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WELCOME AND OVERVIEW OF AGENDA

THE PRESIDENT'S REQUEST AND NBAC PLANS FOR RESPONSE

DR. HAROLD T. SHAPIRO: I would like to call today's meeting to order. First of all, I'd like to welcome all Commissioners to a new year of work, and wish you all a Happy New Year, and hope you all had a good holiday. We have a very busy schedule of meetings during this coming year, as you all know, so I hope it will not be an unpleasant thought to you that we'll be seeing each other more often than we did in this last year. And so, welcome, and it's good to see you all here.

Now, I do want to apologize to the Commission members that for approximately from our break through lunch, I will not be able to be here. [Prof.] Alta [Charo] will chair the meeting at that time. I will be going down to deliver our Capacity Report to [Health and Human Services (HHS)] Secretary [Donna] Shalala at that time, as that was the only convenient time for both of us to do that. So while we're doing

that roughly between 11 and 12-I apologize for my absence during that period and I want to especially apologize to some of the people who will be presenting at that time. But I will certainly catch up through my colleagues and through the transcript of the meeting.

Now I just want to remind you all that last November 14, President Clinton wrote a letter to us, to me as chairman of the NBAC, requesting us to address two issues. The immediate issue concerned a reported experiment involving diffusion of the human cell with a cow egg-a cow oocyte-and he directed the NBAC to report back to him as soon as possible. He was very specific about thatCnamely, at our next meeting-which at that time was just a few days away, as you recall. He also in that same letter requested that we undertake a thorough review of the issues associated with stem cell research, balancing all ethical and medical considerations, and so on. I think all of you have seen that letter before. It is reproduced, I think, in today=s briefing book. And as you all know, on November 20, roughly a week later, I wrote back to the President providing an initial response to the purported, so-called "human-cow" experiment. This was a very brief response. But a copy of this letter has already been widely distributed, and it also is reprinted for your convenience in the briefing book that you have before you. Now in responding to the President's request, no absolutely firm timetable was established for the more comprehensive issue that he asked us to deal with. And just to remind you again, there is a thorough review of issues associated with stem cell research acknowledging that this review would, of course, have to take account of new scientific developments that are cascading upon us almost daily. But I have committed the Commission to meeting this response by June of this year, so we have probably less than six months between now and when I have committed us to give a report to the President.

Now, of course, this issue is discussed daily in various venues. And I think it will be really quite important for us to share, not our conclusions, of course, which will come only after we've had time to think things through and develop our

ideas on that, but to share with others who are concerned with this on a daily, weekly, and monthly basis the issues that we think to be important and ought to be thought through for people who are thinking about this subject and its various dimensions. And I hope that as we go along we'll be able to share this at various points with other parties who are interested in this particular area. There is a lot of background material on stem cell research in particular in your briefing books - indeed, some of it I think is really of very high quality. Indeed, obviously, there have been people out there thinking about this very carefully, and we have certainly not provided you with an absolutely comprehensive collection of materials, but I think a very representative collection of materials. And at least it's clear to me that there are many groups thinking about this and we'll be able to benefit from their work as we try to think through this problem on our own.

Now I want to know one further thing: that is, I had written the President some time ago, perhaps six months ago, offering to provide a brief update on developments in the cloning area. And the staff have been working on that, and we will have a document available for the Commission some time quite shortly, probably within the next few weeks. I have reviewed a draft of that document, which our staff have prepared just for the purpose of updating Commissioners on the cloning issue, because for reasons that will become perfectly obvious as we go through our discussions today, those issues can be directly relevant to some of the issues that we=ll be considering as we go and think about the stem cell research issue. Now today we will be doing a lot of listening, but we'll try to provide an adequate amount of time for questions so that the Commissioners can clarify issues that will be presented before us today. It will really be quite important that we do that, since at the end of the day we want to begin to outline just how we might approach this topic and how - as I said in my memo to Commissioners about a week or 10 days ago, to which there have been various responses and e-mail traffic - we have decided at the very least on the scope of what we're trying to do, although we'll learn as we go also, because things we might want to take on may prove either more or less tractable as we look at these things rather more

deeply. But I think we are very fortunate to be able to attract here today some really wonderful speakers for us, people who are working in this area and are better equipped probably than anyone to help get us started, and I want to express my own gratitude to all of those who have agreed to speak to us today.

Before we begin the formal part of this meeting, let me now turn to [Dr.] Eric [Meslin] to give you a very brief update on other aspects of the Commission's work, which, of course, proceeds in parallel with our work on stem cell research. Of course, tomorrow we will be dealing with another issue altogether. Eric pointed out to me that our speakers today have come from as far away - as he expressed itC@from Halifax to Berkeley, and from Virginia to Edinburgh," which seems like an unusual trapezoid to me, as I try to map this out, but in any case I'm sure we'll all enjoy it very much. So let me turn to Eric to give his Executive Director's Report. Eric.

DR. MESLIN: Thanks very much, Harold. And again, welcome to everyone. I just want to update you on a number of things. First, I want to bring to the Commission's attention that we have some new staff working with us. You all know Dr. Kathi Hanna, who has been working with the Commission for some time, but in the last couple of months Kathi has agreed to take on the responsibility of Research Director for the staff, so she will have overall responsibility for our projects. I'd also like to let you know that I have a new secretary. Her name is Jody Crank. Kathi and the research staff also have a new secretary; her name is Lisa Price. We're also fortunate for a short period of time to have a Presidential Management Intern, Kyle Kinner, if for a very short time indeed. This gentleman also was here for only a couple of weeks with us: Stu Kim, a third-year law student from the University of Wisconsin. We're grateful for the work that Stu and Kyle have done in their short period of time, and happy to have Lisa and Jody join us. Second, as Harold referred to and I'm pleased to let the public know as well, our report on Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity has been completed and finalized. We sent it to the President earlier this week, and as you heard from Harold it will be sent to Secretary Shalala. Dr.

[Harold E.] Varmus can pick up a copy here, but we will be sending it to a variety of others in the near term. We did an initial print run of 50 or so to have it available here, but it will be on our website within the next week and the larger printing will be available within the coming weeks, probably three weeks. If the public would like to get a copy, please just write in to our website, www.bioethics.gov, and we'll ensure that you get a copy.

I have provided for the Commissioners a brief update on our international project. As you all know, this project had been identified some months ago. Obviously, in the wake of our new priorities, we will be rejigging our work. But I have provided a very brief update on the five contractors who we have been fortunate enough to have begin some work with us. Finally, I have added a couple of things to your table folders that you should please make sure that you are aware of, including a statement from the Wisconsin Bioethics Committee, a proposed list of witnesses for our next meetings, and other materials. So please make sure that you have carefully looked at your table folders. I also wanted to draw to your attention that we are going to be joined on the staff by consultants who will work with us on the stem cell project: Jeff Kahn from the University of Minnesota, Anna Mastroianni from the University of Washington, and Leroy Walters from Georgetown University have agreed to work with the staff to assist the Commission on its stem cell project, and other consultants and contractors will be identified as we go along. The last item is to confirm what you all have seen in e-mail, which is that we have revised our schedule for NBAC meetings over the coming months. We will be meeting monthly from now until July. We will next meet in Princeton less than three weeks from now, February 2 and 3. We'll be meeting on March 2 and 3 here in Washington; on April 15 and 16 in Charlottesville, Virginia; in May, we are deciding whether to stay with the plan to meet in Madison, Wisconsin, or move to Chicago to make it more convenient for Commissioners; back in Washington on the 28th and 29th of June; in Cambridge, Massachusetts, the 13th and 14th of July, and then back in Washington in September. Those dates will be available on our website. The locations will be finalized as we have more information. Thanks.

RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS

SCIENTIFIC ISSUES

DR. SHAPIRO: Thank you very much. Any questions for - all right. Let's go on then to the principal topic of our meeting. Most of you I think can recall when we began to address the issue of cloning-that is, somatic cell nuclear transfer cloning-that one of the first things we did as a Commission was to try to take a look at some of the scientific issues involved in their implications, and we are revisiting that in pretty much the same way today. We are very fortunate to have with us as our first speaker today Dr. Harold Varmus, who I think is well known to all of you as Director of [the National Institutes of Health] (NIH) and an extraordinarily distinguished scientist. I once introduced the President of the United States, and after my rather glowing introduction he got up and said, "Well, I hope that God will forgive you for exaggerating and forgive me for enjoying it so much." Harold, I will avoid both of those double sentences today, if you don't mind. I think you are well known to all of us. We are extraordinarily grateful for your leadership and for taking time from a very demanding schedule to be able to help us today. It's the first time that Dr. Varmus has been here with us at an NBAC meeting. We are delighted to have you and look forward to your presentation. I'm going to myself move to the other end here so I can watch with greater care. But thank you very much for being here. It's a great pleasure to have you.

DR. VARMUS: Thank you very much. I want to express my gratitude for a number of things: first, giving me enough time to lay out a number of issues I=d like to bring up to the Commission's attention and to allow for questions and answers as well. Second, I appreciate the indulgence of moving myself from the end table where I feel like a witness at a congressional hearing, to a position where I can feel like an instructor of an enlightened and interested audience. I'm also quite impressed with the

schedule you′ve laid out for the Commission over the next few months. I doubt if I could draw my own advisory committee, indeed my own laboratory code workers, but I want to be able to keep the pace. So why are we here? Well, we′re here in part because investigators, such as those you will hear in just a few moments, have radically changed the landscape in an area of research that has been mocked as the most pretentious kind of science fiction but is now a real eye-stretcher: the generation of work on stem cells by Drs. [James] Thomson and [John] Gearhart, and their colleagues. As you have heard from Dr. Shapiro, shortly after the announcement of the work by the two gentlemen who will be here, and at about the same time, there was a newspaper report of a still unsubstantiated and never published account of an effort to make a hybrid cell in which a human nucleus was introduced into a cow egg. The President wrote to the Commission mentioning the newspaper report on the hybrid cell, and then going on to say that, "Although the ethical issues that surround human embryo research have not diminished, it now appears this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson′s disease. With this in mind, I am requesting the Commission to take a thorough review of the issues associated with such human stem cell research balancing all of that before the medical considerations."And about a week later Dr. Shapiro wrote back pointing out that human embryonic stem cells, although derived from embryos, are not themselves capable of developing into children; the use of human embryonic stem cells, for example, to generate cells for transplantation does not directly raise the same kinds of moral concerns. And we see already the shaping of an argument in which the use of the cells I'll be talking about has to be considered separate, at least partially separated from the issue of human embryo research more generally. And you will see throughout my presentation that theme will resonate. My presentation this morning includes several objectives. I want to talk a little bit about stem cells in general and their potential utility in the goals of the NIH team of researchers, and that is to improve public health. I will talk about how these cells have been generated very briefly, leaving the details to the experts who are following on how they might be produced in the future. I will then spend a good deal of time talking about the role the Federal Government ought to have

and could have in the future in supporting, first, work with the pluripotent stem cells themselves, and second, the generation of pluripotent stem cells from human embryos. And I would like to mention along the way a place where I believe that we can profit from advice from this Commission, both in the short term and in the longer term.

Let me begin by saying a few things about stem cells. The definition of stem cells has remained a bit murky; that is, people tend to use the term "stem cells" without a very precise definition of what those cells entail. And that's understandable because indeed stem cells do come in many different forms. In general, stem cells mark a hierarchy in development, and stem cells are those whose progeny have more specialized, sometimes referred to as "differentiated," functions. Many stem cells have the capacity to renew, that is to keep growing and maintaining their undifferentiated states and proceed to higher levels of differentiation at some later date in response to certain signals. There are indeed many different kinds of stem cells that have approximate definitions. So a cell that has the capacity to give rise to an entire actual organism would be referred to as a "totipotent" or all-potent cell. And consequent to certain cell divisions, we can appreciate the appearance of cells that are referred to as "pluripotent" that is, they may not have the capacity to give rise to an entire organism, but they have the capacity to give rise to all the three major cell types in the body: representing the endoderm, the mesoderm, and the ectoderm. And that's illustrated in this chart by demonstrating that the cell, what we might call the pluripotent cell, can give rise to stem cells that didn't - a mammalian animal, for example, would give rise and turn into more differentiated stem cells that are tissue-specific and lack pluripotency but can give rise to many kinds of cells that populate the blood, muscle cells, nerve cells, the different kinds of cells that make up bone and many other tissues. So this notion of hierarchy - progressive loss of function, the ability to self-renew, and the response to instructions - will lead to more differentiated type of functions that is all encompassed in this set of definitions.

In its most deterministic form, a hierarchy of cells give rise to a mature

organism, reflected in this now classical chart of the differentiation and developmental pattern of the roundworm *C. elegans*. Each of the 959 cells that make up this mature animal, indicated by the end points in this diagram, can be traced back to a series of cell divisions to the primordial or totipotent cell, then gives rise to pluripotent progeny and so forth. This is probably the most deterministic version of development we know. Cells have very limited capacity for self-renewal, and indeed when one compares stem cells in a short-lived, highly deterministic animal like *C. elegans* to the situation in mammals one sees very dramatic differences with our own developmental patterns, seeing more flexible, larger numbers of cells, greater capacity for self-renewal, and more responsiveness to external environmental signals.

PROF. ALEXANDER M. CAPRON: What is the rate of the actual cell divisions?

DR. VARMUS: I'm sorry. Yes, each of these represents a set of divisions; some of these cells have gone through more divisions than others. The end point in each of these lines represents each of the [INAUDIBLE] cells in the mature adult, and you can see that some of the cells actually die during development. They undergo a process called "programmed cell death" that says this cell, having gone through a certain number of divisions, is no longer needed in the mature adult. And as I said, this is the situation - if at one extreme you're thinking about development, in which you have the organisms in which development is very much cued to environmental stimuli-for example, in certain spores it differentiates and they undergo changes that are very environmentally cued, whereas here the genetic program very strenuously draws these organisms into a highly fixed pattern.

PROF. CAPRON: In stem cell terms, is there a certain point where you get the differentiation you say is no longer on this chart for the stem cells? How far up, or how far down does it go?

DR. VARMUS: I think this is a definitional issueCthat is, one could argue that cells, that it's quite far down in this chart, has the capacity to achieve a different status functionally, so it's a precursor to a subsequent cell. One might argue that a true stem cell will give rise to cells of different functions, and has the capacity to self-renew, and that's a capacity that is quite limited in the case of *C. elegans*. This is at one extreme, and rather different from the situation you're talking about in mammals. Well, what has excited the interest of those in this field are the experimental and therapeutic uses of the pluripotent cells that you'll hear more about this morning. A number of people have written about what can be done with these cells, and I want just very briefly to outline the three major areas in which most of us see the opportunities that apply. One of the virtues of the cells you'll be hearing about is that they keep growing in culture for extended periods of time; whether they are unlimited in their growth capacity remains to be seen. I'll come back to that point in a couple of moments. So these cells can be propagated in a dish and there are at least three genres of use that we anticipate. One is to attempt to use these cells to understand what genetic environmental signals are at play when the cells undergo differentiation to form the more mature tissues that lie within these three great sectors: endoderm, ectoderm, and mesoderm. The ability to work in cell culture with cells of this type at this time can=t be overestimated. We are at an extremely exciting moment in the history of biology, a time in which all the genes of many organisms are being mapped and unveiled; a time in which new technologies allow us to look at the expression of essentially all of those genes and to read out of all those genes in a single experiment; at a time in which we have understood many of the signaling pathways that allow a cell to interpret the molecules, hormones, and growth factors in the bathing fluids by changing the way those genes spread out in the nucleus. And we have information about protein products of genes that is truly extraordinary. So the idea of being able to take cells in culture, expose them to certain growth conditions, and ask what is it about the combination of genetic instructions and environmental cues that result in the differentiation of these cells into forms that can be recognized as precursors to many of the mature cells in the body, is a remarkable moment in the history of science.

