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Welcome

DR. SHAPIRO: I'd like to welcome you all to Portland and introduce Senator Mark Hatfield, who is kind enough to make some opening remarks. Senator Hatfield was instrumental in the legislation that authorized this Commission. Senator Hatfield only has a few moments, but I invited him to say a few words to the Commission.

Opening Remarks

SENATOR HATFIELD: Thank you very much, Dr. Shapiro. First, I want to add a warm welcome to each of you for your presence here in Portland. Believe it or not, this little bump on the end of my nose was discovered to be malignant, a little skin cancer, not systemic. People ask me how do you get a skin cancer in Portland, or in Oregon. I want you to know we do have a considerable amount of sunshine in this state, as well as a beautiful green that's created by the rain. I am aware that this Commission has been under very severe stress in getting organized and getting moving. I will not go back to recount the tribulations that we had in the legislative role that I was privileged to play, except to say that Jack Gibbons, who later became the President's science advisor, and really was the great force in bringing forth this Executive Order, should be given the credit of midwifing this particular Commission. I don't think any of us would argue the point that with the advance of science and the rapid growth of so many new areas of science, that such a Commission is a vital part of our ongoing search for truth, and as well as the application of truth in science. I recall when some of the first genetic advances had been made. There was a call in New York City for clergymen from various and sundry faiths, Catholic, Jewish, and Protestant. They met because they were concerned about the application of these new science discoveries and their relationship to ethics. One of the pronouncements they made was that perhaps we ought to halt this kind of science and the direction it's moving. I didn't think that many in the field of science would accept that as an offer of recommendation, or should we? We have had in the past the conflict between science and theology, apparent conflict. In the earlier days, it resolved on the side of theology from Galileo as one of the prime examples. But it was a conservative line, along with many of my colleagues, from the standpoint of not trying to stop science, but to consider the application of science and the role of ethics in that application. I think after the Executive Order was given to create this Commission, you had put upon you a very quick responsibility relating to human cloning. You have responded to that with five recommendations. I think that's the role that this Commission is to play. As you get into more specific papers and activities, I am sure that these other issues will come about with some recommendations as well. I have known the Genome Director, Dr. Francis Collins, and he was saying at the time this was being considered in Congress, we need this just in the genome project itself on the question of privacy of genetics. A woman is diagnosed as having breast cancer, or a man with prostate cancer, is that information private, or does that go to the insurance companies? Those are issues that are so obvious, that as you move into this, I want to congratulate you on the international conference that you held bringing all this together. Because it is not just a national interest, it's an international issue. Recognizing the diversity of cultures, and histories, and religions, and what have you, makes your job all the more complex. But I wish you well and I am very honored that we have Patricia Backlar representing

two institutions here in Oregon as a member of this Commission. I have recognized Dr. Shapiro, and others of you whom I have met in the past and whose resumes I have read, I am just very proud to see the quality, extraordinary collection of talented people that will give us these answers. Now, I have two questions to you, Dr. Shapiro. In 1996, we—I chaired the Appropriations Committee, and we did something quite unusual. We normally do not pass the hat for funding any program around different agencies. But we had no option and we knew we had to launch this Commission, so we passed the hat around to different agencies. I am interested in knowing if you now have your own funding on your own merits and on your own feet.

DR. SHAPIRO: The answer to that is we're passing the hat on our own merits.

SENATOR HATFIELD: Well, that I am sure is something that creates a little sense of uneasiness. The second question I have is, I note that in the Executive Order that this Commission was to expire or sunset in October 1999. Have you gotten an indication about an extension of your life?

DR. SHAPIRO: We certainly have indication. We don't have all of the—it's not accomplished fact yet, but the indications there are pretty good.

SENATOR HATFIELD: Well, not only wishing you well on your life expectancy, but I wish you well on all of these great issues. Thank you very much for your courtesy in inviting me here today. Unless there are some questions I will leave and let you scientists and other extraordinary people get together and do your work.

DR. SHAPIRO: Well, thank you very much, Senator Hatfield. It's a great pleasure to have you here. Before you leave I do want to acknowledge not only your support for the kind of work the Commission is doing, but your support in health science in general for many, many years, which has strengthened that aspect of our society in innumerable ways. So, thank you very much, a great pleasure to have you here.

SENATOR HATFIELD: Thank you very much.

DR. SHAPIRO: Let's proceed with our agenda and turn to Eric for the Executive Director's report. Eric.

Executive Director's Report

DR. MESLIN: Thanks very much. I'd just like to use five minutes to update the Commissioners and any others here on ongoing items coming out of the NBAC offices. I'd like to acknowledge first that in our effort to continue adding more staff to the Commission's expertise, we have contracted for some communications advice and expertise from Andy Burness, who is here in the room. Mr. Burness has provided this advice and consultation to previous national bioethics commissions, the President's Commission, in particular, as well as the Advisory Committee on Human Radiation Experiments. We are delighted to have Andy join the team. We have completed a contract for a consultant editor. And that person, whom I have mentioned to the Commissioners in previous communications, will be onboard within the next ten days to two weeks. I know that staff is grateful to have that person added. The second item that I know

many of you are aware that on the 11th of June, Congressman Shays convened a hearing. He chaired the Subcommittee on Human Resources in the House Committee on Government Oversight and Reform Committee, that is chaired by Congressman Burton. On the subject of IRBs: A System in Jeopardy, we provided testimony. That testimony is available on the NBAC website, as well as testimony from all others who were presenting at that meeting—at that hearing. Shortly after that hearing, legislation was introduced by Congressman Townes of New York, which would require the tracking of research involving children and other persons with mental disorders. Staff will continue to follow that proposed legislation. Third, and this is I think well known to everyone in the room, we have a report on research involving subjects with mental disorders that may affect decisionmaking capacity now in a Commission draft form. It was put on our website a week ago, made available to Commissioners, and sent to about 114 individuals and organizations around the country, who represent a diversity of views and opinions—from scientists, to advocacy groups, to other organizations—in the hope that the input that we will obtain will improve the quality of our report in general, and also demonstrate our profound interest in having public comment. I'm also pleased to report that we have now sent out our requests for protocols and consent forms, a project that we have been hoping to have completed for some time now. We have sent out about 73 letters requesting protocols and consent forms. I am delighted to let you know that Alex Capron and Jim Childress, who initially proposed this idea, as well as Trish Backlar, have agreed to work with staff to form a small working group to look protocols and consent forms, and to provide some summary material to the Commission when they are completed. Obviously, we will not complete the Commission draft on—or the final report, rather, on incapacity until that summary has been completed and the Commissioners have had a chance to review the materials. If all goes well and there is a positive response and the work can be completed, we'll be able to report back in advance of the September Commission meeting. Finally, this was alluded to in Senator Hatfield's kind opening remarks, the Commission was made aware many months ago of the International Association of Bioethics meeting in Tokyo this November. We have now been involved in helping to develop an agenda for the – now the second International Summit of National Bioethics Commissions. Alex Capron has been instrumental on the Commission's side in helping to put that agenda together. So, Dr. Shapiro and his colleagues, co-chairs from France and Japan, Drs. Changeux and Imura, will be co-chairing that session. An agenda is available on the outside table, and is also available for Commissioners. The last item was really just an information item for you, apart from the many staff memos that we provide to you. But Debra McCurry, who, as you know, is on our staff and provides resource and informatics knowledge to us, passed me a note before I left. I just want to read you a portion of it, as it relates to the cloning issue. It is that the May issue of the *Library Journal* published by the American Library Association has issued its annual choice list of "notable government documents." The NBAC Cloning Report is included in that list, although this is a transcript and there isn't a video response I have it in my hand. I can confirm this with a star, "Notable Government Documents: Coverage from Culture to Cloning." So, we made the "A" list of the American Library Association. On that note, I will just remind Commissioners that the Cloning Report that you completed last June, which was so popular that we ran out of copies, and we also noted a few editing changes that needed to be made, is now in the publication process, and we'll be reprinting 10,000 copies. They will be complete within the next—we're hoping within the next week to ten

days, or two weeks at the latest. The Commissioners will obtain copies and we will make them available to the public. It is already available on our website, and any altered version of an editorial nature will also be put on that website.

DR. SHAPIRO: Thank you very much. With respect to being on lists, so if you'd like to be on a list, I usually like to be on a list until I see who else is on the list. So, we'll have to take a look at some of those other documents on there as well. But in any case, thank you very much. Any questions for Eric? Alta.

MS. CHARO: Eric, on the Cloning Report. I have had, on a number of occasions, people ask me about the Commission Papers. I have told them that there are plans for those to be published as an appendix. Is that going to be published with this version that's coming out in a week or ten days?

DR. MESLIN: Yes, exactly.

MS. CHARO: Thanks.

DR. MESLIN: There are three volumes to the Cloning Report. The Executive Summary, the Report and Recommendations, and then the Commissioned Papers, which is a third volume, and all three are being reproduced.

DR. SHAPIRO: Thank you very much. Any other questions? All right. A good part of the afternoon today is going to be spent hearing from a number of distinguished guests that have very kindly agreed to join us this afternoon and share some perspectives with us, which I think will be important. All of us—and I want to express my gratitude to each of them for taking time from busy schedules to be here with us in Portland. I will introduce them separately as we hear from them, rather than do this all at once. The first of these is Albert Jonsen, who is, I think as everybody around this table knows, a pioneer in this area. If there are pioneers, he qualifies, and has been around in bioethics in this country as we understand it today, and has been a key figure in its development for now some considerable number of decades. I had a chance not too long ago—I guess it was last January in Madrid, to share a seminar with him. At that time and as always, came away very impressed with his perspectives and the contributions made to the discussions. So, Al, it's really very nice of you to be here, and thank you very much for coming down from Seattle. We appreciate it. He's going to be speaking to the Commission on the birth of the Belmont Report of bioethics in this country. And as you did distribute some material to the Commission with the—Al, I'd like to turn the microphone over to you. Thank you very much for being here.

The Birth of the Belmont Report

DR. JONSEN: Thank you very much, Dr. Shapiro. It's a great pleasure to meet with you, Commission. So many of you, my friends, and colleagues, and even some students in the past.

Eric Meslin asked me to speak with you about the Belmont Report, where it came from, and where I think it ought to go. I have described the origins of the Belmont Report in my recent book, "The Birth of Bioethics," and you have a copy of that chapter devoted to that issue. That's based on my recollections and on the record, as best I could reconstruct them. I will today add to that account several comments about the influences that shaped my own approach to the writing of Belmont. And then we'll suggest some directions toward its revision for the next bioethical era. A Congressional mandate to the National Commission required us to "conduct a comprehensive investigation and study to identify the ethical principles which would underline the conduct of biomedical and behavioral research with human subjects." The Commission could have been flip about that mandate and simply pointed to the Nuremberg Code and the Declaration of Helsinki as the principles, but we were all sure that Congress wanted more. Indeed, they wanted a more principled approach. A comprehensive investigation and study obviously required a review of the history of the ethics of research. The Commissioners all had copies of Jay Katz and Alex Capron's monumental book on experimentation with human beings published in 1972, which led us into an calibration of that history. A comprehensive investigation also had to include inquiry into the thought of those familiar with the notion of ethical principles. Several Commissioners who had read the ethics literature of that era were aware that the notion of ethical principles was not a subtle and a-simple one, easily transferred from the pages of philosophy books into our recommendations. So, we asked five working ethicists to educate us on the meaning and use of that complex notion, and Jim Childress was one of those five. We received from them an anthology of five excellent essays. Our comprehensive investigation also had to listen to the words of those ethicists who had made a serious effort to identify the ethical principles governing research. Fortunately, the era's most outstanding ethical scholars—one a philosopher, and the other a theologian—had made such an attempt and we had their work in our hands. Hans Jonas's tour de force entitled, "Philosophical Reflections on Experimentation with Human Subjects," which was written for the 1968 Academy of Arts and Sciences Symposium on Human Experimentation, and the first chapter of Paul Ramsey's "Patient as Person," devoted to research with children with discussing the ethical principles of research in general. One could not read all of this material without seeing one principle emerge dominant, the obligation to respect the autonomy of any person invited into research with its corollary moral rule of informed consent. The many scholars who informed our study unanimously repudiated a utilitarian approach to the subject. Jonas did so explicitly when he criticized the words of Dr. Walch McDermott, one of the nation's premiere physicians, who had said, "The core of this ethical issue is to ensure the rights of society, even if an arbitrary judgment must be made against an individual." When Steven Tillman presented a meta-analysis of the scholarly essays on the first night at Belmont, he echoed McDermott's words, saying in summary, "The central question is how to reconcile protection of individual rights with the fruitful pursuit of the collective enterprise." Yet, ironically, none of the scholars had done much reconciling at either the theoretical or practical level. They had come out loud and strong for the principle of autonomy and the protection of subjects. The dominance of that principle is very clearly expressed in some words of Jay Katz, written a few years after the Commission's report. I quote Dr. Katz: "Had the Nuremberg Tribunal been aware of the tensions that have always existed between the claims of science and individual in-violability, it might have

suggested that a balancing of these competing quests is necessary. Even if the Tribunal had been aware of the problem, I hope it would not have modified its first principle, namely, the voluntary consent of the human subject is absolutely essential. It is this assertion that constitutes the significance of the Nuremberg Code then and now. Only when that principle is firmly put into practice can one address the claims of science and the wishes of society to benefit from science. Only then can one avoid the dangers that accompany a balancing of one principle against the other that assigns equal weights to both. For only if one gives primacy to consent can one exercise the requisite portion in situations where one may wish to make an exception for clear and sufficient reasons." The Belmont Report affirms that view. It added to respect for persons two other principles: beneficence and justice. Beneficence and its correlate, nonmalefeasance, was an obvious addition, since all previous statements on the ethics of research from Claude Bernard to Pope Pius the 12th, from Nuremberg and Helsinki, admonished the researcher not to harm the subject. Justice was less obvious, but its importance was suggested by the common, but invidious practice of burdening the indigent sick with research, whose beneficial products flowed to the better off. Tuskegee was the shameful reminder of that practice. However, the larger question of the relationship between individuals and society raised by the words of McDermott and Tillman that I've quoted, which certainly can be framed as a question of justice, was not addressed either at Belmont or in Belmont. Three principles were stated; the Commission does not attempt to articulate the balancing or priorities between these three. Respect for persons, beneficence, and justice, are proclaimed the three formal principles, the pillars that uphold the ethics of research with human subjects. Indeed, it is clear that the first of these exercises dominance or a priority over the others. A careful reading of Belmont reveals that the manner in which beneficence and justice are discussed limits their meaning quite stringently to benefits and harms to individual subjects and to justice in selection of individual or classes of subjects. Neither of these two principles manifest the broader meanings of which they are susceptible. Beneficence does not here refer to utility or the production of social good. Justice does not extend to the claims of a community over individuals of which it is made up. Belmont then does what Katz imagines Nuremberg wished to do. It gives clear primacy to consent. The actual recommendations of the Commission in various areas of research, such as those involving children, the institutionalized, mentally infirm, and prisoners, are somewhat less adamant. The Commissioners believed, as principalists, they worked as casuists. They saw all of the principles, as in the jargon of moral philosophy, prima facie principles, general ruling, but under rare and specific circumstances allowing for exception. This is a respectable doctrine in moral philosophy, but it is also a perilous one. Because both the circumstances cannot be clearly provisioned, and because unscrupulous persons are eager to discover exceptions to their own benefit. Still, even when exceptions are envisioned, as in the very difficult Recommendation Six of the Children's Report, where more than minimal risk is presented to children who will not benefit, and a serious public health problem, such as an epidemic, calls for research, the exceptions are built clearly on the principle of respect. Our social or scientific circumstances rendered the Belmont principles obsolete. Do the three principles need augmentation, reformulation? Should certain trends in moral philosophy, such as communitarianism, dictate a rewrite that would, for example, locate respect for autonomy within

a theory of social responsibility? My answer to these questions is, yes and no. I believe that the three principles should stand. On the other hand, I believe that a new redaction of the text would be advisable. Allow me a metaphor to explain my ambiguous answer. Belmont was first discussed by the National Commission at Belmont House in Elkrige, Maryland, which is a fine old country mansion built around 1802. Now, you on this Commission have traveled to the Pacific to study and discuss the future of Belmont. Most of you flew over the entire route traveled by Lewis and Clark in 1804, 1805, just a few years after Belmont House was actually built. You have ended up about 150 miles from their final western outpost, Fort Clatsa, near the mouth of the Columbia. The Lewis and Clark expedition provides a metaphor for my suggested redaction of Belmont. The original report was drafted with an Eastern Seaboard perspective, a broad forested littoral sloping down to the Atlantic from the rugged but modest Appalachian range. Belmont's perspective on the social and scientific enterprise called "research," was similarly flat and unspectacular. As Lewis and Clark labored westward, they were constantly astonished by the seemingly endless breadth of open prairie, the width and turbulence of the rivers, and above all by the crowning heights of the Rockies. Twenty years of experience with the research enterprise has revealed similar dimensions of height, breadth, and width. We commonly refer to the AIDS experience. Only a few years after Belmont was issued, the nation encountered an epidemic of communicable disease which many experts had thought the civilized world would never see again. The epidemic conditions seem to demand research, perhaps, even at the price of individual autonomy. It also created a situation in which desperate persons demanded treatments as yet unproven and claimed a right to be research subjects. We've also seen changes. We have seen changes in the drug approval process to accommodate these demands. We've seen other epidemics, the appearance of other lethal viral diseases, and the recrudescence of resistant strains of tuberculosis and sexually transmitted diseases. Also, research itself has expanded vastly, as it has moved up. Methodologies have also expanded. A controlled clinical trial remains as it was when Belmont was written, the paradigm for research. But it has been crowded by all sorts of modifications to get at data difficult to enfold within classical protocols. The development of genetic diagnosis challenges common notions of test accuracy and enters personal privacy more deeply than most biomedical research. Research and research ethics now has its Rockies and its Columbia. I believe that a redaction of Belmont for the next generation should retain almost unchanged the current text what the Biblical scholars would call the ortext. But it should surround it with an appreciation of these broader, wider, perspectives. I would suggest that new frontiers can be delineated. The ortext contains three sections: A, entitled, "Boundaries"; B, entitled, "Basic Ethical Principles;" and, C, entitled, "Applications." We might now conceive of adding another section entitled, in accordance with the first section, which is entitled, "Boundaries," entitled, "Frontiers," showing how the simple and straightforward, or what I might call the Eastern Seaboard perspective, opens out into broader perspectives. First, the empirical frontiers, where classical scientific protocols meet other forms of investigation, should be described, and their implications for ethical evaluation sketched. Second, the ethical frontiers, where the three principles meet and challenge each other, how should we describe the frontier, for example, between personal autonomy and social justice? Third, the frontiers where scientific research enterprise encounters the demand of profit and of politics.

