MEETING OF THE GENETICS SUBCOMMITTEE OF THE NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

DR. SHAPIRO: Colleagues, there are just two brief announcements. One of a more personal nature than the other. Let me get to the regular announcement first.

We are as I mentioned yesterday, I may have mentioned yesterday, I cannot remember now, considering meeting elsewhere, that is elsewhere than Washington, D.C. area, for our July meeting. I am going to be asking Bill to look at various possibilities. We have received various invitations from particular locations who would like to have us meet there and I think it is a good idea for us to meet outside of Washington to be able to at the very least to get public comment and so on from people who are not directly in this area.

As Bill reviews these, of course, a key aspect is going to be what kind of support we can get from the location to support our meeting and so on. That will be a key aspect of it. In any case I just wanted to let you know that I am going to have Bill investigating the various possibilities. Any of you who are interested or want to find out about this or want to suggest places, please contact Bill.

Now for the personal announcement before we get down to the business. If any of you see a stray black Lands End briefcase, I am missing one. So I

thought I walked in here this morning with it but in any case if you see one --

DR. _____: Is this it?

DR. SHAPIRO: I do not believe so. That has the --

DR. _____: Are you "HTS"?

DR. SHAPIRO: That sounds like it. Thank you. I knew this would be a help.

(Simultaneous discussion.)

DR. SHAPIRO: Do not auction it off, please.

Tom, thank you very much for the few minutes.

DR. DOMMEL: Before Tom gets underway the seating arrangement is, I am sure you figured out by now, for the members of the public this is a meeting of the Subcommittee on Genetics of the National Bioethics Advisory Commission. So where the name plates are, are committee members, subcommittee members of the Genetics Committee or the invited speakers to join in, in that subcommittee's work or staffers. And then elsewhere at the table commission members or staff will be seated without the name plates.

So any commission member who would like to sit at the table who is not please come up and join us.

DR. MURRAY: Welcome to the second meeting of the Genetics Subcommittee of the National Bioethics Advisory Commission. I am glad we started on such a high

note. We already made a discovery. I refer to my briefcase as my life support system. I would be much less calm about it if I had lost mine.

We have until 10:00 o'clock at which point we will adjourn. There will be a half an hour break and then the Human Subjects Subcommittee will meet from 10:30 until 12:30.

As we had hoped yesterday the full commission gave its assent to our desire to press ahead with the first report on the issue of stored tissue samples. This was a subject that we had picked as one that was appropriate for our intensive work in the first year even as we begin work also on at least two other issues with which we have interest, that is genetic discrimination and privacy on the one hand and gene patenting on the other. But we are going to focus this morning's meeting on the issue of stored tissue samples.

We have asked three guests specifically to join us and make brief comments, about five minutes each, coming from different perspectives. We have Dr. David Korn and I will ask each of them to introduce themselves in a minute. Dr. David Korn, Dr. Mark Guyer and Dr. Debbie Saslow.

We also have two people, at least two people in the audience, who also have a great deal -- who know a great deal about this issue and whom we may feel free to

call upon and they should feel free to add to our conversations. Let me begin by asking you to introduce yourselves.

Would you do that, Dan and Elizabeth?

DR. DRELL: I am Dan Drell with the Department of Energy, Human Genome Program.

DR. MURRAY: Elizabeth?

DR. THOMPSON: I am Elizabeth Thompson and I am the assistant director for Clinical Genetics Research in the ELSI program at the NCHGR and currently on detail to the director's office in the Office of Policy Coordination.

DR. MURRAY: Thank you very much. You should feel free also to be a resource for us if you have anything that you think would contribute to our conversation.

Debra, may I ask you to introduce yourself and to begin by telling us about your work with the National Action Plan on Breast Cancer and particularly the focus group study?

DR. SASLOW: Can you hear me?

DR. MURRAY: Move it very close.

DR. SASLOW: I am Debbie Saslow and I work at the --

DR. MURRAY: Actually would you mind sitting here? That is at the request of other commission

members.

DEBRA SASLOW, OFFICE ON WOMEN'S HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

DR. SASLOW: I am Debra Saslow. I work at the Office on Women's Health and am on the National Action Plan on Breast Cancer which is coordinated by the Office on Women's Health. We have six working groups, one of which has been dealing with tissue banking issues and has spent most of its time on ethical issues and developing a model informed consent form.

I believe you all have a copy of our focus group report which explains some background and history about the project and provides the draft form that was focus group tested. I am going to limit my comments to just a few relevant points specifically about the genetics issue which I think is what you are most interested in.

First of all, one of the premises for this -- one of the early decisions made by the committee that developed this form was that they were only going to address prospective studies. They were going to ignore the issue for now of retrospective studies. I know that came up yesterday. So it is developing a form for any tissue that would be collected from this point on.

They recognize that a lot of genetic research is not different than general clinical scientific

research, however there are some types of genetic research that are different and that do need to be handled differently. Given that this is a breast cancer plan the example dear to their hearts is the Tay-Sachs samples that were used to identify BRCA mutations that are more prevalent in the Ashkenazi Jewish population and that that research has the potential to be used to discriminate not only against individuals but against a group of people.

What they decided to do to address that was to specifically mention genetic research in their informed consent form which other than that deals with cancer research in general using breast cancer as a model.

They start -- this was a long process. I would be happy to answer specific questions about how long it took and who is on the committee. But it started with a much longer form and gradually got whittled down. We also worked with a low literacy translator and genetics. That was an obstacle for dealing with genetics because that is a difficult topic to explain to the general public on a low reading level.

They started with several questions on the consent form. Actually they started with four and ended up with three and may decrease that further. But the fourth question that was deleted was: "Do you give your

consent for your tissue to be used for genetic research?" And the reason they deleted that was for practical reasons. They did not think they could track. This tissue can be used for cancer research but not cancer research that deals with genetics. But they did feel that some mention of genetic research needed to be mentioned in the form itself and that consent for cancer research would include research that involved genetic research.

That sentence that was left or sentence or two did raise some confusion for the focus groups. The committee that developed the form will be addressing the results of the focus groups in the next couple of weeks. They meet by conference call and they are leaning towards developing a question and answer form that would accompany the informed consent and that this consent form would be given to patients a week or two before they needed to sign it so that they could take it home, think about it and discuss it with their families.

Those patients who want more information, who want to know more about genetic research and other issues such as -- the second question was: "Do you give your consent for research other than cancer?" So general medical research. And that question came about because some consumers might object to their tissue being used for such things as behavioral research which is another

topic that came up yesterday.

So this Q&A form would address -- would explain genetic research and why some people might object to it as well as some of the other issues that came up as confusing to these focus groups or that some people might want more information about such as what are these other types of medical research and why should I be concerned about them.

Those are my main points about the genetics issue. I would like to mention that we have another working group that has been very active dealing with hereditary susceptibility issues. Whereas the tissue banking group has used breast cancer as a model for cancer, the genetics group has used breast cancer as a model for genetics. I think that a lot of the work they have done might be of interest or might be able to provide resources to this committee.

We have done a lot of work on genetic discrimination. We have addressed health insurance, employment issues. We have thick notebooks going state by state of legislation. We will be addressing privacy in the coming months. We have address lists of consumer groups, of just a lot of different information that I think might be of interest. We also have a clinical trials susceptibility working group. That is an issue that came up yesterday. A consumer involvement group.

So I would be happy to continue to provide any information I can.

DR. MURRAY: Thank you. This is the first time we will have met as a subcommittee with other members of the commission present and it seems to me to be quite artificial to say that to invite questions or comments from only members of the subcommittee. So I am not going to do that. I mean I will rely on the common sense of other commissioners who are here but not members of the subcommittee.

Please ask your questions if you have any questions of Dr. Saslow at this point. Bette?

MS. KRAMER: Debra, you mentioned that they used the Tay-Sachs material.

DR. SASLOW: Not the action plan but researchers.

MS. KRAMER: That material has been used.

DR. SASLOW: To my understanding that is blood samples.

MS. KRAMER: I mean other than for the Tay-Sachs. They have gone back subsequently and used it.

DR. SASLOW: Right. It is my understanding that individuals who are Jewish and, therefore, gave blood samples to be tested for whether or not they are a carrier for Tay-Sachs, that those stored samples were then used by researchers and that those samples were used

in research that identified BRCA-1 mutations that are prevalent in the Jewish community.

MS. KRAMER: Now did they go back to the donors of that blood to get an informed consent for that? They did not?

DR. SASLOW: No. And that also brings me to the third question in our consent form which is "Do you give your consent to be reconsented if we want to use your samples for something that is not in the original consent form?" We tried to make the consent form as inclusive as possible but left that as an opening.

MS. KRAMER: I was just curious and maybe you know the answer to this or maybe Tom or David: When they went back and used the samples that were taken for Tay-Sachs had that -- was that anonymous?

DR. SASLOW: I believe so.

MS. KRAMER: It was?

DR. _____: It was.

MS. KRAMER: It was.

MR. HOLTZMAN: Were they anonymous or anonymized? I mean, was it theoretically possible to go back to those people or was it impossible?

DR. _____: That I do not know the answer to.

DR. THOMPSON: I do.

DR. MURRAY: Elizabeth?

DR. THOMPSON: Dr. Collins was involved in that research and he after much deliberation, they made the meticulously -- I mean, they anonymized them but there was no possibility of linking them back, none, by anybody.

DR. MURRAY: Zeke?

DR. EMANUEL: At some point early on you talked about the fact that for some tests you were worried because it might be used to stigmatize a group and discriminate and you were in that context referring to the Tay-Sachs and Ashkenazi Jews. I did not understand why that does not apply broadly to genetic tests that might -- we do not know before we start -- track with different racial ethnic groups.

DR. SASLOW: It does. I think my point is that there is also other types of research. You know, genetic research can be defined pretty widely and if you are studying just DNA and not looking at genetic predisposition or genetic disease some people would consider that genetic research. I think Dr. Korn will probably be addressing more of that. That was one example. There are many other potential examples but there are also examples of research that might not have any potential harm or raise concerns to the consumer.

DR. MURRAY: Larry?

DR. MIIKE: Let me get clear about the

process that you are in, in revising the form. You have now asked an additional question about reconsent after the initial with the objective being that once they sign this one they are reconsented for any subsequent use?

DR. SASLOW: No. We are giving them the option to be notified, to be contacted in this case by a middle person in the process of anonymizing samples and not by the actual researcher, but by this tissue banking middle group to recontact somebody to ask them if their tissue may be used for some purpose that turns out not to be covered in the original consent form.

DR. MIIKE: Just let me ask on that specific point then. Why do you ask a question for a yes or no answer when just a simple statement within the consent form informs them that they may be recontacted? Anyway, it seems kind of weird to me that you ask them a yes or no question, that they sign on that says you may contact them when you could simply just ask them or just in the informed consent process tell them that something like that may happen.

But maybe I am not articulating what I am trying to say and I am trying to put forth. But the process that you are going through now you found certain things that need to be improved so you may have added an additional question and then you are going back, at the current time back into the explanatory part of the

document to try to make a better connect between the explanation and the question?

DR. SASLOW: The genetics question was deleted prior to the focus group testing just based on the committee discussion.

DR. MIIKE: I am just looking in terms of the whole revision process.

DR. SASLOW: Right. There was a lot of revision prior to focus group testing just within committee and the committee -- the focus group report was only recently received by the committee. They will now address the concerns raised by the focus groups although based on some preliminary results that were communicated to them during the process we already have some ideas of the direction they will be going to finalize this one.

DR. MIIKE: Is the group also sort of standing back and seeing that at the end of the process can you really get informed consent about this at all? It seems like it sets -- it starts to get into such a wide open consent kind of an arrangement that you just sort of -- I begin to feel that it sort of -- I do not want to use the word -- I guess I better not. But it just seems like it is a -- it is trying to establish a process for something that is almost a disconnect in terms of a real consent. Do you see what I am trying to get at? I mean, it is a consent to such a broadly open -

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DR. EMANUEL: It is overly broad.

DR. MIIKE: Yes.

DR. EMANUEL: Maybe I can amplify it. When I read the statement -- one of the -- we are always balancing things. Are you getting -- you want to make it so that people do consent and on the other hand you do not want them to consent something to so vague that it applies to almost anything. I guess one of the questions is whether number two, the second question, is just so open that in fact you are not really getting consent.

It looks -- I mean, it smells like consent, it is a signed piece of paper, but people have no idea what they are saying yes to when you ask them in that form. So that -- while informed consent is meant to protect people and give them a chance to understand what their tissue is being used for, in fact it is really robbing them of consent when it is so overly broad.

I think that -- Do I have it right, Larry?

DR. MIIKE: Yes. I guess it is a -- I am not following anybody, but I guess it is a deficiency of an informed process that boils it down to a written statement that one signs. I guess that we are stuck with that. That is an issue I really want the commission to look at. Not the procedure that one currently goes through and end up with a piece of paper, but the whole -

- the whole process about can we actually get some reasonable way of true informed consent in the whole process.

It just -- what I am getting at is that since you are sort of bound by the current way of getting informed consent which is an ultimate piece of paper, it seems -- especially when you get into these kinds of areas that I do not really -- I see it as sort of an impossible task to get truly informed consent this way.

DR. MURRAY: David?

DR. COX: I have a comment and then a question to Debra. The comment is a perception, again in a way of trying to protect research subjects in this kind of a setting against unwanted recontact, and in fact -- I will just make a pretty dogmatic statement that something through good wishes paternalism cannot necessarily be good. I know that I am contacted by people constantly for things that I have no interest in because I am on mailing lists and I have a very simple solution to that. I hang up the phone.

So I think that this is something that goes on in our society on a regular basis and if people are recontacted simply because they happen to be on this particular mailing list, i.e. they were on one research thing, then in that specific situation they have a very specific way of saying that they have no interest at all.

Does that really infringe upon their rights as an individual or their privacy? I think that is the kind of issue I would like to explore a little bit and it is along the same things you are talking about, Larry.

The question I had for you, Debra, was if there was a specific reason why your group chose not to deal with retrospective samples because this commission is talking about dealing with retrospective samples and one reason could be it is because you think it is a nonproblem. The other reason could be it is like too big a problem. So whatever -- I am interested in what the reason was.

DR. SASLOW: I think the reason was that it is a separate problem and that they would have to deal with them not together and they decided to take one piece of it. As far as the reconsent I would just like to mention the reason for the question is to protect people who do not want to be contacted but also another piece of this project is principles that they have developed that are geared towards IRBs and that would set out rules for recontact so that you would not be contacted 25 times. There would be some kind of priority and limitation of how many times you could recontact. So this is just one big piece of the project of dealing with informed consent and ethical issues.

DR. COX: Can I do a follow up, Tom? So

then, Larry, in regards to you that this piece in many ways really perhaps is not an informed consent but it is a separate thing in between that is basically dealing with protecting people against recontact and not to -- those sound to me like two very different things in terms of consent for -- broad consent for another study as opposed to consent for recontact.

DR. EMANUEL: Yes, but questions one and two are not about recontact. They are about using tissue.

DR. COX: No. So I am not specifically talking about one and two here specifically but in terms of recontact per se.

DR. MURRAY: Steve?

MR. HOLTZMAN: Let me address one and two and Zeke's question of whether it is done in a written form or some better kind of form, the whole notion of is it possible to get consent for something, a genuine consent when you cannot describe what it is you are going to do because your question goes to that and whether that is possible? So some real life experience. We go out and do a genetic study trying to identify the genetic basis of say asthma. As part of the clinical characterization of that because people -- we take a blood pressure reading and so consequently if you are also doing a hypertension study it might be useful for example if you find the polymorphism to go back and do an association

study back into that cohort that you found in the asthma study. It could be very useful. So how do you handle it?

What I see modeled there at least as the way we have adopted it is you ask for the consent of the person for the use in the particular study that you can describe. The next level is to recognize that if they have familial say asthma that they could have an intrinsic interest in that disease so that you get consent for additional studies within that disease. And then the last is getting the consent for a broader more wide open consent for use in future research.

So in that way you are trying to give people the ability to say how far they want to go. I think you are raising the question is that last request valid?

DR. COX: Right.

MR. HOLTZMAN: And it seems the position at least we have taken in our work is that there are people who by giving the people those different levels of the ability to discriminate it recognizes that someone can say, sure, I am quite happy that my sample can be used in any way to help medical research.

DR. EMANUEL: Well, I think it is in the anyway that requires a certain imaginative capacity on the person who is giving the consent as well as an ability to predict what science is going to hold in five,

ten, twenty years. That is very difficult.

Now, you know, when I wear two hats, one hat as a researcher myself, I understand why I want that. It is a big problem trying to track everyone down, you know, maybe ten or twenty years later, and we could get extremely valuable information. I do not deny it.

On the other hand, you know, I want to say did someone really consent in the way we mean consent when they signed this for something that is going to happen ten, five years down the line in a completely different area. I think, you know, again we are stretching the notion of consent there a little far and we may say that is stretched for a good reason and we are going to accept it. But I think we have to recognize what we are balancing.

DR. MURRAY: Rhetaugh?

DR. DUMAS: It seems to me that the issue to me is informed consent and the farther removed the person is from the initial intent of the transaction the less informed they are going to be. So I think that for me the issue is whether or not in getting some a priori consent far ahead of time you are, indeed, getting informed consent. I propose that you are not.

DR. MURRAY: Carol?

DR. GREIDER: That was exactly my point. In signing this one is giving consent but not informed

consent for exactly the reason that Zeke just said.

MR. HOLTZMAN: I guess I wanted to challenge that. I mean, I can imagine someone coming to me, right, and saying I want to use this sample and I am going to use it in ways in which I cannot imagine this medical practice changes medical research changes. I understand that. I feel fully informed. I feel like I have the basis for making a decision as to whether or not I want to consent or to qualify that assent in various ways such as that is fine as long as it is anonymized. All right.

DR. GREIDER: But you are not the average consumer. You can imagine what some of these things might be down the road in terms of medical research.

MR. HOLTZMAN: Not necessarily, Carol. All right. Maybe what I am saying to myself is if there is no harm that can come to me, for example, if it is anonymized, all right, but I am quite happy it is used in any way. It does not matter to me. So it is a question here really of whether you are going to go paternalistic in trying to make a decision about what constitutes the ability of one to be informed or whether you are going to say can we structure it in such a way that people can exercise an autonomy right to make a decision, whether they have a sufficient ground.

DR. DUMAS: Think about potential harm to community. Raise the issue of what might be perceived as

potential harm to a community who use the samples to show for example some inherent problem in a particular class of people. That could be conceived as potential harm to community.

MR. HOLTZMAN: I think that is a very valid point, Rhetaugh, and that is what is interesting about going back to the samples from Tay-Sachs is that even anonymized, having removed the individual identifiers --

DR. DUMAS: Right.

MR. HOLTZMAN: -- nevertheless you had a characterization of the sample -- the group of samples.

DR. DUMAS: Right.

MR. HOLTZMAN: I think that is a valid issue that one needs to think about.