There is a very practical application that is worth mentioning, and that is that having cells in culture that have extraordinary capacity for specialized function provides an opportunity for turning out pharmacological developments, that is testing drugs for their effect on certain genes and gene products, using cells that have the capacity to move in one differentiation direction or another, to look for toxicity of potential drugs on cells of various types, that provides a new avenue for thinking about drug testing and questions of toxicity that up until now has been carried out either on cells with a much more limited set of instructions or in animals before going to human testing. There is quite a wide range of interest in using such cells in drug development. Finally, and most obviously, there is the potential for taking such cells and learning how to differentiate them into more advanced stages of differentiation so they can be used to either compare genetic proficiencies, treat injured tissues, or treat individuals who have undergone degenerative diseases in which certain organs have been impaired by pathological processes. These include patients who have undergone chemotherapy for cancer; for eradication of cancer in blood-forming cells; in patients who have certain degenerative diseases of the brain such as Parkinson's disease and others; for patients who have severe cardiac disease and loss of the tactile function of the heart, and in patients who have diabetes and have lost the potency of their capacity to produce insulin. In all of these cases, however, there remain two major obstacles - we believe obstacles that can be overcome, but obstacles that nevertheless exist at the moment. The first, of course, is learning how to formulate the chemical cocktails that would instruct pluripotent stem cells to differentiate *en masse* into the appropriate lineage. There certainly have been advances in learning how to do this based on work with parallel types of cells from the mouse, but we are very far from being able to easily induce cells into the appropriate lineage. The other major problem, of course, is one of discompatibility; a transfer of such cells for therapy into human hosts will require that we avoid an intense immune response of the host to any cells that are used in such cell therapies. There are a number of ways one might approach the situation. None of them has been totally established to work. They include developing a tissue bank of many different types of pluripotent stem cells to be more or less a match to potential donors

effort. Alternatively, one might consider efforts to alter the nature of the pluripotent stem cells so they don't encode the cell service proteins or antigens so that it will be rejected by a histo-noncompatible recipient, or again other ways that I may return to in a couple of moments.

Now, we talked a little bit about stem cells in general; I'd like now to talk a little bit about the derivation of such cells as well as the idea of differentiating them. I'd like to begin by talking about what has been accomplished recently, and it's important to remind the audience that the methodologies I'll be describing are not really new. Indeed, pluripotent stem cells have been derived by the methods I've been talking about and will be talking more about later from mice as early as the early 1980's in research that had been authorized for the purpose in a number of vertebrates, including non-human primates. Much of this work, as you all know, is supported by the NIH as an agency priority, and the experience we have had along with the scientific community with the mouse pluripotent stem cells, both the [embryonic stem] (ES) and other types of stem cells, has been quite extensive. There are literally hundreds of laboratories that work with such cells, in part because these cells have been very useful for introducing mutations into the germline of mice, an experimental approach that would not be considered by the NIH to support human pluripotent cells but nonetheless has been extremely useful in making models of human disease with the mouse. Similarly, pluripotent stem cells-ES cells-of mouse origin have been used to give us the greatest disbursement we currently have in attempting to differentiate part of those cells into blood cells, cardiac muscle cells, and nerve cells.

Now I'm going to review the schemes for the generation of pluripotent stem cells, not in any historical order or even order of importance, but in an order that I think will help frame our later discussion about what the NIH is doing in such work. So again, here is a reminder of what we've talking about. And let me illustrate by mentioning the method you'll hear about in more detail from John Gearhart, who has derived pluripotent stem cells by obtaining fetuses from individuals who have elected to

undergo elective abortion of the fetal material, that was obtained and dissected to isolate cells from the genital ridge, which are found in the primordial germ cells, which when cultivated appropriately in culture give rise to this culture for stem cells. This work was supported with funding sources, as you'll hear in just a moment, of the NIH, and NIH is committed to support research on fetal tissue under rules we'll discuss in just a few moments. The second group in the generation of pluripotent stem cells harkens a little bit about normal mammalian development. I remind you that development begins at the fertilization of an egg by a sperm, giving rise to the one-celled zygote fertilized egg, the one-celled embryo. That cell undergoes a series of divisions to form a cluster of cells called a morula. That undergoes a series of further divisions so that by approximately four to seven days after fertilization we have a form of the embryo that's called a blastocyst, in which a collection of cells called the inner cell mass, the precursor to the body of the predestined and eventual baby is developing clustered in one part of the blastocyst, and the trophoblastic cells will go on to form the placenta or another part.

The technology involved in making pluripotent stem cells in the blastocyst form involves taking cells from the inner cell mass, of growing them in the appropriate way, a layer of so-called feeder cells and the appropriate collection of hormonal stimuli giving rise to pluripotent stem cells. Are these kinds of stem cells derived from these two sources identical? We don't really know. They show some differences with respect to cell markers, but they both have the potential to give rise to all three major types of tissue under perfect conditions. The work that you=ll hear described by Dr. Thomson of the University of Wisconsin that made use of blastocysts as a source of pluripotent stem cells was, again, carried out with private funds. This work would not have been eligible for Federal funding under an amendment through the Health and Human Services/Labor/Education appropriation bill. I'll get back to that amendment in more detail in just a moment.

Now these are the two methods for developing pluripotent stem cells that are currently in use and have produced the clear and exciting results that have brought

us together today. But I think it's important in your considerations of this particular issue to contemplate other ways that one might go about making the cells. And one alternative route with which this Commission is no doubt already familiar from your discussions of cloning involved a methodology called somatic cell nuclear transfer. And the notion here is that we begin with an egg, a human or animal egg from which the nucleus has been removed, then fused with a cell. The cell could be embryonic or fetal, or it could come from an adult, and that fusion product would then have the potential to give rise to events in embryogenesis that resemble what occurs after fertilization. We know that this kind of process occurs, and we all know this as well from work that's been done now with sheep and cows and mice and other organisms to give rise to blastocysts, which inner cell mass cells can be removed and to generate pluripotent stem cells. To my knowledge, as yet no one has used this method to develop pluripotent stem cells, but certainly it is a very likely possibility, and it's a possibility that has some advantages that will be apparent to many of you. For example, if the donor here was an adult in need of tissue transplantation, the pluripotent cells derived from this kind of method would be histocompatible with the identical tests to the recipient, and this would obviate the problem I mentioned earlier of histoincompatibility in transplanting tissues.

I don't want to leave the issue here, because there may be yet other means to develop pluripotent stem cells. For example, there has been discussion of doing somatic cell nuclear transfer not into a nucleated egg but instead into a nucleated pluripotent cell, or into a primordial germ cell. And there is preliminary evidence that such methods may have the potential to generate pluripotent stem cells and those ought to be thought about carefully. Furthermore, as we understand the way in which the collection of genes that are present in embryonic stem cells are programmed and deprogrammed, it may eventually become possible to take a cell from any one of our organs and to expose it to the right set of environmental stimuli and to encourage that cell to return to a more primitive stage in the hierarchy of stem cells I described earlier. Under those conditions, one might in fact generate the cell with a great deal of potential as a pluripotent cell from a very mature cell. One might even in fact imagine generating a

cell that's totipotent in that manner. I think things have happened so rapidly in the last few years that we ought to remember that virtually every one of our mature cells - although blood cells and some others are exceptions-but virtually all of our cells contained in the complete repertoire of genes are in principle capable of undergoing the changes that would render them potent for generation of many different cell types.