Without attempting the gargantuan task of exploring these new territories beyond the frontiers, some acknowledgement of their presence and immensity is desirable. It is at the frontiers that serious ethical discourse and reasoning must be encouraged. Perhaps one of Belmont's adverse effects was the impression that the matters were settled. It came to be seen as the strict constructionists see the Constitution. I believe that a redaction should encourage the sense that once principles are stated and their applications noted, the discussion only has begun. Ethics of research is a dynamic, casuistic activity. It is often said today that the excellent system of research review has stalled. May this not be, in part, because it became too automatic, too much the application of principles to protocols, and too little the struggle with the frontiers when the principles confront previously unexpected challenges? In conclusion, I wish to affirm that in the view of this superannuated Commissioner, and I think in the view of my colleagues on the National Commission, the Ethical Advisory Board, which we recommended to be the living oracle of Belmont. Just as our Constitution requires a Supreme Court to interpret, as a writer in the last week's *New York Times* said, "Its majestically open-ended phrases." And if I may allude to my own Catholic heritage, as the Bible requires a living majestarium to interpret its mystic and metaphorical message, so, too, does Belmont, a much more modest document, that either Constitution or Bible granted, require a constantly moving and creative interpretation. It was in the EAB that we envisioned the debate at the frontiers. It was from the EAB that we expected constant refreshing of the perspectives of IRB members everywhere. It was to the EAB that we intended the apparently irreconcilable questions to go, if not for satisfactory resolution, at least for serious study and public exposition. This has not come about as you well know. The EAB languishes in ghostly form as an ignored imperative within 46.204 of Federal regulations 45 C.F.R. 46. I earnestly hope that any redaction of Belmont is matched by a revitalization of the EAB. So, then, in my view, Belmont is an essentially sound proclamation. Its three principles are the right ones, necessary and sufficient, for the ethics of research with human subjects. At the same time, those principles must illuminate wider territories, ethical and empirical, than they now do in the ortext. The written proclamation, what form it takes on paper, must be delivered to a body of responsible interpreters who can make its words come alive in the particular circumstances of particular protocols, public policy, and the changing research enterprise. Thank you.

DR. SHAPIRO: Al, thank you very much for those extremely thoughtful and provocative remarks. I know that our Commissioners might have some questions, if that's all right with you, and we can have some discussion. Let me turn first to Jim, and then to Alex next.

DR. CHILDRESS: Al, thank you very much for that powerful and moving presentation, which will really be very helpful to us as we try to think further today about how we might proceed. Let me raise one question, a question with two parts, perhaps. You mentioned traditions of interpretation of the primary text, and you focused on the absence of the EAB, which was presumably to have been a more or less authoritative body providing interpretation. But in the 20 years that Belmont has existed, there have been different traditions of interpretation. I guess one question would be whether there is any way in looking at other commissions—for example, the President's Commission— or at the way IRBs have used Belmont, that we could begin to see

some things about these traditions of interpretation that might be helpful. Before you address that let me tag on a second part. If I understood you correctly, one might think about affirming the original principles, but then to use—partially my own language, but language I think is consistent with what you presented, we need to think further in the changed context of research about the meaning of those principles. We may have to think about justice, for instance, in terms of—as we've discussed on the Commission, in terms of access, not simply nonexploitation. But we also would have to think further, as you have emphasized today, about how we relate the principles to each other if they come into conflict, if they clash, which should have priority, and what kinds of settings? So the first part would be, could we learn something from the traditions of interpretation that were developed? And then the second part would be, would that be the—in terms of sort of the meaning and the weight of the principles, the primary way in which you would assist to supplement the original text?

DR. JONSEN: Jim, I don't think we know much about the interpretation of Belmont in the actual world of research, evaluation of research protocols. I'm certain that lots of IRBs have never read Belmont, don't know much about it, are surprised by it. In fact, I gave a talk in Portland last year to a group of people who were all IRB participants, and a large number of them knew nothing about Belmont. What they knew was the Federal regulations. They didn't know Belmont. So, they didn't know the higher level of principle. I suppose other IRBs do make an attempt to interpret. But I believe that my guess would be that their interpretation would be a fairly wooden one. And the text, in fact, supports a fairly wooden interpretation. It's not really terribly challenging in circumstances where there are problematic situations to be dealt with. So, I don't know that we know much about the — if you'll pardon again a reference to religious tradition. We don't know much about the Protestant interpretation of Belmont, that is, the believer's own reading of the text. And we don't have any example of the Catholic interpretation, because we don't have any authoritative body doing it. The second question was?

DR. CHILDRESS: The meaning of respective weights of the principles.

DR. JONSEN: Yes.

DR. CHILDRESS: Those would be the two major areas you think we ought to focus on, in terms of amplifying the original?

DR. JONSEN: My belief is, and to some extent this is reflected in my remarks, that people who have thought about Belmont in current circumstance might like to reformulate it much more as a document about social responsibility. I think that might be the primary push for reinterpretation. I don't think that's a good idea. Because I think it would be important for people to go back to Hans Jonas' article to see why that's not a good idea. But I think it would be very valuable to raise the question of research within the context of social responsibility, not to redefine the ethics of research, but to put it up against issues of social responsibility, such as what one should — how one should view research activities in the context of epidemic diseases, which quite remarkably we didn't even think about at the time Belmont was written. We thought they had all gone away.

MR. CAPRON: I'm sure that I speak for all Commissioners in our pleasure in having that historical tour that you provided and the perspective on trying to understand the gist of this, coming from a native Californian like yourself, in redressing the Eastern focus, and your choice to pick Lewis and Clark, rather than the Donner party, as a reference point, means that we should now refer to this as the Mount Hood Report in our new version. I was particularly struck by two of your recommendations: One which you made, more or less, in passing, and I'd like you to expand upon it slightly, if you have any particular concerns, and that was when you were describing the difficulties with casuistry. And you didn't say you were talking about casuistry then, but I believe that you were. You said that one was unscrupulous practitioners, one of the two dangers that I recall your mentioning—that is to say, people carving out exceptions to their own benefit. It seems to me that that is an underappreciated risk in this field, and is a matter of considerable concern as we look at both AIDS research and the like, and the project that has absorbed so much of our time with research with persons with decisional incapacity. So, I would like any further thoughts you have on that. The second one is your strong view that we don't really need to supplement the principles. And as you may be aware, one of the reasons we are talking about this as a topic was early in our work the question of revisiting Belmont came up mostly in the context of the argument that these were principles that had been inadequately attended to. I find myself actually fairly sympathetic with your view, because it seemed to me that the reason that the notion of community wasn't stated, and obligations to the community weren't stated as a principle there -- was that the driving force behind research itself was the notion of benefiting the community through the process of benefiting scientific knowledge, and everything else. The whole examination of Belmont, and so forth, is in effect providing the counterweight to that. We know that that impulse is there. Now are there any principles by which one would govern an ethical response to that impulse? And it is more in other areas, as the Belmont principles got applied to clinical medicine, that one might say, "Wait a second. Do we need a restraint here?" And it's at this point that I'd like your comment about whether we should be thinking about the Belmont Report as something that is more than just a set of principles for research, because Belmont has become more widely applied. And, of course, through the work of Professors Beauchamp and Childress, is addressing the same congeries of principles that has been addressed very broadly. And, secondly, to what extent do you think that the Belmont principles mostly speak, in terms of negative application? That is to say, this notion of protecting people from things, and that the duties that they establish on the correct behavior of researchers, and one might say correlatively the rights that they establish for potential subjects, were mostly the rights of protection against harm. And the difficulty that has been introduced as people have tried to look at the process, in terms of the choice of individuals to have access to, because that is very similar to the issue that arises on the clinical medicine side as people say, "Well, I want that respirator, even if you, doctor, say its use will be futile," a subject on which you have of course written. So, that's the two sets of issues — one around the casuistry and this risk of the unscrupulousness; and the second, reflecting on the community issue and the active rights versus negative rights aspect of Belmont. Thank you.

DR. JONSEN: Thanks very much, Alex. I didn't choose the Donner party, because at least

Lewis and Clark got back home. And I hope you will get back home, too. On the first point, the unscrupulous practitioner—I use the term "unscrupulous" in a fairly—I don't mean it in a very negative pejorative sense in which we usually use it. I mean people who don't have a lot of scruples about sticking to the essence of the law, and so that they'll range far away from it. But I think that the problem with any document, any ethical document that is very—that sets out thematically to say, "This is a tough problem. There are a lot of principles involved, and we have to balance them." That's an invitation to this kind of unscrupulous casuistry. Say, "Well, we've got to balance them, so..." I think the challenge posed to a body like the EAB, if it existed, or if this body were to continue in this function of this is to be very careful about what it does when it balances, what balancing means when you face up to exception, to the question of should there be an exception. So in dealing with the institutionalized mentally infirm, or with children, we had to face that. It seems to me that that can't be done very well in a document. It has to be a living enterprise of people who criticize each other's readiness to make exception. And so, the casuistic enterprise is not very well carried out on paper. It's really carried out in a live-in setting where you have to argue pro and con. And so, that's why I wouldn't like to see the document rewritten in a way that says, "Well, we've got to balance principle." I'd like to see the principles adamant, pretty firm. I think that the reason why principles that I have suggested, and that Belmont suggests, and that I affirm, calls for the task of a very careful examination of the ethical standing of the research enterprise. I think that that is what this unsurpassed analysis of Hans Jonas did. That's an article that we really have to go back to. In his affirmation way back in the beginning of these discussions, we were talking about research and the benefits of research. We were talking about what he called maleuristic goal. But it's very different from the kinds of obligations that we have to protect society against the various things that inferiorate it. And so, the danger of rewriting Belmont as a communitarian doctrine is that it begins to miss that. And you quite rightly suggest that Belmont came into being because that was the position that everybody in the research world was quite happy to accept. McDermott is a very good example of that. Research benefits the world. Therefore, we must have research subjects. And so, the trick of establishing principles that stand very firmly and clearly, and then leaving them open to debate by people who have a sense of the strictness with which you should deal with exceptions. And, finally, I think the very important point that you make, this Commission, unlike the National Commission, is not established just to deal with research. It was established to deal with a broader range of questions. And, therefore, you may want a document that does that. I would only say that let it not be Belmont. You may remember, Alex, that in the very beginning of the President's Commission, there were some brief discussions about whether the President's Commission should not issue a Belmont-like document about the broader range of issues that it had to deal with, and that didn't happen; perhaps, could not have happened given the range of things that we had to cover. What this Commission may wish to do, a Mount Hood Report, a report that deals with the kinds of issues that you have to face. In a sense, it's a reminder of Michael Walzer's approach to justice, saying that when we think about justice, we have to think about justice in terms of various different sorts of social enterprises, in which the concept has to be applied. And it seems to me that it probably is incorrect to think that there is a statement that can cover bioethics. There may

be statements and principles that can cover certain segments of bioethics, or certain sorts of problems. And you may be able to find amidst the things that you have to do here some common thread that merits a report that states principles differently than Belmont, and one that does stress social responsibility. There may—you don't have to deal with managed care, I don't think anywhere. But, certainly, the issue of managed care and the provision of health care in the United States today raises very serious questions about social responsibility and justice in the broader sense.

DR. SHAPIRO: There are two Commissioners who want to speak, then I do want to get on to turn to Jim to tell us a little bit about our own project about Belmont. Alta, and then David.

MS. CHARO: I would like to keep you talking about what seems to be the central dilemma here about meeting the needs of the collective, at the same time respecting the individual. One of the experiences that we have had here on this Commission and many of us in our own work personally, has been to see a kind of “a wink and a nod” approach in the area of research ethics on the subject of personal autonomy. To enroll children in any research, no matter how minimally risky, without their ability to genuinely consent, is to wink and nod at the idea of personal autonomy. To enroll those people who are cognitively impaired in any fashion is to wink and nod. Because we know empirically that most people in the United States are not volunteers for research. So, we can guess with any particular person that the odds are that this person wouldn't volunteer. And anytime we volunteer them without getting their explicit consent under conditions where they can really give it with all of its flourishes, we are fooling ourselves. We build lots of protections in, and we try to make sure it's not expletive and we have lots of special rules about risk levels and review to make it tolerable. But I don't think we often face the fact that really we have simply come to a point at which notions of individual autonomy are just yielding. Now, sometimes I find that these fictions are helpful and it's better to slide by this way. Other times, sometimes, it seems more helpful to name the beast. And, although I'm not yet persuaded on this, I'm truly of no particular mind on this. I'm really interested in your reaction to what would happen if one were to try to make an argument more openly, that there really is a civic responsibility, and that the same kind of civic responsibility that underlies draft, however controversial, is the kind of civic responsibility that underlies this research enterprise, and that you try to minimize its exploitation by relying on volunteers until you're an extremist. But that kind of model, in some ways, more openly acknowledges the dilemma. Perhaps this is the communitarian style. I'm just beginning to get familiar with their work. But I'd like to hear your explanation of exactly how you all dealt with this, and how you came to a conclusion that whether based on principles of intergenerational justice, or notions of civic responsibility, it still wasn't something you'd want to argue as an affirmative obligation on the part of individuals.

DR. JONSEN: I think there are two things that you've mentioned that I would like to distinguish. First, the use of children and persons who are mentally incapacitated, I don't think that the National Commission's approach is a wink and a nod. A wink and a nod would be essentially to do what Helsinki does with children. Helsinki simply says, "You need consent. And if you can't give consent, consent can be given by a proxy." That's a wink and a nod. The National

Commission, I think, very seriously tried to do what I referred to before. They tried to see what the grounds for a justifiable exception would be. And I think that, particularly, the papers in the Children's Report of the National Commission, where the matter—and, for example, the debate between Paul Ramsey and Richard McCormick is spelled out in some detail, is really an attempt to do the most serious sort of ethical work of justifying an exception. The second thing that you referred to is whether people actually do give consent, and whether we ever are able to live up to the principle of consent. I think that is another problem that I guess everybody who has to do with ethics has to struggle with, that is, statements of principle versus empirical reality. If we build our statements of principles on the basis of empirical reality, we probably don't have statements of principle anymore, so that there is at some point a necessity of saying, "This is the way it ought to be." Even though it may never actually be that way, but you try, as you said, to build social structures that would help it to be that way, as opposed to kind of letting it drift into the empirical. And so, I simply suggest that that's the kind of argument that needs the closest sort of scrutiny. And again I say that I think it's Jonas more than anyone else that gave us that scrutiny and before anybody would buy into an argument like that, which do a lot of good things, I think go back and see what the old man said.

DR. SHAPIRO: Thank you. David?

DR. COX: I want to follow up on this point in a way because you mentioned that one of the things that might lead to an evaluation was new technologies, and this Commission is grappling with genetic information and genetics, certainly not the only important issue but one that's taken up a lot of our time. And it's troubling to me to see in the early part of this century that society was very keen on the social good of using genetics. And people could have as many principles as they wanted, and it was like an ant getting crushed by a steamroller. So that even if one upholds these principles, how, in the context of social and cultural steamrolling, does one maintain them? Because I think right now that we see more and more with genetic information that it's consumers that will have a say about it. We see books published pointing out that we can't stop it because people will do whatever they want to with it. And so one can have the Belmont Report and one can maintain this bastion, but how can one be effective? You mentioned perhaps one has this Board, but who's going to listen to it? So this goes one step further than sort of re-examining the points. But how can one think about protection so that society doesn't overrun the principles? Or is that even a worthwhile consideration?

DR. JONSEN: Oh, I think it's a very worthwhile consideration, and it's not something that I feel I could answer with much insight, except to say what I think used to be. What happened in National Commission days was that we had a fairly constrained enterprise. Basically we had the federal government giving money to quite specific institutions to do quite specific kinds of research in the 1970s. And, therefore, you could set up a system of control that was fairly modest that would pretty much do the job. The research enterprise was comprised within that. And you could build into it what most other ethical enterprises never have; namely, you could build in sanctions by taking away their money. And that was pretty neat. You could sanction an institution. Their research would go away, etc. etc., which has happened a few times. But that's

gone, and what you're suggesting is that a new Belmont is going to go out into a world where research is being done by a lot of people outside that setting, over which there are very few sanctions. And that's a great challenge. I don't know what we say about that. That's a different thing than what we had in the past.

DR. SHAPIRO: Thank you very much. I know that there are others that want to raise some issues, but I think we're going to have to move to the next item on the agenda. Al, thank you very much once again. I hope you'll be able to stay with us if your time allows. But let me now turn to Jim to bring us up to date on one of our projects, which is the Belmont Report Revisited. Jim?

