpose that I haven't yet imagined.

DR. SHAPIRO: The reason I raised it was not to get back to kind of our feelings about classified research and how it fits into an academic setting, but whether the experience in classified research in some area really reinforces your finding that it hinders or fails to hinder.

DR. BLUMENTHAL: I haven't studied it so I can't give you a reaction, though I would be quite certain that rates of publication from classified research would be less than rates of publication from unclassified research. And since that's probably the best metric that we have for academic productivity, if you applied the methods that I've used to classified research, you would come away with the same conclusion.

DR. SHAPIRO: Diane, Larry, and Steve?

DR. SCOTT-JONES: I have a couple of questions just to follow up on some of the information that you've provided us. You made the point that industrial funding is typically somewhat shorter than Federal funding would be. But I'm wondering if there are researchers who have over a period of time fairly constant industrial funding the way, say, a researcher might say that his or her lab has had consistent funding from the NIH over 20 years. Would there be researchers who could say that about industrial funding over time?

DR. BLUMENTHAL: There are some. Obviously, they are many fewer in number. There are investigators at Massachusetts General Hospital that have had funding from the Herbst Company for going on 15 years now.

DR. SCOTT-JONES: Then my other question is regarding your comment that this work tends to be more applied than work that would be funded by Federal dollars. By "applied" do you mean that there is some fairly direct commercial use, or do you simply mean that the focus is on a problem or an application in contrast to theory-driven work? Is there some fairly direct commercial use?

DR. BLUMENTHAL: Again, we're not talking about an either/or situation, we're talking about a distribution of work. And I think that the distribution of work that is funded by industry is more likely to involve trying to get the answer to a particular problem or to solve, fill in a gap in knowledge that is crucial to the production of a product. And I think that the smaller the company the more likely it is that the work will be focused around answering a very special or particular question or furthering a particular line of work that has a product at the end of it.

That simply isn't a criterion that's applied to federally funded research; that is, that the result have a product. There is a hope for a product, and in some cases there actually is a product. But it is not as consistently applied as a criterion, I believe.

DR. SHAPIRO: Larry?

DR. MIIKE: It strikes me that two areas in which maybe case studies have been done would be contraceptive research and fertility research, and that those are very different areas in the sense that in fertility research you have the driver of individuals, and that's why you see a rise in fertility clinics, whereas in contraceptive research it's got to be big companies or with the Government. Have there been any studies looking at those two areas?

DR. BLUMENTHAL: Not that I know of, Larry.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: A bunch of questions and observations. Again, I think when you said that they tend to publish less if they have a lot of industrial sponsorship, again that was proportional sponsorship. So those are the people who have the least sponsorship, are least able to get Federal funding—probably because they're not very good may have something to do with why they're not publishing, as opposed to the suppression of publication.

DR. BLUMENTHAL: I agree with you that there are multiple possible explanations for that finding.

MR. HOLTZMAN: Okay. Number one. Number two, and this is from the experience in the last three years or five years of doing about 400 agreements with universities, I can't imagine going to Harold—is Gene Mahoney still here?

DR. SHAPIRO: Yes.

MR. HOLTZMAN:—And saying you have to change your publication policy to work with my firm. They would tell us to walk out, they'd kick us out, and we should be kicked out. And having just served this last year on the working group of the NIH on access to research materials, whereas historically there were problems with firms walking in and telling academic institutions they couldn't be academic institutions, it seems largely not a problem anymore. The people understand that one of the things you do when you work with the academics is, they will publish. If you don't want them to publish, don't work with them.

So I'm wondering how new your data is with respect to the suppression of publication being demanded by industrial firms and being acceded to by the academy.

DR. BLUMENTHAL: It's '95–'96.

MR. HOLTZMAN: Okay. Not consistent, at least with what I heard on the working group of technology transfer people to the NIH.