So with that, I'd like to talk a little bit about the issues that we face as the funding agency of the NIH. Those NIH funds have been used to date for work with human embryos or with cells derived from human embryos, or with those derived pluripotent cells that I mentioned. Nevertheless, the reports we're talking about today present in addition to the traditional concerns we have about human embryo research- may I remind you that in 1994 a panel of some 18 individuals labored on behalf of NIH for about nine months and came up with a series of recommendations for the Advisory Committee to the Director on human embryo research more broadly. But the work we're talking about today does raise a more constrictive issue I'd like to address, and that is, can we support work that uses pluripotent stem cells, cells that are generated by the various methods described? I mean work that is separated from the steps that are required to derive those cells from embryos or fetuses or by somatic cell nuclear transfer. Before we get into the legal issues here, I'd like to remind you of a basic principle on which we work, a principle that was actually reaffirmed by every witness who testified at a recent hearing of the Senate Appropriations Subcommittee conducted by Senators [Arlen] Specter [R-PA] and [Tom] Harkin [D-IA] last month, and that is that this category of research is worth doing, and it is generally advantageous to have public funders such as the NIH in the process. The reasons for that I think are quite obvious to the people in this room: that public funding simply provides more funds, attracts more talent, allows us to get to research goals-a benefit from our talent-more quickly, develops a research environment in which there is a more open exchange of information, and allows a greater degree of oversight on the quality of the research and the ethical manner in which the research is carried out.

Now to date, the involvement of the Federal Government in the kinds of work that we're talking about today have been governed mainly by two things: first, the regulations that provide the guidelines for fetal tissue research, and second, an amendment to the Appropriations bill for HHS, Education, and Labor. In addition, I'd like to emphasize that any actions that we contemplate at the NIH-a body that is publicly funded and provides responses to many of our constituencies-any actions that we contemplate in this very sensitive arena would occur only after consultation with our many colleagues in the Administration and Congress, the public, scientists, and organizations like this Commission. And again, I stress the sense of the deliberations that we undertook in 1994. The Embryo Research Panel is an example of our interest in trying to conduct as wide a discussion as possible about research that we know has many sensitive aspects to it.

Now in response to the recent reports of the generation of many pluripotent stem cells, I requested a minimal ruling from the General Counsel of the Department of Health and Human Services that addressed specifically our ability to fund work that uses these types of cells. All of you should have a copy of that legal ruling recently issued and of the memos made. Let me begin by pointing out two central issues that are contained in the summary, the first concerning a cell derived from fetal tissue. The General Counsel says, and I quote, AThe extant human *in vitro* stem cells are considered human fetal tissue by law. They are subject to the existing statutes as stated by the law; that is, there will be no reason to exclude Federal support or work with those cells as long as statutes and laws are obeyed; that is, no more research exists and are implied by the existing statutes and laws that govern fetal tissue research.@ The second, and more typical, part is the following that applies to cells derived from work with cells that are derived from human embryos, embryos that as I mentioned earlier came from embryos that were residual from efforts made to increase fertility donated by patients and embryos donated with full consent of the parents. The conclusion from the General Counsel was the following, and I quote:" Statutory prohibition on the use of funds appropriated to HHS for human embryo research will not apply to research

utilizing human pluripotent stem cells because such cells are not a human embryo within the statutory definition." In other words, the Administration holds that it is legal to use Federal funds, and NIH funds, to support work on the existing work on stem cells.

Now I would like to elaborate on three points: I'd like to talk in a little more detail about this ruling, I'd like to consider briefly how the NIH intends to proceed to initiate funding of work on these parts of the stem cells, and I'd like to outline the kinds of advice that we seek from your Commission. First, we seek to deal with the fetal tissue research guidelines in general, and with respect to substantive use of these cells in transplantation. I have a handout for the Commission that talks about the existing Federal regulations on fetal tissue research. Turning to those pages, the Health Research Act specifies that fetal tissue means tissue or cells obtained from a fetus after a spontaneous abortion or induced abortion or after a stillbirth. There are three provisions covering the use or transfer of this tissue: first, there's a criminal prohibition against the sale of human fetal tissue. Second, there are restrictions on fetal tissue transplantation research, and those restrictions are good in that there must be informed consent of women when donating the tissue, a statement by attending physicians regarding that consent and the method of obtaining the tissue, a statement by the researcher about the source of the tissue, and a clear indication of directed donations of tissue for transplantation. It's forbidden. Second, let me say a little more about the embryo ban as it exists in our appropriations bill as an amendment - that too is in your handout. In the last few years this amendment or a moderately different version of it has appeared in our bills; the current version is in the handout, and it states that none of the funds made available to the agencies concerned can be used for, first, the creation of human embryos or embryos for specific purposes, and second, not to use for research the human embryo or embryos destroyed, discarded; or knowingly subjected to risk of injury or death greater than that allowed in research on fetuses *in utero*, under 45(c) of Article 6, and Section 498 of the Public Health Service Act.

Essential to the legal implications of this amendment to establishing the use of pluripotent stem cells in culture is the definition of human embryo. And in the law, human embryos are defined to include, and I quote, "any organism that is not protected as a subject under 45(c) of Article 6 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means for one or more human gametes or diploid cells."

So the question arises: are pluripotent stem cells embryos? And then the question becomes, are pluripotent stem cells organisms? And we have determined by consulting both the legal and the scientific texts that since an organism is individual, it is constituted to carry out all of the life functions of the species. Pluripotent stem cells, while not an organism, do carry the potential to develop into an organism and can't develop into a human being, even if it's introduced into a receptive womb. Therefore, an embryo is said by law to be an organism, and if a set of pluripotent stem cells is not an organism, then it is also not an embryo and is not subject to the law.

So, given this ruling, how will the NIH proceed to fund research with these cells? First, let me emphasize that no funding of such projects will occur until procedures for this work have been outlined and established, and advice has been sought from the many parties. There is a three-part plan, if I understood it, and I suppose I'm seeking advice on this plan from you. The first is to develop clear guidelines that lay out what work cannot be supported with Federal funds. And it is made clear to our investigators what it is that this legal decision permits us to support. Second, we will be disseminating those guidelines to our current grantees and to any prospective future grantees so everyone is clear about what these guidelines say. And third, we'll be assembling an administrative oversight panel to validate legal use by any of our grantees, guaranteeing that the plans that are envisioned by anyone who is likely to receive funds from us are consistent with the law, consistent with the guidelines we provide them.

Now we're working inside this mechanism for oversight of our funding on work with stem cells with a careful look over the next couple of months. In the interim, we'll be consulting with the public and Congress on some issues. We come to you today in part to ask your advice about the kinds of considerations to be placed in the guidelines, and we would hope tohave any advice from you on this issue within the next week or so and out on March 1. I'm asking that you would consider separating this narrowly focused issue of the terms with which we have provided guidance to investigators who would like to do work in this area with appropriate Federal funding separately from the longer term type of issues that come before you now. I think we all appreciate that the results from the research on stem cells that I've described as they stand at the moment present issues of much greater complexity and sensitivity than the work toward pluripotent stem cells themselves. At present the Federal government can support derivation of pluripotent stem cells from fetal germ cells, but not by other available methods such as derivation from inner cell mass, human embryos, or by stem cell nuclear transfer. So the eternal question arises and I'm sure will be a major topic for your considerations over the next few months, of what methods for the derivation of pluripotent stem cells should be supported by Federal funds in the future. As you will note in your reading of the Human Embryo Research Panel's report from 1994, these issues were already very clearly on the table and are described in some detail in that report. And we expect that, consistent with the President's letter to NBAC in which he awaits guidance about how to balance the ethical and medical considerations that may have changed in view of recent advances, a reassessment of the appropriateness of Federal funding for methods for the derivation of pluripotent stem cells will be a part of the task you're undertaking. I would point out the Administration does not at this time seek any changes in the law, but we await guidance from you about whether the recent advances should alter our position in this regard. I would suggest from a personal point of view that you consider some of the problem issues that you've been dealing with already, and I'd just like to put on the table some of the things that certainly have become questions for me as NIH looks to deal with these problems. The first has to do with the importance of distinguishing between different objectives of research that may