Proposed Future Project: The Belmont Report Revisited

DR. CHILDRESS: Thank you, and if Al can stay around a few minutes, it would be useful also to get your input at some point in our discussion of Belmont Revisited. In your mailing you received, we're focusing on Tab 4C, where there are a couple of pages headed "Belmont Revisited." The Belmont Report was approved in 1978 but was published in the *Federal Register* on April 18, 1979. And as we're coming up on the 20th anniversary of the publication of the *Federal Register*, Harold had asked Eric Cassell and me to draft a proposal for NBAC to consider how we might revisit Belmont. And Eric Cassell and I did that with substantial and regular input from—and very important input—from Eric Meslin; and then at Cleveland, an opportunity to get Alex Capron's input over dinner. That was very important as well and relates especially, but not only, to the second part of the proposal. So you have here a two-part proposal, and the first one is an attempt to get at what Harold had suggested might be particularly useful, and that was to have a conference sponsored by NBAC, along with other groups, to look back at Belmont but also to look forward regarding Belmont's future. And so the proposal will be to have a conference in the Spring of 1999 with substantial funding from outside groups—and I've already explored some possibilities there, if there is a fair amount of interest in seeing such a conference occur—and if NBAC agrees that it would be useful to go that direction, one proposal we have would be to think about revisiting Belmont in a conference, followed by a publication that would look at three major general areas. The first would be in part for historical purposes, but also to eliminate the present and the future, to cover some of the ground that Al covered today and look at the background, the development, and the content of the Belmont Report; that is, especially the three principles. What was the nature of the report as a product of public policy deliberation, as an exercise in public philosophy? Those principles, why those principles, etc., and a lot of questions have been raised on the material you received under 1B about those principles and how they related to existing documents and discussions. We'd be interested in hearing the kind of story, a version of which Al presented from his own experience today of those who were involved. And we'd be thinking about contributors from those on the Commission, from on the staff of the Commission, as well as from outsiders who have a variety of perspectives on the background, development, and content of the report. But then, as you've already heard today, Belmont has been around and traditions and interpretations have developed. How has the report been used? How has it been

interpreted? How has it been incorporated into regulations, guidelines, IRB decisions—and we heard from Al that we'd probably have to have a lot of information there—over the last 20 years? And some examples of the kinds of ways in which we might look at this—particularly, for instance, getting chairs or staff members of other major commissions to reflect on the extent to which, if any, Belmont or Belmont-like considerations entered into their deliberations and recommendations. We've already heard some discussion today about the institutionalization of Belmont in modern bioethics. What role does it have there? What role does it have in clinical medicine? What role in international discussions? And that would be looking at the way in which Belmont has been used, interpreted over the last 20 years. The third part would look at the future of the Belmont principles. What is their promise? What problems do they appear to have as we move into the 21st century? And a few examples of the kinds of questions that might be raised here under three. Some of these have to do with the possibilities and limitations of the principles as such. Some have to do, as we've already discussed today, with the possibilities and limitations of these three principles and where there's a need for additional principles, such as a principled community, principles that were called to our attention at the very first invite meeting, or for reinterpretation of the principles as received. As we think about cross-cultural and international issues, are these principles relative to particular sociocultural groups or are they universal? What's the relevance to the different areas of research like public health, epidemiology, genetics, and so forth that have emerged, particularly over the last 20 years? Those are some of the kinds of issues that came to our attention as we tried to think about a possible conference. So I think if I may share with folks on just the first part of this before turning to the second, that one question is whether you think it will be fruitful for NBAC, in collaboration with other groups, to revisit Belmont. And then, second, whether you think doing so along the lines that have been suggested here might be useful. And obviously, though we have already begun to develop a list of possible contributors, at some point—I don't have time today—but it would be useful to get your views about possible contributors to such an enterprise, which again would occur in a conference format with the goal of publishing the proceedings.

DR. SHAPIRO: Thank you very much. There are a number of views on these issues, but let me turn to the commissioners first.

MS. BACKLAR: I want to put another question to your question. Something that you said, Al—I'm really delighted that you are here and, yes, I am one of your students, as you know. It's a great honor to have you with us. You said something at the beginning that really does concern me and that I don't think that we can address this without thinking very seriously about it. And that is the relevance of Belmont today and how it is used and who is reading it and who is thinking about it. And if we're going to start on an enterprise like this, which I endorse, I think we have to think very carefully before we spend a great deal of time and energy and thought and bring other people in to give us their time, energy, and thought, about how we're going to frame this, how we're going to make certain that perhaps by updating Belmont, revisiting it, that we will draw attention to the significance of the issues that we wish to address. And in that, I think that David and Alta said something that was extremely important. I'm very concerned, Alex knows, about the "wink and nod," how we look at consent and how we bring subjects into research

protocols, and also that this research industrial complex has its own pressures, as David points out, so that these are issues I think we have to think about very carefully before we start this enterprise.

DR. CHILDRESS: Let me respond in part because it seems to me that, while I appreciate the concerns you're raising, they are particularly relevant to the second proposal, not as much for the first. That is, to have a conference that we co-sponsor in which we deal with a variety of these questions. The questions you are raising are not as critical to that as they are to the second one. And that is, if we as a Commission, decide to go and revisit Belmont in terms of trying to come up with our own Commission statement—the other is not a Commission statement. The other is the Commission co-sponsoring a conference that would address a variety of these issues. And Alex and Eric Cassell in particular thought that this was something the Commission and NBAC could and should do. I'm a little less sanguine about the prospects there, but that's something we need to turn our attention to as well. It's not necessarily something we need to resolve because it will require—we have our table full—and we are already getting criticisms from a variety of federal agencies and departments, as well as members of the public, about the tardiness with which we produce reports, so I would hesitate to say that we ought to put something as important as Belmont on the table until we get some other stuff out. However, this is the sort of thing that could be pursued, number two of the second page of Tab-4C. That's something that could be pursued by individual Commissioners or a subcommittee to see whether it might be possible to revisit it. So I want to distinguish the two projects. One is a conference—some of your questions are relevant to that. But they are particularly relevant to the second; that is, whether we as a Commission want to go that direction.

DR. LO: I wanted to follow that line of thinking. I must say, as I try and explain to my colleagues what I'm doing, the question I keep hearing over and over again is "So, what have you done since the cloning report?" And I think I would view this as a matter of what are the opportunity costs. I mean, these are fascinating issues. I would love to go to a conference where people like Al think about these issues in depth. I'm just concerned that . . . our real charge, it seems to me, is to address the issues that really make a difference to the IRBs and the investigators and subjects, and we've tackled two big topics and we haven't really finished them yet. I think there are a host of other issues. Alex has started us thinking about international ethics. There's an incredible controversy going on about whether IRBs are doing anything other than just sort of soaking time and resources. And I think, unless we can sort of address some of these topics on a level of practical solutions to problems that IRBs and investigators and subjects face every day, I think we're getting off track. It would be nice to have this done. I would like to encourage some other organization to lead and for us to attend and to participate and to learn from it. I'm just concerned that this . . . I'm questioning whether this should be a major focus, given that we really haven't yet produced some of the documents that many in the country are waiting for.

MR. CAPRON: I share some of Bernie Lo's concern, and I wanted to put Jim's comment on the relationship between what he's calling sort of Part 1 and Part 2 of the proposal in a

different light. If other people around the country, Bernie, are interested in doing the Part 1 part of the document, of the proposal rather, which is principally an historical piece with some attempt at reinterpretation or understanding the place of the report in today's world but not addressing the report in either a highly worked out, Protestant fashion, where people tell us everything and how they've interpreted it and we get sort of a common-law buildup of understanding, or the magisterial Catholic fashion. I think that that might be, as you say, a worthwhile enterprise, but it doesn't seem to me it's for this Commission to do right now given its time constraints. And I think the notion that it would go on and we would be involved in some way, we would be fooling ourselves if we didn't think both in terms of Commissioners' time in terms of thinking about and reading all that material that would be produced and going to the conference, it would still be substantial if we have a backlog of other things. I thought it was relevant to think about that, however, if we were going to do the Part 2 part. I mean, in other words, if we're going to say, just as the National Commission found it useful—and Al describes in his book how—I think he quotes Pat King as saying this—that once they'd had a chance to talk about those principles, it was then easier for her to understand what her fellow Commissioners were saying substantively on a lot of other specific reports, not that they had to have agreed on all of them, but that it helped to draw things together and it made the work go better. And then we get to the question that Patricia has raised, which is "Is the report then going to be a document which has some life in the world after the Commission?" And I want to tie this in with something which is on our plate already, and that is the notion of an ongoing governmental process that is at a higher level than the present OPRR process and that involves outsiders from the government similar to ourselves in that process, which is one of the proposals that we have discussed for recommendation on our general oversight function and how the government should handle this. We might think that if that project is really likely to come to fruition, if we think it is possible to generate the will, either in the Legislative or the Executive Branch or both, for that kind of move, that that project, that organization, that that ongoing entity would be ideally suited to actually take this task on because it could use this task as a springboard for its interaction with the actual process that IRBs and others are going to carry out. And so the timing is bad, Jim, I realize, because we kind of have to make a decision about this sooner rather than later. So to summarize, I would actually prefer, if I thought that that process was going to be forward, to put this on their plate and say, "This really ought to be your high agenda item to get your ball rolling." If we think that's too problematic and we feel we have to make a decision now, I'm really only interested in Part 1 as a Commission activity if we're going to do Part 2, which I guess I'm in exactly the opposite position as you. You think Part 2 is maybe too much for us and drag us down. I think Part 1 is a nice academic exercise but not for this Commission, hard-pressed for time and resources, unless we're going to really make use of it as the springboard for our own work.

DR. SHAPIRO: Okay. Thank you. There are a lot of people that want to talk, but we're going to make, if you'll permit me, a change in the agenda. I've just been told that a few of our guests who are here need to leave by 3:30 for the airport, so I want to just hold this in abeyance and turn to them right now because I appreciate very much the time and effort they have given us. So let me . . . our agenda, of course, calls for us to hear from Allen Buchanan about the work he's

done for us as well as other work he's done in this area, and Frank Dukepoo, also from Northern Arizona University, wants to address us on issues. So let me turn to them right now, if the Commission doesn't mind. We'll come back to the issues that pick up this discussion a little later on. Professor Buchanan, let me turn to you. Thank you very much for being here. Hello. Dr. Murray, we have you on the conference call now. Okay, Tom. Welcome. We're about to hear from Allen.

DR. MURRAY: Thanks very much. It's good to be here even if it's only in voice.

DR. SHAPIRO: Okay. Thank you. Professor Buchanan.

An Ethical Framework for Biological Sample Policy

DR. BUCHANAN: Thank you. I'm honored to be here. Since we are short on time, I'll leave it up to you to cut me off at the appropriate point. I want to definitely hear from Frank. And I think I have the advantage of having already given you a large text, whereas he hasn't, as I understand it. First let me briefly thank Tom Murray and Eric Meslin as well as the members of the Genetics Subcommittee for helpful guidance I received in writing the paper. I benefited from the transcripts of the Subcommittee quite a lot. Let me mention a couple of fairly minor changes that I intend to include in the final version of my paper. First, as some members of the Subcommittee have pointed out and as is noted in Courtney Campbell's commissioned paper, there's one item that should be added to my list of interests that weigh in favor of more liberal access to samples. The interest that some individuals who may be sources of samples take in contributing to medical progress and scientific research . . . I talked about the societal interest in medical progress and scientific research, but I didn't give any explicit attention to the fact that there are definitely some individuals who have strong commitments to contribute to that process. Second, with respect to previously collected samples that are individually identifiable, but which were collected without adequate informed consent, in the fourth draft of my paper I proposed that sources be given a choice of either having the sample rendered nonidentifiable to them or giving a blanket consent to identifiable uses of the sample with various safeguards and with the possibility of a requirement of specific consent for certain sensitive uses that might fall into what I call the "special scrutiny category." I'm now inclined to add a third option, though I'm not certain about this, namely that the source be given the right to have the sample destroyed after being given a suitable explanation of the possible cost to himself or herself and to others that the destruction of the sample might entail. This seems to me to be at least a plausible suggestion if we're talking about cases in which the sample was not collected under conditions of anything approaching informed consent. Now those are two modifications, for those of you who've had a chance to read the paper. Before hearing their comments and attempting to answer any specific questions, I'd like to take just a few moments to iterate the strategy of my approach and to address the issue of how the various interests I identify are to be weighed against one another in order to determine sound policy recommendations. And I'd also like to explain briefly how my analysis supports what I take to be several recommendations toward which the Committee's deliberations seem to be pointing. First of all a word about strategy. My strategy is to dig beneath or behind the usual rhetoric about

rights to privacy and confidentiality versus the value of scientific progress. That's the way the issue's often framed. My strategy depends upon an assumption, which I defend in the paper and which I'm prepared to defend at greater length, namely viewing rights as protectors of morally important interests that individuals have, either as individuals or as members of groups. Given this assumption, the appropriate procedure is to identify all the morally legitimate interests that weigh either in favor of greater control by the source over the sample's uses or in favor of wider and less constrained access to the sample for various uses. And here perhaps a cautionary word is in order. It's not a matter of taking an interest-based approach versus a morality-based approach. I'm only identifying what I take to be morally legitimate interests and then the moral analysis comes in trying to see what the relative weights of these interests are. So although I talk a lot about interest, it shouldn't be understood to be simply a kind of might-makes-right approach or looking at which interests are most politically powerful or anything of that sort. It's definitely a moral analysis. Now let me also comment very briefly on the sense in which the approach that I advocate in the paper is a secular perspective on the ethical issues. It's very important that this is not to be misunderstood. It's a secular perspective in the sense that I have not explicitly invoked any distinctively religious principles or ideals in the analysis. However, this is not to say that there's anything in my analysis which should be controversial or repugnant from the standpoint of any of the major religious viewpoints. I focused exclusively on the interests of persons that are at stake in the policy debate concerning stored biological samples, attempting to illuminate what sorts of broad policy options would best achieve a fair balancing of morally legitimate interests, a balancing that reflects widely held and defensible moral principles. Given that we live in a pluralistic society that contains many ethical perspectives, not all of which are religious in nature, as well as many different religious perspectives, I can imagine no plausible alternative to an approach to the ethics of public policy than one that focuses primarily on the interests of persons. And again I don't want that to be misunderstood in an overly individualistic way. Sometimes the interests of persons that are most directly relevant are their interests as members of groups that are very important to them and with which they identify. But having said that, that is that the focus in on the interests of persons, this is not to say that there's anything in my analysis that could not be framed in distinctively religious terms by individuals whose primary ethical perspective is religious. It's just a matter of which way of framing the issues is most appropriate for the public policy debate.

Now let me say something briefly about the big task, the task of weighing the various interests that I identify. I identify a lot of interests that speak in favor of more control over the uses of samples, more confidentiality, more protections for the source. On the other hand, a number of different interests that speak in favor of wider accessibility and more types of uses by more types of individuals of the samples. Let me say something about the problem of how to weigh these. We cannot simply count up the interests on each side and say that we go with the approach that has the greatest number of different types of interests in its favor. The matter is not that simple because some interests should count for more than others. Some are more morally important. And I think we can give reasons to explain why this is so in particular cases. Let me give a few examples of a number of places in the paper where I give some indication of what the

relative weights of various interests are, or at least of how one would go about arguing for what the relative weights are. And also what kinds of considerations are relevant to determining the weight of various interests.

First, consider the interest in avoiding insurance discrimination. This is an example of an interest whose weight will vary depending upon how high the corresponding risk is, the risk of insurance discrimination. Risk is usually understood as the magnitude of a possible harm times the probability that the harm will occur. That is, how bad is the bad outcome and how likely is it to occur? In a system in which there is no risk rating for insurance coverage, the risk of insurance discrimination is zero, at least from any reasonable perspective. In our system the risk is greater than zero because we do have risk rating for insurance that many people get. People are sorted into different groups according to their risk of ill health. But just how high the risk is—more specifically, how great the probability of discrimination is—is a matter of dispute. Moreover, the risk of discrimination may vary depending upon the type of information that is made available to insurance companies. The main point I try to make on page 12 of the fourth draft of the paper is that how weighty the interest in avoiding insurance discrimination is will depend on the nature of the institutional arrangements, and these can change. That's why we shouldn't think in a static sort of way. What the weights of these morally legitimate interests are will change as our institutions change. And they're changing now in some cases. Another example. Consider the interest in avoiding stigmatization. If there's a high probability of serious discrimination, serious stigmatization, then clearly this interest counts for a lot relative to other interests that might range on the other side of the balance. But the risk of stigmatization can vary as cultural attitudes change. Information about some disease conditions may be, at a particular time in our history, very stigmatized. Information about other disease conditions may not be very stigmatizing at all. If our society does a better job of educating people to the fact that everybody carries several genetic mutations, for example, perhaps stigmatization will eventually not become so significant a factor. And to that extent, the case for restrictions on access to samples will be correspondingly weaker.

Third, consider the interest in controlling the profitability of one's samples. Sometimes samples that are taken from people are used to create immortalized cell lines that are used in research and sometimes profits result from this. If there were a clear, institutionally recognized property right that people had in their samples, then this interest, this interest in controlling the profitability that arises from uses of one sample, would be very weighty. It would also be very significant, this interest in profitability, if there were a well established practice, regardless of any legal property right, a well established practice of sources sharing in the profits derived from uses of their samples. But neither of these conditions is satisfied at present. So comparatively speaking, the interest people have in controlling profitability that stems from uses of their samples is not very great.

A fourth example, finally. Consider the interest in being able to control what happens to one's sample, independently of one's interest in avoiding discrimination, independently of avoiding dignitary harm, such as not being treated respectfully, and independently of avoiding

nonconsensual bodily invasions. Call this the interest in control, or in choice per se. To say that whenever this interest is not fully satisfied there is a violation of a person's autonomy would be hyperbolic. As a normative concept, the concept of autonomy is better reserved for domains of choice that really matter, that affect a person's important interests and aspirations. Not everything that gives more choices increases autonomy. And that's why it's very important not to make the mistake of assuming that the interest in control over samples per se is a very weighty kind of interest, especially compared to some of the important interests on the other side.

Now let me conclude very briefly by saying how I think my report bears on some conclusions toward which the Commission may be tending, at least from what I've seen from the transcripts.