Another question is, you said Bayh–Dole requires greater dissemination than will come. And I'm curious, one of the things that came out when we talked to Thomson, the last one was that the funding of the initial work was not under Geron, that is, under nonhuman primate. It resulted in a patent covering human primate. It was exclusively licensed by the university to a commercial firm. So, therefore, that there was

Government sponsorship as opposed to private sponsorship didn't affect the question of accessibility. So I was curious what it was under Bahy–Dole that requires additional dissemination that you were thinking of that an industrial sponsor—how it was different?

DR. BLUMENTHAL: Well, there are potential—

MR. HOLTZMAN: Other than the Government's reserved research use right.

DR. BLUMENTHAL: Well, there is that, number one. And if I'm not mistaken, there are also matching opportunities that the Federal Government has under certain circumstances, and I don't know the regulations in detail. But certainly the opportunity for the Federal Government to gain access, and also the requirements that the Federal Government puts around disclosure and other monitoring of conflict of interest that goes on in the context of application for Federal funding, so at least the peer review groups know about the conflicts that the scientists they're about to fund are involved with. And I think that provides, though it may not be operationalized very often, it provides a kind of check on the funding of university-based research that isn't true of industrially based research.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: You mentioned to us that your study of secrecy in genetics research is funded by the NIH. Who funded your study of the consequences of industrial funding?

DR. BLUMENTHAL: Also the NIH.

DR. SCOTT-JONES: Okay.

DR. BLUMENTHAL: It's actually Eric's old program, the Human Genome Project, the LC program.

DR. SHAPIRO: Kathi?

DR. HANNA: David, have you thought about, in the context of stem cells specifically—this is a hypothetical situation, we don't have any evidence that this is occurring yet—but I'm hearing from some people in the scientific community that they have concerns about Geron having a "monopoly" at this point, and that material transfer agreements that any university-based scientist would have to negotiate or a university

would have to negotiate to gain access to these cells seems for some reason to be the big uncertainty. And I'm not sure whether this is unique, if this happens all the time with other types of patents or intellectual property agreements.

DR. BLUMENTHAL: I think it could happen with federally funded research. That is, if a university like Johns Hopkins or Princeton had done this work with federally funded research, it would be free to exclusively license it to Geron or another company and that would convey the same monopoly that all patents and exclusive licenses provide.

Now my knowledge of what the Bayh–Dole Act requires gets fuzzy, but a number of licensing agreements that universities, at least that we wrote with companies when we did licensing agreements, basically said, "If you don't use this, we're going to take it back." There was a sort of clause that breached the exclusive license if the result of the research wasn't used effectively. And I really don't know whether that's a university-specific condition or whether it's something that is required by Bayh–Dole.

MR. HOLTZMAN: It's a university. It's not required.

DR. SHAPIRO: It's what?

MR. HOLTZMAN: It's not required by law.

DR. SHAPIRO: That's right. At least that's my understanding. I shouldn't say that's right, but that's my understanding as well.

MR. HOLTZMAN: The concern Kathi raised, there was a meeting at the National Academy of Sciences last week talking about these issues. And it's really an issue of not necessarily just patents, but the issue of when you have a rare know-how, stuff, okay, what are the reach-through licensing conditions you require of someone in order for them to gain access to it? It's typically a company would say, "I have to be free to use any improvements; I need to be free to use any new uses you discover," and then there's a haggling, if you will, over my rights of license to use substances you create using my stuff.

DR. HANNA: My point is more, I think, having to do with the Federal, where there are Federal funds commingled in there and the relevancy of Bayh–Dole, and we need to look at that. I know that the Senate Judiciary Committee is going to revisit Bayh–Dole for these very same issues. So it's clearly something that people have questions about.

MR. HOLTZMAN: So it goes to the issue of how university OTLs [Offices of Technology Licensing] are licensing the federally funded inventions. The Warp team at Wisconsin, for example, was advised that they ought to engage in a nonexclusive licensing strategy because it was such a basic research finding. They chose to do an exclusive licensing strategy, albeit to the best of my understanding, time limited exclusivity.