DR. COX: Steve, it seems to me that your argument -- okay, if I got it right -- was that sure this is fine because it will not do any harm because things are anonymized. In fact, if they were completely anonymized so you did not even know the group that they came from too, then like totally anonymized, then I could see your argument. But otherwise if they are not anonymized then we know that there is -- whatever the probability --

(Technical difficulties.)

DR. MURRAY: We have lost sound.

DR. SASLOW: I just wanted to mention --

DR. MURRAY: We have lost sound. Can you hear me?

DR. _____: Yes.

DR. MURRAY: We have sound. Go ahead, Debra.

DR. SASLOW: I wanted to mention that members of this committee included consumers, that those consumers in this case just happened to be Jewish as well as breast cancer survivors and that they were looking at from the perspective of, you know, when I got my breast tissue removed, this is how I feel the community issue was discussed.

DR. MURRAY: Thank you. Larry?

DR. MIIKE: Having started off the way I did now let me change tracks a bit. It seems that what you are -- faced with the dilemma that you are faced which we just discussed, it seems that what the group is trying to do is to say there may be times in the future where it will be used for things unknown and we are asking you for broad consent to recontact you. I would feel comfortable if there is a recontact process and if at that time those are initial consent were then provided enough information to then make a subsequent independent decision about their reuse. That I assume is what is being attempted in this revision of the consent form.

What you just said is they are just giving permission to be recontacted. It is not a blanket

provision to be -- to use their tissue in anyway. Is that correct?

DR. SASLOW: I think the second question deals with other medical issues that we can understand now and that would be addressed in a separate, not in the actual consent form, but in a separate like Q&A or brochure for those who want the information which goes back to the broader issue of the informed consent. A lot of these focus group participants do not want all the information and that has been a difficult thing for us to deal with. As far as the reconsent again that is a piece that is a start for either IRBs or this group or some other group to take off and come up with rules about reconsent.

But the idea is that there may be something in this consent form that is not covered and something that researchers want to do with the tissue and they should not automatically be able to call up somebody and say, hey, can I use your tissue for something else. But if that is okay with the person then they can give the consent to be recontacted again with the -- under certain rules that are yet to be generated about -- but that would not be a call every other night from any researcher for any purpose.

DR. MIIKE: But with the intent that when they are recontacted they are then given another

explanation of the specific use of them?

DR. SASLOW: Right. There would be a whole another consent form for whatever, you know, would be appropriate at that time.

DR. EMANUEL: May I? We have been talking about anonymizing the tissue samples and all. But as I read this consent that is not part of it, right? I mean, part of the whole point of this consent is to keep all the medical history that goes along with that tissue sample so you have the richest pool of research data possible.

DR. SASLOW: Without the person's name and keeping in mind that this is cancer research where they would want to know, for example, with breast cancer was a person estrogen positive or negative, did they relapse, et cetera.

DR. EMANUEL: I have to say I still do find number two -- I think it needs more thought. I mean that is just my reaction here. And again as a researcher I absolutely understand why one wants to have this and I can see that it is hugely important and it makes things efficient. But I think we need to think about under what conditions might it be permissible and do you need more information in this kind of consent before -- about how it is going to be handled, et cetera, before that consent can be considered informed and legitimate.

DR. MURRAY: Carol?

DR. GREIDER: I guess I also have a question between question two and question three. Question two reads, "I agree that my tissue may be kept for research about other medical questions." And question three, "I agree that someone may contact me in the future to ask me to take part in more research." If somebody signs yes to number two, why would they even need number three?

DR. EMANUEL: They might need a different tissue for example.

DR. MURRAY: I would like to make a distinction that goes to why we invited you here. We have been focused, I think appropriately we have been focused on whether or not this kind of particular form would be satisfactory, that is whether it would, in fact, as a -- you know, given informed judgments by people sophisticated about this kind of research and about the ethics of human subjects research, whether this particular form and process would be adequate.

We also though invited you here not so much to judge the form and process, and I just have to note for the record as far as I know most consent forms are not developed with this kind of care. So if this is -- if we can raise these kinds of complaints about one that has been developed with excruciatingly detail and care heaven help the rest of them.

We also invited you here though to find out what it all means to the people who are asked to sign the forms. What do they understand when they are told that this tissue -- that there are tissue banks and at least one of the comments indicated that, you know, the banks -- people make money in banks and there are lots and lots of interesting interpretations that your respondents made in these focused groups.

It goes -- there are comments about the motivations. Why people would agree. There was interesting information about the question of -- we had the question yesterday whether individuals as sort of isolated, atomistic persons who just make these decisions in the full glory of their autonomy, or whether in fact they see themselves as situated in families and they want to talk to their families, and you have information that pertains to them. My gloss on it is that yes they want to go talk to their families for the most part. They do not see themselves as making these decisions entirely in isolation.

Is there anything you want to stress to us about how they understand genetics and how they understand what it means to give -- to provide tissues for research or should we just -- the data can speak for itself. But if you would like to say anything more to us I would like to give you that opportunity and then we are

going to take you off the hot seat.

DR. SASLOW: Okay. I think as far as genetics there is not good understanding about what the concern is so even if they understand genetics they might not understand the implications. I think that there is a lot of people who do not want to know, who just want to sign it and do what you want and there are others who want a lot more information, and so again our response will most likely be here is separate information outside that consent form. If you want it, it is here. Again a practical issue, we foresee the informed consent form being delivered and presented to the consumer by a doctor. We wanted a doctor.

Presumably their surgeon with some explanation, with some conversation, do you have any questions, do you want to discuss this, here are the things that, you know, commonly come up. But also with the understanding that a lot of doctors do not take the time to do that and just hand it to people as they are being wheeled into surgery. So we are providing the information but with the hope that there will be more.

I also want to underscore that one of the biggest goals of this project was for the consent to be informed and not to develop a consent form, but for the consent process to be informed. And that was behind a lot of this and I think the report speaks for what the

public is responding.

DR. MURRAY: I see Bette wants to say something and David wants to say something, and then I think we are going to -- we want you still here but maybe sitting there and we will invite Dr. Korn to come up and speak next.

Bette?

MS. KRAMER: Debra, when we spoke a few weeks ago I think you told me that your group was developing an informational video. Has that -- do you intend to use that along with this or --

DR. SASLOW: That video is on genetic testing for breast cancer. It is done by the different working groups. It deals with the hereditary susceptibility issues. The informed consent deals strictly with donating tissue for research. So there is overlap --

MS. KRAMER: So it did not pertain to this issue.

DR. MURRAY: David?

DR. COX: Since this commission as Tom -- at least the subcommittee in particular is very interested in finding out what the public's perception to stored tissue banks is I found it very interesting in the focus groups that one of the conclusions was that the participants were suspicious about the motivations behind tissue bank research.

So what were they suspicious of? Because the -- I would be interested in that.

DR. SASLOW: We were told by experts that conduct focus groups that we should give as little as information at the outset as possible who we are sponsoring. So I think that there was a lot of suspicion there. Again there were cultural differences. The African American community was very suspicious about, you know, the whole -- you know what those researchers like to do with our tissue and they will take -- all the groups, but particularly on some of the Baltimore African Americans were very suspicious about profit and about using tissue for unethical reasons. I think there is a lot of misunderstanding or a lack of information about what research is and how it works.

DR. MURRAY: Thank you very much, Debra.

Dr. Korn, would you be willing to join us at the front of the table for a bit?

DR. KORN: It does not seem to improve the quality of the sound system I am sure.

DR. MURRAY: Let me just switch the cards around. Dr. Korn has consented to join us. I gather you are usually in California but you are at the Association of American Medical Colleges now as a distinguished research scholar if I recall correctly.

DAVID KORN, AMERICAN ASSOCIATION OF MEDICAL COLLEGES

DR. KORN: Yes. Well, thank you very much for allowing me to be with you today and feed you some fuel for your debate. I will just say that I have been a faculty member at Stanford for 29 years. I was chair of the Department of Pathology for 17 and vice-president of the university and medical school for 12 -- 11. I am on sabbatical now with the Association of American Medical Colleges undergoing rest and rehabilitation, and it has been very successful.

Let me try to give you a somewhat different perspective on this issue of tissue issue. I will talk about --

(Technical difficulties.)

DR. KORN: -- although it is not just generally recognized by the public, and we can argue and apologize for that forever but it is a fact, our nation's hospitals and especially the academic medical centers collectively contain an enormous archive of human tissue samples that represent a unique resource that reflects the prevalence and protein expressions of human disease over time. It is a document of human disease over time that goes back to the time that these materials began to be collected over a 100 years ago.

The specimens were all removed for medical reasons under sparing general broad consent language that usually provided a proviso for research and educational

uses and were submitted to the path lab for diagnostic evaluation. That is why they were removed and submitted to pathology.

Although they were not collected specifically for research purposes these specimens have, in fact, served as a rich source of materials for clinical pathological investigations that again as a fact have provided most of the vocabulary and much of the foundation of modern medicine. That is what modern medicine has evolved from.

The results of the studies because of the technologies available have historically been of public benefit, not private. And thus of little immediate consequence to individual patients from whom the tissues have been derived. Accordingly and admittedly the practice and standard of informed consent for this vast body of research, vast body of research, has been minimal and I would say in the context of present understanding inadequate.

What has changed of course has been the introduction of dramatic new technologies like monoclonal antibodies and polymerase chain reaction which allows investigators to go back to these fixed paraffin imbedded section tissues and examine genetic abnormalities either in gene structure or expression and infer whether these changes are as they commonly are of somatic origin and

therefore not inheritable or on occasion of germ line origin and therefore inheritable.

The power of these approaches provides unique insights into the mechanisms of human diseases. For example, neoplasms is as evident from just reading the contemporary medical literature that I believe cannot be obtained by other means and they offer enormous promise of advancements and diagnosis and prognosis and therapy, and even prevention. At the same time, however, by their nature the results may be construed to have major predictive consequences for individual patient sources and their families and this fact has rested the entire topic of research on human tissue from a historic state of peaceful repose to sharp prominence in the public consciousness.

Now a lot of the committees and groups have been wrestling with these issues. Many of them under the sponsorship of the ELSI program and a number of proposals have been circulated or published in the last couple of years. I think that these efforts -- I think very strongly that these efforts have suffered from a lack of broad based scientific input. I think this is reflected in the proposals which many of my scientific colleagues and I find to be disappointing and unduly threatening to an entire class of promising research.

I would like to make four general

observations about these processes which are personal and then offer some specific recommendations that I realize will be controversial.

First I think that the deliberations have failed to distinguish between two different issues. One of them is genetic testing which I think should be defined narrowly and which raises considerations of definition and appropriate informed consent. The other is genetic information that can be obtained or inferred from a myriad of clinical and research sources and which raises concerns of privacy and of the protection of the confidentiality. I think secondly it has been too readily accepted. In my case the genetic information is unique and different in kind from all other private, sensitive, often predictive, often stigmatizing information that can exist in a medical record.

I argue that the difference is not so much qualitative, it is one of degree, and I think the distinction is important in devising appropriate and workable, and I underline workable mechanisms for protecting confidentiality.

Third, I think it is disappointing then in attempting to deal with issues that heavily center on preventing the misuse of genetic information obtained through research so much effort has been expended not in trying to strengthen the protection of the information

but in burdening the conduct of genetic inquiry and erecting barriers to the ongoing creation of the knowledge base.

I think the proposals thus far have a very commendable input of bioethical and legal perspective but an inadequate input of scientific perspective. I think they come down too heavily on the side of private interest at the expense of public benefit and thereby destroy the delicate equipoise that must always be respected in research involving human subjects. So let me make a couple of specific suggestions. Fuel for discussion if you will.

First of all, I think that much more attention has to be paid to the definition of terms in order to achieve precision and avoid confusion and adverse unintended consequences. In the context of contemporary molecular biology terms like genetic research, genetic sample and even genetic tests colloquially used are exceedingly broad and so inclusive and imprecise that it is inadvisable to attempt to use them as the basis for new research guidelines or regulations.

I would respectfully suggest that an example of the semantic contortions that one gets into in not dealing with these definitional issues is beautifully illustrated in the scholarly commentary to the genetic

privacy act by George Annas and his associates. I commend it to your attention.

Secondly, I would argue that genetic testing appropriately defined should unarguably meet a high standard of informed consent. But again the definitions proposed are too broad and overreaching and I think they should be narrowed to focus on the purpose of the study rather than on the kinds of research methodologies that are used. For example, I make no pretense of being a geneticist as David Cox knows, I would suggest that such a test might be one that is carried out on individuals to determine the presence of particular inheritable risk factors of established predictor significance for purposes of genetic counseling and/or medical management or on populations for epidemiologic purposes.

I think the research studies on human tissues removed for medical reasons ordinarily should not be construed as genetic tests even if they involve examination of gene structure and function. The results of such studies should not be considered diagnostic, should not be entered into the medical record ever and should not be communicated to the source of the tissue ever. There appears to be general agreement.

Third, that the informed consent protocols used for research on human tissue specimens must be strengthened and that different stringencies of informed

consent perhaps should apply depending on whether samples are anonymous or linkable to patient sources. I would point out that research on samples that are coded but linkable to patient sources -- I would argue, excuse me, that research on samples that are coded but linkable to patient sources should continue to be eligible for approval under a general informed consent mechanism under specific circumstances that I will address in a second. But I also would suggest in any new consent protocols developed for use in the clinical setting must be clear and simple, and provide the patient with a clear yes/no option.

I do not know how many people in this room have been in surgery. I have. And I will tell you that facing surgery on the instant of the anesthesia you are in no mood to get into a elaborate dialectics over potential future uses of your scraps of tissue. You simply are not. That is not informed consent. I do not care what the language says. That is not informed consent.

I would argue that the language should be crafted in conformity with the principle of general informed consent. I know that is controversial. That it should be based upon the premise that the national tissue archive has always been and should remain a public resource dedicated to the public good. And not a

depository like a savings bank of private property.

I know fourth that efforts are underway in the Congress and many states legislatively to strengthen the protection of clinical genetic information and prohibit its misuse in discriminatory fashion. I believe that many of these initiatives are hasty, ill considered and inadvertently over reaching even at the same time that they contain substantial loop holes that undermine their intended purposes. Much more thoughtful effort must continue in this arena and similar efforts must be initiated to secure genetic information created in research.

Now elsewhere I have suggested and I am not sure it is a good suggestion that a mechanism like the certificate of confidentiality mechanism or some new mechanism from statute might be developed to protect as a class all genetic information created in research and that such protection could be conferred on research institutions through an assurance mechanism that required those institutions to have in force an institutional confidentiality policy that met specific requirements including the provision of severe sanctions against violations of that confidentiality rule.

Finally I would urge the subcommittee to broaden participation in this important debate by reaching out to the scientific community and especially

to those who are increasingly employing the tools of contemporary molecular biology and molecular genetics to tissue samples of human origin to gain unique insights into human diseases that are major burdens to our society, both in terms of human suffering and resource consumption.

I think I will stop there. I have a handout which you have and I would just point out to you again for a fuel for your discussions that there is a model consent language that I tacked on to the end of this statement just to give you an idea of the other extreme if you like from some of the proposals that have been attempted or circulated by other groups.

I would like to just point out to you that when you think of the tissue archive there is no way as some of the people on this side of the table have already said to predict the kinds of research applicability that might be -- that might arise months, years or decades later than the collection of that tissue.

So if you really believe in informed consent where every potential use of this material could be presented honestly and completely to a patient in advance, it is impossible. It is impossible. The only other alternative that you would have then is to go back to each patient or their next of kin on every single specimen that might be identified as interesting for some

study of the disease in question or whatever else might be useful for those tissues. Most of those tissues are used longitudinally to study the diseases for which they were removed. In general that is what happens to most of them.

That is how our knowledge of disease is developed. It is the mechanism by which the knowledge of disease and its manifestations, its classifications, subsets of disease and how they respond to different therapies or do not respond is accumulated into the medical literature. That is how it happens.

This resource is an irreplaceable, invaluable resource that has to be maintained with maximum accessibility for the public. I urge you to try to keep that point in mind as you get into these very, very difficult issues that you are wrestling with. I wish you luck with your deliberations. Thanks.

DR. MURRAY: Thanks. Let me invite questions or comments.

DR. COX: Dr. Korn, as one of the members of the scientific community that does use this information I would like to say that I really think that your analysis of the historical present of this versus the present time is a very apt and interesting one and that is where I would like to come into this discussion.

If I heard you right you said that

historically that this information really was used -- it did not have applicability to individuals and that what is different if I heard you right is that with the new technology now there is a perception that the new technology will have applicability to individual.

It strikes me that that is where the discussion and where the turf is divided up really lies because if, in fact, we are in a new time where information does have important consequences to individuals then this distinction of information as being research versus practice becomes a blurred one.

It again strikes me that that is really where the discussion lies in terms of whether we even need to have a different view of dealing with stored tissue samples. So I would very much like to hear your views on that particular point because if we are in a new time where the historical tissue archives now have different implications for individuals, first are we in that kind of a time and, if so, then how do we deal with that?

DR. KORN: Okay. Fair enough. First of all, implications I think -- would you agree that implications are particularly relevant to the discussion if you are picking up something that is germ line?

DR. COX: I would like to go even broader than that just in terms of implications to the individual whether they are germ line or not. I think that the

specific -- it is, is it information that the individual could or should use for making personal decisions?

DR. KORN: Well, it is my -- again, I want to emphasize that being in the jobs I have had, and I have gotten deliciously distant from some of the front lines on this, so if I misspeak I hope you will correct me. But I do not really believe that the study of somatic changes in tumors, for example, has very much in general particular interest to the patient sources. I think that information is much more pertinent to developing an understanding of the progressive changes that lead to the transformation of the normal cell to a malignant cell.

It is of interest I think that as far as I can recall not a single proposal except the one that came out of Dr. Holtzman's genetic testing task force, not you, the Johns Hopkins Holtzman, even mention the difference between somatic and germ line mutations. It is never mentioned in any of the documents and proposals that have been circulated, including George Annas' compendium.

Now, yes, if you are doing research on tissues and you pick up a germ line mutation, yes, you definitely could argue that this has significance for the person and probably the family of the individual who has submitted that tissue. But I think that in order -- I guess the way I come down on this is that I want to keep

access and use of the research of the tissue archive as unencumbered and unburdened as we can.

I am willing to trade off on certain conditions in order to accomplish that and one of the conditions that I personally would be willing to trade off on and again I am sure that this can be debated is that this material, this information is never diagnostic, it is never entered into a chart, and it is never communicated, and nothing needs to be identified with a particular individual.

Most researchers as far as I know who are using tissue for these kinds of studies have no interest whatever in the name, address and social security number of a patient. There does have to be linkability because a lot of this data is very -- of very limited value unless, for example, you can go back to the clinical record and find out it is what the biological correlates are. That can be done through a protected mechanism like a tissue repository mechanism where the investigator need never have access to the chart but would go through a secure linkage point or request through a secure linkage point the information.