First of all, the question, "Is it permissible to use nonidentifiable collected samples without consent?" My understanding is that at least there's some sympathy in the Commission for an affirmative answer to that. My paper supports that affirmative answer; that is, I think it is permissible and I think I can give good reasons why it's permissible to use nonidentifiable collected samples without consent, except in certain cases. And the main exceptions to that general principle are where the collection of the samples itself involved human rights violations, as with some seriously immoral experimentation. And the other case that might be an exception to this general principle would be where a use of the sample falls into what I call the "special scrutiny category." For example, that the sample may be used in research on the genetic bases that certain kinds of antisocial or criminal behavior and there's a long record of racist or other misuses of this kind of research and where certain groups have good reasons to feel a special vulnerability. In those kinds of cases, some special scrutiny, which I talk about in some detail in the paper, might be advisable even though the sample is not identifiable individuals, because it may be identifiable as to the group from which the individual comes, and the group and the members in it may be vulnerable for historical reasons to negative stereotyping and other kinds of discrimination.

The second question, which as I understand it the Commission may be at least leaning toward a positive answer to: Is it necessary to achieve prospective consent when the source of the sample can be identified? I understand that there's some sympathy for an affirmative answer. I agree with that, though it may be that blanket consent, combined with special consent, for special scrutiny cases would be the most appropriate route there.

A third question to which an affirmative answer, I think, seems appropriate: Can the Commission's recommendations all be accommodated within the existing regulatory structure? I think the answer is yes. I don't see anything in my paper which would call for any new structures. I do mention various places where existing structures, including institutional review boards, might play new roles, but I don't see any need for radically new institutional arrangements.

Finally, concerning collected samples where there may be a possibility of identifying individual sources: Does a greater probability that the source might be identified necessarily require greater safeguards? Is there a kind of one-to-one correlation between the probability that the individual source can be identified and having more procedures, more safeguards and hurdles in place? I don't think so. I don't think that the relationship is that simple. I think that my analysis

of the relevant interest indicates that in some cases, even though there may be some increased probability that the individual source will be identified, that's not necessarily a sufficient reason for added safeguards unless the interests which would likely be harmed by the identification occurring are sufficiently weighty.

Now, I had intended to go through this summary of the main conclusions which I provided the Commission with, which isolates about 14 different summary points. But since you already have that and since we're running short of time and I don't want to cut into Frank's time, I think I'll forego that and just open for discussion now if that's agreeable to you.

DR. SHAPIRO: Thank you very much. Let's take just a few moments for discussion now; then I'd like to turn to Frank. And then if there's more time left afterward, we can have further discussion. Maybe just one or two short questions right now.

MS. CHARO: One of the things that has come out in the discussion so far is that the existing regulations provide a balance of protectiveness of individuals with the need to do the research in the form of a waiver of the usual requirement that you obtain consent. There are many conditions for that waiver. One of the conditions is that the research only be minimal risk. And it's occurred to many of us that there is an insufficient understanding of the idea of minimal risk in this area of nonphysically invasive invasions of interests. And, although you haven't been prepped on this so it may be unfair, I wonder if you could speculate, based on your list of invasions of interests, on how one might get a handle on the usual measure of minimal versus nonminimal risk, which is by reference to our experience in everyday life. How would you evaluate the experience of invasions of those interests in everyday life as a kind of benchmark against which to measure this extra invasion by virtue of research?

DR. BUCHANAN: Well, that's an extremely important question. I think you're really entering into new territory here in trying to think about what counts as minimal risk where it's not risk of some physical mishap like bleeding from venipuncture or something like that. I mean, it's curious in a way. One of the developments in the idea of informed consent has been to extend it from just protecting basically against batteries to protecting against what I call "dignitary harms" and against other kinds of psychosocial harms. And yet there hasn't been a corresponding refinement of the idea of what counts as minimal risk there. And I don't try to do that in this paper. Perhaps I should, but those of you who struggled through 73 pages are probably thankful I didn't try to do any more than I did.

I think that my analysis helps to some extent because it at least excludes certain kinds of . . . it points out and sets aside certain kinds of misunderstandings that might come into play in trying to determine what counts as a more than minimal risk. Just the interest in choice per se, in having control over what happens to the sample, it seems to me is not an interest whose thwarting or lack of satisfaction constitutes harm in any significant sense. That's certainly true. Is the risk of insurance discrimination a more than minimal risk? I'm not sure there's any general answer to that question. You might have to look at different disease conditions and find out whether—because you're really talking about what the risk is, what the magnitude of the harm is of an insurance company finding out that you have a certain disorder and what the probability of that harm is. I

think we have remarkably little information about this. As I point out in the paper, there are empirical surveys of what people think they've experienced by way of genetic discrimination—and there clearly is some genetic discrimination and discrimination on other grounds that are not genetic either, just knowing that you've had cancer or something like that, reporting accurately in your family history of the disease. As more and more of us find out that we have potentially deleterious mutations in our genome, which we all do, and especially if insurance coverage begins to extend to genetic testing and to dealing with genetic conditions when they can be treated, then both stigma and risk of discrimination will go down.

So I guess what I'm saying is I think you're on to a hugely important topic. I think my paper provides some of the initial materials for tackling it. But the main lesson to be learned at this point is that it's probably going to have to be a pretty piecemeal kind of approach which looks at a number of these different interests that I've isolated, and ask, in particular cases for particular groups of individuals, how serious is the harm if it occurs, and how probable is the occurrence of the harm? And that requires a lot of empirical data which we don't seem to have at this point.

DR. SHAPIRO: Thank you. With everyone's permission, I know Bernie has a question, others, but I would really like to turn to Frank just to make sure to give you a full opportunity to say what you would like to the Commission.

As you know, we've been talking from time to time on community interests, what this means and how we think about it, if we should think about it, and so on, a whole series of issues. And Frank is going to talk to us regarding sensitivities and concerns in these kind of research areas from the perspective of Native American communities.

Thank you very, very much for being here. We're very glad to welcome you here and very anxious to hear what you have to say.

Sensitivities and Concerns of Research in Native American Communities

DR. DUKEPOO: Thank you very much, Dr. Shapiro, and thank you, Commissioners, especially Dr. David Cox and Eric Meslin, who were very instrumental, and Pat Norris, in getting me here, and thank the audience for coming.

In Indian country, sometimes we're very blunt. When I go there they have three questions for me: Who are you? Why are you here? What do you want? So I'm going to answer those.

Who am I? I'm Frank Dukepoo. I'm a Hopi from First Mesa in Arizona. I'm one of two Indian geneticists in the country. The other is Cliff Pudry, who is now at NIH. He's a Seneca Indian. So there are only two of us in this area since 1972.

Why am I here? To share with you some concerns about some sensitivities that Indians have about human genomic and botanical research. I want to say at the onset that I do not represent the Indian voice. I do not represent any tribe. I just want to convey the concerns that I've been dealing with since 1972. So it's a collective 25-year history that I bring to the table about the concerns that Indian people have had.

And why am I here? Well, I'll share that in some of the recommendations. What do I

want? I'll share those in the recommendations I have.

The Indian concerns that have been conveyed to me I've presented to the Commissioners in three papers; one that I submitted to AAAS, the other two to international journals. And I know you have a lot to read, I trust the Commissioners have read those. And if you have, take out a pencil and paper and I'll give you a little quiz now. Just kidding.

Anyway, these are papers in which I do present the concerns. The concerns that Indians express are very similar to what other people have expressed about what is going on, but the concerns that Indian people have are very unique and their uniqueness is based on a background of a 500-year history with the U.S. government, a history that you can read for yourself, filled with many things called treaties and even patents. Over 500 treaties, agreements have been made with the U.S. government with Indian people, not a single one of which has been honored to the letter. So that has significant import on written documents, especially informed consent documents. Their uniqueness is very special because of their history, background that Indians have that other racial ethnics in this country do not have—reservations, language, culture, customs, and so forth.

The general concerns we have concern the research subjects, serving again as research subjects, and what is going on, which is very similar to other ethnic groups. But the unique concerns we have and the reason we have those are presented in that paper.

Now let's just talk about some of these.

Cloning, for example. Indians are very much against the idea of cloning because they feel this is totally in disregard to the things that we hold as spiritual and unique, the sanctity of life.

Patenting is another issue that Indians are very concerned about because, in my experience in talking with thousands of Indian people, I haven't met a single one who was for patenting. Not one. Both cloning and patenting. The idea of patenting is abhorrent to the Indian population because it connotes a lot of things about ownership. I think the U.S. government has itself declared that you cannot own another person; hence, slavery is a thing of the past. But Indians present these views in a different way because it's a type of ownership of one person when we patent that genetic material, especially when we patent these materials that are derived from cell lines.

These cell lines are technically just cell lines, but to Indian people they are immortalized cell lines; in other words, part of that person is still on the earth, part of that person is still in the laboratories of many institutions. So I've heard many Indian people express that they don't like the idea of grandmother being around where everybody can sample her and she doesn't know about it.

The idea of commercialization is abhorrent to Indian people, too, because the idea of making profit off of another person doesn't fit. Because the Indian perspective is you can't own the land, you can't own the air, and you certainly can't own each other or another part of that person. The idea that some of the tissue, part of that person may be immortalized in these cell lines upsets many people because many Indian tribes hold a strong belief that you can't be buried

with a portion of you wandering around the earth; you must be buried whole. I understand Jewish people share that same feeling and belief.

We also have concerns about botanical research into our native plants and the indigenous knowledge that goes along with that.

The idea of conformed consent I think presents some problems, too, because in our past history, again referring back to the 500-plus treaties and agreements, Indians look at that and they say, "Well, we just can't believe what is written on the paper." Because, in our experience, this has not been our case where they've been honored. So what we put on paper, how can we really trust the White man?

There's an important lesson, too. It used to be that in Indian camps they used to talk about past histories and great battles, now the common story that they share is John Moore and the important lessons that we learned from the John Moore experience. And I trust that most of you know about John Moore. If you haven't, go ahead and read it because it certainly impacts on Indian people and their perceptions and their concerns about what is happening or potentially could happen.

The Indian response to what is going on: Since 1972, there hasn't been much response or interest, and then all of a sudden in 1991, when the Human Genome Diversity Project became newsworthy in the Indian country, there was a slight response; followed by 1993, when we had the first meeting with the Human Genome Diversity people in San Francisco, and then seven years later with more Indians, ten from the U.S. and ten from Canadian First Nations, but that meeting, held in January of this year, resulted in an impasse because of unclear goals.

The Human Genome Project, on the other hand, by NIH, has had an interesting history, benign perhaps on the onset, but you can see what happens now at the recent meeting we had in Virginia. You had the Five-Year Planning Committee, which I attended. There was a lot of discussion about what was going to happen in the next five years. I attended that session on diversity and SNP activities. And it came as no surprise, and Indians were expecting this, because from the Indian perspective, you look at NIH, what they have with personnel and technology, we, the Indian people, had reasoned that it wouldn't stop there with mapping and functional genomics. It was not a question of if they would turn to diversity studies, but when they would. And, certainly, this has happened.

So Indians are very concerned about what is happening with the NIH Human Genome Project and their diversity and SNP activities. It is very evident when you attended that meeting that the decision has already been made that they would go ahead and do diversity studies. The question I raised at that meeting is, did you bother to ask whether or not they wanted to be included in those studies? And the answer was, no.

There are many concerns that Indians have about the NIH and their activities and also with the Indian Health Service. There are many studies that are ongoing in both of these entities. These concerns have resulted in Indian country meetings, conferences, e-mails, so forth, that have resulted then in proclamations, declarations. Recently, the National Congress of American

Indians, which represents about 150 tribes, in 1993 put out a proclamation absolutely condemning the Human Genome Diversity Project and related human genomic research.

The Indians have then evolved into their own communication network. Through conferences, they have developed, and many are developing, their own IRBs and their own Indian protocols. Noteworthy among these are the Akwesasne model, the Mohawk model, the Cherokees have developed their own, the Navajo, the Hopi, Shoshone-Banok, and numerous tribes in Montana. The reason for this is that they are now assuming more autonomy in what goes on in their own communities regarding human genomic and botanical research. It is a statement of self-determination.

With regard to the patenting issue, Indians have looked at what has happened in the South Pacific with the Solomon Islanders and the other people there and have taken a lesson from that. Some tribes have said we should declare Indian reservations, Indian communities as patent-free zones in response to the patenting issues.

I want to emphasize here that there's a new concept, and I heard it mentioned around here, about community and ownership. A lot of the tribes are now turning to this new concept of community ownership in the form of tribal DNA, that is, the tribe is now claiming that as their own property, which presents a lot of interesting things legally, a lot of legal issues. A new concept. In other words, how do we deal with certain people.

With other ethnic people, you don't have these kinds of issues, but with Indian people you certainly do. If you declare DNA as tribal property, then it becomes the property of that tribe. For instance, if there was some specific activity that I wanted to get into and my tribe says no, then I would respect that. The tribes are also incorporating these into their own IRBs and their protocols that you must consider this. That even though you want to do research, you must go through the tribes and get their own opinions, their own approval. And these documents have been very well thought out, so that even though an individual may want to get involved and the tribe says no, then no is the answer. So it's a new concept in this community, especially with the tribal DNA, if they claim ownership of that.

The present situation, where are we? Well, Indians are quietly forming to discuss these issues. The Montana meeting we had last year, we had over 1,200 people there, and they had a declaration, "The Heart of the People Declaration," which is in the documents I submitted to you. The first of August they are going to have another meeting in Northern California to continue these discussions. The researchers, on the other hand, are gearing up in their own way because of the activities that they want to pursue.

The issues we face now are not Indian, they are very human. The ELSI issues, certainly, but we also have sociological and spiritual issues involved here, social responsibility, as one speaker mentioned earlier.

Where are we headed? This is a more important question. What kind of legacy are we going to leave? This is important for the Human Genome Diversity Project. I think if you read the literature, you see that this was a public relations disaster. What kind of legacy has the Human

Genome Diversity Project left? Well, you can read that and maybe determine that. It's status, where is it going? We don't know.

What about the Human Genome Project out of NIH? I conveyed this in my concerns to the Human Genome Project people—namely, Dr. Collins—and I asked him this question, and it's a very important one, because we stand on the threshold of something very, very unique and very, very significant in the history of this country: What kind of legacy are you going to leave? Are you going to contact these people? Are you going to respect then this is what their wish is? And only history will determine what kind of effort you make in that regard.

What about NIH? I've been talking with Peter Bennett and he is making concerted efforts to reach the Indian community. I had a meeting with him recently within the past week and had a long discussion. He is very sensitive about the concerns.

IHS, we're lucky to have Dr. Bill Freeman, who is very concerned about these issues and has continued his discussions with me and others, and has made serious attempts to communicate with the Indian community.

Now, as far as the pharmaceuticals, we don't know what kind of legacy will they leave.

Which brings us now to the issue at hand, what about the Commission, what kind of legacy will they leave? While I appreciate you inviting me to this Commission, there are other questions I have about the composition. As I read through the composition of the membership of the Commission, I see no Indians on the Commission. And I raise that question, why not? Do you have any plans to include Indian people on the Commission?

You have held meetings in various parts of the country. You delegated at one time to the CHPS people meetings to get information from specific groups and communities. You held meetings in Richmond and Honolulu, two, as a matter of fact, San Francisco, this is a CHPS meeting, CHPS meetings, San Francisco, Cleveland, Ohio, and Miami. You've held regional forums in several parts of the country. But Indians are curious to know whether or not you plan to have any forums in Indian country, whether or not this Commission is planning to have any forums in Indian country. If not, I think maybe this is something you should consider.

So we are down to some basic issues, and they have been raised around the table, and they are not scientific issues. They have issues that deal with trust, honesty, decency, and respect. Indians have a saying, this came from an old Shoshone medicine woman who was 108 years old, I asked her for some advice, and she said, "Son, wherever you go, walk and talk with decency, respect, and wisdom." So that's what we are looking at. Those are the values that we share.

The problems we have are not unique to Indian people but I think Indian people bring to the table some unique concerns that you should consider. Discussions, fine, the documents, the pamphlets, the booklet you publish are very nice and very attractive. But there is another challenge. While the discussion is important, there is a key word here that I think we should all consider. That after all the study and all the recommendations, the key word starts with an "I" and has to do with implementation. So that is a challenge that we bring to the table from the Indian

people is talk is not enough. We want to see what is some implementation of some things brought to this table.

I'll cut my remarks very briefly because I want to get through it very quickly. But I think there are some important issues here that maybe you have not considered, or maybe you have considered, that Indian people want to convey to you. Again, these are not my own comments, my own personal comments or feeling about it, I want to emphasize that these are comments that we bring from the Indian people. Thank you.

DR. SHAPIRO: Thank you very much for your thoughtful comments and, once again, thank you for being here.

Let me now turn to questions from Commissioners, either for Frank or Allen, as the case may be.

Larry?

DR. MIIKE: For the last speaker. The issues that you raise don't seem particularly pointed at genetic research but just their relationship between what Indian peoples have suffered in terms of the American government. I thought you were starting off by saying that they want no participation. But it sounded more at the end like it was a self-determination issue and control over those kinds of things, if I'm correct on that.

DR. DUKEPOO: Yes.

DR. MIIKE: I'm more interested in you as a geneticist and your dealing with Indian peoples. How do you handle all of the issues that you have raised from your own perspective as a scientist working with your people?

DR. DUKEPOO: I've been asked that question many, many times. Prior to about three years ago, I was busy in a 30-year project in my own research on albinism in Indian people, albinism in-breeding. I was on the verge of doing some collaborative research to map the albino gene with some animal model studies.

So this issue came up about human genomic research and I made a decision, and a very important one. What did I do? I put a moratorium on my own research. Why? The answer is easy, I was an Indian long before I was a scientist. And since there are only two of us in the country, I felt my allegiance to my Indian people. I couldn't conduct and continue my research with these issues at hand, so I had to make that decision about what direction I'm going to go. And Indian people need my help.

So this is my role now, a more important and probably a much more exciting role than just sitting there mapping genes and constructing pedigrees, is getting into discussions like this, because Indian people have turned to me to do a lot of interpreting of what's going on here. We don't have the person power to deal with these issues. But Indians are very glad for this, that the Indians are becoming much more aware and concerned about what is happening in genetic research.