DR. BLUMENTHAL: I wanted to say, you had asked me previously about how we could have found what we found about restrictions on communication that results when universities would be likely to kick you or some of your colleagues out of their offices if you tried to include them.

I guess I have two points to make. First of all, I can't exactly reconcile that except to say that stronger universities are stronger in their insistence on not having those restrictions. And we didn't confine our study to relationships between Ivy League universities or major technology institutes and companies. We looked at the whole gamut of American universities, number one.

Number two, I think companies differ a great deal. Some companies, especially larger companies, are much more used to dealing with universities than smaller companies, and companies that are founded by university scientists are probably more likely to, or that have strong links to universities are more likely to, follow or allow for university norms than others. So I think there's a lot of variation among companies.

And third, I don't think that in public forums people are likely to be honest about this because it's not an acceptable thing to say, "Yes, we make our scientists be quiet, the ones we fund in universities." And we, of course, guaranteed our respondents anonymity. So that I think we may have gotten a more representative view of what goes on in the real world than you would get from listening to conversations in public settings.

MR. HOLTZMAN: I guess, you know, I don't mean to react so violently. It's just that Habenmoss in the mid-1970s wrote about the co-optation of the university that would take place as a result of this industrialization. I've been doing this now for close to 20 years; I haven't see it happen. I've seen a lot of hard work by a lot of well-intentioned, good people on both sides of the aisle, or whatever you want to call it, who recognize that without the academy there is no biomedical industry that has a prayer of transforming basic research into things that will help mankind. We have assigned to the private sector in our form of economy the role of translating that stuff. We have an elision taking place between applied and basic research in the biomedical world, and I think there are important safeguards and protections that people try to erect. But to get

up here and say that the reason we need federal funding of stem cell research is because otherwise big, bad industry is going to rape and pillage I just think is false. I think there are a lot of good reasons—

DR. CASSELL: I didn't hear that.

DR. SHAPIRO: I didn't hear that, Steve, either. I understand what you're saying. I didn't hear that.

DR. CASSELL: That invalidates your own comments when you do that.

PROF. CAPRON: Or something of that ilk.

DR. SHAPIRO: But anyway, we exclude rape and pillage.

There are a number of people who want to speak, and I have some other questions also. Alex, then Diane?

PROF. CAPRON: I hadn't previously noticed the resemblance between David Blumenthal and [Jurgen Habenmoss], but—[Laughter.]

MR. HOLTZMAN: Go back and read it.

PROF. CAPRON: It's stronger. I wanted to know whether—I guess I took from your comments, and maybe my notes were wrong, about the restrictions on publication that you weren't looking only at nonpublication but delays in publication. Is that right? And I wonder whether we have either from your work or others' comparative data on the delay in publication when a scientist working either with university funds or Government funds or private funds or some mixture comes to a finding that would be patentable and decides what to do vis-à-vis the timing of publication working with the universities and/or the other sponsors' intellectual property people. Do we know whether there are dramatic differences in average—

DR. BLUMENTHAL: I can't answer that. I only know what the companies tell us or told us they sometimes request, and that is delays beyond the time that is required to file a patent. And whether those delays are important, whether they have any—and I'm not saying that's the rule.

PROF. CAPRON: Have they quantified those? I mean, is it, "We need a month in order to figure out what we're going to do with this," or to have an IPO [initial

public offering] or some other process that is corporate-related as opposed to whatever the university—

DR. BLUMENTHAL: I can't quantify it for you. And I can't tell you that it's important scientifically. That's another thing. I think that's another potential criticism of the work that we've done, that we can't show that the differences we observed—

MR. HOLTZMAN: Are significant.

DR. BLUMENTHAL: Are matter for the progress of science.

MR. HOLTZMAN: Right.

PROF. CAPRON: And just that I understand, the situation where there wouldn't simply be a delay or a difference in timing would be when the corporate sponsor would decide to treat the discovery as something of a trade secret variety rather than a published but protected case.