Now I do not know whether everybody in the room understands what I am talking about but let me give you a very simple example. One of the vexing problems in modern medicine is the inability of clinicians and

pathologists who receive a minimal breast lesion detected by mammography let's say to know whether or not that lesion is going to be a problem to the woman from whom it has been removed.

In many, many cases removal of that minimal lesion is a cure. But there are other cases in which it will not be a cure and those patients need aggressive chemo and/or irradiation therapy, and maybe tamoxifen, and all kinds of other interesting things. We cannot really tell which of those minimal lesions. The same thing is with prostate in males for example. If we could find particular genetic markers that would reliably predict benign behavior or aggressive behavior in these now confusing lesions which are so abundant it would be an enormous public benefit and an enormous benefit to patients. That is a kind of genetic research that I think we do not want to hinder. We do not want to hinder it.

DR. COX: David, I completely understand that and that is in the --

DR. KORN: Yes, I know you do.

DR. COX: -- sort of historical model. But in the context of where information can be used by the individual to make decisions then it is difficult. I would just say with respect to somatic mutation, and I am not an oncologist, we have an oncologist here, but I

think that there are clinical decisions made based on the distribution of somatic mutations in terms of what your therapy is right now and medical practice now that has direct implications to a specific individual in terms of what their somatic mutations are.

So I am not saying this is easy and I certainly understand the paradigm that you are talking about which has been, as you very eloquently state, has been the historical basis of all of modern medicine. But I think that if we are in this modern time which I did not hear from you whether you think we are or not, where things are different, then we have to deal with -- then do we have to deal with those differences? The trade offs that you spoke about which you are willing to give up to be able to maintain the historical way of doing things. I think that is what this commission is looking into is should we be -- how do we adjudicate those trade offs.

DR. KORN: I respect your point, David, and I do not really disagree with it. I do not believe the current standard of informed consent is adequate. I have said that and I will say it again. I think it has to be strengthened. But how it is strengthened and how one goes about doing this I think is critical and I think there are two very serious issues -- three serious issues here.

One, the emotional state of most people who are going to be asked to do that consent. They are not going to be sitting around a desk having an intellectual discussion about genetics. They are going to be scared to death about what this thing is in their body that needs to be removed.

Two, it is impossible to predict what kinds of applications, technologies and questions might be benefited from using that tissue over a long stretch of the future.

Three, I think that how you ask questions, as many of you know better than I, has a very, very big impact on what kind of answers you get. There is something magical about the word "genetic" right now. It reminds me, a senior citizen, very much of the furor in the early '70s when recombinant DNA came along and there were enormous -- there was enormous hysteria about the threat to the ecosystem that was going to be offered by recombinant DNA. There were mass meetings and the banning of research in the City of Cambridge and other places. I mean this is a kind of -- we do not want to fan that kind of hysteria. I think that leads to no good end whatever.

DR. EMANUEL: I -- you have said twice now that you think the standard of informed consent that we had used is inadequate. As I understand it there is --

when you come into a hospital there is generally among the papers, certainly in academic hospitals a statement that your medical record and other related information could be used for research, and that is usually the carte blanch on which we have done a lot of this medical records and related work.

Why is that inadequate in your view?

DR. KORN: I think it is fair to say that what happens with tissue is that buried in the operative consent form which most people do not read is a sentence or two that says any tissue not required for diagnosis may be used for educational research purposes. I just do not think that is informed consent.

I think that that -- I mean, I am not saying you should adopt this thing that I tacked on to the statement, but some separate statement that says that these kinds of tissues have been used very importantly in developing medical information and progress. That we would like to be able to use your tissues for such studies now and in the future years, and I think it is important to deal with this issue of property interests.

I do not believe that people have property interests in their scraps of tissue. I know that is also debatable but that is how I feel about it. I know there is only one really good case to my knowledge that has adjudicated this which is the Moore case out in

California. But I do not think that people should have ownership of their scraps.

DR. MURRAY: Steve Holtzman had a question.

MR. HOLTZMAN: Not so much a question as a comment. First I would like to thank you for your presentation. I think what we as a committee are getting here is in some ways the beginning of a conceptual road map of all the kinds of distinctions we could profitably draw and clarify. So, for example, genetic tests. Somatic mutation looking at that or changes in transcriptional profiles of genes is very different than looking for inheritable mutation. The latter is your paradigm. The kinds of concerns you have are very different than if what you are talking about is looking at anonymous samples for transcriptional markers.

The kind of question David raised is has the technology changed the nature of the relevance of the investigations of the individuals. I am not sure, David. For example, the idea of doing longitudinal studies looking at morphological changes which has classically been done in terms of pathology studies. You could find something that says if I see that change it is relevant to the individual.

Another aspect is, is there a difference when the collection of the sample is in the context of a research study, which at least is my paradigm with doing

genetic studies and you can go through this consenting process, versus when it is in the context of the pathology getting the scrap of tissue. It seems to me that there may be important differences. I know that the pathology departments right now also, as we deal with them as a commercial firm, they do not know what to do. They find themselves looking for guidance.

Does it matter that it is the investigator down the hall who wants to look for a molecular marker versus it is a commercial firm that wants to look for a molecular marker? Does that make a difference? On the other hand the investigator down the hall finds the molecular marker and that institution turns around and licenses it to a commercial firm. That does not seem a problem.

So I think -- again we need to get into these distinctions and try to get some clarity.

DR. MURRAY: Steve, do I recall correctly that you were trained as a philosopher before you went into --

(Laughter.)

DR. GREIDER: I just wanted to -

DR. MURRAY: -- good philosophical work there.

DR. GREIDER: I just wanted to address the practical issue that has been raised a couple of times

between the difference between a somatic change and a germ line change. I do not think that that would be a useful distinction to make because we do not want is going to happen in the future in research.

For instance, there are examples where you might want to cross a somatic change and then later experimentally discover that somatic change is due to a germ line mutation. For instance, mutated phenotypes and other such things. So I do not think that we could, you know, prospectively say that we know that a somatic change has no implication on the germ line.

DR. KORN: I would like to make just one other clarification of what David Cox asked me before. I believe that if a particular genetic marker is identified as and accepted as a valuable diagnostic indicator in a particular disease it moves rapidly out of the research setting into the diagnostic -- armamentarium diagnostic work up. In other words, if one knew that a particular marker in a prostate lesion had important prognostic or therapeutic interest then the path lab would begin doing that test as part of the diagnostic work up of the specimen submitted to it by the surgeon.

Now I would call to your attention that because of the semantic problems, the definitional problems, if you read literally and in good faith, a number of the proposals that are out there to date, they

would require not only informed consent for any particular or potential use of research -- in research of the tissue, but it would require informed consent of a whole host of diagnostic tests that become part of the routine evaluation of specimens.

In fact, unless the surgeon or the clinician knew in advance exactly which of those tests were going to be necessary for that particular specimen, which usually does not happen until the first pathology look is made, you would have to keep going back and forth to the patient and say, well, now we have got to do another test and we are going to have to look at another gene, and let me explain all this to you.

I mean it is cumbersome and I do not think that is what was intended by any of the working groups. They were not trying to get into the diagnostic process. The language has a way of seeping into very unexpected corners when you are using very broad and vague terms. I think that is a problem.

DR. MURRAY: David, you framed things usefully, even starkly when you said that this is -- one could understand this debate as an effort to strike a balance between private interests, the protection of private interests and public benefit. That is a legitimate way of framing it. I am not sure it is the only way but it is certainly a useful way.

So I have been thinking about what are the sorts of private interests, or to put it another way, the concerns of subjects that might be at issue here and let me just -- in the spirit of Steve's comments let me try to list what strikes me as a few as I recall them from reading the various statements in the literature that I have read.

One is discrimination not just for self but also potentially against family. A second is privacy which is not again subsumed under discrimination but also concerns about information about me but also about my family again. A third is the possible uses in research that I would disapprove for whatever reason because it involves research into group differences because it involves research into behavior. You know, on can just let your imagination run on this. That is a possibility.

A fourth is commercialization which David Cox keeps reminding us is an issue that people have concerns about and that can take different colorations. It could be not getting my share although the evidence I saw from the work that Debra Saslow has presented to us indicates that not everyone is concerned with so much getting it for me but there would be some reasonable use which again was sort of second cut on commercialization might be a kind of unjust enrichment without appropriate return to the people -- the categories of people or to the public.

You get unjust private enrichment rather than public enrichment. So commercialization is for me the fourth large category.

And then the fifth which you framed as a kind of generalized property interest, people maintain property interest in bits of their tissue.

I am not arguing that all five of those are legitimate or that they are widely held, but they strike me as at least five different and I would invite other members of the commission if they had other thoughts if they wanted to extend there. That seems to be the kind of -- I am sure we can generate a laundry list and we can look critically at each of those kinds of concerns or interest. Some of them might strike us being much more legitimate. Others as well. Maybe the sorts of things that might appropriately be sacrificed in the furtherance of the larger public interest of research.

MR. HOLTZMAN: Well, one of the things that Alta raised yesterday is that how people feel about all those things might -- it also might make the difference which tissue is at stake. All right. The reproductive tissue. But if you then look at our societal practices, you know, it is pretty odd when you think about it that organs you can only donate, blood you donate, blood is fractionated and the plasma is sold. Plasma on the other hand is purchased when you go to a plasma phoresis

center. Urine, which is also used to find markers and whatnot, people do not seem to have the same relationship related to their urine in quite the way they are related to their blood and to organs.

When we just jump into as our paradigm highly charged areas like breast tissue and cancer I think we get ourselves confused and in the most well meaning way we start to lay down paradigms of how this should be handled then it is problematic. We really need to lay open all of the different relationships and look at the historical -- how we do things with all these different kinds of tissues, the different circumstances under which we as a society collect them and use them.

PROF. BACKLAR: I am interested that the only talk about the negative aspects. Your list is all negative. There are no positives. I have concerns about future generations. My obligation to future generations and information that they may wish. There are many people I believe who might want to be linked to their tissue. I think we should start to explore that side of the issue just as we have explored the negative.

DR. EMANUEL: Can I amplify that? I mean, it seems to me that certainly when I wear my clinical hat one of the things almost all patients who come in want to know is if there is going to be research on their tissue if they might benefit. The idea that this research is

only negative, and I cannot talk about it in terms of generalizable for people who are not sick, but certainly when they are sick they are very concerned about the latest potential advance that might be to their benefit and whether their tissue might contribute in that way.

So part of what I was going to follow up on the idea of putting it as individual interest versus public good may not fully capture it because many people as individuals have an interest in the public good being advanced. A personal interest as well as a general interest.

PROF. BACKLAR: This is Eric's -- the individual in a context.

DR. EMANUEL: So I think I would -- well, it seems to me that this might be an area where we should urgently and promptly commission a paper to think through these balances and interests because it might help us. I mean, if in fact what we are going to end up doing is balancing individual interests, community interests, researcher interest, having those spelled out in the way you have done and talking about their strength and saliency may help clarify in all of our minds rather than just each of us doing it on one foot in five minutes.

DR. MURRAY: I agree completely, Steve. Yes. Larry and Alta?

DR. MIIKE: Actually this is the genetic

subcommittee part of the day but this is most useful to me for one of the two areas where I wanted the Human Research Committee to look at. Getting back to the informed consent thing, it seems to me that it is sort of like trying to fit my shoe and my foot in my baby's shoe.

In a sense that -- you know, I mean we talked yesterday about the change in the paradigm of research and yet we are still stuck in all modes. This is what is coming to my mind here is that I do not think there is any -- we are not even satisfied with informed consent in the traditional way because as you say the way it is applied is you never get really informed consent.

So it seems to me that from this standpoint here we need to look at two things. One is whether -- regardless of what the legal system now says we are required to do, I do not think we should be restrained by that in terms of the informed consent process because I think part of our mission is to look for some major change in the way that even the legal system looks at things. We talked about that in the patent area.

But I think the side that we need to look into in this base is what are we trying to prevent, what kinds of harm are we trying to prevent, and how we can do that without just sort of being stuck in the informed consent process? So when we get into these kinds of issues to me it is too narrow a way to look at it if we

just sort of limit ourselves to the current requirements that we must go through in order to try to fit this unfittable thing into a legal type of situation.

DR. MURRAY: Thanks, Larry. Alta?

PROF. CHARO: Thanks. First an apology because I may something that somebody else said. I was spending half my time scribbling to the chair of my own subcommittee.

I had the good fortune of spending a fair amount of time with Gail Geller last spring who works on the breast cancer stuff and although we have not actually written it up we found ourselves talking a lot about a phenomenon we called inflicted insight. A phrase that she thought McFadden might have coined in which people are given information that actually causes harm by virtue of having been given the information.

It arose in the context of breast cancer because there particularly information about your genetic predispositions tended to be coupled with complete confusion or absence of information about what one ought to do with that information. So its overall result was to provoke anxiety without any real constructive purpose to which it could be put, at least one that was confidently known.

And it strikes me that this is the thing that might distinguish genetic information from other kinds of

information, Dr. Korn, if only because the amount of information that is available through tissue samples through genetic testing as opposed to the other kinds of testing traditionally done is greater and the uncertainty about what that information means is greater at this time in history.

So I find on your list of things to concern yourself with, Tom, particularly in light of the difficulty of informed consent when you do not know what you are consenting to, which is particularly true in this area, that perhaps an additional thing to float through your subcommittee would be to take into consideration the degree to which we are talking about obtaining consent from people in a process that in and of itself, to the extent that it tells people we have information that may or may not be a value in disease identification or predisposition identification might itself constitute this kind of inflicted insight problem. That is not to suggest you should not tell people because I understand if they turn out to be valuable in the end they may come back and say why did not you tell me.

We ran into specifically this problem at Wisconsin with regard to samples that were stored in a research context and they were sampled and tested and then years later better test developed, earlier on presymptomatic but for a disease for which there was no

presymptomatic therapy that had any proven value in preventing or ameliorating onset, and we were totally stuck as to what to do. So I am not suggesting any answers. I am only adding something to your list.

DR. MURRAY: David, do you have a comment?

DR. KORN: Yes. There is another phrase that I would urge you to keep in mind that I was told about by an epidemiologist called "uninformed denial." And I think that is -- you know, you have got informed consent, inflicted anxiety and now uninformed denial, what you are trying to do is steer a path that is not going to get on any of those reefs and I think it is a tough problem.

Well, I really appreciate the opportunity and very much respect the challenge that you have got.

DR. MURRAY: Thank you very much. Let me ask Mark Guyer to join us.

MARK GUYER, NATIONAL CENTER FOR HUMAN GENOMIC RESEARCH

DR. GUYER: I am Mark Guyer and I am with the National Center for Human Genomic Research and my title is assistant director for scientific coordination.

DR. MURRAY: Were you planning a coup, a demotion or what?

DR. GUYER: No, it just -- it is a historical statement, not a predictive one.

Tom asked me to come here today and talk about the experience we have had in dealing with some

human subjects issues in relation to collecting material for the Human Genome Project for determining the human DNA sequence, large scale DNA sequencing. And specifically I want to talk a little bit about what led us to developing a policy which we promulgated last summer and then some of the reaction to it without talking about the policy itself which I understand you have all seen and I am assuming that you have read.

The background is that as the Human Genome Project began and was conducted for the first several years before the stage where we had to really consider producing sequence I think it had been all along assumed, it was clear that it had been assumed all along that the sources for the material which was eventually going to be sequenced were going to be numerous and that -- and anonymous, unlinked at least to the individuals who donated the materials to make the cell lines or the clone banks, or so forth.

And so with that assumption in mind we did not really focus on some of the questions that would be raised by having large amounts of information about individuals in the public domain. I think there are some similarities in what we are doing to some of the questions that have been raised this morning and some differences. I think in listening to what I am saying it is important to remember that what we were doing is

specifically collecting samples to develop a resource, a research resource that is going to be widely used, widely distributed, and presumably will be used in ways that are now unanticipated. And so some of the questions that came up earlier today I think are entirely relevant to this.

When we -- about -- just about two years ago now the Genome Project started to move into a phase where we were developing the capacity for doing DNA sequencing on a large scale and testing ways that would eventually bring us to the point where we could really go into production on developing this first human reference sequence and we called for grant applications.

Again assuming probably without thinking too deeply about it that we were going to get proposals that involved a lot of different resources, a lot of different sources rather. And then as it turned out that was not the case and when the applications came in, and there were almost a couple dozen applications, most of them involved a very limited number of DNA sources because as it turned out that is really all there were. The technology for doing DNA sequencing had come to focus on a new kind of vector system and there were really very few clone libraries that had been made using that vector system. Probably only two or three really that were readily available to the people who were proposing to do

this research.

And so all of a sudden a year or so ago we realized that some of the assumptions we were making about how the source issue was going to be handled were not correct. So the policy that we then developed was very much stimulated by the need to try and understand the issues that would be raised by having the human DNA sequence, the first reference sequence, come from a very limited number of individuals and as it turned out in some cases even made from -- developed from clone banks that had not been collected even with appropriate informed consent.

The policy that we eventually developed, and this is -- make sure that everybody understands it, this was a policy developed jointly by the NCHGR and the Department of Energy Genome Programs, but only in the U.S. This was not a policy that had its development internationally even though the sequencing program is an international program.

The policy that we came up with was based on our conclusion that, in fact, given what DNA sequence information is and that DNA sequence information is uniquely identifiable with an individual that some of the standard approaches for human subjects protection involving anonymity did not pertain in this case, that ultimately with DNA sequence information, maybe not now,

but sometime in the not too distant future, individuals could be identified and that in -- even in the reference sequence if it had been derived from just a couple of individuals there were clearly going to be ultimately genes carried by those one or two individuals identified which had mutations and raised many of the questions that we have all been discussing about implications for health status and so forth.

So the policy that was developed really had a two pronged approach to the problem. One was to increase the number of clone sources that would be used for sequencing so that ultimately this -- that we would return to the model that we had assumed in the first place. The reference sequence the Genome Project was developing would actually be a mosaic that would be comprised of DNA from as many individuals as possible therefore limiting the information that theoretically could be derived about any one of them to as minimal as possible.

The second was that with every attempt to keep those individuals identity confidential on top of everything else but realizing that we could not guarantee anonymity, to really focus on trying to -- on the informed consent of getting the donors of this material to indicate and to provide them with as much information as possible about what they were donating and the project

that they were donating for, and what the potential risks were including this issue of unanticipated use and therefore unanticipated risk.

So the guidance and the policy that I presume you have seen tried to incorporate that. It was issued publicly last summer. In terms of reaction to it I did not even know how I was going to fill up the five minutes of time. There has been very little reaction.

There were a couple of articles in the press about it, a piece in Science, a two page piece in Science, that generated two published letters in Science and that is basically the extent of the public reaction.

We have not had calls, as far as I know the DOE has not had calls. Francis Collins tells me that nobody has come up to him in private and said anything. There have been -- there were some concerns originally on the part of the people who were involved in the DNA sequencing, a concern that whatever we might do would slow down the research. I think that was a risk that we were willing to take. But even that does not seem to have been a particularly significant problem because we addressed that by not prohibiting the use of the existing libraries until the point at which the new libraries could be made available. The existing libraries. But we did require that those people who had been involved in constructing the existing libraries go back to the donors

and obtain what we called consent for continuing use basically as a stop gap until new libraries that were made under more acceptable conditions could be developed.