As I see it—when people ask me where I stand, I say, I've made some decisions about it. But I think it is important to know, and I want to share this with the Commissioners and the public, too, that as I see Indian country, if you can imagine a bell curve, you have three areas of the curve that we look at. On both extremes are populations in Indian country.

On one extreme, you have a population that says no, absolutely not. The NCAI, with their 150 Indian tribes, says no, absolutely not, we don't want to deal with any of this kind of research. So the answer in dealing with that population is very simple, again getting back to respect, the answer is leave them alone.

On the other hand, you may have a small segment of the population of Indian people that say yes, we want to do this research because there are some things in it that we would like to see. Certainly, the Pimas have been involved in this and the Cherokees, for numerous reasons. You can't throw out the whole thing because some Indians do see some beneficial aspects of this kind of research. Take, for instance, the whole idea of the diabetic issue. That has been enhanced by genomic technology. In other words, now insulin is available through genomic technologies. Indians understand this.

So there are certain Indian tribes that do want to get involved for various reasons that are biomedical and perhaps biogenetic. And the answer for those is, if you're going to do it, let's do it right. In other words, you have your IRBs, the Human Genome Diversity Project people came out with their MEP, the Model Ethical Protocol, which I think is very impressive, and that's maybe the way research should be done. But Indians are now devising their own IRBs and their own ethics protocols that I think should be respected and looked at. And I think that's going to be a big challenge to Western scientists. The reaction already has been very interesting and not unexpected. They are saying, "Why? Why do we have to do this? We never had to do this in the past. I just don't understand why we have to do this." Well, that's the very point—times are changing. We are taking control of what goes on in our own communities.

But the larger population in that curve that I described is probably what describes the population out here, that many of you don't know enough about the issue to make a decision one way or another. So that it is incumbent upon the agencies and institutions to look for innovative ways to communicate what's going on in your different agencies, your different organizations. So the key here is education.

My own response is I'm not out to tell them what to do or which direction to go. I want to give them enough information so that each tribal entity can make a decision that they can live with. Ultimately, it gets down to the tribal level and you have to deal with tribes specifically and perhaps individually on each project.

DR. SHAPIRO: Trish?

MS. BACKLAR: I'm hoping that we have a few minutes while you and Allen Buchanan are still here, because you bring up something that is extremely important for our deliberations—and we are, by the way, very honored that you are here and it is very important that we listen to your rebuke as well as the information that you are giving us—and that is the issue of community.

You appear to come from a well-delineated community. But even in a remark that you made to us about the Indian perception of how they felt about human cloning, you said something that was very clear is that there was one perspective on this. But we actually received, while we were writing our report, some communication from another Indian community that actually spoke about how human cloning might be beneficial for a group of people who may not be reproducing as much as they would wish to be and to continue their presence on this earth.

So I would like to ask you both to maybe give us some insight into this issue of how we deal with community. What does it really mean? Is it something that we can delineate, or is it something that is going to be so amorphous that we're not going to be able to get answers? Because even in the community you delineate, you also indicate that there are individuals or groups who don't have the same agreement.

Dr. Buchanan and I were speaking before we started, and I'm very interested in the possibility that the communities may end up being disease communities. I don't know if that is something that you could discuss about this with us.

DR. DUKEPOO: Well, there will be a variance in response from the different Indian communities. What they say and what they actually do remains to be seen whether they want to get into cloning or not.

MS. BACKLAR: But what about individuals? Can you really speak for your whole community?

DR. DUKEPOO: They have discussed this and there are discussions now ensuing saying, if we determine as a tribe that this is something we don't want to do, then it should not be done. And all those investigations that are done illegally against the tribal wishes are null and void. That is not research. And that gets back to this whole thing of respect.

DR. SHAPIRO: Allen?

DR. BUCHANAN: Could I just make a comment? Because I think we're kind of on the same wavelength here. I take it the question you're asking is, is there a discussion of which things should be in the control of tribes when individuals dissent, and which things should not? To say, well, the tribe has now decided so an individual may not choose to participate, and if he chooses to that will be overridden, is already to make assumptions which some people might contest. I was struck by something Frank said earlier, that, in general, Indian people don't have an idea of property in biological material. But there is another way to put this, and that is they have a very definite idea of property in biological material; namely, a collective property right on the part of the tribe. So it's not a question of whether there is a property right in biological materials, the question is whether it's an individual property right or a collective property right. That's just a different way to put the issue.

But I think it raises this issue; that is, of course, if there are tribal governments, they have a proper domain of jurisdiction over many different decisions, but the question is which ones when it comes to the uses of biological materials or other kinds of research participation? And

who decides that? Well, you might say that maybe the tribe decides it. But then what are the processes by which the tribes decides what the proper jurisdiction of the tribe is.

And questions about representation and all that kind of thing come up at that point.

I'm sorry, I spoke out of turn. I'm a political philosopher by training, and so this is the way I tend to look at things.

DR. SHAPIRO: That's very helpful.

Alta?

MS. CHARO: Following on this, actually. Dr. Dukepoo, I'm interested in understanding how much you believe your comments can be generalized to other communities in the United States that are not, in fact, organized as independent political entities? Much of what you've described in terms of decisionmaking seems potentially quite closely linked to the fact that you exist as a series of independent nations with governments that are subject to their own kinds of rules and constitutions and charters, et cetera, and that are recognized on a variety of topics as being sovereign over their citizens, however they define their citizenship, through enrollment, et cetera.

Those seem to me to be distinguishing characteristics. If we were to look, instead, at the community of people who are Ashkenazi Jewish or people who are all first degree relatives of somebody with breast cancer, which are two other kinds of communities that we talk about, how generalizable do you think your experience is or how much do you think it is linked really to the political agenda of the decisionmaking?

DR. BUCHANAN: Who is that directed to? I hope it was directed to you.

MS. CHARO: It was.

DR. DUKEPOO: Well, I hope, and this is good because Indians may serve as a model because of their uniqueness, and whatever we learn from that experience I think would be very beneficial to other communities. Now, the Ashkenazi Jews, for example, members of that population have said, hey, we have similar sentiments and concerns about people in our community, about stigmatization and so forth.

So, it's gradually emerging. This is going to be very interesting to keep your eye on to see how this emerges. The question of how are you going to deal with Indian people is going to set the precedence of what happens in the future with other communities. And it could be that other communities will start to bind together and voice their concerns collectively. We haven't heard from the Hispanics, the Blacks are expressing their views, we don't know too much about the Asian Pacific Islanders. So maybe this might be the stimulus for the other ethnic or community entities to get together to express their concerns. And they should be written. I think we've got to see what they're thinking.

On the other hand, it is incumbent not only for the other populations to express their opinions, but it is also very important for the project designers and entities such as this to put

down their expressions on paper so that we know exactly where you are. It comes down to, if you're going to come to the table, let's do it openly; here's what we have to offer, here's what they have to offer, and let's sit down and discuss it. These things about decency, respect, honesty, trust are all a part of this.

DR. SHAPIRO: A number of other Commissioners want to speak; however, I'm conscious of your plane schedules and I don't know if we've run out of time or not. You'll have to advise me. If you have, then we'll just thank you and we'll continue our discussion and perhaps communicate in other ways. So, Allen, I know, but if you both have to go, I certain —

DR. DUKEPOO: It's been my pleasure to be here and I appreciate the time. And we've only scratched the surface. And I want to leave on a note that I'm really hopeful that things can be worked out and I'm really concerned about the legacy that this Commission will leave as well as I am for the other entities that exist out there. What kind of history will you leave? Will it be a continuation of the 500-year history we've experienced, or will it be something new? And this is the something new that I'm really excited about because it could be sociological, it could be a big sociological breakthrough. How do scientists interact with their research communities and their research people, that's the question. And I think that's what we have on the table.

And I want to leave also with this whole thing of where I stand. I want to help you. So I want to continue the dialogue. We've only scratched the surface. If you're up to it, we can continue it some other form or fashion. I'll be glad to comment on some of the reports you made. You have my articles. You're free to cite those as you write up your papers. So let's continue the dialogue and let's continue the discussion.

I would urge you to maybe invite more Indian people, or actually go out to Indian country and hold a meeting in Indian country. A good example would be in Montana because they are very much aware of this. And I think that's part of your education. It works both ways; we can educate you, but you need to educate us. And I think that would be a way to do it is go out to the people and demonstrate your concern about what is happening in Indian country, and that would reflect on other ethnic populations as well. Let's set a good role model, a good precedent.

Discussion of Staff Draft: The Research Use of Human Biological Materials

DR. SHAPIRO: Well, thank you very much. I propose that we take a break until 3:45, that would give us about a ten or fifteen minute break, and then we will return to our agenda. Our next agenda item is the human biological materials staff draft. I'd now like to discuss the July 10th memo. Some chapter material put in the appendix and so on. But the report, the draft that you have from the staff in front of you, attempts to cover all aspects of our discussion, save the really critical aspect, namely, the recommendations themselves. That is, what are we to make of this field currently described in chapters 1 through 4, which deals of course with this—I think in a pretty comprehensive way—with the general environment within which we're going to try to make some recommendations.

The memo then goes on to think about possible conclusions and recommendations. And that's where I think we should focus our discussion here today. We really would appreciate

comments from the Commissioners also on the first four chapters—I'm not going to deal with those right now. But when I say we really would appreciate it, I really mean it. We are not receiving a lot of feedback from the Commissioners that are detailed and in fact helpful to us in moving this forward. And that's an absolutely essential aspect of trying to get us on schedule here. So, while I'm not going to pause for it today, if you have marked-up copies of the first four chapters, if you have comments, perspectives, whatever way you want to describe it, please give them to myself or to Eric or any members of staff and they will receive very careful attention. But it is really quite important to get that feedback if we're going to move this forward in a timely basis.

My current anticipation is that I would like, in fact, to issue this report this calendar year, which means that we should have a complete staff draft by September, which is at our next meeting. And hopefully that will be sufficiently close as a result of our discussion there to be able to move toward a public comment period and so on and so forth, much as we're doing with the capacity draft right now. And so that's at least the objective. And I don't see any reason why not, right now why we shouldn't be able to achieve that, pending some fundamental disagreements which may be generated by our discussion and need to be ameliorated or . . . What we do not, incidentally, in any of these drafts have to reach is a complete consensus on all the issues. It's not even clear that's a good idea, but we'll just see how far we get.

Now, with respect to this particular July 10th memo, which I think we could use at least as a way to begin our discussion, under possible conclusions and recommendations the first one dealt with there deals with what I think is a very important decision for us to make in this area. Namely, whether we think that, by and large, we can work within the existing structure and simply by clarifying what are things that are truly not very clear under current regulations, to clarify them and therefore improve the structure and level of protections that are involved in the use of human biological materials. And in some sense this is that point of view at least, that's summarized on top of page 3 of this memo, which you can read for yourself. It's the first complete paragraph on the top of page 3. That's not to say that no regulations have to be changed or that we might not say that within this overall structure that provides on the whole pretty good protections if appropriately implemented and understood. It may be that there are regulations we do want to change, but that would be very different from saying the structure is just not adequate, we just can't deal with it, we have to start constructing a new structure. Just to tell you where I'm leaning on this and just as a way of getting this discussion started is, I think, the existing structure is adequate for us to deal and improve the situation, given my own particular views on what has to be done here. But that's an issue which is open for discussion. Others may have quite different views of that, and I'd be interested and perhaps we can start that way. Let's see how the Commissioners feel about that. Larry?

DR. MIKE: It's not specifically on the guidelines whether it's the same process to begin with. In the taking of clinical samples . . . In the informed consent process for clinical samples, the issue about use of samples for research is so buried in the informed consent process that I don't see how that's any kind of consent. So I think that we have to address explicitly, especially in a

research setting since there are going to be research subjects, is a very different issue. But just the fact that it's buried in there. And I think a simple solution is to just separate it out and make people sign twice or separate it out, put it at the very end. They can . . . Some means has got to improve that process.

DR. SHAPIRO: I think that issue, that is, the quality of the informed consent process and what we might recommend to make that process more real, so to speak, more genuine—put it that way—is an important issue which we certainly need to discuss. And I think in my view of things it qualifies as being within the current structure but something that needs specific improvement. And perhaps that recommendation or another might be suitable. But I think that's an important issue. I agree. Bernie?

DR. LO: How can you sort of conceptualize this? As I read this through, it struck me that I thought you were trying to kind of get us to see the big picture and are things basically going pretty well versus a complete overhaul. I was finding it very hard to sort of backtrack from the much more specific topics we had been talking about with our grids and such. But I'm just wondering—do we have a sense of closure or agreement on those issues? I think if we do, then we can easily go back and say, "Well, are we basically just saying the general framework is there and we just need to clarify, give guidance, so forth?" I just find it hard to get to your bottom line, Roman I versus Roman II versus Roman III, without having some sense of whether we agree on the much more sort of detailed, specific issues that we've been discussing at other meetings and in other drafts.

DR. SHAPIRO: I don't know if my response will be adequate. First of all, I'll certainly give you my judgment of this. I'm not the author of this draft, so I don't want to speak for that. Unfortunately as you know, for health reasons, Kathi can't be with us today who's supposed to lead this discussion. My own view is that the basic structure of the protections that are currently involved is quite adequate to deal with all the issues that were raised in those, as you say, more detailed discussions. As we go through particular recommendations, we'll get to those and deal with them one by one. I don't think that nothing has to be changed or nothing has to be added and no clarifications have to be given. But I am myself, at least at the moment, convinced that taking the existing structure and simply clarifying and perhaps adding a few regulations as necessary. Maybe something about the informed consent process—there's a whole series of things we'd have to go through here—would in fact meet that objective.

MS. CHARO: Let me also try to respond to this. The way I read the big picture of the current scene, current situation is as follows: We define the people who are considered to be the subject of research very broadly so that it includes people who are obviously personally identifiable to the researchers and people who are not as obviously identifiable but could be with a lot of work. And then we take a fairly protective stance and we say for this very large universe of people, their tissues can be studied only if they give consent. And then we make one fairly big exception to that: we have a provision for waiving that consent requirement if two key conditions are met—it's minimal risk, whatever the heck that means, which is a good area for us to work on, and it's not practicable to get their consent, whatever the heck that means. Another good area for

us to work on. So that the current situation tries to create a balance between protectiveness of the fairly broad universe of people with some kind of large-scale exception carved out to permit research to go forward. And I've been struggling all along to figure out whether I think that that existing system, with some content better developed for those key terms, provides the appropriate balance between protectiveness and fostering ease of research. And for the moment, what I have not seen is good evidence that the current system can't work well and serve all of our various purposes if we focus on giving some content to these terms. I agree with you, though, that it would be nice to get a clear consensus around the table about that very, very basic issue.

MR. CAPRON: This is just a question for information. What is the relationship between the document with the recommendations in it dated the 10th and the staff discussion of protection of groups from harm and when do you plan to take up these different aspects?

DR. MESLIN: The former is the cover which we used as a model in the past to help the Commission focus its attention. The latter is a summary of a longer piece of writing that staff was asked to do following the Cleveland meeting on the subject of community and harm. Andy Siegel from our staff took the lead in preparing some of that material. And since it had been sort of buried in the longer text, we wanted to pull it out since it had been an issue that the Commission wanted us to focus on.

MR. CAPRON: What I really meant was for the purpose of this meeting, I understood that the chairman was asking that we really go through the cover memo as it identifies conclusions and recommendations and sign off on them or correct them or whatever we need to do so that we come out of the meeting with something that approaches chapter 5 of the report. And I wondered if, since it's not unrelated to some of the things in there, we were going to pause during that and discuss the group harm issue or if you thought, because that's really part of the text for the earlier chapters, you were at some point during today or at a future meeting, going to do that. That's all I was asking.

DR. SHAPIRO: I want to get to group harm today or tomorrow morning. That issue. Community and group issues is something that we've been talking about. We need to focus some attention on it either of these days, so I do intend and hope we'll get to it.

DR. MESLIN: Allen, just a reminder on page 4 of the cover memo, we mentioned the memo, so it could have been picked up at that point.

MR. CAPRON: That's what I wanted to know. Are you going to do it at that point?

DR. SHAPIRO: Yes. Larry.

DR. MIIKE: Just picking up on—and you tell me if I'm interpreting it correctly. We spent an inordinate amount of time in our subcommittee meetings going over a grid about previously collected samples, future collected samples, etc. I look at that as still valid. This is the overarching thing and we can use that grid to say from the sample point of view, how are we treating these and how do these things apply? So I don't see this as replacing that. I still see that as part of the discussion, although I don't see it in the current draft.

MR. CAPRON: I thought we dropped it after the meeting in Tysons Corner.

DR. MIIKE: What I'm saying though is that it's all well and good to talk in these grand, lofty terms, but researchers and everybody else are going to know what was meant in terms of a specific biological sample, and I think we need that.

MS. CHARO: I'd like to emphasize that the researchers currently organize their work around the existing regulations, which are not focused on the status of the sample. It's focused on whether or not an individual is identifiable. So the issue is not whether or not a sample is identifiable; it is whether an individual is identifiable by virtue of research being done. And to that extent, the grid is not in fact the way researchers would figure out how to apply some set of rules. They're going to be looking to the regs. Now, again, we could change how we approach this, but my personal preference would be not to go back to the boxes because I found that in the end it did not add to clarity and it did not dovetail well with the existing regulatory system, which, unless we're going to scuttle it totally, we must work with and we must insert our work into.