be carried out with one methodology - for example, using certain methods to develop cells and tissues that we work with in culture and that we use in therapies as opposed to generating cells that could be used to try to produce a new human being. I'm referring specifically to somatic cell nuclear transfer, where the many distortions and distinctions between using the methods to generate cells has come to be confused with the use of them as a way to generate new organisms. Second, I would encourage you to consider the different ethical considerations that are posed by methods for deriving human organ stem cells. We as an institution, of course, face this issue as we think through what kind of values to provide to our investigators. We propose the use of pluripotent stem cells, cells that have more properties that come from different sources that you will hear about - how cells are derived from fetuses, from embryos, with very different legal restrictions incurred by these procedures. This approach is consonant with the ethical concern. Third, I'd like to think about the distinctions between so-called pluripotent cells that are derived by sexual means, that is by fertilization, as opposed to being derived by asexual means. Should cells that are derived via somatic nuclear transfer in human eggs be regarded the same as other cells? If you consider the equivalent effort in deriving by fertilization, if you were able to generate a pluripotent cell by changing the growth conditions, it has yet to be discovered whether that cell has the same moral status as a cell derived by fertilization. Those are some of the things that I would hope you would think about as you consider the difficult task of embryo research.

DR. SHAPIRO: Thank you very much. I very much appreciate the care you've taken in bringing these issues before us and the preparation involved in the statements of the presentation. I will get back to my seat in just a moment. Let me first of all turn to the Commissioners for any questions they have.

PROF. CAPRON: Beginning with your third question to us about the difference between pluripotent cells created through somatic cell nuclear transfer and those created through sexual intercourse or [*in vitro* fertilization] (IVF) procedures, you asked whether we would look at the potential difference in moral status between these. I

can begin with a question of whether you thought that the answer to that depended primarily on the scientific data, which you said isn't yet available, or is there any scientifically discernible difference between these cells or if you were thinking that the major reason for differentiation had to do with the intent in creating a cell, that is to say if one were using the somatic cell nuclear transfer to create cells that would be just incompatible for transplantation or other therapeutic cellular purposes. That, say, the usual purpose of an IVF, where the aim is to create a child for a couple. So is it a scientificCis the basis of your question that we're likely to be able to turn to you and your colleagues a few months or years from now, and you say there are actually no discernible scientific differences, or do you think that those differences are improbable and the major difference is a difference in intent?

DR. VARMUS: I'm concerned at the moment, and I'll try to put this quickly, that evaluating whether or not cells and their scientific nuances may not yet be apparent and their use may be quite similar one to the other, so it should be taken into consideration the result of the mode of generation. In other words....

PROF. CAPRON: I understand your question. But it primarily, do you think-if you were to think of it now, it's just that this is an inquiry worth having that we're going into-do you suppose that the major difference that we are likely to find between these is the intention with which they're created as opposed to a likelihood that there are scientific differences between these cells?

DR. VARMUS: I think it's a combination of intention and the issue of whether we hold in greater regard a cell that is generated by fertilization than a cell generated by an asexual means.

PROF. CAPRON: Yes, the latter is the question you're asking.

DR. VARMUS: Right.

PROF. CAPRON: Do you hold it in greater regard? I'm asking whether in asking it, your first thought is because they were created for different purposes, we may hold it in a different regard, as opposed to because they are created through different means they are in some scientific sense....

DR. VARMUS: Well, there is a fundamental difference with respect to the content of the cells, so that in one case a cell might be construed from the standpoint that there's no difference in any cell in the body of the donor.

PROF. CAPRON: But the quality of totipotency, which might be achievable by even simpler means in the future without using an egg as opposed to the deliberate combination of these generated by IVF. The second question I had was, when it comes to the advice you had on the prohibition of Federal funding for cloning human beings, would it be fair to say that the present memorandum for the President that went back to March of 1997, which was a flat ban on any Federal funds being set for any cloning of human beings, is a much broader ban than that which was proposed by the Commission and which was translated to Congress by the President?

DR. VARMUS: Our restriction - the one that we recommended - had only to do with what we colloquially refer to as cloning to create a child, as opposed to cloning techniques used for basic research. That's why I suggest that attention be given to the ultimate goals of research, that is [INAUDIBLE] last year to the bills in the Senate [INAUDIBLE], because it cut off over the use of human embryonic tissue in stem cell research [INAUDIBLE] was a consideration similar to the one we're facing now, where we must contemplate the uses to which these will be put and focus on the goal of those Federal policies.

DR. SHAPIRO: Thank you. Alta?

PROF. R. ALTA CHARO: First, I'd like to add my thanks for the

valuable presentation that Dr. Varmus made on behalf of the NIH. Speaking to the point you mentioned about federally funded research projects, I'd like to make sure I understand what would be possible under various conditions. First, what is the range of research that you envision with the existing supplies of stem cells and their progeny, and which experiments are *not* impossible with existing stem cell supplies? [INAUDIBLE] And second, regarding the nuances, what kinds of differences are there among the stem cells that are generated from primordial germ cells as opposed to embryonic sources?

DR. VARMUS: Well, to start with the latter question, as far as we know [INAUDIBLE] more details, but at the moment [INAUDIBLE]. With respect to your first question, we know that cells that have been generated in the two laboratories do undergo a large number of cell divisions while retaining their copies of theDNA. So it's clearly the case, as is true for work with pluripotent stem cells in organisms such as mice, that the cells that have been generated could be applied to a number of studies or a variety of cell types.

It's important to remember that research on mouse embryonic stem cells shows us very clearly that we can't expect the cells that have been derived to become embryos. Indeed, those who have made use of such cells know that they are subject to sometimes indeterminate changes of unknown provenance, such as loss of potency to the differentiation of various cell types - and no one knows why that happens, but it makes the cells unusable. Therefore, there are a number of stem cells of mouse origin in use around the world that have been used to produce for years, while others have been known to fail after a couple of rounds cell division.

People have asked whether I believe that the technologies available will increase the demand for fetal tissue. I think it's clear that the many thousands of people who object to the use of human embryos have concerns.

DR. SHAPIRO: Thank you. Larry?

DR. LAWRENCE H. MIIKE: I have a series of questions: if the NIH is not able to respond on stem cell research, What would be the effect on research?

DR. VARMUS: Well, obviously we've been doing this research for a long time, and without having too many pluripotent stem cells at our disposal. So we have been able to live without stem cells, rather than...

DR. MIIKE: Well, I understand, I understand.

DR. VARMUS: Yrespond to potential years.

DR. MIIKE: Right. That's what.

DR. VARMUS: Y And we would clearly be limited. However, as I have indicated, we have reached a conclusion, based on law, that it is appropriate for NIH to support this research and we intend to do so once the appropriate methodology for clearing our investigators, informing them of the guidelines they will still be required to work under.

DR. MIIKE: Well, that's my next question, which is, given the fact that you can fund stem cell research, and there is one avenue in which you can fund the derivation of stem cells, which is through the aborted fetus - that's what I understood you to say - does that give you enough leeway that you think that the agency would be politically hampered in being able to address all of the issues that have now arisen out of stem cell research? In other words, is that one avenue of resources for new stem cells adequate? And then, second of all, is that - from what I understand you are saying, and I don't want to make you uncomfortable about it, I just want to understand your opinion when you say that it's supported. If some researcher did a somatic cell transfer and ended up with a stem cell one, and that researcher then came to the NIH with funding for stem cell research along that way, your General Counsel's opinion says you can

fund it.