The only other element in terms of reaction that I can think of is on the part of the people who are going to go out and make the new libraries. There really -- there are only a couple. Maybe three or four. Three laboratories in the U.S. that I know of that are involved in making the new libraries. They have actually been very responsive to this policy. They have both worked with their IRBs locally and with us in terms of developing the consent forms and protocols for collecting specimens for making DNA libraries in ways that we have found acceptable.

DR. MURRAY: Thanks, Mark. I am pleased to hear about the reaction, your sense of the reaction of the scientific community. I am surprised because I was assailed by a very distinguished and well known scientist for what he described -- he used fairly flowery language to criticize this document and others. And I guess he has been -- which -- it was interesting since I had nothing to do with the preparation of any of them and had not read them at that point. This was several months ago.

DR. GUYER: Whatever your response was it must have been very effective.

DR. MURRAY: It must have been very effective, I guess. Yes. Well, I hit him is what I did.

(Laughter.)

DR. _____: And he is now dead.

(Laughter.)

PROF. CAPRON: But we have used his tissues.

(Laughter.)

DR. MURRAY: I got his consent on the way down. Yes.

(Laughter.)

DR. MURRAY: Thanks very much, Mark.

We have a little time for questions or comments with Mark, a little dialogue with Mark. Here is my plan: Two hours was not very much time to begin with. I would like us to take the last ten minutes and I am going to let us -- I am going to count that from 9:55 to 10:05 since we did start about ten minutes late. But I do not want to encroach too much on the break or certainly not on the next subcommittee. So we will end at 10:05. I would like to give us ten minutes just to briefly begin a conversation about future subcommittee meetings. We will make a recommendation. And also about the products, beginning the process of having what sort of products we want to commission through the NBAC staff. So we will start that at 9:55 so we have like seven minutes to talk with Mark.

DR. COX: I just wanted to make a comment, Mark, is that with respect to the Genome Project at the very beginning for years the press have been asking whose genome is going to be sequenced and the scientific community, myself included, blew that off pretty easily because it was obvious to me we were not going to be sequencing one person's genome. It was quite a shock to me to realize that we actually were sequencing that person's genome. So perhaps the scientific community can -- in broadening their context and looking at what the public concerns are can sometimes head things off at the pass and this was an interesting lesson that I have chalked up on that science personally.

DR. MURRAY: Harold?

DR. SHAPIRO: I have really some simple comments and reaction. First of all I want to thank Dr. Korn for that wonderful phrase "repose and obscurity" which is in your paper which I think is a kind of wonderful phrase and it can be used in many situations. But that is a part of the sentence which talks about research that cannot be accomplished by any other means as I recall that testimony.

That is an important sentence and I just want to observe that that is not well understood. I mean it is well understood by scientists. I am not trying to say that scientists do not understand it but it is simply not

well understood and therefore in balancing the costs and benefits to whatever solutions are reached I think, Tom, we need to do something in the educational role of our commission to make sure that people can understand just what the importance of this is. I think there are many examples. I do not want to take time now to go into that but I think it is something we have not attended to very well just in that area and I hope that I can do something about it going ahead and going forward.

The second issue which I would perhaps ask any of the people who have presented today to respond to is in all these issues of trying to balance the costs and benefits and interests of various kinds here even if one assumes that in an initial situation that you have the appropriate informed consent, that people think the benefit is worth the cost for providing their tissue under whatever circumstances.

We are always faced with the issue as a number of our speakers have indicated this morning that there are unanticipated costs and benefits out there. That is since we do not know what the progress of science is going to be and we are accumulating this archive there is by definition a stream of unanticipated benefits and unanticipated costs.

Now no one is going to worry very much about the unanticipated benefits because it is only a benefit.

If that happens that is great. There is no controversy. It is the unanticipated costs that attract people's attention and can be responsible for what Dr. Korn talked about as a kind of scare situation. You looked at the early 1970's with the recombinant DNA scare. I think we have to be very cautious about that because there is no end to the long list of unanticipated costs one can imagine.

There is any kind of scenario you can develop in this without limit and I think -- I just hope as we go ahead that while we have to be conscious that that possibility exists of course that we have to be careful not to over emphasize or inappropriate -- I do not want to say over emphasize, inappropriately focus on that as we go ahead.

DR. MURRAY: Thank you. Any other comments or questions of Mark in particular?

Thank you. Should we have another -- when should we have the next subcommittee meeting? I have not really spoken with you about this but let me make a -- float a proposal. The next full commission meeting is March. What would you think about a subcommittee meeting and we would try to coordinate it with the other subcommittee, have them back to back if at all possible, in April? Why April and not February? Well, because February is next month and scheduling with damnably

difficult.

Number two, I would like to have us have some products to look at before the next subcommittee meeting and I wonder if you think -- I mean, my sense is we ought to be able to commission at least a couple of the conceptual papers and have them in the commissioner's hands by at least last March so that we have a couple of weeks to look at them and think about them before we got together again in April.

That is my proposal. Please tell me what you think.

DR. COX: I quite agree getting some things in our hands now is very important. I was struck by what we have seen already in the context of focus groups and with the public views with respect to the stored tissue samples, but rather than providing answers that to me can provide even more of an impetus to have such focus groups specifically with respect to our own interest in this subject. So I would really like to see that go forward pronto.

DR. MURRAY: More focused report.

DR. COX: No. Focus group addressing the public perception of stored tissue samples in banks and I think that what that is going to require just as what we have seen from -- in the breast cancer case are thoughtful questions and professionals organizing focus

groups that provide open ended questions so that we can get a better feel of how the public perceives this issue.

DR. EMANUEL: Can I ask in that light, Dr. Saslow, were you or your office intending any more generalizable -- beyond focus groups usually you go to surveys of particular groups on some of the issues raised?

DR. SASLOW: No. Our next step is to after we revise this to pilot test and then actually we will not be doing it. We are hoping through the NIH grant process.

DR. MURRAY: Harold?

DR. SHAPIRO: I have two comments. One is the April time frame seems fine, but if that is what the subcommittee decides to do I think it might be helpful to consider that when you commission a paper from an individual that they may, in fact, report to us in some kind of initial way in March when we are all here so that we can have some impact, we meaning the subcommittee, I apologize, can have some impact and some interaction with whoever it is the paper is commissioned from.

In some cases that may not be possible but where it is possible, we will leave it to the chair to decide that, that might be very helpful in getting the work so when the product arrives in April it will be well understood by the subcommittee members. That is one

comment.

The second comment is that in deciding eventually just what papers or projects we ought to commission there will have to be some kind of iterative process where we know something about the time it will take to do something, whether that has got to be a long-term project or a shorter term project. As I am just sitting here right now, I do not know how long you have spent on these focus groups, how long it took you to mobilize it and do it, that would lead you to do it faster the second time, most of us would.

But that may -- we are going to have to reiterate around a bit as we look at the portfolio possibilities and look at just what we can do in the various time frames we have laid out.

DR. MURRAY: One of the things we will need to do, I believe, is draw up a kind of work plan.

DR. SHAPIRO: Right.

DR. MURRAY: And, you know, start from next October when we will have a report and figure out what we need to have each month or so however to reach that goal. My -- having -- you know, I write conceptual papers and not empirical papers myself, it may still take time for whatever reason.

DR. COX: Tom, in Harold's point, I mean I guess there is professional groups that do these focus

studies and they can make it very simple.

DR. MURRAY: Absolutely.

DR. COX: They call one up and they say it is going to take us two years. But that is what I would like to know. Is it going to take us two years or three months and how much money?

DR. MURRAY: I agree.

DR. _____: Three months is the --

DR. MURRAY: Three months. Part of the work plan is figuring out what each of the proponents realistically is going to take to get a product and where optimally it would fit in our own deliberations and report drafting, et cetera.

PROF. CHARO: Excuse me, Tom.

DR. MURRAY: Alta?

PROF. CHARO: I think this is my staffer background coming out again but I recall lots of very complicated rules about financial limits above which you were not allowed to single source something so you have to put it out for bid which would drag the process on further. So I am not sure I understand -- I do not remember what those numbers are, but depending on what it is you are planning to do you may not be allowed to just single source and that might make the whole time frame particularly complex.

DR. MURRAY: Steve?

DR. EMANUEL: As I recall it is $25,000 and probably for these focus groups depending upon how elaborate you want to get them you should be able to get in well under that.

DR. MURRAY: It will be hard to find an ethicist to write a paper for less than that I imagine but we will just have to --

PROF. CAPRON: Especially a conceptual paper.

DR. MURRAY: We will have to scrape the bottom of the barrel but we will manage.

MR. HOLTZMAN: Tom?

DR. DOMMEL: And time for the IRB review and approval of the project with the focus group.

MR. HOLTZMAN: A question, Tom, it seems to me we said we were going to start by looking at the issue of retrospective samples knowing full well that we would draw morals from that in terms of processing such as consent and use for future samples. You have suggested maybe we start with a conceptual paper.

I am almost inclined to say where I would like to start is by learning out about what are the samples we are talking about? What are these different collections? Under what conditions were they collected with respect to consent and other aspects? How are they now being reused under what understanding about how they may be reused?

Because clearly the pathologists have a very different understanding than the public health authorities who are in possession of the blood spots from infants. A very different understanding than say the people who have the serums from the Framingham study. Under a very different understanding of for profit clinical pathology lab or genetics testing lab. So I think that would be a good place to start, is to know what it is we are talking about here.

DR. MURRAY: By conceptual I just meant conceptual as opposed to going out and gathering original data and running subjects like focus groups. So a descriptive paper, that would have been a more accurate description on my part. I think that also we could commission very rapidly. I would like to see that.

Let me just -- we did this yesterday and then we had some good feedback about extensions, refinements, additions. It is 10:00 o'clock so we have just a few minutes and I think this can only be the beginning of our conversation which will have to continue via e-mail, telephone calls and other things. That is fine.

But let me see if I have -- I have at least this list of the sorts of things we would like to see done in order for our own work to continue. One are -- one or more descriptions of what these tissue collections are like, what uses are made of these tissues. This is

something we would like to have done quickly I note and also that we should attend both to sort of public collections and also private collections. Someone had suggested that. So that is one -- at least one component with maybe more than one subpart.

A second component would be this analytical paper about cultural, ethnic and religious views and how they might differ in the U.S. about the use of stored tissue.

A third thing would be the focus groups which thanks to the work that Debra Saslow has reported we can focus primarily on public perceptions of tissue banks, uses of stored tissue, et cetera. That is a third component.

A fourth component is called a conceptual paper. It is a kind of normative analysis that would be based in part on the position papers that we have seen but also would try to raise the list of concerns that people might have, the private interest versus public benefit and not limited only to objections on the private side but also to, you know, people's interest and positive views about having their tissue stored. That I suspect would be one paper but maybe not.

We want to have some kind of international perspective, that is a collection and review of international statements and the dates going on in at

least a few other places about stored tissue samples. So that is the comparative international piece.

We may or may not want someone to sort of take this together and give us a sort of policy analysis of what the reasonable options seem to be, at least to deliver to the commission for the commission's own deliberations. That is it. Those are the pieces I had.

We did originally have in mind from the subcommittee meeting the possibility of an opinion, a public opinion poll, up to ten questions. I did not hear a lot of enthusiasm for that yesterday. Now let me -- but we did not do an all things considered view of it.

Are there members of the subcommittee who would like to see some public opinion poll data on this?

Bette?

MS. KRAMER: Tom, I would like to suggest that you question some professional person who can give you some feedback as to the relative value of focus groups versus public opinion. Obviously you would not want both but I think you want to try and find out which one is going to be more productive for us in this instance.

DR. MURRAY: Yes. I left one thing out which is it was -- I guess it started with Alta's suggestion that if we wanted to find out what -- sort of a sampling of what the public felt about this in a more opinion poll

rather than focus group fashion, rather than just asking the general public we might look to groups of people who have, in fact, had stored tissue and who have been sort of -- who have had occasion to think about it. That remains a possibility.

Zeke and David?

DR. EMANUEL: Yes. When we think about the public opinion survey there are a variety of ways of doing it. One is our own survey. One is tacking on questions to an already existing survey which is incredibly cheap actually and many of these big survey groups are going to particular populations.

So if we are very interested in certain subpopulations they are doing these kinds of surveys for all sorts of other governmental, et cetera, reasons and we may be able to get good minority looks or looks at what minority groups think of it for example.

I think that there may be some groups already looking at certain specific populations, maybe not in relation to tissue samples but in relation to genetic testing, et cetera, that we may again be able to tack on some questions either to their surveys or to their focus groups.

DR. MURRAY: At least one of the major national opinion pollsters does offer this sort of service where you can do it. You can pay for questions.

DR. EMANUEL: Exactly.

DR. MURRAY: But for us the question would be are there -- this is getting to be the question, the third question, the third use of the concept question. Do we have a question or a set of questions that we want to ask to the general public? What I heard yesterday was not a lot of -- not a certainty that we have those questions. I would like to leave that as an open possibility for us and maybe that should be something that we continue to dialogue on.

Steve and David?

MR. HOLTZMAN: What I would like to suggest is the one danger with saying what you are going to do is follow up Alta's suggestion and go and talk to groups about their experience thinking about the question of stored tissue samples is typically the groups you will have will be people who have the kinds of diseases that are highly charged. What we are talking about are a broad sample here.

We need to -- so I do not have a problem with going to those groups and maybe what you need to do -- but then you start -- you have to cast the net much wider because the kinds of samples Dr. Korn is describing come from all different kinds of patients and under all different kinds of situations.

Again it is much like when one talks about

what is a genetic disease if your paradigm is a highly penetrative disorder which you cannot do anything about with a single gene, it is very different than if you start to talk about the more kinds of common diseases that are polygenic. And if you ask people to identify themselves in terms of a genetic disease versus those with these others you get very different impressions.

DR. MURRAY: Yes, that is a good reminder, Steve. You are going to have, except for my closing comment, you are going to have the last word out of fairness to the next subcommittee.

Yes?

DR. COX: I hope it is worth it. I agree with what Steve just said and with respect to Bette's comment I really do think we need professional input about what the best way to get information broadly from the public is and not just from specific interest groups. But I will say I learned something from Debra's focus group already and I think we should always build on what already exists.

What I saw from your focus group is that people were suspicious because they did not what stored tissue banks were about and it is pretty hard to get public opinion polls from people asking about things if they do not know.

So in my own view I think I would like to see

the commission work with whatever professionals we have to come up with scenarios with which we could not direct what the answers are going to be but at least have scenarios that encompass some of the things that we would like to get answers back about.

DR. MURRAY: Thank you very much. We will try to -- Jim?

DR. CHILDRESS: Just a question since this concerns both the subcommittees. We have not talked about whether to try to have a meeting prior -- of our subcommittees back to back prior to the next meeting, at least I have been in and out of discussion this morning so I am not sure that has been discussed.

It seems to me that might be useful to do while we have virtually everyone present if the staff does not object, is to see whether we could find some dates and actually move forward because if we are expected to make some kind of report at the March meeting, only about eight weeks away, we really do need to have a meeting of the subcommittees prior to that. At least that is my view.

DR. MURRAY: What I had proposed, I guess you were out of the room, Jim, what I had proposed was that we not -- our subcommittee not try to meet in February, but the time would be better spent for us reviewing materials and commissioning various products which we

would have at least preliminary reports on at the March full commission meeting, but then a chance for the subcommittee to have more polished versions of for an extended meeting in April.

DR. CHILDRESS: All right. We will raise it with the next subcommittee too and see what it says.

DR. MURRAY: I do not have a strong feeling about that. It just struck me that might be a sensible use of our time and give us a reasonable amount of time to get report -- initial reports in.

Bill hands me a note and also from Margaret Quinlan to consider some dates. I do not think we should try to schedule at this time but just keep these in mind. The third and fourth of April, the 17th and 18th of April, and I have to tell you I am probably teaching those weeks. Our semester ends in mid-April.

So we might also -- if you would be willing to accommodate me think about towards the end of April or the beginning of May. That would be a possibility for many of us or even in May. But we should not try to set dates. We should get that -- each and everybody should fill out their calendars.

What I am going to propose to do is with the help of NBAC staff prepare a kind of just brief description of these components, these products, and when we would like to try to get them in, and get it

disseminated to all members of the commission, get your feedback on it rapidly so that we can then go -- you know, if you approve or if you want to modify them we can commission them.

Thank you very much. I want to particularly thank Debra Saslow, David Korn and Mark Guyer for coming and spending the morning with us, and all the members of the commission, particularly the subcommittee.

We will reconvene at 10:30.

(Whereupon, the proceedings were adjourned at 10:11 a.m.)

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MEETING OF THE HUMAN SUBJECTS SUBCOMMITTEE OF THE NATIONAL BIOETHICS ADVISORY COMMISSION

Friday, January 10, 1997
10:35 a.m.

The Madison Hotel
Washington, D.C.

EBERLIN REPORTING SERVICE
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Silver Spring, Maryland 20906
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I N D E X

P R O C E E D I N G S

DR. CHILDRESS: In order to use the full two hours most efficiently I think we ought to go ahead and get started even if we have to interrupt it at some point to talk just for a few minutes about additional scheduling.

This is scheduled to end at 12:30 and since people have travel plans to meet we will certainly try to do that.

I should also mention that Bill Dommel will be out for the next little while and Margaret Quinlan will be handling everything from the staff's standpoint.

Harold Shapiro, anything you would like to say before we get started?

DR. SHAPIRO: No.

DR. CHILDRESS: Okay.

Well, you will recall from our discussion yesterday the Human Subjects Subcommittee is interested in working on different levels, one considering general perspectives, principles and concepts, and the other looking at specific areas of concern particularly for policy development. And in the specific areas one of the most important has to do with cognitively impaired research subjects because of the gaps in federal regulations and guidelines for this particular area.

There is a consensus not only in the Human Subjects Subcommittee but also in NBAC and also in the literature that this is one gap that ought to be closed if possible.

I quote from two 1996 publications: "The new National Bioethics Advisory Commission should act promptly to develop more precise principles and procedures to guide future research on mentally disabled subjects."

The second one: "There should be a federal policy for the ethical conduct of research on persons who by reason of mental or behavioral disorders are vulnerable and that they are not capable of giving adequate informed consent. The policy should be formed by a national advisory group modeled after the National Commission for the Protection of Human Subjects."

Well, those two 1996 challenges to the National Bioethics Advisory Commission came from our two panelists. The first from Rebecca Dresser and the second from Robert Levine. We are delighted that they could join us today despite adverse travel conditions and complicated schedules, and share with us some of their reflections about the issues involved in thinking about cognitively impaired subjects and the kinds of policies and guidelines that might be developed to more adequately protect them.