DR. LO: I'd like to express a concern I have about trying to decide, "Can we make it work by coming to agreement on what's minimal risk and what's identifiable?" I mean, I've looked through the briefing book. The folks at Mayo Clinic have spent a lot of time thinking about it and say categorically they don't think genetic research per se is minimal risk for a whole lot of reasons. Then you're bound and determined today saying that if he doesn't see any reason why genetic research by and large can't be minimal risk, I think we're going to play this nod-and-wink game where you have the regulatory grid laid out. The researchers, because of these wonderful diagrams that staff has drawn, now understand what the regs say and they know what they want to get. They want to get to do research on samples without going back to patients for their consent finally, because it's just a lot of hassle to respect people's autonomy. They're going to figure out a way of saying "This is really minimal risk. It's impractical to do it. Therefore, by algorithm, table 3, I don't have to go back." And I'm not sure we're going to come up with a convincing way of saying, "Yes, this is minimal risk in these circumstances but it's not here." I think there's a lot of confusion out there about minimal risk and part of it is it's a very tough thing to define. I'm not sure we've done it in the other report either. We've struggled with that. I think it's the same thing. When I have a specific protocol, can I reliably say that most of these are going to go through a deliberative process and come up with a reasonable principled decision why it is or is not minimal risk? I have real concerns about that.

DR. SHAPIRO: And the implication of that is what, Bernie?

DR. LO: Well, I would like to go back to what are the issues that investigators are bringing to our views that may raise issues as to whether you should get consent from individuals in certain types of studies or not and give them some guidance on prototypical issues that come up. And we've had a lot of discussions here about the paradigm that I think David, you and Steve laid out for us where you have 100,000 samples that someone collected for some other reason; you go through to get a candidate gene, or several candidate genes; and you get down to a thousand and you want to go back and recontact. It's a real-life dilemma. I'd like us to try and figure out do we agree that you can go back and recontact those folks without their having

consent in the first place? Is that minimal risk? Those are the kinds of issues that IRBs are facing, and I think if we're going to provide guidance on that level, I'd like to see us provide some guidance.

MS. CHARO: You know, Bernie, I don't think what you're asking for is at all inconsistent with going through what has been laid out as a potential way of answering, and here's why. The boxes aren't going to answer your questions. The boxes were just a way of explaining 1,000 different versions of traceability of a sample back to individual. They were a useful tool for figuring out how it is that individuals can become identifiable, but they don't tell us anything about the risk levels. So if we're working within the universe of individuals that we understand to be identifiable—and that actually—there are a few bumps and grinds here, but mostly that's manageable under the current regs. We're going to be spending all of our time on exactly what you're talking about, which is how does one provide content so that we can achieve a goal. Now I don't know whether your predilection is to be more, less, or equally protective of people's privacy than is currently the case. I don't know what your goal is when you discuss whether or not we should be making it easier or harder for these researchers to recontact folks, but that's exactly what we'll discuss if we were to discuss the meaning of minimal risk or the meaning of practicable to get consent again. So I think all of your concerns would come out.

MS. KRAMER: I'm wondering if, as a matter of process, if we go through these points and we bring the document to a sufficient point that we feel that we can sign off on it and put it out for public comment, if we might not then invite the appropriate persons or organizations to take a look at it and say, "Looking this over, can you come up with an example where the researchers or the IRB will not have sufficient guidance?" as we're putting this out there. For instance, to take the example you just raised, Bernie. Would there be sufficient clarity in the document as we put it out there to guide them as they need it? And try to approach it from that way.

DR. SHAPIRO: Let me just remind everyone in that respect that what the plan is here—I don't think we're going to reach today or tomorrow a sufficient degree of closure on this to send it out for public comment. My objective is to try to get enough sense of where the Commission would like to go so that we can produce, so to speak, a final staff draft for us in September, which would then go out for comment if we were satisfied with it. That's just the logistical arrangements. Now, I think it's useful to get comments from others at any time, so I think that's a very useful suggestion. David, you had . . .?

DR. COX: I very much like the idea of following through on discussing these recommendations. I, number one, think that there's a lot of—my foundation concern is Bernie's, that basically people want to do something and they'll find a way to do it. In order to obviate that, I believe that the best thing to do is to clear ambiguity in the regs. If we can clear up the ambiguity in the regs, it closes loopholes and it allows us to say what our major principles are. Right now by reading through this I think that it leaves very vague what our major principles are as a Commission. But I think that we can define those if we go through these different points. But as a starting place, to say what is ambiguous or what are ambiguities in the regs right now is a

really safe place to start because that's something we have to do no matter what. And in doing that I believe that it will help us define our principles. And as we define those principles, it will close loopholes. So as I think about all the things I'd like to see get done, I think that this is a very efficient way of doing it.

MR. CAPRON: In an attempt to move us along, on page 3, Guidance 1 suggests that HHS and the other participants in the Common Rules need to describe the types of research that are included in the category of research that uses identifiable information. I have two comments on this. The first is what this says to me is that our contribution on this issue is going to be commentary which would be useful to that process but we don't feel that we can come up with refined enough language to do that job. I guess that may be the case, but I would hope that our commentary would push that process almost to the brink, even if we don't want to take the time to write the regulatory language. I mean, it would be strange if we spent three years talking about this and cannot be pretty clear about that identifiability.

The second question is what about this aspect of risk? Does it come in at this point or not? And I'm not sure I understood the response to Bernie on this. I may not have. But Allen Buchanan's argument was, it seems to me, that one has a lesser interest in being identified if the harm that may come from being identified is going to be very, very small. And therefore, that the same kind of consideration—nonidentifiability—which allows an exemption from the consent requirement, might be applied even with identifiability with small harm. I'm not in favor of adding that aspect as sort of a modifier to the identifiability. I think that invites the kind of complexity that Bernie was complaining about. It's worthwhile talking about it, I guess, in the report, as we now do a little bit, but it seems to me that in the end we should not be encouraging HHS to modify identifiability that way.

So I'm basically in favor of Guidance 1 as it's written here. The only part of it—I would like our commentary to push along the idea of identifiability in a very commonsense way. It seems to me that identifiability means that, through facts about you or your name or your social security number or date of birth, you can be linked with the information that's been developed by the researcher. And I think we are right to try to point out that now it is incorrectly thought by people that if you have a code you're not identifiable. And we should be saying that that's wrong. I don't understand the last paragraph of this section, which says, "Finally in developing this guidance, consideration needs to be given to the aspects of protocol design that are intended to slow or prevent the flow of intermediate or even final findings back to the tissue donors and treating physicians." New? I mean, what does that say to me? Yes, if you put up rules and say identifiability means you need consent and you say, "Well, wait a second. We're putting in this kind of coding so we can get back." Well, that's a good reason for having coding, but in our rationale it's a good reason also for requiring consent. So I . . .

DR. SHAPIRO: First of all, on that latter sentence I don't know what it means either. I haven't the slightest idea what it says. I tried to figure it out the last day or so. I don't know what it means, so I don't know the answer to that.

But the two other issues you raised, however, are very important, and I want to at least

give you what my sense of that is and Bernie has something he wants to add, too. One, I think we should push identifiability as far as we can. Whether we can complete it in the right regulatory language I don't know, but you just can't wave a flag here and say here's something you salute and tell us how to do it. I think that's not adequate. I completely agree with that.

Second, and I think equally important, issue that Alex raised and which I very much agree with what I think is your perspective on that; namely, that we don't want to open the possibility here by just dealing with identifiability by making this more complex. It's either identifiable or it's not. And when it is, you fall under a certain regulation; when you don't, when it's not it's not. And so I think both of those issues that Alex highlighted there I think are important ones in this area. And if Commissioners disagree with that or that general kind of thought, now's a good time to engage in this discussion. Yes, Bette?

MS. KRAMER: No. Just as a point of information. Do I hear you recommending then that we say that information that is coded, or samples—I'm sorry—which are coded, are identifiable?

DR. SHAPIRO: That's my view. Absolutely.

MS. KRAMER: Okay. So it's on the table that you're proposing that this is what we say: "Until such time as there is an encryption scheme that does all these . . . gets to them."

DR. SHAPIRO: We'll get to that later. I've also tried to do some investigation in that area, but we'll come to that later. Bernie, I'm sorry. I don't want to talk so much.

DR. LO: I just want to say that Alex, as sort of clarified by Harold, goes a long way to addressing my concerns. Here's an issue, guys; figure it out. Here's another issue. I'd like to push one step further. Codes don't make you—if you're coded, you're still identifiable. Even if you strip what you think are all the identifiers—this goes back to, I guess, David, your comment from Framingham that even in large data bases, just by knowing things like the zip code, the number of children, you can often identify people. And that may be of particular concern in genetic research when you have knowledge of a pedigree in the family. So that I'd like to suggest that we err on the side if you're not sure, treat it as if it's identifiable rather than I think what a lot of scientific may want to do, saying, "Well, it's not iron-clad nonidentifiable but it's good enough that we can consider it nonidentifiable." I think, if anything, there's going to be an increased ability, either using computers or more sophisticated dramatic analyses, to make things more identifiable than they were deemed to be.

MS. CHARO: Now I'm keeping in mind that the reason we're talking about this is because as soon as we call somebody identifiable, this whole panoply of protections is going to come into place. And my question is going to be: Do we want to make this a definition in which the key is whether somebody is identifiable to 100 percent certainty? Or is it more probabilistic than that? There was an example of somebody who was put into the staff draft of somebody who gives the samples of a Family Jones that are made up of people who have the gene for a particular form of dwarfism, to a researcher with nothing saying Jones. The only thing that's on there is family physician, father, mother, daughter, son, maternal aunt, etc. And at this point, in fact because the collection knows that it's Family Jones and the researcher knows that it's mother-daughter, there's

a high degree of identifiability but it's not 100 percent because if there were several daughters and you've got several samples that are all listed daughter A, daughter B, daughter C, you can't link a particular sample to a particular daughter. But you can link them to two people who might be daughter A for a particular sample. So I want to understand how far you want to push this. If you want a bright line, you might want to make it 100 percent reliable determination of who the individual is. If you want to make it fuzzier, then we need to discuss exactly how we're going to make that fuzzy line.

DR. COX: I'd like to be as specific as possible. Coded means identifiable. Having said that, there are other situations where one needs to be sensitive because, even when you think you're not being identifiable, you might be. But we can't deal with all the situations, and we're just asking the people to be thoughtful . . . That's the place of most wishy-washiness on the part of researchers right now. If this Commission says coded means identifiable, that's what it means. In fact, that's what we saw at the regs meeting. So let's say it. With respect to these other issues, it's going to be extremely difficult to ever be 100 percent or not 100 percent, but we just have a discussion about it so people are sensitive to it.

MS. CHARO: If I may . . . David, being sensitive to it is a wonderful position to take as far as what the ethics of the researcher ought to be, but please keep in mind that on an implementation level the significance is that you do or do not have to go through anything having to do with the IRBs. If you say it's unidentifiable and you want people to be sensitive, you're saying, "Please be sensitive while you don't go to an IRB. Please be sensitive while you don't go through any of these protections." And if that's what you're advocating, that's fine; but I want to make sure that's really what you meant.

DR. COX: And that's what I meant, because unless we can define the specific point of what we want people to do or IRBs to do, we are fooling ourselves to think that it's going to get done. So if we can't be specific enough to say these are the things, that's why I bring up this point about coded. It's clear what a code is. If somebody holds a code, then we say that this is identifiable. But on the other hand, for some of these other issues, it's not so quick. I'd be happy if we could come up with clear points where my four-year-old could implement them. I think that's the level that we have to beat, the clarity that we need here.

DR. SHAPIRO: Okay. There's a number of people who want to speak, including myself, so . . .

MS. BACKLAR: I just want to start. When we are talking about coded, we mean the researcher may know the code or the repository may know the code, anywhere that that code is. Yes? Is that what we're meaning?

DR. COX: That's what I mean.

MS. BACKLAR: Okay. That's all. I just wanted that point made clear.

DR. BRITO: I share with David the fact that we had to say coded is identifiable. But I also understand Alta's concerns. And I'm not sure if that's not addressed, that concern's not

addressed in the third recommendation on page 6, or the suggestion for the third recommendation on page 6: "Where research is conducted on kindred, special attention must be paid to the extent of identifiability of family members." And maybe here we can just use stronger language and recommend that where's there a possibility of identifiability of family members or other affected individuals, there may be a requirement for it to go through the IRB process. That way, when we talk about coding as identifiability, that's 100 percent all or none, and then when we get to the recommendations, specific recommendations, this might take care of Alta's concern.

DR. SHAPIRO: Alta, did I understand your concern? That example that we, the following type—I may have misinterpreted what you said, that should we consider identifiability to be someone who's saying I'm 50 percent sure it's you. I'm just asking if that's the question.

MS. CHARO: My concern was raised when Alex and Bernie began saying that they wanted an expansive definition of identifiability. Now, saying that coded samples are identifiable is not expansive; it's reiterating what's currently the case. So I began to hear that they wanted something even more expansive and I got concerned that at that point they were going to go past the boundaries of certain identifiability and get into this "I'm 50 percent sure it's your stuff," where it gets very tricky.

DR. SHAPIRO: Let Bernie respond first. I have a view, but let Bernie . . .

DR. LO: I must say I find these little charts extremely helpful. I only wish they were sort of color-coded rather than gray. But the way I read it, it's "will information be recorded by the investigator in such a way that it cannot be linked to the subject?" You have to say "yes" to be exempt. If you say, "no," even though there's a pretty high chance, a pretty good chance it won't be, then you ask, "Is it more than minimal risk?" and then you get expedited IRB review. I guess one of my concerns, Alta, is that I'd like to keep the IRB involved in the questionable tough cases if only to look over and say, "Yes. We agree with you that it's identifiable or not, of minimal risk or not." What I'm concerned about is if you have a complete bypass of the IRB, if you just say it's not identifiable or using the more regulatory language, there's a tremendous incentive to answer that question a certain way. And if the expedited review is really expedited review but it's an outside person looking over the investigator's shoulder and saying, "Yes, we've had a lot of experience dealing with these genetic issues and we think it meets the not-linked-to-the-subject and it doesn't involve greater than minimal risk. Who's your expediter?"

MR. CAPRON: I also need a little clarification of that. If researcher A goes to repository B and says, "Do you have any families of dwarf samples, tissue samples from a family of dwarfs?" They say, "Yes, we do. We've got a mother, father, maternal aunt . . ." "Could you give those to me and label them as to which is the mother, which is the father, and which is the aunt, and so forth?" Other than that, this could be a family collected in 1900 or 1998. It could be from Europe; it could be South America; it could be the United States; it could be anywhere. And he doesn't know anything. And that sample isn't coded; it's an anonymous sample. The fact that the person, if he knew the family, could say, "Oh, you're 3-1/2 feet tall and 6 feet tall, you must be the dwarf here." I don't get the identifiability.

MS. CHARO: No, no. It's that the collection knows that it's Family Jones. It might be from 1905; it might be from 1995; but they know it's Family Jones.

MR. CAPRON: But they give it over to the researcher with no code on it. They're simply saying . . .

MS. CHARO: Each sample is labeled by the position within the kindred.

MR. CAPRON: But that's not coded.

MS. CHARO: I agree with you that it's not coded, Alex. My point simply was that we have a difference of opinion here, a real difference of opinion between David and Bernie about whether or not how we want to be treating this in terms of protectiveness. It's not coded. And as we currently understand these things, it's not necessarily going to be subject to the regulations. But in fact, by putting together just the name of the family. I don't even meet them. The collection can say it's Family Jones, and I know this sample . . . I have a sample in front of me that's labeled mother, and between my information that this sample has this particular gene in it that I'm looking at in my lab and it's labeled mother and the collection's knowledge that this is Family Jones, we've now in fact identified this individual. Okay. That's identifiable under the regs. If I'm looking at daughter and there's more than one daughter, there may be a question. I know this sample belongs to a daughter in the family, but the best we can get is a guess that it's one of two people in the family. We don't know which one. I'm understanding Bernie as saying that he wants an IRB to have an opportunity to think about whether that meets the definition of identifiability. I'm hearing David say, no, he just wants the researchers to be sensitive to that. And all I'm saying is that if we're going to want to send it to IRBs, we're going to have to come up with some very good language to explain to researchers when they have to go to the IRB for that extra look. In no case was I talking about meeting up personally with Mr. or Mrs. Jones.

MR. CAPRON: Okay. If I can pursue this one step further. I really thought you were using Jones to mean a name that they just make up a name.

MS. CHARO: No. A Family Jones.

MR. CAPRON: This is Family Jones, so the researcher, the person who's conducting the research, is told this is the McGillicuddy family, to use a more particular . . .

MS. CHARO: They're not told. But the collection knows that it comes from the McGillicuddy family.

MR. CAPRON: So are we now saying that the only thing that is not identifiable are anonymous samples? Because I had not understood that.

MR. SHAPIRO: I'm sorry. I didn't hear that last one.

MR. CAPRON: Are we now saying that the only thing that counts as nonidentifiable are anonymous samples? In past discussions of this—we've had so many discussions that we've brought different things, I suppose—I had thought, to go back to those much-feared charts, I had thought that at some point we were distinguishing between those things which are provided with a

code, meaning I write down that this is from Mrs. Jones and I put a code number 1 and then I give it to the person with a number on it and they can come back to me and I can figure out who goes with that. And that we were calling identifiable, potentially identifiable. Are we saying the only ones are those in which the researcher, when he pulls them off the shelf, doesn't even see a name on it? Even if he sends it over and doesn't put a code on it. Excuse me, the repository. Thank you for your question.

MS. CHARO: I think, again, that we will confuse ourselves if we focus on the samples and on the details of how the samples are being managed and the details of the coding schemes. If we focus on the individuals, I think we're going to be on stronger ground. The question is always whether or not the individual is identifiable, not whether the sample has a code. That's just one way of making an individual identifiable.

Now, there are these weird gray cases in which an individual is identifiable without a code. That's no problem. The regs say that they're a human subject; the panoply of protections comes into place. Great. Then we have the second set of weird cases where an individual is not completely identifiable, but we can move it down to a level of certainty where we can look at two or three specific people in the world and say, "We know it's one of you." The question is do we want that to be subject to this panoply of protections. That's what I'm just asking. We're going to try to suss out what identifiability means. I'm only asking is it enough to say we know that you're one of one or two or three. Or does it have to be "We know you're the one?"