DR. BLUMENTHAL: Where there wouldn't be a difference in timing?

PROF. CAPRON: Where there would be a difference—would be a difference not just of the speed with which something is published but the actual nonpublication of a finding because the company says that, "We don't trust the patent process; we want to treat that as a trade secret." Can you quantify how frequently that happens for work that's conducted out of house, that is to say at a university or other research lab?

DR. BLUMENTHAL: We know that trade secrecy is more common in industrially funded research than others. And the order of magnitude, now about 15 percent of scientists funded with industry funding will say that a trade secret, that is something kept secret to protect its proprietary value, has resulted from their work, whereas that will be true in about 5 percent of scientists who don't get industry funding.

PROF. CAPRON: And again, we don't know the scientific importance of the findings and whether they interfere with the progress of science.

DR. BLUMENTHAL: We don't know if it's temporary, that is if it's a two-month issue or a six-month issue or a ten-month issue. And I again want to say that I'm not opposed to industrial funding of research in universities. I simply believe that a

balance is essential. It makes the industrially funded research more productive and it makes the federally funded research more productive.

DR. SHAPIRO: Okay. And Rachel, did you say you had some quantitative information to deal with this issue?

MS. RACHEL LEVINSON: I'm not sure how germane this whole line of discussion is, but it could be to what may happen to a new field that is experiencing some interest from industry. But to give you some information: Roughly five years ago the NIH did a review of all the sponsored research agreements in response to a proposed agreement between Scripps and Sanders. And what they found at that time was that there was a great big passel of questions for university grantees from the NIH, and what there found was they were a range of requirements from companies as to delays in publication. But most of them, even at that time, were between 30 and 90 days, which were about the same as what the university offices of technology licensing required once a patentable invention had been disclosed to them to review it for patentability.

And since the publication of those results, there has been a greater degree of uniformity across these agreements between different kinds of universities and companies, because I guess the bargaining chips have become more or less equal.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: Steve mentioned instances in which a lab would receive funding from industry and from Federal sources. Did you find that it was typical for labs to have particular balances, say 10 percent industrial, 90 percent Federal, or 50–50, or 90 percent industrial and then 10 percent Federal? What was the typical way that a lab—

DR. BLUMENTHAL: Most labs have a third or less of their funding from industry. And I think that makes a lot of sense from the industrial standpoint as well, that the industry is able to leverage the findings that result from federally funded research. Roughly speaking, I would say it's probably 70 or 80 percent have less than a third of their total funding from industry.

DR. SHAPIRO: Eric?

DR. ERIC MESLIN: David, I just had a question that sort of asks you to think hypothetically on a different issue about the ethics of what you have been describing. Steve has given you some food for thought. And I just wonder whether, given that the Commission is writing a particular report on one case study in a very large

area of investigation, what lessons should the Commission take away when thinking about the ethical issues that would have to be addressed to make clear that some of these concerns have been considered, if rejected or if adopted? You mentioned secrecy, you mentioned disclosure, you mentioned ideas of collaborative relationships. Are there some specific themes that have come up in your research that are more normative and more prescriptive that you might speculate on? I don't want you to go beyond your descriptive data, but I know you've thought about this a bit.

DR. BLUMENTHAL: Well, I sometimes have trouble differentiating between ethical norms and norms that are meant to get the most out of what we're doing, that are more productivity-oriented. And my approach to academe–industry relationships has always been to ask what sets of relationships give us the biggest bang for our buck, our investment in science? And that's why I come with this idea of a combination of sources of funding as being the most productive way of spending our money as a society.

People tend to invest academic norms like openness with ethical content. And I don't know whether they are appropriately regarded as ethical norms as opposed to characteristics of universities that render them best suited to furthering public purposes. I tend to see it in the latter light rather than the former, because I'm quite willing to admit that there are cases when classified research is necessary to serve a larger purpose or secrecy is necessary to serve a larger purpose.