Let me say a word about each of our panelists. Rebecca Dresser holds the John Deaver Drinko Baker and Hostler (?) chair in the School of Law at Case Western Reserve University. She is also a professor in the Center for Biomedical Ethics, School of Medicine, at Case Western. She has taught in the law and bioethics area over the last 15 years and is the author of numerous articles in medical journals as well as co-author of a Case book, Law and Bioethics.

Robert J. Levine is professor of medicine and lecturer of pharmacology at the Yale University School of Medicine and chairperson of the Institutional Review Board at the Yale Newhaven medical center. He is a former editor of Clinical Research and the current editor of IRB, Review of Human Subjects Research, and has been involved as a consultant in several and international agencies involved in the development of policy in this area.

I mentioned in my memo that his book, Ethics and Regulation of Clinical Research from 1986 is one of the most important works in this area.

So we are delighted that they could be with us today.

Our procedure is the following:

We start with Bob who as a staff member of the National Commission for the Protection of Human

Subjects was deeply involved in the discussions and deliberations surrounding the whole range of issues covered by the National Commission, but including for our purposes today the institutionalized mentally infirmed subjects.

And as soon as he finishes his eight to ten minute set of remarks we will ask -- give everyone to raise a few questions for clarification and then before proceeding into substantive discussion we will ask Rebecca Dresser to present her remarks and then have an opportunity for a few questions for clarification, and then have both of them involved together in our substantive discussion because both of them have really focused in this area in important ways that can illuminate what we are about.

So, Bob, we will start with you and then we will turn to Rebecca.

ROBERT J. LEVINE, YALE UNIVERSITY SCHOOL OF MEDICINE

DR. LEVINE: Well, thank you very much, Jim.

It is a pleasure to be here with you. I take it as a great privilege to be invited to participate in your important project. If I may so, though, getting here was not half the fun.

Jim tells me that you probably all have read the various readings that were sent to you to prepare for this meeting. That then frees me up of any

responsibility for giving you details. I am going to instead try to provide an overview of the big picture.

Understand that this consideration of dealing with people with cognitive incapacity or suspected cognitive incapacity has two purposes. Firstly it seems to be part of a larger project to consider the meaning of vulnerable as it applied to prospective research subject populations.

Secondly, it is an important consideration in its own right, it being the only field of individuals that the old DHEW regulations defined as those with limited capacities for consent. The only category that does not have any federal regulations guiding the conduct of research in them.

The reason that these people were identified or the reasons in general that people or populations are identified as vulnerable is that in general there is some reason to suspect that they lack the capacity to give informed consent. In the case of the category defined by the National Commission as those institutionalized as mentally infirmed there were two elements of this capacity that at least had to be suspected of being absent.

The first is that for many of them they lack the cognitive capacity to be properly informed to reach what the Nuremberg code calls an understanding or an

enlightened consent. The second feature is that they are in positions of dependency so they lack what the Nuremberg code calls the capacity to provide a voluntary consent.

In particular, as the commission was addressing not all people with competent disability but only those who were institutions. There is a consideration that simply living in an institution for a long period of time made one quite dependent regardless of one's cognitive ability. So that influences the recommendations that were made by the National Commission.

Now dependency is also extended in some of the international documents but not in the American regulations to cover people who are subordinates in a hierarchical structure. So, for example, when Major Walter Reed invited buck privates to be bitten by yellow fever mosquitoes this was considered potentially coercive in that buck privates in those days rarely would resist any recommendation made by a major.

The same would go -- similar considerations are applied to students. You probably have already heard about the problems of psychology departments in universities requiring in some cases requiring undergraduate students to serve as research subjects and giving them course credit for doing this.

So to leave the general issue of vulnerability and to focus more specifically on those institutionalized as mentally infirmed I want to first call attention to the fact that the Congress asked the commission to deliberate about those institutionalized as mentally infirmed.

The commission introduced the word "as" to show its skepticism. It was their belief and it was probably correct that there are a goodly number of people who are institutionalized as mentally infirmed even though they do not have mental infirmity. I do not know if empirical work in the 1990's would support that vision but it did in the 1970's.

The structure of the recommendations and what became the proposed regulations is characteristic of the National Commission's approach to dealing with vulnerable populations.

They first defined one category of research in which all of the procedures taken together present no more than minimal risk. You are all familiar with the definition, I trust you are familiar with the definition of minimal risk. Many of my colleagues have analyzed this concept and find it very unsatisfying. It really is a nondefinition but it is the one we are stuck with.

Now once you get beyond minimal risk then the National Commission recommends that regulations be

developed as they did for their earlier recommendations for research involving children. But you should categorize the research -- or no, not categorize the research but categorize the components, the procedures, the interventions that are going to be performed in terms of whether they hold out the prospect of direct benefit for the individual subject. They do not refer to therapeutic research or nontherapeutic research.

I was troubled to see that most of the documents circulated to this group today rely on that distinction and I can give you many, many examples of how this distinction leads you into conceptual snares. The American College of Physicians Statement, for example, which relies on this distinction finds it impossible to give advice on how you would treat cognitively impaired subjects who are being enrolled in a placebo controlled trial.

You might argue that the drug, the active drug arm would be therapeutic or would hold out the prospect of direct benefit. But this could certainly not support applying the same standards to the placebo arm. This is the sort of conceptual ambivalence that confronts you every time you use this distinction.

Alex Capron has heard me say that before.

We have discussed it in print.

Now if the procedure that presents more than

minimal risk holds out the prospect of direct benefit then according to the National Commission recommendation and also according to the children's regulations the justification of imposing this risk is just like it is in medical practice.

You have got to find that the procedure itself offers consequences or the expected benefit is at least as good as anything else out there in the practice of medicine and that nothing superior is being withheld. Aside from that justification there are no additional procedural protections apart from what is necessary for all minimal risk research.

Now the other category is when the intervention or procedure does not hold out the prospect of direct benefit. In that case you have got to apply more stringent standards to the justification. First you have to find that the information being sought is of vital importance to the solution of the problem and, secondly, in the case of children they said that the procedure would present experiences that were commensurate with what the children subjects would experience by virtue of their situation, their disease, for example. I can give you more detail if you like.

Now also when you are dealing with procedures that do not hold out the prospect of direct benefit there are additionally stringent requirements for committee

review, for checking with the treating physician to see that the participation in research will not interfere with the course of therapy, and various other things that you could read about.

There is also a requirement that the increment above minimal risk must be something that can be characterized as a minor increase. If it is more than a minor increase then it has to be removed by the Ethics Advisory Board, parenthetically I trust you know that there has been no such board since 1980 when its money was given to the President's Commission.

Now I think that they should have found the same amount of money for the President's Commission but they also should have kept the Ethics Advisory Board.

Now are these recommendations relevant in 1997? I think they provide a good structure, a good logical system for thinking about the problems. However, some changes are necessary for two reasons. The first reason is that the commission was focusing on people having two problems and one of them was institutionalization.

My recommendation is that you come up with a set of standards that would apply to all people who might have incapacity by virtue of cognitive disability or suspected cognitive disability and for that reason the recommendations would have to be revised to accommodate

those who were living out in the world and not in institutions.

A second reason for revising some of these recommendations without departing from the conceptual structure is that in the 1970's we were living with this attitude of protectionism. There was a prevailing presumption that research was dangerous, that you know you could get hurt. We were still living in the shadow of the Nazi war criminals and many people writing at the time thought that what the Nazi research physicians did was typical of research.

Subsequently we have gone through a great revision in our perception of research. Now all too often it is portrayed as being totally benign and beneficial. As I have written and perhaps you have read, I think the current attitude is just as wrong headed as the old attitude was.

It is not only dangerous and exploitive and it is only benign and beneficial, but good can come of it for individuals as well as populations. We should go forward with it while maintaining our vigilance to see to it that any potential exploitation or injury, any potential for exploitation or injury is minimized.

One closing remark: I think the greatest problem presented in the field of doing research on people who have disorders that can produce cognitive

disability is the problem of what has come to be called drug free research.

Placebo controlled clinical trials, placebo washout periods, and one additional thing would be the so-called probe studies where drugs are given in order to explore the pathogenesis of these serious disorders such as schizophrenia where drugs are given to see whether or not they will exacerbate the condition, to see whether they will bring about a transient increase in symptoms.

These studies are very valuable but they are also very frightening to deliberately induce symptoms in people who may have questionable capacities to understand and in case you induce the symptoms you might have a problem with assuring the subject's freedom to withdraw at any time, you know, as is required by all ethical codes and regulations.

If you like I am going to talk more later during the discussion period about this drug free research business but I believe I have occupied a little bit more than my time line.

Thank you.

DR. CHILDRESS: Thank you very much, Bob.

As I mentioned at the outset let's just take a few questions for clarification only, not to engage in a substantive discussion yet. We want to involve Rebecca in the substantive discussion as well. So if there are

any questions for clarification since Bob had to cover a lot of things in a short period of time?

MS. FLYNN: I am not sure it is appropriate at this moment but I wanted to ask you for just a little bit more information about your statement that the current structure provides in your view an adequate framework for us to then move in whatever additional directions that we may see fit. Are you speaking in terms of the way in which we have characterized and classified the vulnerability or the way in which we have characterized and classified the risk itself? Can you just enlighten me a little bit more as to why you are feeling that the current framework is, in fact, strong enough and adequate to build on?

DR. LEVINE: Well, thank you very much for the question. When I refer to the framework I am referring to the conceptual structure. I think it makes sense when dealing with vulnerable populations to categorize research as minimal risk and then to recognize that there is a second category of research in which some of the procedures or components could hold out -- could present more than minimal risk.

I think that it is a good idea within that category to analyze the specific procedure intervention that is presenting more than minimal risk and if it has a reasonable prospect of providing therapeutic, diagnostic,

prophylactic benefit then the proper method of analysis or justification of this risk is very close to the method of justification in the practice of medicine that it is bringing to this individual advantages that are on a par at least with the best known alternative.

If on the other hand the procedure presents that more than minimal risk is not beneficial, not therapeutic, then I would impose stringent restrictions on who can do it.

I will give you an example of an actual clinical trial which was analyzed as therapeutic research. It was one of the early phase TIMI trials. That is thrombolysis and myocardial infarction using enzymes to dissolve clots in the coronary arteries. Clearly therapeutic. However, one of the components in the placebo controlled arm was to insert a catheter into the coronary artery for purposes of infusing placebo.

In a study of that sort if you are analyzing things according to therapeutic research you get what I call the fallacy of the package deal. Just because one thing is therapeutic you cannot justify everything in the same way.

Now to get to the other component of your question, no, I am not claiming that we now have an adequate definition of vulnerability. I would expand it to include the things that are in the CIOMS World Health

Organization document recognizing that members of hierarchical -- subordinate members of hierarchical structures, and you can read all this stuff. I am also not recommending that the term "minimal risk" is in its present form useful.

I tried to write an alternative term in 1976 and failed seriously. So you better call on someone else to advise you.

DR. CHILDRESS: Since not everyone may recall the definition, you just mentioned it in passing but did not -- go ahead and state what it is at this point, the definition of minimal risk that has been used and is problematic.

DR. LEVINE: There is no such thing as "the" definition of minimal risk. The National Commission wrote definitions of minimal risk that were peculiarly relevant to each category of subjects. In my view none of them were adequate. But what the HHS or in those days HEW regulation writers did was homogenize them all so that they could put one definition in the mainstream of the regulations.

What it does is it says that minimal risk is the degree of risk that is -- I am paraphrasing -- on a par with that expected in a routine medical, psychological or dental examination covering all the basis. And that one should also take into account the

circumstances of the individuals expected or accustomed life experience. Both components of that are problematic. You would have a different standard than for linebackers, you know, and for violinists if you take into account the circumstances of their life.

When you say the risk is on a par with what one encounters in a routine medical examination the problem you were discussing in the first half of this morning, genetics, where you are developing very private information about people, one could argue, well, that is what doctors do when they take a history. So genetics is minimal risk why didn't you start your meeting at 8:30? And these are the sorts of problems you have to contend with.

DR. CHILDRESS: Any other question for clarification only?

Okay. Thanks again, Bob, and we will have the subcommittee discussion in a moment.

Rebecca, welcome.

REBECCA DRESSER, CENTER FOR BIOMEDICAL ETHICS, CASE WESTERN RESERVE UNIVERSITY

DR. DRESSER: Thank you. I am very honored to be here with you.

Just in light of what we were just discussing I have here the actual definition in the regs of minimal risk. It is the probability and magnitude of harm or

discomfort anticipated are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. So it also refers to just, you know, walking outside, driving the car, that kind of thing.

Okay. Again I am going to assume that you have read my article so I am not just going to review it. I wanted to highlight a few points and then add some things that I was -- I thought of just trying to be a little bit creative about these problems.

I think one central problem here is the varied nature of the people that we are talking about. Not only do individuals in the different groups that we are talking about vary substantially such as people with dementia, I mean there is just such a range of capacities and situations, certainly people with psychiatric disorders. Also the groups themselves vary. For example, with dementia you have a condition that is eventually going to end in death, progressive. You do not have that in the other major groups with developmental disability and mental disorder. So that is a difference.

The fluctuating capacity that people -- that many people with psychiatric disorder have going. At one point they are capable and at others they are not. That

is also the case with people in earlier stages of dementia. Not so often the case with developmental disability. But it is just such a complex group.

I think we have to accept that policy probably cannot address all the specific problems of these different groups. We can try to get some general principles but there is also always going to have to be a lot of supplementation. Perhaps what this group ought to try to do is prepare some of the supplementary material to enrich some of the specific issues that are only going to arise with certain kinds of research in this area.

Also, you know, inevitably I think we have to rely on the good faith of IRBs and investigators at some level. We want to try to provide them a lot of guidance but there is the fine grain nature of these issues that is going to make us have to rely on individual examination of studies and subjects, and so forth.

Now I want to mention seven substantive points. First, capacity, assessment and subject representatives. There are a couple of basic problems here. One is that capacity assessment and information disclosure have to be individualized to each subject. And the other basic problem is that you want to select a subject representative who is appropriate for the subject who is incapable.

I think it might be possible to address both

those problems with a mechanism that requires somebody who is independent otherwise of the research project to be involved in this. First in terms of assessing whether the subject is capable of understanding and can make a voluntary choice, whether the subject understands the information, the actual disclosure process, the substance of the disclosure, being involved in that process, and also then being involved in that process when a subject representative is involved.

The current federal policy requires or says that incapable subjects may be involved in research with the informed permission and consent of a subject -- a legally authorized representative, and then it does not define that. It leaves it up to state law. Most states do not address this at all. So who is that?

So one issue is should this be a legal guardian? Even as a lawyer I do not really think that that is such a great mechanism to use. Legal guardianship is fairly general. Probate judges make decisions to make people guardians. It is typically people could have legal guardians and they would have been appointed without any discussion of research involvement certainly a specific project that might be proposed. I just think it is way over broad and then the expense and costs are probably unnecessary in terms of protecting subjects.

Again I think if you have the involvement of an independent person who is speaking with the subject representative, giving the information, assessing understanding and assessing the ability of the subject representative to follow the standards that that representative ought to follow which is making decisions based on whether they think the subject would agree to participate if the subject were competent or alternatively doing things that are in the subject's best interest.

I think education, working with the individual subject representative is a better way to protect subjects than to just say, oh, well, everybody has to be a legal guardian. I just do not think that addresses the problem adequately.

I would say with both of these areas this therapeutic misconception is a major, major problem and really requires a lot of attention. In all human subjects research there is a tendency for people to confuse being in research and being in treatment, and thinking that people who are doing things to them for research are doing what is best for them. And it is just so important to be very clear with people that even in research that offers perspective direct benefit there will not be the individualized attention typically say to a dosage to catering the intervention to the individual

person that that person would get in the clinical situation.

I almost think that when research projects are proposed, even potentially beneficial research projects, people should put on a different color coat. They should take off their white coat and put on a red coat or something, or something that really reduces this possibility of confusion between this is my doctor who is there to do what is best for me and this is a researcher who certainly is concerned about me but the overall goal is to produce knowledge that will benefit others.

Okay. Second area, advanced directives for research. Now this is attracting some support. I have a lot of reservations about it. I do not -- I think that choosing -- just designating a future surrogate decision maker is not as problematic as asking somebody to issue specific instructions about research participation. In the language of advanced directives that is the proxy directive is not as problematic as the instruction directive.

Problems with the instruction directive are limited subject ability to be informed ahead of time of all the information that is necessary to make an informed decision about research participation. If you look at the regulations there are all these requirements that people have to understand before they make an informed

decision to enter research. The longer the time lapse between the person's competency when the person is asked, well, would you like to participate in this project, and the time when the person becomes incompetent, and the advance directive takes effect, the more likelihood new information would have arisen about the study, about the subject's condition, about lots of things that the subject would not have been aware of at the time the consent was elicited.

So I just think this adequate information is a problem and then somebody is going to have to then represent the subject once the subject becomes incapable and then it just kicks into the usual situation where you have an incapable subject and a representative.

The other thing is research is a -- research participation is a process. It is not an event. Giving consent at one point is not enough. There has to be continuing consent all during the project. Everybody has to have the ability to change their minds once they are in the middle of it and saying, wait a minute, I do not think this is for me. So again you are going to have to have a subject representative to do that for an incapable subject.

For somebody to give binding consent to participate in a future research project we would not accept that for a competent or I do not think we should

accept it for somebody who later becomes incapable.

Now an interesting issue here is whether -- if we are going to set limits on the risks to which incapable people can be exposed, should it be appropriate to allow people who make an advanced directive saying I am willing to be -- I am very concerned about dementia. I am in the early stages. I have seen it in my family. I am willing to expose myself to moderate or high risks in the future because it is so important to me to find a cure for this or whatever. And allow greater risk to be imposed on somebody like that than we would on somebody who never makes a directive like that and is entered into a dementia study.

I have real problems with that although I know there are different views of this. It really raises the conflict between honoring the competent person's autonomy to consent to future severe risks versus our duty to protect people who are incapable at the time those risks or burdens are imposed.

I would say when we are talking about research my preference would be to err on the side of protection but maybe we will talk about that here. I also think it is important as a practical matter to realize few people will make these kinds of directives. I mean we know that very few people or relatively few people make advanced treatment directives.

If we are talking about advanced research directives where people are consenting in advance to accepting significant risks when they have dementia or perhaps when they are incapable because of a psychiatric disorder, I do not know that that many people will be interested. So I hope that we do not spend too much attention and time on that. I think it is always going to be a very small group of people. In terms of getting enough subjects for research I just do not see that that would be a workable way.

I know I am going on too long.

Assent and experiential assessment for incapable subjects. I think it is really important to remember that once people become incapable they do not lose the ability to express their preferences. That is they can show us in a number of ways physical resistance, just evasion, avoidance, as well as linguistic ways. but they do not want to be involved in a research project.

Now this issue of whether we should ever impose interventions, because a lot of these things such as shots, being physically restrained for a limited period of time could be quite upsetting to somebody who has dementia or a mental disorder, or a developmental disability.