MR. SHAPIRO: If I could interrupt here, maybe I could say something that'll be helpful. I don't see how we could get into a situation. What we have to decide is whether the probability of 1/3 versus 1/30 versus 1/100 versus 1/10,000,000 is going to be an issue in deciding whether or not the panoply of protections come in or doesn't come in. So my own view is that what we have to focus on—I want to come back—let me focus on the individual first. It is whether it's identifiable or not. And just how it's identifiable is not a critical issue, but identifiable in my view means identifiable. I think it's 50 percent sure it's you or I'm 1/1,000 percent sure it's you. And it seems to me that can work in a fairly straightforward way. A much harder one, which gets into the next issue, is does identifiable refer only to individuals? Then you can say, well, does it refer to family, does it refer to group, some other kind of group or something. That to me is another kind of issue which we need to address. But for the moment, if we stick to the individuals, it seems to be that the best way to go is to say—I guess I'm just reiterating what a lot of people have said already—that it's either identifiable or it's not. And identifiable means "could be identified." And as technologies get better and you can identify with different kinds of information, then we have to adapt to that as it goes along, things we could not identify 20 years ago, we can now identify. And so something would have to change. And this will be a moving target as we go along. And it seems to me—but we'll get to the nonindividual case, that is, family or group, community or whatever it is in a few moments. Let's not try to redo that.

MR. CAPRON: May I ask Alta—do I take it then that the distinctive thing you were saying there—I agree with Bernie that we ought to have the presumption in favor of potentially identifiable, which means some probability you can do it. After all, that's the whole possibility that

lies behind this. You have a coded sample, and it's unlikely that the code is going to be broken. But it's potentially breakable. That's why we say we should call it identifiable, and you should go through this review process to see where it comes out. And if it were potentially identifiable with a very high-risk, high-discriminatory factor subject being studied, you'd say, "Whoa. You're going to need consent to do that because potentially if that ever came out, that person would be very badly harmed." If it's something of low-risk or of minimal risk, then you may be able to not have all of those attached, but you still have the initial IRB review. You're still subject to the protection.

The question that your example raised was in making it members of a family, you really have already identified the collection of samples you have, and you don't know if it's sister A or sister B. You've got the 50 percent probability. You're potentially right if you took a guess; you could be wrong. But you know that it's either, to use your name, one of the Jones girls here that you're looking at in this sample. If a researcher says, "I want to study XYZ gene in people who have had thyroid cancer," and he goes to his colleague who runs the lab and says, "Can you give me 26 samples of people from whom you extracted thyroids because they had thyroid cancer?" And he says, "Sure." I say, "I don't care if they're male or female. Just give me 26 samples." And he goes into his lab, and as he pulls the samples, he remembers his involvement with each of those patients and he remembers Mrs. Jones and Mrs. Smith and Mr. Johnson, and so forth, one after another. And he has all those. And he sends them off but they're just labeled A to Z and he doesn't keep any record as to whether Jones is A or whatever, so they're not coded. He just separated them into 26 categories, A to Z. But he remembered these 26 people. We don't call that identifiable because when the research is done, he won't know who you're talking about. So what was distinctive in your example was the fact that it was a family and we knew that much of the identity of the group of people. Is that the point of the example, because otherwise the result would be that, if you don't have your repository only having anonymous samples, you'll always have "identifiability" because the researcher may know the people from whom they came.

MS. CHARO: Yes. No. Of course. I mean, the example was constructed to meet Bernie's concerns and to test out where we . . . I don't disagree with Harold's conclusions about we ought to come out. It's actually my preference as well, but Bernie seemed to be advocating for a broader definition of identifiability, and I wanted to put an example on the table.

MR. CAPRON: The presumption in favor of review rather than . . . In other words, if there's the potential of identifiability, we ought to have a review process. That's all.

DR. SHAPIRO: Could I just ask Bernie a specific question? You said something, Bernie, I wasn't sure that I fully understood it. And it had to do an aspect of IRB review. Did you say that you wanted decisions with whether something was identifiable or not? A decision of deciding whether something's to be subject to IRB review . . . I think that's the . . .

DR. LO: Where there's some legitimate question, I'd rather have a really expedited IRB review where someone in the IRB looks at it and say, "Yes, based on . . ."

DR. SHAPIRO: You don't want to leave that decision to just the investigator. Okay. I just

wanted to make sure I understood you.

DR. LO: Well, I think the expedited review should really be not very onerous. So that from an investigator's point of view, I don't want there to be a huge incentive to have it exempt. And I think that may require some changes in the way IRBs are run.

DR. SHAPIRO: Okay. I just wanted to understand that. Thank you very much. Bette?

MS. KRAMER: Just to address some of Alex's last remarks. Alex, I'd be very surprised if any repository would ever send out samples without knowing the individuals or without making some record of the cases from they sent it. So it seems to be that if they're identified at the repository, they're going to be at least coded and therefore identifiable.

MR. CAPRON: If that's an accurate description of what they do, then the answer is they're all going to come under that. And that only exception would be those which start off being anonymous. And they say, "We sent you sample number 471, and we don't know who 471 is. But if they did it the other way and just said, "We just sent them over. Here's the list, but we didn't write down A next to so-and-so, so we can't tell you." When you come back to us and say "We want more of A," we say we don't know which one it was. We'll send you the 26 samples afresh, but we can't tell you which is which.

DR. SHAPIRO: Let me suggest that we move on here. I think I have a pretty good . . .

DR. LO: If I could make one quick corollary to just sort of flesh things out. I think, if people take this bypass where they say it's nonidentifiable and therefore exempt from 45 C.F.R., the implication would be that you then can't later go back and say, "We want to contact the subset because they're genetically interesting." So with David Cox's example, you either say, "It's really unidentifiable" and live with it or you say "It is identifiable" but I think it's minimal risk and I'll go to the IRB.

MR. CAPRON: And just to be clear, on Table X. On the right-hand column where the question is, "Will information recorded by the investigator in such a way that it cannot be linked to the subject?" And then it's yes and then your example, or no. We almost want to drop a footnote to the "no" and say, "And that includes maybe or almost certainly not." In other words, if there's any doubt, have that issue reviewed. And then underneath know there's the—or maybe we do need the maybe category. There should be IRB review of the question of nonidentifiability. That's what we're saying, isn't it Bernie? I'm trying to identify places where we're in effect suggesting to this HHS process that we say should be operating what they should do and one thing they should clarify the regulations to say "It's the responsibility of the IRB to confirm that it's nonidentifiable" or that that determination has been made correctly.

MS. CHARO: Alex—and I guess also for Bernie—just by way of information, you're discussing these in a way that makes me infer that you believe this is not already the case. But the way it works now is there's an initial judgment that has to be made by an investigator as to whether or not her work constitutes research and whether or not there's a human subject involved. This is the inevitable first point of self-regulation that cannot be evaded under the current scheme.

These investigators then voluntarily present themselves to the IRB. They're already supposed to in cases of ambiguity consult with the IRB chair or administrator for an informal ruling as to whether or not it needs to go through the IRB. And when it's genuinely ambiguous, that person often will say, "Let's go to the committee and have everybody talk about." So I have objection to what you're suggesting, but I wouldn't want to put it on the table as if differs somehow from what's currently going on. What you're perhaps suggesting is that there ought to be strong language urging people to take it more seriously, that there ought to be examples made of what constitutes an ambiguous circumstance that people should recognize as such, but we already do exactly this.

MR. CAPRON: Well, you're describing the University of Wisconsin at Madison. We do not know what goes on in the other several thousand IRBs and the Inspector General's report would make me think that they don't all look like that. The alternative here would be to say that that issue ought to be an issue that gets at least administrative review in each and every case.

MS. CHARO: It can't be. Somebody's got to alert the IRB to the fact that there's a research project out there. That has got to be the investigator. There's nobody else who can do that.

MR. CAPRON: Excuse me. You know this, I'm sure, from submitting things for funding to HHS and NIH. When you sign off on that, you say you've gone through the regulatory process. If you can now check yourself as exempt because it's not identifiable, that's different than saying that the IRB or the IRB chair or the IRB administrator has checked you off as exempt. Now we could say that a better protection would be that before you can submit, you have to have their signature saying, I looked at the protocol and this is truly one of those nonidentifiable situations. It doesn't have to be only the research.

DR. MESLIN: Perhaps as a point of clarification, as a former Project Officer at NIH, it might be helpful to raise the following suggestions. That if the issue is at what point ought sensitivity be raised as to whether or not this would go somewhere, it could be helpful in our guidance were we to make precisely those points. There are a number of places where individuals might need to pay special attention to the fact that this kind of issue would benefit from IRB assessment. There are more than just investigators. When you go to Project Officers, oftentimes you haven't gone through an IRB. And your approval for funding will be dependent upon an IRB approval. So it's not either one or the other. There are several instances in which that alert should be provided. I think that's why we are opposing that the Commission consider the guidance that is developed indicate those areas of ambiguity. They says nothing about whether the Commission ought to find and formally find that coded equals identifiable. These are not mutually exclusive suggestions.

DR. MURRAY: The one question I had about this section, page 3, the first full paragraph. It looks very reassuring about the existing regulations provide adequate protection, etc., and I think I agree with Harold that that is true insofar as it pertains to research which would come under IRB review anyway. What about research that takes place purely in the private sector, no government funding, that might otherwise escape regulation generally? I guess my point is that I

think the regulatory regime is generally satisfactory, the framework is satisfactory for research that is currently covered by the framework, but there is this world of potential research which currently lies outside the framework. And I don't think we should reassure people that all research is covered if it isn't.

DR. SHAPIRO: I take that point, Tom. That's correct.

MS. KRAMER: On page 2, that bottom paragraph, the 4th line from the bottom. It says "except when carried out by private investigators, etc." I made a footnote, a note that it seems to me that it would help this if we fleshed out something about the scope of that. I mean, there's . . .

DR. SHAPIRO: Okay. That sentence I think should read "investigators and organizations not currently covered" because you can be covered if you're part of an organization that's covered even if you yourself don't have government funds and so on. But I accept your clarification. I think that would be really helpful. David, I'm sorry. I have your name on my list. I apologize.

DR. COX: Arturo first I think.

DR. BRITO: It's very frustrating. When I originally read through these guidance—I want to stick to what the guidance principles that were recommended were—on page 5, and I'm going to go back to Guidance 2 with this, and after hearing what Alta was saying, I think this might help a little bit. One of the problems I had with this is that minimal psychosocial risk. I think that any time there is a potential for a group, someone outside the individual, group, community, kindred, somebody in the family, etc. to be identified, then you are no longer "minimal risk." Psychosocial risk for the most part is not the minimal part; it's greater than minimal risk. So I haven't had enough time to think about the language, but if we go back to the second Guidance 2, and in here, somehow put in here, as part of our guidance make it very clear, that when there's minimal risk to an individual, but the information or the protocol might implicate another individual or group and there no longer is minimal risk. And then we go to Table X and say that any research that implicates another individual is no longer minimal risk, therefore would require full IRB review. I don't know how that relates to all the other conversations that went on afterwards. But I was hearing more about implementation problems than actual wording. What I'm getting at here, what Alta's talking about, when you can identify other family members, or a group of people, then you pose a problem where it's no longer just a minimal risk. It's greater than minimal risk; and I think that would take care of it itself worded correctly by having that required to have IRB review.

DR. SHAPIRO: Okay. That's a helpful point. But let's come back to that in just a moment, Arturo, when we get Item 2 and we can bring in five more issues like that. But do you have something regarding the first item?

DR. COX: I do indeed.

DR. SHAPIRO: I do want to move on to this area.

DR. COX: Yes. And I hope this will allow us to move on. The vast majority of the samples and the situations that we're talking about in terms of people as individuals are going to be coded individuals. The vast, vast majority. Right now, that there's ambiguity, genuine

ambiguity on the part of most researchers in terms of whether those individuals represent something that should go to the IRB or not, because they say to themselves—in some Machiavellian, but in most cases totally clueless—if I don't know who that person is, then they're not identifiable. Well, it turns out that those researchers were wrong, but they don't know that they're wrong because nobody ever told them they were wrong. So we need to tell them. So I would just like to emphasize that point.

DR. SHAPIRO: Well, I don't know if we're doing something monumental, but I think we'll do that.

DR. COX: Because it's not clear to me, Harold, that we are going to be able to do that, but if we do that...

DR. SHAPIRO: We're going to do. What the world will do is yet another matter but I think I don't really hear any dissent amongst us on that issue. I think we're really completely agreed on that. And I think we've heard enough and had some very interesting useful suggestions regarding this first item, which will enable us to articulate it more carefully in a more helpful way, and I want to go on to what is called here Guidance 2. Do you have something before we do that?

DR. MESLIN: The only thing I was going to ask is it helpful if we were to add a finding, an actual statement that preceded the guidance of the kind you've just described, such as the Commission finds that coded equals identifiable—don't take that language identically. Because from what Alex had said earlier, we don't want to simply say there ought to be a guidance, and from what Bernie has said, state the finding, the finding within the contexts of the regs which we feel to be appropriate. That allows us to say there is inadequate information of the kind that David Cox's investigators ought to have. I raise that now because for each of these guidances, you may want to have statements of finding of that kind. The Commission finds that...and as a result we recommend the following.

DR. LO: I think we really don't want to do that because that will be a sort of richness and the tale of the text that will make it much more useful. And since this is the commentary to the principles that Al Jonsen was talking about earlier, showing what we mean in various ...

DR. COX: What are the frontiers, we want to concentrate on the frontiers.

DR. LO: And sort of underlining what the issues are, so not only do I know what I need to do but what the implications are for other things I might be able to do.

DR. SHAPIRO: Alex, last comment on this because I want to

DR. CAPRON: It seems to me that with Guidance 2, we have three situations. The easy situation is one in which the sample is identifiable and therefore has to go through an IRB process. And what we're saying is the IRB ought to consider the possibility of group harms and comes to the conclusion that the group harms have been resolved in a way that's satisfactory to allow the consent of the individual. The hard cases are the opposite sides of that. On the one hand, Arturo, we get to the situation right now there is no process for IRB review of something where the samples are not identifiable. They are anonymous samples that came from an identifiable group.

That is to say they were samples collected during Tay-Sachs screening that you now want to use for BRCA-1 screening, but they were just numbers and you don't know who the numbers refer to. The repository doesn't know so you don't have a problem with their passing them on, there's no coding to people. The question is, the present regulations wouldn't provide to the IRB to even see that, so the first question is should we say that if there's any potential that samples could yield results which would reflect upon a group or community that they have to have IRB review. I can understand an argument for that but it really would require a big change. And then we have the opposite side where you have the IRB look at this and say wait a second, this is going to harm the XYZ group a lot if it's done this way and the results come out. But all the people who are members of that group whose samples are going to be used are eager to have the research done. And the researcher's a member of the group, too, and they all want to have it done and they're all ready to go. Do we stop them because of that? Do we have any authority to say that this research should not be done because one of the harms that would be weighed on the scale is a harm to a group of people who are not research subjects. And that's...on that latter issues, I think that the staff memo suggests no, in the end, you really can't.

DR. BRITO: Isn't that when you get community consultation? Isn't that ... but that's my point. Should the IRB be determining whether or not they think it's harmful to the group. Should it be somebody....

MR. CAPRON: Well, but even for them to say you have to have community consultation, you go through community consultation for two purposes. One is to get advice from the community about how to do the research in a way that minimizes the harm. But if in the end the community says it would be harmful to have it done but the researchers think that there'll be great value and the subjects are all willing to have their samples used, does community consultation mean well, nice to talk to you, thank you very much. Or does it mean the community can go back to the IRB and say we went through the consultation and we still don't want it done and they're not willing to change it sufficiently to make us agree to it. Does that...and I'm not prepared in that situation to say the research should not go forward. Mostly because I don't think that the process of community consultation is going to be precise enough to end up with answers of what the community is and how it's going to be.

DR. BRITO: Right, so I have that fear also, and anxiety, about the community representative. But then what you're saying is you're leaving it up to the scientists to decide what research should be done that may identify community and up to an IRB that has no community representative.

MR. CAPRON: It may or may not, that's true, there's no requirement because in most situations there are a thousand communities, as it were. You can break up communities in so many different ways. So I would be inclined to think that it might well be worthwhile to add another question to this flowchart, and the question would be will the research produce results that will identify characteristics of a community. And if the answer to that is yes, even though it's not identifiable to the individual it ought to have IRB review just so that they get a chance to see that the risks have been minimized at least. Because in that case you're not dealing with the

consent. All those people whose samples you used might be equally alarmed if they knew that there samples were going to produce information that's harmful to their group but they don't have to be asked because we don't know who they are. You see, you don't have the argument that you have in the other dilemma that in that dilemma, at least you're operating on the informed consent of individuals who say, we think this information is worth getting even if it comes with a price. There you don't know that, you have no such guarantee. And the only substitute for that would be some kind of a—which we talked about before—going back to that community and saying well what do you think of this, we're not asking for your individual consent because we don't know if it's your sample. So you go back to the temple where the Tay-Sachs screening was done and say what do you people who happen to be here today think of this research using your former congregants' information from 25 years ago. I mean that would be the only way to go about that.

DR. SHAPIRO: David, then Alta.

DR. COX: So I come down on this issue number two the same way I came down on issue number one, guidance. Right now, if you have a group identified, and in large part what we're talking about here are clearly defined racial groups, there could be many other groups but right now, at least in terms of genetic work, people are identified by their skin colors in terms of group.

MR. CAPRON: Broadly, you mean population groups.

DR. COX: Population groups. But let's....

MR. CAPRON: Racial may be the wrong word.

DR. COX: Yes, but that's how it's designated.

MR. CAPRON: Colloquially, right?

DR. COX: Now, and heretofore, there's never been any consideration of this. If you don't identify the individual, no big deal. Well, sometimes it is a big deal, sometimes it isn't a big deal. But the IRB isn't necessarily a representative or any better than anybody else, but at least it's a body that's sitting there looking at it and trying to deliberate on it to have the researcher think about it in terms of whether there's risk involved or not. So it's being considered. That's certainly a better situation than what's going on right now. I quite agree that going and getting community consultation is not practical, but on the other hand not having somebody even consider this if the group's identified strikes me as irresponsible. So, just to simply say if the group's identified, the IRB looks at it is a simple, straightforward recommendation. And I support it.