I also believe that secrecy is an inherent part of the scientific process for limited periods of time and that we can't avoid that and still motivate people. And that one of the reasons I got interested in secrecy independent of academic–industry relationships was that I was continually told that industry was not an important factor in secrecy, that really what was an important factor was people's interest in priority and holding on to their research. And I think that in fact a lot of what goes on in science has little to do with the actual norms of science and a lot to do with a kind of barter system where people exchange information when they expect to get something back personally rather than doing so because it is "the right thing to do."

So I guess I have trouble talking about this ethically as opposed to seeing it as the right way for us to conduct a profitable line of research. Some of my sociologic colleagues will tell me that for every norm, Newtonian norm, there is a counter-norm, and that those counter-norms are actively entertained at the same time as the norms, and that scientists are inconsistent and not logical about their ethical precepts and what operates day to day.

So I'm hesitant to invest those norms with more than they deserve. But I do think they are certainly things that we carry around in our head and that have been associated at least in a formal way with a period of great progress in science, and so we don't want to discard them willy-nilly.

DR. SHAPIRO: Thank you. Let me make two observations, and then I think we need to wrap up this afternoon. We've been at it since 8 o'clock this morning. One is directly related to this issue of technology transfer, knowledge transfer in biomedicine. I just want to observe that it does take place through research contracts of one kind or another between various kinds of institutions, public and private. It also takes place in an important way not through contracts but through consulting arrangements of one kind or another where enormous amounts of knowledge are transferred daily, and to good effect as far as I know. But it is another major source of the way knowledge is moving from one sector to the other.

But I think the main lesson of what you told us for the issues we are addressing here is really an interesting one, one I find perfectly convincing, although you made many other very stimulating remarks—namely, that if I understood you correctly, there was a great deal to be gained by mixed strategies on all sides, for everybody. Institutions gain, science gains, corporations gain, everybody gains with the pursuit of a mixed strategy. You suggested a particular combination but there might be other combinations that work; I don't think you've suggested it in any detail. And I think that is important, that observation, to the extent we find it convincing it's important for us as we go ahead to think about what's in front of us right now.

So I thank you very much for being here. I am very grateful to you for having persisted through a canceled flight and arrived here today. I hope we can welcome you back here to Princeton another time. Thank you very much.

DR. BLUMENTHAL: It's a pleasure. I enjoyed the questions. Thanks.

DR. SHAPIRO: We look forward to getting copies of your report. Thank you.

If I could just cover a few logistical items for the committee members. First of all, tomorrow morning we will begin at the same time, the same arrangements as today. That is, for those of you who are interested there will be a continental breakfast available over at Prospect House starting at 7:15. There will also be a van over at the Nassau Inn for those of you that have bags and would prefer to have a drive over here and want to check out early, there will be a van there roughly around that time, which will go back and forth for any of you wanting a lift over. It's a very short walk, but—

PROF. CAPRON: Will there be someone in this building at the time that we come over from breakfast so that we could leave our bags here rather than hauling them to breakfast?

DR. SHAPIRO: Yes. Yes, there will be someone here.

Second of all, so that will just make it easier tomorrow. There will also be, for those of you staff members and Commissioners coming to dinner over at Lowery House tonight, it's probably easiest to take—there will also be a van around 6:20. If it's not there, it's because it's making a trip and it will come back and pick you up. So you can wait for it there at the entrance to the Nassau Inn. It's a very, very short drive, but in case it's raining again it might be better to wait for a van drive.

Third, I do want to carve out some time tomorrow morning, and I'll have to think this through a little bit, to revisit the Human Biological Materials Report, see where we were and to make sure we understand jointly where the issues are that we didn't come to resolution on. We really were quite unsatisfied where we were and we're asking you for a reconceptualization. Some of the issues we've resolved, some we haven't, and I just want to make sure we leave with a common understanding of where that is. So I would like to take about a half hour out of tomorrow's session to deal with that. And I think there's enough discussion time to do that.

That's all I have. Thank you very much. I hope to see most of you later on.