I think we should have a low tolerance for forcing research interventions on research -- incapable

research subjects who indicate any kind of resistance. Maybe a short term giving somebody a shot is one thing, particularly if it is in a project that offers them direct benefit. But I would prefer to be very conservative on this. Also on the other hand very liberal in interpreting their communication that they do not want to be involved in a project.

Research burden expected benefit assessment for incapable subjects. This is a big issue for you all. I think one thing we really need here again is a monitor, a research auditor in the words of Jessica Berg. Again because these things are so individualistic. For some incapable subjects being -- getting a shot, being restrained will not be upsetting. For others it will be. Somebody has to be there watching to see how the individual experiences it. So again this might be a place for an otherwise independent person.

I was thinking we now have this mechanism of the clinical ethics consultant who is there to kind of back up the hospital ethics committee and to go on site and to observe individual cases. Perhaps we could develop something like that for the IRB, that is an individual who is very trained in these issues who could either go between the actual research process, the disclosure process and so forth, and then going back to the IRB and reporting.

Risk limits, again if you do decide to adopt risk classifications and limits I hope that this definition of minimal risk and minor increase over minimal risk can be enriched. It is a very slippery thing. I am not surprised that you were not successful.

One thing that I think might be helpful is to develop some case examples that IRBs and investigators could look at. Just giving examples, here is a situation where we think it is minimal risk. Here is a situation where for this subject it seems like greater than minimal risk. Here is a situation where it is beyond a minor increase over minimal risk.

Again because of the complex nature of these individual situations I think perhaps stories, case examples, narratives are going to give better guidance than trying to put things into conceptual definitions.

Finally, I would just encourage -- oh, an examination when we are looking at potential benefits to incapable subjects that again we think about, well, what are we -- what is the exact benefit? Here is some questions: Is it acceptable to expose an incapable subject to a potentially lethal risk if the research offers a prospective direct benefit in terms of improved cognitive function? That might be the case with say some dementia drugs.

Is it acceptable to expose such subjects to a

risk of a physically disabling injury in research that offers the subject possible improved functioning or extended life?

To what extent is extended biological life a benefit for somebody who has moderate or severe dementia? I think we have to think about that.

There is the big danger I think of being too liberal about accepting risks in research that offers subjects direct benefit and we really need to scrutinize what the value of the potential direct benefit is to the individual subject and not just take it at face value.

Then finally I would just encourage developing some mechanisms for greater consumer involvement in the planning and the carrying out of this research. I just think that people who are in touch with the problems of these populations are going to be aware of issues that even bioethicists will not. It is just very valuable to avoid problems to have their input.

Then finally this individualized model of decision making that we have had. That is somebody goes in and gets the information and makes the decision, goes forward. I just think that is really not suited to actual real life decision making. Even people who are capable tend to have family members they may want to involve. Incapable subjects may have more than one subject representative.

I think it would be good if we could incorporate that even though I know it is very messy and could be practically very difficult. I just think it reflects the messiness of actual human decision making and we ought to be at least open to it.

Thank you.

DR. MURRAY: Thank you, Rebecca. Any questions for clarification only at this point?

Alex?

PROF. CAPRON: I wanted to know whether you were saying in describing the state law situation about legally authorized representative whether the uncertainties you were identifying were if who is the representative or who is an appropriate representative, or this question of the authority of such a person to consent for research which involved anything more than minimal risk for the subject?

DR. DRESSER: Well, I guess there is both. I mean, you know, a lot of states now authorize family members to make treatment decisions as surrogates.

PROF. CAPRON: Right.

DR. DRESSER: But what does that -- what implication does that have for research which is so different?

PROF. CAPRON: Having looked at the state --

DR. DRESSER: Yes. Actually --

PROF. CAPRON: -- law as well as statutory law, do you think most states have not addressed it or they have addressed it and they have left you with answers that are unsatisfactory? I was not sure what you were saying.

DR. DRESSER: I do not think most states have addressed it at all. If they have addressed it, it has only been in the clinical situation and not the research situation.

DR. CHILDRESS: And let me also say we welcome Alex officially to the Human Subjects Subcommittee. People have wondered about Alex as the floater but we have him now so we are delighted.

(Laughter.)

DR. CHILDRESS: This discussion is open to everyone obviously and not simply to the Human Subjects Subcommittee, but any other questions for clarification only before we move into the substantive discussion involving both our panelists?

MS. FLYNN: Just follow up a moment on Alex's issue. Do we -- are you aware of any information as to how well the advanced directives for treatment for cognitively impaired patients are actually working? Are they? Is this something that is growing? Is this something that is being viewed as useful? Is it, in fact, being implemented in large measure? How is it

playing out in the real world?

DR. DRESSER: Well, I think one of your colleagues has a lot of information on that. Trish Backlar who has written on that. So I would defer to her to answer that question.

PROF. BACKLAR: I am embarrassed to say that, Laurie, you are going to have to repeat your question. I only heard about advanced directives and I did not know if we were talking about the psychiatric treatment or for research. I am presuming it is for research.

MS. FLYNN: Actually I was asking the question that her comment raised. What do we know about how well and to what extent advanced directives for psychiatric treatment are actually being implemented? I have certainly anecdotally heard a variety of experiences but I wonder if this is something that is moving along and becoming accepted, and being increasingly utilized, and being adhered to or honored in the actual situation or not?

DR. BACKLAR: Well, I actually have an article that came out in Psychiatric Services in December.

DR. CHILDRESS: Could you share that with us?

DR. BACKLAR: On a survey, a preliminary survey that we did in Oregon. There are a number of states that have -- we start to describe what the

situation is with advanced directives for psychiatric care. There are a number of states and I am unable to list them for you but there are not very many that actually have legislated approval for an advanced directive for psychiatric care treatment.

There are a number of states that incorporate within their advanced directives for health care generally the possibility of one choosing psychiatric treatment. In Oregon we are one of the first states that did pass legislature and our document was passed in '93 and came out in January of '94. We have had it in place for two years.

This preliminary survey told us that very few people know about it, point one, that most of providers know very little. But we did find out that it had been used a number of times for people when they were in crisis and in those times when it was used when they were in crisis, I am talking not in quotation marks, their wishes were honored.

Our document provides for a proxy or surrogate decision maker and we were interested to find that only in the documents that we were able to find out that had been made out, not just used, less than one-third appointed a surrogate decision maker, which was of some interest to us. Most families reported that they simply did not know what we were talking about. They

found the document quite confusing and they thought that perhaps it meant they needed an attorney.

I think that there are a number of issues about advanced directives generally. But I think there are many advantages for an advanced directive for psychiatric treatment which we have not begun to understand. One is they are very different from an advanced directive for end of life care and I was talking to Rebecca before when we were coming into the hall. Advanced directives for end of life care is -- you prepare something for you do not know what is going to happen. It is unknown until it occurs pretty much. We do not know what is going to be our end of life issue.

But an advanced directive for psychiatric treatment, in fact, should be only for somebody who has had an experience of a decompensation or psychotic period, and it might be a great advantage for them to be able to say that this is what works for me, this does not work for me, and to make sure that that is going to occur. On the other hand you are going to have issues to do with privacy, confidentiality. How do people if you go into a hospital somewhere out of your state or even in your state, how are people going to know about it? There are lots of issues to do with this that have not been well looked out for.

The other big advantage is that certainly if

one works well with one's health care provider and your family member or surrogate decision maker, there is a wonderful opportunity for really truly informed consent in terms of medication, understanding one's illness, becoming involved in one's "recovery."

Laurie, I know you know what I mean by recovery in terms of mental disorders.

DR. CHILDRESS: Well, let's view this as the first substantive area for discussion now that it has been put out on the table and let's talk a bit more about advanced directives, their role, their ethical and practical problems, what kinds of different views we have on that and then we will move into other topics as members of the subcommittee and NBAC wish.

Rebecca, Bob, anything else you would like to say about advanced directives?

DR. DRESSER: I think I used my time.

DR. CHILDRESS: Oh, no, this is for our --

DR. DRESSER: Yes.

DR. CHILDRESS: Anything else you want to add? Bob?

DR. LEVINSON: I think that it is a good idea to encourage advanced directives. Rebecca mentioned that you would not want to allow people to make binding commitments, even people with mental, full cognitive capacity, but I do want to point out that in psychiatric

practice and to a limited extent in research we do acknowledge the validity of what has been called Ulysses contrast.

The contrast is taken from the -- you know, from the myth where Ulysses or Odysseus as you prefer wanted to sail past the place where there was this irresistible lure of the sirens and so on, and what he asked is that his crew bind him to the mast of the ship and leave his ears unplugged so he could hear this without being lured into this and he had the crew cover their ears. This has been used in psychiatric practice where people who have intermittent psychotic disorders can sign a paper, a Ulysses contract, saying next time this happens put me in the hospital for my own good. It bypasses the necessity for formal commitment proceedings and things of this sort.

In research it has been used more in doing research on such things as alcoholism where people when they are sober sign a contract saying next time I get really roaring drunk it is okay if you draw my blood to do some research. I have not seen it get into any of the really heavy considerations.

The point that has had long experience with advanced directives for research is the clinical center at NIH. I think it is correct if my memory is correct that they drafted the first -- what I call -- research

living will. That is not what they call it. Back in the early 1980's and they have been using it ever since. It applies not only to the people with mental disturbance, Alzheimer's, but also to people who will lose capacity because they have septicemia, a bacterial infection that is overwhelming and things of that sort.

DR. CHILDRESS: Other points about advanced directives?

DR. DRESSER: Just for those of you who might be interested, the International Journal of Law and Psychiatry in '96, I did not write down the exact volume, there is a really thorough analysis of research advanced directives for people with mental impairment. And they give it a qualified endorsement that say that it should be limited to minimal risk research and it is very thorough and it kind of goes through a lot of the pros and cons.

You know, I just think it is very important to remember advanced directives in treatment are people issuing instructions about their future care, what is in their best interest in the future. When we are talking about research we are talking about doing things for the benefit of others and these authors express some concern and I think it is legitimate that once -- if we put a lot of weight in this mechanism, will there be pressure put on subjects in these groups to sign these directives?

Will they be, you know, highly encouraged? Those kinds of things. Will capacity judgments be compromised? That is people will be deemed capable of making these directives because there is an incentive to get them into the research.

So I think those are all legitimate questions.

DR. FLYNN: Does the NIH experience that Dr. Levine referenced -- does the NIH experience with a form of this kind of advanced directive for research shed any light on what the actual practice has been? Because I hear your reluctant, Rebecca, to seeing this as a useful tool and if I am hearing Dr. Levine correctly he is saying that there has been considerable experience at NIH with this kind of approach.

DR. LEVINE: I wish somebody from the NIH Clinical Center Bioethics Office was here. So let me suggest that for updating on this you might contact -- well, Ezekial Emanuel, where is he?

DR. CHILDRESS: He just left.

DR. LEVINE: All right. Well, when he comes back ask him about it. Although he has not been there enough, but several like Evan Duranso would --

DR. CHILDRESS: Gary Ellis might.

DR. LEVINE: But Gary is in a whole different thing. Gary, do you know about that?

DR. ELLIS: Dr. Allison Wickman would be the one --

DR. CHILDRESS: Allison is not here today.

DR. ELLIS: Dr. Levine is quite correct in parsing out the bureaucracy. Dr. Allison Wickman would --

DR. CHILDRESS: You are near a mike but you are not using it.

DR. ELLIS: Dr. Allison Wickman would probably be able to answer that question.

DR. CHILDRESS: Thank you, Gary.

DR. LEVINE: While you are waiting for more complete information there is quite a number of safeguards built into this. Curiously the pivotal role is played by the -- an individual designated in their policy as the Clinical Center Bioethicist and when in doubt you clear things through this individual. This could be Allison Wickman or some of the others in that office.

I think that as you are weighing the safeguards -- what I have heard so far today and what I am accustomed to hearing when these matters are discussed is primarily focused on getting the best possible assurances of the autonomy of the individual research subject. I think if you want to read an extreme example of that sort of thing you can look at the regulations for

what was then called those institutionalized as mentally disabled that were proposed by DHEW in 1978.

These evoked a massive outpouring of protest from what was loosely called the public. You have got to calculate the costs. The way they have it set up is for doing research on some categories of subjects. You would have to get the go ahead from seven separate agents and agencies. And the researchers simply said too much, you know. We will ignore those with mental incapacity because it is so much easier and less expensive and less time consuming to do research elsewhere or with other people.

So I would caution you about excessive focus simply on autonomy of the subjects and try to balance the considerations. We have been through the experience in the United States of developing what came to be called the therapeutic orphan phenomenon which was applied to children. But subsequently it has applied to women and this population too.

DR. CHILDRESS: Alta and then Alex?

PROF. CHARO: This is not about advanced directives. Is yours, Alex?

DR. CHILDRESS: Okay. Thanks.

PROF. CAPRON: My question is to Rebecca. You have expressed in other contents very eloquently your skepticism about the concept of advanced directives

because of the nonidentity of the individuals to whom they will apply once incapacitated with the individual who is expressing these now. I would like to have your reflection on that as it applies to this context.

I would also like your further reflection on the comment you were making about the problem in the research context with the choice that is being expressed which is the choice to say I am willing to give to others in the future and I am willing to take some risk on behalf of the greater good because it seems to me that in a certain way one could say that that choice is the sort of thing where it makes more sense to use an advanced directive than about any particularity.

I mean, you did express and I would agree with you a preference for proxy directive and instructive directives on the argument that particular instructions that one will give is going to be so contingent on the actual conditions as they develop and it is better to have a proxy who is there, who is situated and can see what has happened.

But as to this basic fundamental choice which is either I am a person who is willing to have some risks -- to take some risks for the benefit of others so that others can learn from my condition, something which a competent patient is understood to be able to do and of course is at risk of being exploited and being pushed

into.

But what we see in some ways as a chance for ennoblement and gaining meaning from a serious illness that one cannot defeat, at least I can allow this to help others, you know, in a way is a person who is facing the prospect of a mental incapacity because of Alzheimer's or some other deteriorating condition. Not really entitled to being able to make that choice and isn't that the kind of choice which it does make sense to say you either want to put yourself in category A or B. But then again that circles back to the question is it fair to allow me now to choose for my future self. So you see the relationship between them.

DR. DRESSER: Well, you know, I think you articulate the values conflict here. Certainly we think it is good for people to be altruistic. I guess for me the policy question is do we think that that is so good and do we think that the rewards that competent people could gain from volunteering themselves for future harmful research balance the harms that would be imposed on the person as an incapable subject who no longer appreciates those earlier values of altruism. That is, is just experiencing something very negative and harmful.

You know, I think as a society that is the choice we have to make and it is one balance when you are talking about treatment, and I have some of the same

concerns there. But when you are talking about research where these people are being imposed on to advance the needs of others, as well as to advance their former values, I just think it gets even more -- of more concern.

DR. FLYNN: Is your objections to this specific to the cognitively impaired? In other words, you would not hold this concern for individuals who are -- have other disorders but are not necessarily cognitively impaired?

PROF. CAPRON: They do not need advanced directives.

DR. FLYNN: I understand.

DR. DRESSER: Yes. See they can always -- no, I think that competent people should -- I mean, of course the regulations require IRBs to only approve research where the risks are reasonable in relation to the anticipated benefits to the subject and/or society. So there is even a view that people with full autonomy should not be exposed to extreme research risks unless there is a good reason. Certainly that should apply here. But I also think that there should be perhaps a greater examination when you are talking about imposing risks on people who do not really understand why they are in the project now.

I mean they just -- it is -- if you are

talking about a psychiatric disorder, I think it is a little bit less troubling because if somebody who has been through decompensation, been through the research experience, and has fluctuating competency I guess I would have less problems with that person saying, okay, well, I am willing to go through that again in the future when I am incapable because that person is familiar with what it is going to be like.

I still am not totally convinced that that would be the best outcome. But if you are talking about dementia where this, you know, the person who has the mild dementia or has dementia in the family has no idea really except based perhaps on observation of some other --

DR. FLYNN: Well, you have made the distinction that I was interested in because I think that is an important distinction that people with psychiatric disorders fluctuate as you said earlier in their ability, capacity and autonomy. That is quite different than the -- as you pointed out, in the course that we see for people with dementia. I wondered whether that affected your view of the potential utility of these approaches.

DR. CHILDRESS: Bob wants to respond and then we will shift gears to a different topic with Alta.

DR. LEVINE: Point of question, when you asked will you apply these considerations only to those

who are cognitively impaired, there is all too common a problem of thinking about the cognitively impaired as those who have been labeled with psychiatric diagnoses. During the last few months of life many people are cognitively impaired.

I also -- I am not going to elaborate that but I am going to say that there is a set of studies done by Barbara Stanley and her colleagues where they evaluated the capacity to consent to research in voluntarily committed patients in a locked ward and compared it with the patients in the general medical ward of the same hospital. I believe it was Bellevue hospital. And the involuntarily committed uniformly did better for whatever that is worth.

DR. CHILDRESS: Alta? Did you want to tie into this?

DR. CASSELL: Well, on that topic.

DR. CHILDRESS: Okay.

DR. CASSELL: Let me wait until Alta is finished.

PROF. CHARO: Are you sure? Really?

DR. CASSELL: Yes, I am sure.

DR. CHILDRESS: Altruism?

DR. CASSELL: No. I want to extend a comment and I do not want her jumping up and down.

DR. CHILDRESS: All right.

PROF. CHARO: No, I am calm.

DR. CASSELL: No.

PROF. CHARO: I would like to shift gears if I might because although this has clearly not been mine completely and there were a number of other substantive issues that are of great interest, I am personally very interested in the notions of benefit and what in the world direct means as well as issues of risk.

In order to focus my mind on the constructive possibilities in the commission setting I would really love to get the benefit of kind of a road map of the obstacles, whether they were political within the government, political within the research community, within the patient community, all three, or if there was indeed a single or two substantive issues that truly prevent a consensus that have prevented any movement on this issue since the time of the National and President's Commission and now in order to just -- because there is a tremendous wealth of literature on all of the issues we are talking about that has been developing and improving over the years. But in order to figure out which one to focus on most intensely I would love to get a road map of what the problem has been in moving forward.

I know you wrote a little bit about the beginning of it but since then.

DR. LEVINE: I think you have an excellent

resource on the history of obstacles in Alex Capron. The exchange of letters between the President's Commission and the Secretary of Health and Human Services I think highlighted the problems. I will go back before that just a bit.

PROF. CAPRON: Could I say those are published letters in the President's Commission's reports on research ethics and it really is I think going to be a necessity, Bill, for this subcommittee to have copies of the report on compensating research subjects and the two biannual reports.

PROF. CHARO: And if I may before -- Bob, before you begin, see you are doing what I do.

DR. LEVINE: I am going to jump up and down.

PROF. CHARO: Right. And without stopping from summarizing it you present in the piece that was distributed a nice summary of the initial problems that took place before the National Commission and DHEW and these letters then take us up through the time of the President's Commission. But that is still more than a -- I mean, like that is still 15 years of history and these proposals have been out there, the literature has been out there. The model drafts have been out there and I am desperately curious to get, especially for now, current feelings. Although I know what the history is but you want to also -- what is holding this thing up?