DR. VARMUS: We're speaking in respect to our General Counsel's opinion about work with the pluripotent stem cells themselves, not the derivation of the cells. We try to make a clear distinction between those two acts.

DR. MIIKE: That=s what I understood. That's why it's working.

DR. VARMUS: If stem cells were derived by somatic cell nuclear transfer, when we could not under current appropriations law have supported derivation of the cells, cells once generated could be used for NIH-funded research under the same interpretation of the law I have provided for the research with cross-derivation of pluripotent stem cells from so-called spare embryos.

DR. MIIKE: The first part of my question was that given your current legally approved method of gaining stem cells, what is your assessment about that as being adequate?

DR. VARMUS: Well, I think when we're doing it-the moment we state that it's something we will support in the future will make it happen with or without Federal funds from fetuses and without Federal funding from embryos and stem cell methodologies, but our funding will focus primarily on work that is carried out with the stem cells. It would require a change in law before we could fund work derived from stem cells from embryos by somatic cell nuclear transfer, and that change of law would only be pursued by us once we heard from Congress on it.

DR. MIIKE: But you can fund research that derives from stem cells from aborted fetuses, right?

DR. VARMUS: That's correct.

DR. MIIKE: My question was, what's your assessment about the adequacy of that given the current restrictions on the other research?

DR. VARMUS: Well, I would prefer personally to be able to have greater flexibility as to research methodologies, but that's unlikely now and depends on the assessment of the situation by the Administration.

DR. SHAPIRO: Thank you. Jim?

DR. JAMES F. CHILDRESS: Thank you very much for that helpful presentation. In your discussion of NIH plans, developing clear guidelines, disseminating guidelines, and then developing an administrative oversight panel, I'm reminded of the experience with the RAC. And I just wonder if you would comment on your sense of what you might have learned from both the success and the failure that holds for how you would go about this particular enterprise.

DR. VARMUS: It's useful to consider what we're doing here in relation to a number of other issues, whether it's the definition of death that is required for tissue and organ transplantation or the way in which we provide oversight for common DNA activities, or for gene therapies, and where we are just trying to set up an oversight on transplantation. It's important to remember in what we're talking about at the moment that research on stem cells doesn't involve patients, that is, we're talking about cells that have been generated by other means. We are not talking about cell therapies, because cell therapies would require other realms of oversight including [Food and Drug Administration] (FDA) approval and possibly other institutions. And what we're trying to do is to ensure that our investigators are following the law, and that they're following the set of guidelines that you will design according to the kinds of advice you receive over the years and expect to receive in the next few weeks. We'll be looking back at the 1994 Human Embryo Research Panel, and it is extremely likely that we will require that individuals working with cell lines, for example the cell lines

described today, have been obtained with the kinds of careful precautions to send appropriate attention to fetal tissue regulations that have been the case for the work earlier described.

DR. CHILDRESS: Could I just add a follow-up? When you described it as an administrative panel, I guess I wasn't sure whether it would simply be, in a kind of narrow way, to make sure these guidelines are followed, whether you'd say that it's involving also public representation. How public would the activity be?

DR. VARMUS: We expect that the determination of the guidelines would be a more public activity. Funding for this research I expect will come in three forms. One is the network of existing grants to the NIH, the one using funds they currently have to change some of the work they're doing to involve research on stem cells. It is traditionally the case that our investigators receive their grant money with the expectation that the original plans they had laid out are subject to changes as the science matures. So we would welcome them to make deviations in their plans for doing research. There are also supplements to existing grants and we expect people to make new grant proposals to provide all three genres of funding to be subject to its regulatory oversight because we believe that there are insufficient guidelines about what the law says and what is considered a legitimate job to do, and thus this process should be one that says carefully what we're seeing. The administrative process would include people from within the NIH staff, and then others from the outside. But I don't envision the work to have the same kind of complexity of the evaluation process that we've seen in recombinant DNA, or in the early days of congressional oversight. Now as you know, as recombinant DNA work evolved, the issues became much more administrative and much less interesting to the public. And I think that, at least at this stage, the issues will be - once the guidelines are defined - it will become a routine matter of assuring that the investigators must understand where the boundaries are and what they must do to comply with the law.

DR. SHAPIRO: Thank you. David.

DR. DAVID R. COX: Dr. Varmus, what are the three ways of making stem cells, and which is the way that hasn't been talked about very much but has raised considerable public and political concern about, which is somatic cell nuclear transfer. We don't have any research publications to evaluate that work. Another thing that came forward was the scientific difficulty of not having matched mitochondria. What is your view of the potential of this approach, that there is any potential in it, and what is NIH's view of the relative merits of creating pluripotent stem cells?

DR. VARMUS: Well, as I mentioned when I described somatic cell nuclear transfer, the nature of the cell into which the nucleus is transferred is not necessarily determined by - it isn't variable, and most that's been written is about transfers that employ the same species as the donor nucleus. But one condition is of the recipient cell being a number of things: it could be a more advanced cell, a stem cell, an egg, or a cell from another species. And there are a number of other reasons including histocompatibility that determine the success of that venture. The species [INAUDIBLE] transfers carried out and you know it's actually cell fusion [INAUDIBLE]. [INAUDIBLE]. And I think it's premature to engage the virtues of different methods. One virtue that has been very clear, and that I remarked earlier, is that usually, before you go to the stem cells as a source of tissue for cell therapy [INAUDIBLE] interest in using stem cells [INAUDIBLE].

DR. COX: So right now it is scientifically premature to judge the merits of any of the three - any one being scientifically superior.

DR. VARMUS: Right. I think it - s important to remember that a somatic cell nuclear transfer may be an umbrella for many different approaches that are influenced by the source of the donor cells and the source of the nucleus being modified.

DR. SHAPIRO: Could I ask a question? I'm not sure, frankly, whether this is an interesting or a trivial question, but I will try to ask it anyhow. The cell lineage map you put up I think gives me a good way to ask the question that was on my mind. I understand that particularly what you have there is a special case, and I don't mean to generalize it to other organisms. But as you see the developing science as it's developing day by day now, are we either close to a situation where one can imagine that any cell of any type could be brought up and down the hierarchy, so that you could restore a specialized cell to any spot in that hierarchy? And I understand we can't do that right now. We don't know enough about the instructions, and so on. But does it seem to you a reasonable prospect - I don't know how to give a time frame on this at all - that therefore we ought to face the fact as we think about this that cells in that sense are undifferentiated, because wherever we are we can pull them back and forth, up and down that lineage map?

DR. VARMUS: I think this is a very important issue for us all to think about, because if you would have brought this before this Commission four or five years ago many of my colleagues would have said somatic cell nuclear transfer of a non-totipotent cell is not possible. So everyone's notion has been changed. Its important to remember that it's not as though a mature cell has all of the genes ready to be reprogrammed, because there are chemical changes that occur to our genes by a process called methylation that, while potentially reversible is not in fact readily reversible. So, it may not be the case that every cell might be brought back in the way a sponge can be brought back. But I do think that it's important to remember that essentially every cell in our body has a full complement of genes and in that sense is potentially totipotent, and so this raises some rather serious issues - among other things, that by transferring the nucleus from a mature cell from an egg into one that is a potentially totipotent cell, but of course in the case of humans, it would not be tested. The only test that we have available is [INAUDIBLE] human being stem cells, and that certainly in NIH's view is prohibited by law and not on the table. But the notion of what the totipotency of any cell is [INAUDIBLE] going to end up in a situation where any cell with the potential to

be a human being, and, therefore, every time we include cells from our bodies where the natural process of cell death occurs that [INAUDIBLE] this notion that obviously brings to our conscience the fact that our biology has changed, and the way we think about each cell in our bodies. Our perspective on life has changed.