MR. CAPRON: If you're the IRB, the question is what do you do when you look at it.

DR. COX: Well you know what, Alex, it's situational. And since it is situational, I go with Bernie on this. We have some examples of what we would do in different situation, what we would recommend as guidelines. But there are not going to be clear-cut, push button A and you get answer C on this. We're not ready for that, and we don't know what those answers are. But this is one of those frontiers and the frontier where the IRB tries to make some statements. If it looks at it and it says we don't know, we don't see any risks here, if no member of the IRB sees any problems, then you go forward. But not to have it reviewed by the IRB if the group's

identified, I think, is a mistake.

DR. SHAPIRO: It seems to me, and this is in response to your question, as Alex says, what do they do besides lose a night's sleep, and it seems to me I thought you really mentioned what they should do before. They ought to look at this and say if there is a potential harm, the design is such that it minimizes that.

MR. CAPRON: Yes, exactly. But I guess my example, I was being rhetorically but not entirely about going back to the temple. Suppose, take the most extreme example. You have the research is going to be carried on at the Mother of Perpetual Sorrows Hospital, a Catholic hospital with a Catholic IRB and so forth. And it's going to involve a Jewish community, Jewish samples. And the Catholics look at it and they don't see any problems. It turns out that there's some particular sensitivity that has to do with cultural or ethnic differences that relates to...they don't have access to that. It's not that they're not being conscientious. They look at it and the basic parts of good design are there, and the researcher is sensitive to not do broad generalizations, but he's out to look if there's a Jewish gene is the way he's looking at it, that's it. And if you went back to the group that was in some ways involved, they might think of something that you didn't think of. So have you added anything by going to the IRB? Well, in nonextreme cases, you probably have, I mean, if you don't have this chasm that I described. A conscientious IRB might be able to suggest ways of modifying the risks or tweaking it or doing this or that, or do you really have to do it this way or that? And the researcher might say no, I don't really, and they could get around that problem. But sometimes if you don't take the next step, then in the end you don't have any sense that the people involved gave consent. When we talk about an identifiable sample, the people involved are the people from whom the sample came. And my view is that that person can override the group interest if they're not being persuaded by.

DR. SHAPIRO: I agree with that.

MR. CAPRON: If you don't have that person exercising that judgment, who him or herself might have some sensitivity to the thing that is of concern to his or her group. Do you try to seek a surrogate for it? Sometimes you might have a surrogate. It might be a temple. If it's not, if the samples are just random Jewish women who came in for this procedure and you now want to test their samples for some other thing, do you know who to go to? Do you go to Hadassah? Do you go to the AJC? I mean who do you go to in that case? It is a dilemma, what's your community.

DR. COX: Alex, in advice, simple advice to the researcher, if the group is identified, it's the onus on the researcher to say I've identified this group and I've thought of the fact that it's identified, I've thought about these issues and this is why, this is how I feel as a researcher about that. The IRB looks at those statements, it doesn't come blank where the researcher says it's up to you IRB, I don't take any responsibility for this. So you have a discussion about this where the onus is on the researcher. And that's not the situation right now, let's make that the situation.

MR. CAPRON: So you're saying that's a step forward, even if it's not perfect.

DR. COX: That's correct.

DR. SHAPIRO: And I think the problems raised, myself, identify a group and then are just too overwhelm any benefits you get, as far as I... Excuse me, Trish and Bernie.

MS. BACKLAR: One of the things that's interesting in listening to this, I'm harking back to our other report and how we dealt with this, these people that have mental disorders. And how we say to the IRBs, or we're going to say to the IRBs, that you have to have a record. When you're looking at this kind of issue, you should invite somebody from this group, either an advocate or a member of this population, relative of this population, to sit on the IRB and think through the issues at that if you're addressing this kind of thing. And wondering if we might not look at this in the same way and consider making the same kind of suggestion, depending on the populations being looked at. Because one of the issues that's so interesting to me when we look at the communities in these populations, they're not just ethnic, they're not just religious, they also maybe diseased populations. And more often than not, that is what we are going to be because we're going to find these things everywhere. And this might be a simpler way of dealing with it. Taking that model, that template that we're already using, with a diseased population, with a variety of diseases within that particular population.

DR. SHAPIRO: Bernie, then Alta. Alta, I missed you before, I apologize.

DR. LO: First I'd like to say this, the dialogue we've been having, needs to be in this chapter because I think it makes it much richer and much more helpful. So I hope the recording's working. I just want to point out a problem that I'm going to keep trying to flag which is brute, putting on the shoulders of the IRB a lot of important new things. And there's a lot of criticism now that IRBs are having trouble, at least some IRBs, are having trouble doing what they're really supposed to do. I think at some point we need to try and address that, lest what we suggest not ring true. I have a question with regard to the points Alex is raising about, and Arturo raised before, sort of taking into account community harm. Are we saying that we don't want to put this as a regulatory proposal for regulatory change, but we want to put it forth as kind of best practice to be adopted on a voluntary basis by the most conscientious lawful IRBs? Because this is a departure, it seems to me, from current regulatory structure. And I think it's an issue I'd raised before. Are we saying it's going to be such a hassle to change the regs that let's not try and push for regs? Or are we really saying that it's a little too early yet but we ought to try it? IRBs like Mayo Clinic ought to be commended for adopting what I think is essentially Alex's approach, but to really be inspirational rather than regulatory. I think there's a good argument to be made that there are enough regulations as there is. And finally, I'd like to introduce the concept of best practices, that there are a lot...it struck me as I've been thinking about what we've done—you know it's taken a lot of time—but we've heard some thoughtful people, I think, really try to grapple with what's going on. So some of the folks at Heart/Lung, some of the folks at Mayo, the breast cancer group, are really trying to push this forward. And where we can highlight a best practice example without saying everybody has to do it, I think it will give some incentive for other folks to do that. So you know, it seems to me what, what's his name, Vogelstein at Hopkins has done, is really a real-life example of the kind of thing that Alex was talking about. I think what's interesting about that example is sort of a converse to what Allen Buchanan argued in

what's now chapter 3, that because we can't predict the future and things that seem real bad now might not be so bad later, it works the other way. The things that didn't seem so bad starts to get really bad. Where people say I didn't mind when I just had Tay-Sachs but now I've got this gene and that gene, and my kids are asking me are we all going to die prematurely. So that I think because it's unknown, the best investigators, the best IRBs are going to want to have a very low threshold for going to the community and at least talking to them. I mean, again, David's principle that let's get the bulk of what's going on. Right now investigators aren't thinking about it and aren't making any effort to talk to anybody who's related. These questions, while we don't know what's the exact representative to speak with legitimacy, talk to anybody and you'll probably get some ideas you've never heard about. It's a dialogue. When this gentleman from Illinois, I was going to say, they never even talked to us, they never came to explain. I mean that's part of what's going on. I think, again, to go back to the AIDS examples, you know it's that dialogue you start and if you really are there and you listen, you go back and think and you lose sleep, but you change what you do over a period of time and it's not a matter of saying who has absolute political power.

DR. MESLIN: Bernie, we may come to this later, but we have two proposed recommendations on page 7, Recommendations 7 and 8, which may get to what you're describing. One is this language of recommending that the scientific community should agree on a set of standard practices. That could be a way of encouraging them to describe what already may be best practices. And recommendation 8 is a way of us referring both the consent document documents that we've received and heard from the others on, the NHLBI, the National Action Plan on Breast Cancer. And that's what was meant by that language. We would attempt to reference them, not to endorse them as models, but to encourage people to go and see who has already made great strides. So the language is there. It could certainly be developed as a textual form if you thought that was appropriate.

DR. SHAPIRO: The...Bernie, I want to ask you. You said two things today which—you said more than two things, but two things are on my mind right now—that stand a little bit, perhaps I don't fully understand, which is most likely the case. You've just said that one of the strategies we could take is to be inspirational and inspire people to do better by best examples, and I think we certainly should do some of that. On the other hand, both you and David have said over and over again that people will do whatever they can get away with, and that leads me to think that inspiration is not, may not be so helpful in this community. But can you...both of you raised this issue and I'd be interested in your observations. I believe in inspiration for the most part.

DR. LO: I think we have a spectrum of things. But one thing is very clear in saying you guys have been interpreting the regs wrong, this is what we think they mean, this is what the implications are, this is how you interpret these slippery terms. And we get 80 percent, 85 percent of the cases just because everyone thought you didn't even have to bother, coded meant unidentifiable. Then as we get to the really tougher cases where we're not wise enough, not experienced enough, or the field hasn't developed enough, rather than trying to be proscriptive I

think we should just say keep working on this, keep thinking, keep talking, here's some good examples of people justified to do that. So that it's sort of a multipronged approach where we can be fairly clear and sort of definite about what we think should happen, I should say that. And when we're less certain, we should say keep trying to do what the best people are doing and we'll get to it eventually.

MR. CAPRON: If the requirement were a well-informed review, and then the examples would be well how do you go about getting that well-informed review, you might follow Trish's example sometimes. And if you have representatives of the community, bring them in to sit with the committee, the IRB. Other times it might be telling the researcher he or she has to go out to certain identifiable organizations. And it could be any number of things, these best practices.

MS. CHARO: Two things, as a detail, we can certainly suggest to HHS that they provide the resources for OPRR to actually follow up on those IRBs that attempt to implement any of these in order to learn from those experiences in preparation, perhaps, for regulatory change in the future. I don't think OPRR currently has the resources to do that, and so we should accompany that. More substantially, just so we understand where we're coming out here, I understand that nobody here is suggesting that any form of community consultation gives any member of the so-called community a veto power. But I haven't heard us decide whether or not an IRB should ever in its own judgment decide to deny approval of a protocol because they feel that it is too psychosocially or politically damaging to a larger community, although it otherwise meets all of the necessary requirements for approval. And that's a hard...I just don't think I've heard anybody say anything about it. And so my question is what do you want an IRB to do when they've concluded that a particular piece of research is psychosocially, and I really mean socially, damaging. And I'm thinking about so many, it's not just race and it's not just disease, thinking about Simon LeVay and Dean Hamer's research on homosexuality, which engendered such controversy within the gay community on both sides of whether or not this was helpful or harmful to that community's effort to gain political equality. And I'm really interested in hearing people discuss how they think an IRB should react to something like this.

MR. CAPRON: What's your answer?

MS. CHARO: I'm not sure yet.

DR. SHAPIRO: Could I ask a clarifying question? Are you thinking of cases, Alta, where people, the subjects, have individually given consent already, or are you thinking of cases where they're....

MS. CHARO: No, I'm limiting myself to the moment to Alex's example in which we're working with genuinely anonymous samples. You give Simon LeVay a bunch of genuinely anonymous slices to use. So there are no individuals who can stand as the decisionmakers. And we're suddenly asking the PIs to go to the IRB for the very first time for this kind of discussion. And the IRB looks at it and says, you know, there ain't no good going to come from this. This is only going to pour fuel on the fire, or whatever.

MR. CAPRON: And the traditional view is that you can't stop it for that reason.

MS. CHARO: Absolutely, the traditional view is that that is irrelevant. I can imagine for a beginning, that faced with this kind of political consequence, the IRB could have a much more rigorous insistence on scientific validity of the experiment itself to justify the psychosocial harm.

DR. COX: What a concept.

MS. CHARO: So the bad sociobiological research wouldn't automatically get approved because it doesn't hurt anybody because we'd actually be paying attention to whom it hurts.

MR. CAPRON: But if it's good design, and "bad policy," bad social policies, that's hard.

MS. CHARO: That's the hard case, that's the hard case. And I understand everybody's concerns. Every time I see another study published about why women are congenitally able or not able to do certain things, I feel implicated now because everybody wonders now if I'm able to see a triangle versus a square. You know, so I understand this and at the same time I'm very nervous about censoring science.

DR. COX: But Alex, 99 percent of studies that are bad social policy are even worse science, right? And so if you use that as the criterion, you're in great shape, right? I am very hesitant, though, if you have good science for social or cultural reasons to suppress that. You know Galileo would roll over on his grave. So if you just use the quality science criterion, you will solve 99 percent of these cases.

MR. CAPRON: May I ask just a ...if there were no samples in tissue banks that satisfied the need of the researcher, and the researcher went out to the group in question and said, I need to collect samples, and they said what's the research and he described it, and all of them said well, we're not going to give samples for that reason, would that change your view? They couldn't do it, then, in other words, but now we're saying would it change your view if that hypothetical were applied to anonymous samples which conveniently are there and you don't have to ask anybody about. That's what...in the back of my mind, that's what worries me.

DR. COX: But Alex, I have other...there are other social controls for that. And one of the best examples is in this situation when there was an NIH grant for criminality. Now, I actually...and it got taken away right for that conference. Now that was a conference, and because of that social pressure, that grant, it was basically withdrawn. Ultimately it got re-funded but there are lots of other social controls over things that are going to be good science. So even if it's good science, if it really, you know, gets up people's noses, they're not quiet about it. So I think the IRB is sitting there in the context of looking at the science of it.

MR. CAPRON: You say if it's a political objection it should be handled in the political process.

DR. COX: Exactly, that's what I'm saying.

DR. SHAPIRO: I would ...that's my own view, also. Even though it's not an easy question, that's what I would....

DR. COX: But see, the reason why I'm so comfortable with this is that almost all of these,

if we just used the scientific criteria which IRBs are supposed to be about, that these things would go down the drain. The point is is that the scientific quality isn't paid enough attention to. And so the researcher needs to show that, and that's why you have experts on the IRBs that are supposed to judge the time.

DR. MESLIN: I don't know if it helps, but in the report that we'll be discussing tomorrow, we have an extension section on the ethics of study design and it may be useful for Commissioners to review that before coming back to this draft tomorrow to see whether an equivalent section might be inserted into this draft. I see no reason why questions about the selection of subjects which we raise on the report on subjects with mental disorders that may affect decisionmaking capacity could not equally address the issue of why one selects groups or individuals or kindreds. Because the issues of scientific design which David mentioned are already discussed in another commission draft.

DR. COX: And how can you justify it? Because Al Jonsen said it, how many people...I mean the scientists, they may be pretty smart in science, but you know they're busy. They need this to be simple. They don't want to have to read the Belmont Report to figure out what is it they're going to do. So we need clear guidelines on this.

MR. CAPRON: All eight pages of it.

DR. SHAPIRO: Alta, then I want to move on.

MS. CHARO: Trying in my head to kind of summarize how this would work, let me see if I understand this. For research using both samples that are anonymous, meaning unidentifiable, and research that involves samples that are being used with the explicit permission of the sample sources, in both individuals, it encompasses a concern about the community. And second, and contrary to current practice, when you're working without single, explicit human subjects (i.e., you've got anonymous samples and no identifiable person), that the investigators will be asked to go to the IRB anyway, if their research is about examining a salient characteristic of an identifiable group in order to allow the IRB to do that risk-benefit balancing. And it's in that risk-benefit balancing that you'd get the review of the scientific value of the research which is tied up with the integrity of the study it's on.

MR. CAPRON: But they would never disapprove something purely because they object to the potential findings, if the findings are legitimate conclusions from the science as designed.

MS. CHARO: So when you're doing a risk-benefit balancing, any valid scientific finding is considered a benefit that outweighs the risk of social harms.

MR. CAPRON: No, not really.

MS. CHARO: Any valid scientific finding.

MR. CAPRON: Oh I see what you're saying. You're saying overall in terms of there are limits.

MS. CHARO: Right. I mean it could be a completely trivial scientific finding that has tremendously controversial political repercussions. I'm actually, despite this, extreme and on rare

case willing to go along with this, but I want to make sure we're really clear what we're saying here. There's a risk-benefit balance in which any iota of scientifically-valid result trumps social harm.

DR. SHAPIRO: Well I like...let me talk to that. I usually phrase this in a somewhat different way and it may not get around the issue you raised, and I know where I'll come down from it if it doesn't get around it. When I try to write or think about this, I think of scientifically valid and scientifically important issues which the IRB has to deal with. Just because it passes a statistical significance test doesn't mean anything to me. That's important in some context, but it has to also have to be scientifically important, that is it answers or is on the way to answering something of some considerable importance to somebody. And if it satisfies that, in my view, this may not be shared by other Commissioners, that's right. This is not a group that should be...this...the IRB should not be speculating and governing the scientific agenda by their particular views of what causes harm.

MR. CAPRON: I think Alta should be writing headlines for the *Washington Post* because you've taken a recommendation which basically said most of the bad stuff is going to fall out on science crowds, said well, if it's good science, any little tiny finding will justify doing terrible harm to a group, says National Commission.

DR. COX: Harold, can I comment on that, because the standard peer review practice in reviewing grants isn't just if it's scientifically sound. It's is it important? Because that's how these things get sifted. So scientific review, peer review, it has a series of values to it that the IRB is looking at too in terms of the scientific merit of it. And it's not simply validity. Validity's one component of that. But I really agree with the way you put it, Harold, with those two components.

DR. SHAPIRO: We are unfortunately running out of time this evening. I'm going to...and so we do have to adjourn. We're supposed to adjourn at 5, it's now 5:30. And we have other commitments. Let me suggest that we come back and spend some more time on this tomorrow morning. I don't think we've allocated enough time to this, we'll have to somehow spend...now what is everybody's schedule tomorrow morning? Is it possible for us to start earlier or is that, because we've published the agenda, impossible? We can put out a new agenda which gives more time to this discussion. Why don't we... I don't know how successful we'll be, but why don't we try to start at 7:30 tomorrow morning. And somebody can get double caffeine coffee or something somewhere. And we'll try to do these other things as well but I think there's still quite a few things and we're getting to a sense where we can help ourselves here and I want to continue on. So let's adjourn here, let's reassemble tomorrow as close to 7:30 as our ... as we can.