DR. LEVINE: Well, let me venture an opinion. One, this is not the only area where individuals or groups of individuals have lobbied the federal government for improving the regulations in substantial ways. We have the repeated eloquent arguments by John Fletcher about why we really need that Ethics Advisory Board back and that has -- I do not know if it has fallen on deaf ears but it has not elicited any action.

I think in the field that we are discussing here there is inaction because there has not been a powerful movement insisting that the regulations be rewritten or written. And I am hoping that this commission can be the powerful force that will cause something to be done.

But what we have seen since the President's Commission adjourned finally in 1983 is that there have been occasional individuals or small groups calling for regulations in the field and what they are calling for are very different things, some want this, some want that, but it is not like -- we saw regulation writers mobilized a couple of years ago when a lot of different groups formed a coalition insisting that there be some accommodation in the informed consent regulations that would enable research in emergency circumstances and the -- you know, you must know the history of this. But that is what I am trying to say. It is a coalition of people.

And then what happened was the writing of an amendment to the regulations, public comment and so on, and now it is a final regulation, and this continuing unhappiness on the part of some participants in the discussion. But at least something happened.

PROF. CHARO: But, Bob, to be really specific if I am hearing you correctly what you are saying is that more than anything else since the initial set of difficulties we are faced with a situation of inertia, not positive active opposition on the part of any part of the government but simply inertia, and a lack of consensus among interested people that would form a single force that would push. I would then like to know around which specific issues in those regulations the lack of consensus can be attributed to.

DR. LEVINE: The lack of -- I think those who have been pushing hardest for developing regulations in this field have been more or less in agreement. In my judgment they have generally erred on the side of calling for what I consider excessive oversight and I would not have people monitor research on people with incapacity which presents minimal risk.

The arguments I have seen published generally do not distinguish minimal risk from other categories and generally do not distinguish the reasonable expectations of a procedure that would present more than minimal risk.

They all too often say, well, for therapeutic research do this and nontherapeutic do that.

So there are people talking about it. I think that is all I can say about it.

PROF. CHARO: So there is resistance on some parts for the excessive protectionism of others as perceived?

DR. LEVINE: I do not think -- you know, I --

PROF. CHARO: I just do not understand what the --

DR. LEVINE: You are asking me to read the mind of regulation writers.

PROF. CHARO: Okay. All right.

DR. CHILDRESS: Laurie wants to get in on this.

DR. FLYNN: Again at the risk of being inappropriate, I think there are a couple of things that have gone on in this arena. We are dealing at least with many of the cognitively impaired with individuals who are disadvantaged not only by virtue of cognitive impairment but are often quite impoverished, Medicaid and Medicare recipients often living in circumstances where the kinds of organized advocacies that have gathered around other disorders has not been so easy to create.

It has -- I think then an issue that my own organization of families largely and consumers who have

these disorders has come to over the past several years because of the kinds of issues that have come up through the media. And I will tell you as someone who is widely regarded in the psychiatric community as an avid research advocate and truly a believer and participant in research that I have been astonished at how threatened and resistant much of the research establishment has been by the notion of examining and perhaps extending protections in this arena.

When I press on it they raise two issues. They raise the one that you did and quite properly because some of the proposals out there really are burdensome and excessive, and I think restigmatize in some ways the whole enterprise. They are also very concerned about the fragility of the research enterprise around these disorders, that these are difficult to engage subjects, very difficult to understand disorders. The protocols are often complex and there are many very controversial issues particularly with respect to those that have the most severe incapacity and disorders, compounded by the sometimes fluctuating nature of that lack of cognitive awareness.

So it is a difficult field and a field that is in some ways at some breakthrough points in terms of basic understandings of the disorders and some real advances in clinical treatments. Folks are very afraid

to have anything upset that.

But unfortunately the way it has been perceived often by people like myself is that there is an arrogance in that community about, you know, what is best. We have been used to being in charge of these folks who have not had organized advocates. We are not bad people. We are a long way away from the climate you described in the '70s. Why are you coming now when we are just kind of getting somewhere and asking these questions of us? So it has been surprising to me the depth of that resistance in the research community itself.

DR. LEVINE: Let me agree but add one thing. And that is a constituency that is impoverished does not have much of a voice. But the constituency in the one area that we have seen a dramatic research, research in emergency situations, there is no constituency of research subjects. I mean, the people who will be the subjects of this are people who will get hit by a truck and have head trauma. We cannot round up this population in advance. But people who will need cardiopulmonary resuscitation.

So one of the things that dramatizes the fact that there is no constituency is that FDA put into this regulation that you can only use this emergency exception if you consult with the community. Well, where is that

community to consult with? As the person who first wrote up the maneuver, the procedures for community consultation, I never had this in mind. I had in mind a community that you could find.

DR. CHILDRESS: Rebecca, do you respond before we --

DR. DRESSER: I was just going to agree with Laurie largely. I think that part of it is because it is such a complex area. For example, what Bob just said about not having an independent person monitoring research that is minimal risk, in this population research that maybe prospectively looks like -- first of all, we have all agreed that the definition of minimal risk gets pretty vague so what is it. And even if you defined it, in this population something that you think would be minimal risk to an individual subject might turn into greater risk, that is it might become more experientially burdensome than you thought it would be.

So it is more difficult I think to make prospective judgments about how subjects are going to experience these things as individuals. That is just one example why there is a lack of consensus I think because it is so complex.

DR. LEVINE: I have to respond.

DR. CHILDRESS: A brief response.

DR. LEVINE: You said what we need is case

histories to exemplify what we mean. And I would suggest that a typical research project on somebody with severe cognitive impairment might impose the burden of having the blood drawn once or twice a day. I agree that this can be experientially burdensome to a small subset of this population.

However, as experiential burdens go it pales into insignificance with the other experiential burdens they have every day like maybe getting someone to bring them a toothbrush or getting someone to wheel them into the room where they can get their breakfast. Drawing blood is trivial in comparison to what these people go through lobbying for rights that most of us never even think about.

DR. DRESSER: Well, I guess I just think that substandard conditions should not be a justification for rationalizing research risks. But I do not think that we should --

DR. CHILDRESS: This is interesting and important. Let's get some more comments.

DR. CASSELL: Well, I have to leave shortly. I did not have to leave shortly when I had my hand up.

(Laughter.)

PROF. CHARO: I am sorry.

DR. CASSELL: But I think that there is never a lack for people to write regulations. So if you see an

error in which effective regulations have not been written it is not for lack of regulation writers. There are some things that -- there are some things where the difficulty posed by the problem is just unresolvable and the basic problem that is posed here is shifting cognitive capacity. And who, in fact, can be responsible for somebody tomorrow who today was one thing and tomorrow is another? Am I the same person today as I will be tomorrow if my cognitive capacity shifts, and I promise you it will little by little?

But, in fact, everybody who is sick is in that situation but we have not the knowledge about that. As Bob pointed out there is a piece of work done on sick people in an ordinary medical world. I have done work that shows that there is impairment in people's thinking with all serious illness. And that somebody who is -- and that somebody who is well now and signs a consent is not the same person one day post operatively as they were when they signed that consent. They simply are not.

On the other hand they are not a different person. There is something about them that is not at all different. I do not want to get into that old philosophical argument of how do we know whether they were the same or not.

But what we come to here is realizing that the person cannot be their own spokesperson, that there

are circumstances in which the person cannot be their own spokesperson. On the other hand, when we attempt to get a monitor in we find out that if you get a monitor into enough situations you cannot do the work. So now we have -- there is no way for the person's cognitive impairment to be accounted for on a day-to-day basis. There is no way to have somebody supervising other people's work and then what do we do in the absence of that because the research has to be done for the very people who are cognitively impaired I mean in other words.

And Laurie says she is an advocate for the research. She is not an advocate for research just because she loves research but because she knows the nature of the problem of the persons who are sick.

So then we begin to see that -- something we have already discussed in the subcommittee. We begin to see a changing relationship and the need to make happen, not to wish into existence, but to make happen a changing relationship between investigator and subject that has more benefit for the subject than any monitor will.

Now I would like to say that all research, all human endeavors for that matter, depend on a degree of trust. In fact, persons are good and true, that they will do what they say do, that they will be responsible for sick persons.

Rebecca brings up another very important

point when she points out the inherent conflict of interest between the investigator as the seeker for knowledge and the investigator as a caregiver. There is an inherent conflict of interest. It cannot be otherwise. It must not be otherwise. On the other hand is to say, well, we have to solve that in some way.

If we will just accept for the moment that this mind bending problem has to be solved and cannot be solved in the way we have done it in the past, that is to try and figure out another way of writing the regulations that will somehow change the cognitive shifts that go on in the human mind if we will just accept that that is not going to be our solution. Then I think we actually have a chance of moving forward.

Just as an anecdote years and years ago when I was in the air pollution business everybody was trying to get, you know, what number of amount of sulfur oxide in the air could we write that would make everybody protected if it was below that. And in those days I did epidemiologic research on air pollution. I bent my head about that? What number? Well, finally the conclusion was no number. Give up the idea that there will be a number. The idea, in fact, it will not be numbers, it will be process.

Here I think we are going to come to much of the same kind of conclusion. If you say when I am

finished speaking with reason, well but that is a vague -- you do not have to have a solution when you start out. You have to have a direction.

PROF. CHARO: Eric, I am not going to dispute a word you said about the kind of core substantive issues that applies to many of these people. But I do respectfully differ with your underlying premise. Yes, there are lots of regulation writers. But actually writing the regulation is a major pain in the neck and nobody wants to do it unless they are forced to. I mean, the routine to get it through is just nightmarish.

It strikes me that where the regulation came down is because, in fact, in essence there was no patient group at the table. Either people did not see themselves as potential subjects because they could not recognize that in themselves, kind of thing you were describing with the emergency stuff, or the patient groups would dismiss out of hand.

The prisoners, well, they are a very identifiable group, they confide in one another, they know they are going to be targeted, but nobody is going to pay attention to what they say anyway. And, in fact, they are not even allowed to vote if they are felons.

Pregnant women routinely dismissed because as the Researcher announced yesterday they are physiological sound to be absent minded and basically cognitively

impaired. I loved that announcement.

As a result I think that in some ways the problem here as weird as it is to say, you know, the morning news is wonderful, the problem is as weird as it is to say is that there is a patient group, it does not know how to find itself, it does not know how to identify itself, but in this case because of the very substantive problems that have been identified, the variability of the patients, et cetera, they have a voice through their allies, their families, but the voices are not uniform. They are conflicting.

So there is not a consensus that can allow that patient group to sit at the table and so you do not get anywhere. Without the patient groups we have nothing but elites and that is the French bioethics model and it works beautifully. They make much more progress than we do.

DR. CASSELL: Alta, you cannot have a patient group where the people who will be uninjured the day after tomorrow.

PROF. CHARO: Right. But that is an advantage in many ways because it allows just the elite, the researchers and the lawyers, and the regulators to sit down and make progress and do it without the fuss and muss of the public.

DR. CASSELL: Is that what you are

suggesting?

PROF. CHARO: No, it is not.

DR. CASSELL: I would be slightly surprised if that is the conclusion you came to.

PROF. CHARO: What I am asking, though, is if we do not want to cut the public out, that we do recognize the lack of consensus from them at the table is going towards your efforts to regulate I would be really interested if there is some way to splice this public and find the core group that do have a consensus on certain kinds of subjects and kinds of settings, and work on those things where regulation probably could be adopted, and then continue to work on the areas that are not yet easily regulated because there is genuine difference of opinion.

So, for example, you made a big distinction and everybody else has about people who are experienced with various forms of cognitive impairment or emotional impairment, and now are currently competent and might go forward, et cetera, et cetera, as opposed to those who are unfamiliar with the experience, it is going to be a long-term experience, a permanent experience and they are going to be incompetent to the point where even things like assent are unrealistic.

It strikes me that in those more severe cases actually there might be some consensus around an

extremely protectionist attitude. And that the real debates are circling around the more problematic cases of partial competencies, sporadic competency, degrees of risk, et cetera. Maybe it is possible to split off populations and find the ones where there is a consensus within the patients and patient allies, have them work with the researchers and the regulators, and move forward with some portion of the puzzle.

DR. CASSELL: Alta, if you go and solve the problem of changing competency in all the other groups where competency has been taken for granted up until now all you do is protect a small group.

PROF. CHARO: Yes.

DR. CASSELL: If you stay in the same model, the same model that was there before, not as you rightly pointed out, if it is impossible to find it, let's go get where there is a group and do that.

PROF. CHARO: Yes.

DR. CASSELL: That is the only problem with it. It may, in fact, be necessary for certain groups where no matter what solution you find that works for everybody else will not work for patients --

PROF. CHARO: I agree. It is a classic dilemma, democracy is a messy business. You heard the American President at the movies, "Democracy is hard work. America is hard work." And the question is

whether you want some short term gains while you do the rest of the hard work or that the short term gains are not working.

DR. CASSELL: Well, but in the past what happens in this is what people have done in a conclusion like that is take the small group, write regulations for the small group and leave the basic problem untouched.

DR. CHILDRESS: We have a scarce resource of time. We have only about 15 more minutes before -- Tom, will you be around until the end? We will need to pursue some of the questions we talked about over break about the future. So we will have about 15 more minutes for our substantive discussion. Laurie, do you want to tie into this particular part?

DR. FLYNN: I just want to endorse the point of view that Eric is espousing both in earlier comments about the -- I think based on the discussions we have had and the interactions we had yesterday, looking at some new ways to deal with these issues that engage the broader community in creative ways that further the dialogue and ultimately create a messier, if you will, process that may, indeed, help us get to some of the most difficult solutions that have alluded us so far.

I would be worried about -- as much as I see advantages in trying to move forward on those areas where there would be agreement because I think the bigger

problems are the ones that are plaguing us now are the ones that are affecting large numbers of individuals and where we can no longer afford to be silent. We have to wrestle through this and I think Eric is pointing in a direction that would be very helpful to us as we attempt it.

DR. CHILDRESS: Yes?

DR. COX: At the risk of being repetitive this really hits a key with me, too, and the -- an easy way to deal with research is to make it very separate from medical practice. I was really struck by something -- I understand why you did it, Rebecca -- of saying, in fact, you know, let's have the researchers wear red coats and let practitioners wear white coats. That is a way of basically keeping this irreconcilable conflict from having to be considered.

But I really think that this is where the action is, is because it is not so clean, and we have to be willing to deal with the mess of this because it is adjudicating a new relationship between research and medical practice, whether it is for, you know, particularly vulnerability groups or not. I am not looking forward to the mess but I really do completely agree with Eric and other spokespeople in this, but that is almost certainly where the solution is.

PROF. CHARO: There probably should be some

pink colored ones too for the nurses.

DR. CHILDRESS: Harold and then Trish.

DR. SHAPIRO: I was just going to make a remark that given American history red coat is not a very good idea.

(Laughter.)

DR. SHAPIRO: Try some other color.

DR. CHILDRESS: All right. Trish? Okay. All right. In the last 15 minutes what are some of the issues from people we have not heard.

Alex?

PROF. CAPRON: Just to pursue this question, putting aside the color of the coat, do you have thoughts about what kind of separation that would need to be between a person in a professional role who plays the evaluative and to a certain extent representative function with the incapacitated patient in terms of making sure that the incapacity really is not correctable in the near future so that the patients could give consent making evaluating the risk/benefit and so forth from the patient's point of view, how you would set up a relationship in terms of who appoints this person, who funds the person's efforts and so forth that would make them sufficiently separate from the research enterprise that they would not be kind of captive of that enterprise?

For example, in the transplant area some people worry about the doctors who are making determinations that death has occurred are too closely related to the transplant team and the law tried to specify, no, they should be completely disconnected from it and so forth. In the end they are likely to be paid for that effort by the transplant team and so forth. I mean, those kinds of things can arise.

So have you given thought in this context of how that would be done? Would one need a separate funding mechanism, separate appointment mechanism, et cetera, et cetera, and would it be possible to have a person playing that professional role and yet a separate person playing the surrogate role, the proxy role for the patient who is not a professional but is either the relative or the court appointed person who, in effect, would turn to this expert for advice but the expert would not be the decision maker.

That is really two sets of questions about their role and their independence.

DR. CHILDRESS: Rebecca, do you want to respond first?

DR. DRESSER: Sure. This is a tough one. I think some of the things Eric was saying were suggesting that it would be possible for some members of research teams to adequately fulfill this role of accurate

disclosure and assessment of capacity and, you know, just the decision making process. I think that is certainly true. I think that some researchers could do this. And on the other hand I think that having somebody independent of the research project is not a guarantee that that person will adequately do this.

So it is just a question, I think, for policy purposes of if you create this separate role are you more likely to get what you are interested in than if you tried to assign it to one of the members of the research team? That is the question and, you know, I think you can figure out how to think about that as well as I can.

In terms of funding, I mean it is sort of the same issue we have with hospital ethics consultants. I mean right now coming out of general funds there is some concern about, you know, should this be factored into patient fees and all these questions. Where is the money going to come from? I guess there really -- should it be written into a research proposal as a cost? Obviously investigators are not going to be thrilled with that idea but that is one avenue.

I do not know if there could be a creation of a separate fund, you know, for issues.

DR. LEVINE: I am glad, Alex, that you are attentive to the problems created by so-called unfunded mandates. There has been an extensive literature

developed on having third parties superimposed on the research process where there is an expectation that there could be a conflict of interest. I think the person who first wrote about it at length was Harry Beecher who recommended in the process of getting informed consent that he would have consent discussed by somebody other than the investigator. He also talked about separating the role of physician and investigator.

This then provoked me to review what had been written about it and there is a passage in my book where on review of all of this I come to the conclusion that if you assume that the researcher and that the treating physician have differing motivations, irreconcilably different to the extent that you separate the roles, then you want to be awfully sure that the investigator is never left alone with the subject.

I mean, after consent is done they are the investigators on his or own to savagely abuse the subject. My conclusion was and remains that the only way to assure that there is a physician around every time the investigators can contact the subject is to have them both and have it the same body.

DR. BRITO: From personal experience I would say that even when they inhabit the same body there can be a conflict.

DR. LEVINE: Of course. But if you want to

find any human beings that have unambiguous univocal approaches in problem solving then we really are going to have an unfunded mandate.

DR. BRITO: I have a general question about regulations, et cetera. One of the main problems I have with informed consent, this goes along lines of informed consents not just for cognitively impaired but just in any situation, is that -- and I brought this up before, it seems like we always put the onus of the responsibility on the person signing the informed consent, and it just seems something very basic that if we put more of that responsibility on the investigator by having he or she sign an informed consent that applies to that specific research project it would make rather sense there. Does that -- is there any legislation that requires --

DR. LEVINE: Albert Reese, a sociologist, wrote an elegant paper showing how the consent form was an instrument designed to protect the institution against the subject. Basically what it is, is a receipt so if the subject comes back some day and says you did not get informed consent from me, you can give me the information, you can say, "Oh, yes, I did and I have got a signed receipt for that."