DR. SHAPIRO: I'm going to ask a simpler follow-up question of narrower type. As you have reviewed, or as perhaps you know others have reviewed the evolving literature in, let's say somatic cell nuclear transfer, whether in any kinds of mammals, and so on. And they do use particular cells, of course, nucleus of cells for that purpose. Do you sense that there is any category of cells that somehow works better than other categories of cells, either for particular animal models, which is, of course, the only thing we have available now, or has that not really been investigated yet?

DR. VARMUS: Well, our experience is so limited, but there are cells in the [INAUDIBLE] that do seem to have given a greater degree of success in [INAUDIBLE]. Obviously, since mammalian species have at least 200 different types of [INAUDIBLE] different cells, it's not going to be possible to carry out these laborious efforts with every cell type. But I do think that the nature of the donor cell, the conditions under which the cell is maintained, the conditions under which the fusion is carried out, the period in the cell cycle in which the cells are derived all are likely to have important effects, including on the methodologies of somatic cell nuclear transfer.

DR. SHAPIRO: Thank you. Other questions for members of the Commission? Steve?

MR. STEVEN H. HOLTZMAN: Dr. Varmus, I have two questions. One goes back to your response. And second, if one were to take the product of that fusion and derive ES cells from it that work with that fusion [INAUDIBLE].

DR. VARMUS: Well, certainly at this point, the NIH does not fund research derived from cells like that. We would have to consider that, while we can't say with certainty that these are human embryos, it would be sufficiently likely to develop into a nuclear embryo [INAUDIBLE]. If such cells were generated, then the same argument applies to cells derived from inner cell mass stem cells.

DR. SHAPIRO: Bette?

MS. BETTE O. KRAMER: I'm concerned with the ultimate cost to society if funding from the federal sector is not permitted for this kind of research. And I wondered if you can interpolate from denial of federal funding over the past several years in the area of embryo research and comment on what might be the cost to both the scientific community and society at large if restrictions were placed on-similar restrictions were placed on this one.

DR. VARMUS: First of all, before I answer that let me point out that this really is a very difficult question to try to answer. But the question does embody one very important point that sometimes we ignore the argument, that is, the ethical evaluation of these issues, in my view, has to take into consideration the benefits that we'll derive from such research and that would accrue to living human beings, as well as consider the ethical issues that surround the use of other materials that either are intended for storage and disposal or research. It is pretty difficult for us to evaluate exactly what has been lost by the ban on human embryo research and methodologies. Certainly many investigators have been dissuaded from doing such work, others have tried to seek support from the private sector, from pharmaceutical companies and other private industries that have been very active in this area. And under the situation their involvement has been useful in adding to the literature. On the other hand, everyone would acknowledge that a number of issues having to do with the number of investigators working on these problems, the amount of funds available, the open communication issues that are involved in technology transfer in the research

community - all are affected by the way in which the funding is carried out. It's clear to my own sense that there is much to be gained here. Patients have injuries, diseases, made to evaluate the impact of the few years in which this cell research has been accomplished.

DR. SHAPIRO: Thank you. We'll just take one more question now because we do have the next panel, which is due to start in a few moments. But let me turn to Alta for a final question.

PROF. CHARO: Dr. Varmus, this is more of a technical question. You discussed earlier that somewhat down the line the prospect of cell-based therapy for use in transplantation. And you mentioned three different approaches to dealing with the problem of immunological incompatibility, multiple cell lines being developed, somehow denaturing cell lines so it doesn't generate immunological reaction. And, finally, having matched cell lines based on derivation of somatic cell nuclear transfer. Can you describe for us the state of the animal research in those areas now that would help us understand in a very speculative way the likelihood that either of the first two methods will turn out to be satisfactory as a way to go forward with cell-based therapies in the human species?

DR. VARMUS: Well, with respect to the first [INAUDIBLE] of cell lines that provide an [INAUDIBLE] tissue from those people [INAUDIBLE]. I don't have human outlines yet. It comes mainly from efforts to try and use tissue donors for organ transplants in humans. We know that there is tremendous variation within these populations. Some individuals need to screen a million prospective donors or more to find the appropriate match. Others have much more common types, however, may not be a complete match, necessary if appropriate levels of compatibility as is the case today. This may vary from one tissue to another. So I think that's a matter that needs some careful technical thought to envision whether or not it's possible to develop a bank that would satisfy, say, the needs of 70 percent of the population, or 30 percent, or

95 percent. With respect to defusing the antigenic status of the donor cells, there are some promising things to think about. For example, we now know that it-s possible to use a methodology called targeting to introduce into pluripotent stem cells a change in the cells. So one condition of moving the portion of a given chromosome that encodes the most, the strongest of the so-called histocompatibility engines, so the cells become a type of universal donor, or one could imagine introducing the [INAUDIBLE] as genes to make them into single cell types, a single line, a wide variety of cells that have histocompatibility markers.

DR. SHAPIRO: Thank you very much. Let me once again, Dr. Varmus, express on behalf of the Commission our great gratitude to you for being here today. I want to move directly on to our next panel and welcome Drs. Gearhart, Thomson, and Smith. If they could just sit up there in any order they would like, I'd very much appreciate that.

Let me begin by once again expressing on behalf of the entire Commission our gratitude for this morning's panel to be here. Dr. Smith, I especially appreciate the long distance you have traveled to be here this morning, and thank you very much for being here to all of you. I'd also like to express to all of you our enormous admiration for the work you have done, which has surprised us in so many ways. So thank you very much for, all of you, for being here. Each one of you has a very long [*curriculum vitae*] CV, and I'll plead the same excuse I gave Dr. Varmus: I'll try not to exaggerate or embarrass you by reading them. I can't help but notice, however, one not so well known aspect of Dr. Thomson's *vitae*, which I want to particularly highlight: namely, that he was an [National Science Foundation] NSF undergraduate [INAUDIBLE] while at Princeton University. I just wanted to highlight that this morning for some reason.

DR. MIIKE: What university is that?

DR. SHAPIRO: A good one. So thank you very much. I don't see the reasons are too serious the order in which we start, so let's have Dr. Gearhart, Dr. Thomson;, and then Dr. Smith. So we'll proceed in that order. If I could ask each of you please to keep your remarks to 15 minutes, so we'll have plenty of time for questions. So let me turn first to Dr. Gearhart.

DR. JOHN GEARHART: Thank you for the opportunity to come and tell you exactly what we've done. [INAUDIBLE]. It's a letdown to follow Dr. Varmus, since he seemed to cover everything we have under discussion. But I'll try to at least give you some of the nuts and bolts. Everything that I will tell you has been published or has been written for your access, and I'd be happy to provide you with any material that I would talk about that you don't have access to. I have chosen to show some slides, if I may. And if it's okay, I'd like to go in that direction.

DR. SHAPIRO: Please, feel free to wander about as things seem appropriate to you.