If we really saw these instruments as something designed to serve the subject's interest we

would do it more like a product warranty. We would have a piece of paper that the investigator signed and hand it over to the subject so the subject would have the receipt. We are still stuck with that to this day. But I do not see informed consent as being such a large justification for research. It tends to be the thing that is most often discussed.

I think some of the international documents have a better perspective saying first look at scientific design; second look at the confidence of the investigators; third look at the balance of risks and benefits; and after you are done with that then you decide -- then you -- if you pass those three tests now it is time to discuss the informed consent. We begin with the informed consent.

DR. CHILDRESS: I have Laurie and then Rhetaugh.

DR. FLYNN: I think we could profit just parenthetically from a whole session with you folks on the issues of informed consent that we have identified. I want to move to a slightly different issue and it may be addressing in some of your writings, which I confess have yet the experience of really delving into and I am very eager to read your book.

What is your view or what is your assessment of the -- some of the concerns that we have just

articulated around the vulnerability again and special needs of your population as we look at the variability of IRBs and your experience in dealing with these kinds of protocols, in the wide range of training and knowledge that may be available and the make up of these IRBs, a variety of ideas float around, everything from there should be some super perhaps national IRB or special regionally designated IRBs that specialize in certain of these areas so that there is a growing capacity to make those distinctions.

My own organization has a great interest in seeing IRBs that do substantial work in psychiatric research recruit and significantly involve members of the community of concern, family members, advocates, patients who have recovered and live in the community to be direct participants in some of that.

What is your view of how we might -- given what we have all identified as the very difficult issues here, how might the IRB system or structure, or mechanisms perhaps help us address this?

DR. DRESSER: A lot of what was -- what has just been discussed, I keep thinking about this UCLA schizophrenia study where, you know, one of the problems that the federal officials investigating saw was that the researchers were the care givers and that was not explicitly dealt with as it should have been. But, you

know, I believe that one of their -- I do not recall whether it was a requirement or a recommendation but it was that the UCLA IRB include someone who was a consumer representative or community representative.

I really support that. I think that community involvement on IRBs -- to do it effectively it is difficult. Any people who have been on IRBs know that lay members are often very intimidated and it takes a while to -- I would say a year or two to get the hang of it and, you know, sometimes it works and sometimes it does not. It depends on the person. It depends on the support that that person gets from the other people. So it is not a panacea but it can be helpful.

DR. FLYNN: Dr. Levine, did you have a view on specializing IRBs? In other words, certain IRBs sort of becoming a regional or national repository for this kind of research that falls in the area of perhaps most impaired, greater than minimal risk might be reviewed?

DR. LEVINE: I think that the National Commission put together a very sophisticated analysis of why have these sort of general practitioner IRBs located right in the institution where the research will be done. Part of it has to do with you cannot write it all in regulations. You have got to be right there on the scene to know which members of your staff need watching more than the others. Although you do not see that written

about very often I think most people on IRBs know that they have to individualize that sort of oversight too.

Let me get back to an earlier --

PROF. CAPRON: Bob, could you stop right there. Do we have -- you say it is not written about very much and people are nodding their heads that it is a sensible idea. Do we have any basis on which we could say that has proven to be an important mechanism because certainly the notion of centralized and localized review is greatly buttressed by the notion that there are these intangible benefits.

The kinds of manifestations of that in terms of individuals -- IRBs refusing to allow its center to participate in a multicenter trial because the investigator at that center, the oncologist, happens to be not reliable whereas at another institution he or she is. Or consent monitors being widely prescribed for people.

I mean how would one get tangible evidence that IRBs have done this or is it simply a matter that they read the protocols? I mean, has anybody written about it? You edit IRB --

(Simultaneous discussion.)

DR. CHILDRESS: We have one more question and we have to get on before we --

PROF. CAPRON: I am just very concerned with

this kind of -- I am really desperate for information or for something that --

DR. LEVINE: There are no data. What there is, is the armchair anthropology of people like me and a couple of others. What we talk about is instead of having monitors, what we have within the institution where the IRB has established itself as a credible unit we have a system of informal monitoring that would be vastly experience to purchase.

We get medical students, nurses, professors walking in and saying I think there is something funny going on over there, would you take a look at it. You respond to all of this. This is not -- this is the sort of behavior that would confound sociologists who are obsessed with power imbalances.

One thing we had a couple of years ago was a medical resident came in to say that he thought that there was coercion of an elderly woman, female, research subject in a protocol where the principal investigator was an associate dean. As it turned out there was and as it turned out the PI did not even know what his fellows were doing. But we got it straightened out in a real hurry.

I am seeing George Caspara (?) sitting there and it makes me wonder if we are going to get inspected for this.

DR. CHILDRESS: Unfortunately, we are at the end now. I have to get Rhetaugh's question and that will be the last one.

Rhetaugh?

DR. DUMAS: I do not want a question.

DR. CHILDRESS: Or comment.

DR. DUMAS: I had a comment on another --

DR. CHILDRESS: Could you make your comment and this will be our final word and then we will need to talk just a bit about procedure.

DR. DUMAS: I do not even really -- I do not think it is appropriate at this point. We have gone beyond it.

DR. CHILDRESS: Okay. All right. Thanks very much.

Please join me in thanking our two commenters for such a --

(Applause.)

DR. CHILDRESS: We hope we can call on you again for written contributions or other contributions. This has been a most helpful session. We, unfortunately, identified several areas where we need a lot more information.

Several of us have talked a bit about the future in passing. One of the things we might consider for our subcommittee is -- given what we have heard

today, if we have another session, I am now making this more specific, for them to get some of the people, perhaps Jonathan Marino from the University of Pennsylvania, Center for Bioethics, study of informed consent which is also moving in the direction of trying to talk about guidelines for the cognitively impaired. And the possible Maryland legislation and Dr. Schwartz and others have been involved in.

These would be two more specific versions that would take what we have heard and try to focus on things more generally in a more specific concrete direction.

If that is something that the subcommittee would find appropriate we might try to schedule at least an hour or so on that, perhaps two hours, at a subsequent session. Is that, subcommittee, appropriate?

PROF. CHARO: Can we add to your task list over time?

DR. CHILDRESS: Oh, sure. Yes. We will need to.

The second thing that some of us have talked about in passing is what kinds of papers to try to commission if we could. These are some that have come up in the discussions. One would be to get something if we could identify the right sort of person or persons for the discussion about vulnerability.

A second would obviously be to focus on issues surrounding community and how taking that kind of perspective might lead us to rethink some ways to reinterpret the Belmont principles.

A third, obviously something that would be another possibility too would be to make it feed into a report would be to get -- maybe we have enough in the literature from the contributors we have heard from today and I think Harold Levine and others have contributed in this area, to talk about the shift in paradigms or the changing context, the nature of research, but that might be another possibility. Those are at least some that we could think about and there may well be others as well.

PROF. CHARO: I would like to add just two things that I think are really concrete that might be quite do-able. First can we get some -- can we get a commitment to get a copy of the agency reports within X number of days, X whatever, and a commitment among subcommittee members to read it and be ready to discuss an evaluation of it while other work is proceeding in parallel so that we have the possibility of doing something with those. That is A.

And, B, in light of today's discussion, and I was nodding, Alex, because I recognize the situation because I thought it was a good idea, could we through e-mail perhaps accumulate a list of pieces of information

about the actual operation of IRBs that we have all noticed and then send a letter to the institutions that have multiple assurances at IRBs that we do know about and invite their chairs to submit written comments of any sort that they wish but notifying them that these are already areas we have identified in which we really lack information.

And so to the extent that those are things they would like to talk about it would be particularly appreciated. This is not a survey. This is a very targeted invitation for written input that might provide some of the stuff that we cannot get from commissioned papers because we do not have the time or money.

DR. CHILDRESS: Right. That would be useful and also I will get the National Reference Center for Bioethics Literature to give us as much as they can in this area as well.

DR. DRESSER: One thing you might think about, we did not talk about the New York Appellate decision today.

DR. CHILDRESS: Right.

DR. DRESSER: Even though that did not apply to federally funded research in the federal regs I think it raises a lot of issues about the regs and it might be worth it for somebody to go through that very carefully and point to the issues.

DR. CHILDRESS: Right. Good. Thank you. And everybody has that packet of material.

Okay. Any response to Alta's suggestion and the others?

PROF. CAPRON: Yes. I would like to say publicly what I said to you privately and then you can get feedback either now or otherwise from other subcommittee members. I think there is great urgency if we are going to have useful meetings to -- and be able to produce a report -- to commission papers very soon and the experience of the National Commission which was operating on a very short deadline as to its first report on fetal research is an experience which is now 20 years old and the world has changed, and the people who you turn to are busier than they were then. But there was less going on.

But for an important presidentially appointed body that is mandated to look at a subject I think it is possible to get good people to do work on a short schedule even if what they present to you first is a brief written outline and then an oral presentation of their issues. You know, we have had the benefit in effect of asking Rebecca and Bob to do that for us today but they are not commissioned to then write reports. We have got to have that kind of fodder. Frankly, if the staff and others are going to be able to turn out reports

you need that kind of work and we need it in March and we need it in June whenever we are meeting.

I just want to say I am very, very hopeful that once whatever funding commitments are necessary for Bill and others to get the secretary to sign the contract that those people be already identified and contacts be made with them and that we get the four, or five, or six papers that you just described under way so that they are there when we need them.

DR. CHILDRESS: And also --

PROF. CAPRON: And that those reports -- I am talking about something that will not just come back to our subcommittee but would be someone coming to talk to the whole commission that we would have arranged that we have a substantive discussion with people who can really take us deeply inside some of these issues.

PROF. CHARO: Alex, but no matter how fast you make it, it is already getting late. Can't we be our own analytical staff until we have one?

DR. CHILDRESS: I do not think they are mutually exclusive. I would propose we pursue both simultaneously if the subcommittee agrees. Are those -- those topics we have heard, those -- what changes or alterations would you want to make in those and I will depend on you e-mail and otherwise for getting names and suggestions?

DR. DUMAS: I am concerned about what we are planning to do by March and I do not know what Alta has suggested is intended to be part of that March report. I thought I saw the IRB issues on the lower end of the list of priorities. So I need some orientation about (1) when we are going to meet again and (2) what are we going to do between now and then.

DR. CHILDRESS: Well, I think in terms of the IRBs appearing low on the list of priorities mainly that was for purposes of being able to complete a project but several of these things overlap and we will be pursuing along the way. It was my impression of the way we are approaching the priorities that there is so much of a need in the area of informed consent and IRBs that we are probably not going to be in a good position to have a strong recommendation by October. But we need to be carrying that process forward. Obviously those two overlap substantially, the informed consent language, that was the area we talked about today. So I do not know, does that help?

DR. SCOTT-JONES: This is on a different topic so you can go ahead.

DR. CHILDRESS: Okay. Anything else along those lines. Is that --

PROF. CHARO: Can we -- we could commit for the day before the March meeting if we wanted to try to

convene a subcommittee. We could commit to having reviewed the agency reports and come back to discuss them, and if there is a consensus about an evaluation, find that consensus. And, second, to discuss the language of the consensus if one exists about the need for universal coverage of protections from research regardless of the mechanism that is chosen and to submit that for the March meeting for the full committee.

DR. CHILDRESS: We need to do that. I quite agree. Regarding another meeting, this was something that Tom and I have had some passing conversations about. There are several possibilities.

DR. SCOTT-JONES: If you are ending I would like to just go ahead and say what I was going to say.

DR. CHILDRESS: Please. I am sorry.

DR. SCOTT-JONES: Well, first of all, I agree with Alta that we need to move towards products and I just wanted to say that the three topics that I have noted that you have said, Jim, would be good for commission papers, vulnerability, community, and shifting research paradigms.

I think that because we have discussed those at length and we were not quite in complete agreement on them, but if we were to commission papers that we probably should try to develop a paragraph or two on each one of those ourselves and circulated them and make sure

that we are all agreeing and asking for the same thing. I would be especially interested in working on the -- well, any of those three as far as developing a paragraph that would say what we really need and what we would really be asking for.

DR. CHILDRESS: That is very important because that has to be done obviously before we can get someone to sign on. And then the other part would be trying to have them -- if all this could be arranged, trying to have them available for a March meeting or a late February meeting, or whatever, at which time we could -- I am not talking about the large meeting, but a separate -- at which time we could work with them in further refining the direction of the project. That is to say the paragraph will be important to get them started, but then as they get into it we need to interact with them in that direction. Does that make sense?

So do others want to take -- you will take primary responsibility for getting a first draft started on --

DR. SCOTT-JONES: Are we trying to assign that now?

DR. CHILDRESS: I thought you were ready to volunteer for one of those.

DR. SCOTT-JONES: No. I mean, I would be happy to work with Arturo on vulnerability.

DR. CHILDRESS: Oh, good, okay.

DR. SCOTT-JONES: I would be happy to work on the --

DR. CHILDRESS: Okay.

DR. SCOTT-JONES: -- whatever --

DR. CHILDRESS: Any other? Okay. I will start the first draft then on the third topic. Okay.

DR. BRITO: So did we decide on the meeting and --

DR. CHILDRESS: No. That is something we have to do but make sure we cover this first. Anything else on the three papers?

Okay. Now, Tom, what thoughts have you had about the meeting matter?

DR. MURRAY: About whether to have a meeting before March?

DR. CHILDRESS: Yes.

DR. MURRAY: We had as some of you heard a brief conversation at the end of the first session this morning about whether to have one and there had seemed to be a consensus, which was really apparent and not real, not to have one before the March meeting of the full commission.

Zeke Emanuel came up to me afterwards and expressed a view that he thought it might be useful to get together even if we just got together for half a day

or a day to sort of -- as he put it a schmooz meeting to sort of schmooz about what the various topics were. I said, "Well, what if we actually could have the contractors who are writing papers identified and have them be present for part of that conversation." He said, "Yes, that sounds like a good idea."

So I am quite willing to try to see a meeting occur as you say perhaps in mid to late February where we bring at least two or three of our potential paper writers, contractors in to sort of think aloud about what ought to be in their papers. They might have an initial sort of very crude outline at that point. We could respond to that and raise our own consensus. I would be happy to see that happen if it is something that could be put together and if other members of the subcommittee thought that it would be a good thing.

I see some nods of affirmation on that.

DR. CHILDRESS: What about the Human Subjects Subcommittee? What is your rule on that? Does that direction sound useful? Let's get some feedback and see what people think.

DR. SHAPIRO: Jim, can I --

DR. CHILDRESS: Please.

DR. SHAPIRO: A number of very critical things have to happen in both subcommittees in the next week or ten days. Just to name the most obvious, it is

mobilizing our own intellectual capital in some kind of effective way so that every member of every subcommittee can be expected -- can be asked by the chairman to do something and to harness their own intellectual capital. Individuals have to be identified for those areas which the subcommittee chairs feel that we have to identify papers as Alex used the unfortunate word of fodder for our thought, but in any case certainly to help us think more clearly through some of these things.

Within now and a week from now or ten days from now I believe it will be true that both Tom and Jim will have a much clearer notion of what can be available for useful discussion at what time. So my own suggestion is, Jim, for both of these subcommittees, is that we spend this next week or ten days in e-mail, telephone and other kinds of contact so that you can better feel your way as to how useful another meeting would be either before or after the March meeting.

If we are fortunate we can meet before the March meeting in which case the March meeting will be all that much more effective. What I would wait to do before setting the agenda for the March meeting is to be in contact with people, see where you are going to be if you are going to meet before or after because that will impact the agenda of the March meeting itself.

So my thought is that we cannot easily settle

all of these things here today but that we take that as high priority must item to do in the next week or ten days at the most to settle these issues and to try to schedule something which is convenient for the various subcommittee members. It is an extraordinarily important time now if we are going to meet our October aspirations.

So my thought is if you and Tom would agree that we could leave it that way, that puts a lot of responsibility on my shoulders, yours and Tom's shoulders over the next ten days, but I do not know any other way to get a conclusion here.

DR. CHILDRESS: Is that satisfactory from the members of the subcommittee standpoint?

DR. MURRAY: One thing could we do, could we ask the staff to do right away is to resurvey the group just to see about availability in late February?

DR. SHAPIRO: Yes.

DR. MURRAY: Because we could start that right now.

DR. CHILDRESS: Larry?

DR. MIIKE: Until Harold mentioned the March meeting I was going to say that we need to know what we were going to talk about the March meeting. We are putting in these interim meetings post the March meeting without any discussion about what the March meeting is. I think we are coming fairly rapidly to an artificial

distinction between our regularly scheduled meetings and ad hoc meetings. So I would rather look at the March meeting as just another one of the meetings around these overall issues and not reserve it for any particular --

DR. SHAPIRO: Larry, it may, in fact, work out that way. It may, in fact, work out that what the March meeting comes to be is something for us to work on these issues. But there is at least one other possibility for the March agenda, at least for part of the March agenda, which I expressed yesterday, but if it turns out it could be postponed for another meeting, and that is I do want to give an opportunity to certain groups to address the committee regarding issues that we are addressing that have not for one reason or another taken advantage of the public comment session and that reach out to invite them to come and speak to us.

Now it would not have to be the March meeting. So that is just one of the other items which we have room in the March meeting we will try to accomplish.

DR. CHILDRESS: And as we discussed there might be ways to focus some of those contributions to some of the areas we talked about this time. Yes, absolutely.

DR. MIIKE: One last comment is that we need to build in some redundancy here. Having done these kinds of things before one cannot depend on commission

papers and expect that they are going to be valuable. So I think that -- I see Alta nodding her head over there. So we have had a whole bunch of --

PROF. CHARO: As both author and the requester of such papers.

DR. MIIKE: So I think that in our planning we should be prepared that a certain number of these are not going to be useful.

DR. CHILDRESS: I think you are quite right and I would hope that this interactive process that we are talking about of providing direction and selecting the right sort of people we hope and then giving them feedback and process as well as having them give us feedback might well produce a better product because quite often these papers are commissioned with just a brief statement and then the author is sent off to prepare the paper.

At least what we have been talking about, Tom, I think it is correct to say would be a much more interactive process if we could do it, which I think would be mutually beneficial.

Bill, Harold, anything you folks want to say?

DR. SHAPIRO: No.

DR. DOMMEL: We will resurvey all the commission members and -- we will resurvey all of the commission members as to their availability for meetings

in February and March, April, May. I will ask Emily to take the lead on seeing that everyone gets the federal agency responses by mail and you receive those by Wednesday. Except for Alta, I have hers right here.

(Laughter.)

PROF. CHARO: And it is full.

DR. CHILDRESS: Harold, do you want a final word?

DR. SHAPIRO: Thank you very much.

DR. CHILDRESS: Thank you very much this morning and again, Rebecca and Bob, thank you for --

DR. DRESSER: Thank you.

(Whereupon, the proceedings were concluded at 12:41 p.m.)

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