DR. GEARHART: Okay. What has brought me into this arena has been a longstanding interest in developmental genetics and particularly the aspects dealing with Down syndrome research. To summarize it briefly, many of the events that go wrong go wrong very early in development. And to get a better understanding of this, you either use human embryos or you try to have access to tissue that could give you appropriate answers. In 1992 and '93 we began a program of first considering using embryonic stem cells and then going through a process that took almost two years to get the permission from various committees to go forward on this. I won't review much in the way of stem cells again and the source of them. We have a number of options available to us. We have taken some of these options, but we want to concentrate on stem cells from very early mammalian embryos, and I wanted to distinguish between the two procedures that were used by Jamie Thomson and myself by giving them an ES and [embryonic germ] EG as the acronym that one can use. Our consideration in the early

1990s was, do we attempt to derive cells from the inner cell mass, cells that become known as embryonic stem cells, through the mouse work? Or could we take a new route that was actually derived or designed and carried out by Peter Donovan at [National Cancer Institute] (NCI) at the time and Bridgid Hogan, both in the mouse. Upon our review of the availability of preimplantation stage mouse embryos - I'm a part of the assisted reproductive technology program at [Johns] Hopkins - we do have embryos available to us. But I was concerned about the quality of these embryos and the fact that at that time, how well could we grow very healthy, viable preimplantation stage embryos? We then looked carefully on the other side of this, that is the cells derived from primordial germ cells that Peter Donovan referred to as embryonic germ cells, or EG. We reviewed the mass literature to see: are they equivalent? Are they equal? And this is an important point and I would urge you that we don't know an answer to this. I think that both arms of this, or both options, should be left available for research. Over the years what we have learned is that there are differences between these two groups of cells. We can talk about that later. But they do have similar properties in that in the mouse they can both form germ line chimeras, they can both differentiate in the dish to form a variety of cell types. And they both can form tetracarcinomas these tumors that are a mixture of different cell types when placed subcutaneously in appropriate mice.

Now we ran into our first series - I won't refer to them as obstacles, but certainly of review. It has taken us actually a several-year period to put into place many of the requirements that were necessary to pursue the work. I wish that we had had at our disposal a committee, like Dr. Varmus, who could give us a determination on this in a period of a few months, perhaps. But through our university council, various officers at our school, we began to review everything that we had to do to do this right. We got involved in patient consent through [the Office for Protection from Research Risks] (OPRR) at the NIH. The FDA has a series of guidelines if you're going to do fetal tissue transplantation. What are the requirements for this, the record-keeping, etc.? We have a fetal tissue committee at Hopkins. We have two[institutional review boards] (IRBs). Hopkins, like everyone else, is developing our own talent, and we have different

hospitals involved so we had to go before the internal review boards of various hospitals. And then the dean's office, as soon, for example, as the banning that went into effect in 1996 came up, it was a concern: well, does it apply to our research? And the determination was that it didn't. Our work was fetal tissue research. Patient consent forms - we have extensive patient consent forms outlining many of the points that Dr. Varmus had made about what the tissue would be used for. We had payments of money, etc., not permitted. A conflict of interest committee now oversees all of our involvements with the private side of interest there and, for obvious reasons, security was involved. And all of this is still evolving to a certain degree, but it did take us a period of almost two years before we could get started.

A little embryology so we can now be talking about what embryonic stages we are collecting from. We know in the mouse work that's a very defined window in which these germ cells, these primordial germ cells, can be collected and can be, let's say, are amenable to the derivation of the embryonic stem cells from them. We didn't know where these stages were or what these actual times were in human embryos and we had to determine this.

This is a drawing from Emil Vecci's work in 1948. This embryo is during the fourth week post-fertilization. Crown rump length is about 3 mm. and germ cells first become discernible in an extra embryonic site. You have to stain for them, but one sees a cluster of 50 to 100 of them. Over the next couple of weeks these primordial germ cells, through a process of embryonic folds and active migration, actually make their way, then, to the gonadal ridges. These are structures that will develop either into an ovary or a testes. This is during the fourth week. If you look at a little later stage, again a drawing from Vecci, which indicates where these germ cells are as they come from an extra embryonic source, migrate through the gut, through the gut mesentery and into this long tubular structure here, which is actually the developing ovary or testes. It rounds up eventually into a structure that you can recognize as such. This is a period in the fifth or sixth week post-fertilization. As these cells migrate, they also divide. By the

time they reach the ridge there are probably 25,000 germ or primordial germ cells in that embryo.

I want to show you a few photographs from Marjorie England's atlas to give you a feeling of what this tissue looks like. This is a stage about 35 days post-fertilization and we're interested in the structures here, we're looking into the left side of the abdomen. The crown rump length here is about 7 mm. We see structures that are associated with what's called the middle kidney or the mesonephric kidney, which is in the form of a ridge that has tubules. It has two ducts, the mesonephric ducts and the paramesonephric duct. And we have a little structure here, which is a developing gonad. We go to a later stage and see now that this gonad-fortunately these are numbered-number three here is actually the gonad at about six and a half weeks or so. And underlying the mesonephric kidney-it'll make the pancreas, etc. And then finally, at around eight weeks, one begins to see textbook-type structures, if you will. This is a female embryo growing ovaries, the forerunners of fallopian tubes, the vaginal primordium, rod ligament, kidney, and adrenal gland. Our time frame in collections, it turned out, we did from five to nine weeks post-fertilization; crown rump lengths of 5 mm. up, really up to 40 mm., is the time in which we collect this tissue. The tissue is in the form of a ridge with some mesenteries. We dissociate this tissue. Now this tissue consists of stroma elements that are formed, either the ovary or the testes plus the primordial germ cells. This tissue is dissociated, placed in culture under certain conditions that are defined in our publications, essentially on a sheet of what we call feeder layers and in the presence of a number of growth factors and sera, etc. And we're now working on improving these culture conditions and we can go into those in detail if you like. But nonetheless they require certain growth factors to survive, to divide initially when one plates them. Here the comparison is between Peter Donovan's work on the mouse, showing that when you plate a primordial germ cell you get [INAUDIBLE: assessed?] types. We see them in humans, or you see cells developing these huge [INAUDIBLE: filopodia?], which move across the surface of the feeder layers. In a period of 14 days or so one can begin to see colony formation of these cells

and I think you can see that these are clusters of cells and they can be small or they can be large. From here we then go on to a series of markers that are now fairly well accepted as to representing pluripotential embryonic stem cells. We won't go into detail on these other than to say it's not any single marker in and of itself, but the group of them that's important. And we certainly want to make sure that these cells have a normal karyotype and that they have developmental potential. So these are standard assays that we have done. This again is in the publication showing that these cells react against specific antibodies or are positive for specific antigens. We are obviously very interested in passages. We have had in straight culture conditions some of our lines lasting as long as nine months. Others are in between as we continue to study them, and these are encoding.

One of the differences I should tell you in FDA requirements versus the use of standard fetal material in a lab is that if you're going to go to transplantation, you've got to keep records of where that tissue came from. We code it, but it has to go back eventually to a patient if necessary. This is a very important difference when we start talking about privacy issues and patient issues. These are different codes that we use. We have found that we can generate cells that are both male and female and that they have a stable karyotype, which is important to us as well. Most of you know the mouse work; generally you can only generate Y cells or X-Os. Jamie [Thomson] has also demonstrated in the nonhuman primate that this is the case. And this is a normal female. We do karyotyping on all of our cultures at different passage numbers. Importantly then, the excitement here comes in in the developmental potentiality. There are several ways of demonstrating this. One, we can look at differentiation in cell culture. We can look at structures called embryoic bodies or one can grow tumors in an immunocompromised animal. And we have done the top two on this. Now there appears in the press this term "Aembryoid." This is a pathologic term; these are not embryos. These are structures that in 1936 were first identified in a human: teratomas. They seem to be free-floating structures that have a resemblance to embryos. And under a light microscope you can see these structures. They are very small, not more than a

few millimeters in diameter. If one does some histology, you can certainly begin to see it looks like germ layers, etc.-that these are abnormal embryos, if you will. They are not capable of forming a being out of it. What we did was to take a large number of these and then section them, and using antibodies and different reagents that would recognize specific cell types went through and showed that we have neural precursors, muscle precursors, etc. I won't bore you with that kind of data. But these are early stages. We could show hematopoietic precursors that are in these embryoic bodies.

Let me show you this type of an example as well. There are ways of treating these cells in culture where you can enhance or select-we would hope some day to direct the type of differentiation. But at this point it doesn't occur. But we can derive cultures in which we see predominantly neuronal type structures. It is also possible and it can show that these are neurons that are stained with an intermediate filament that is specific for neurons. We can also show that it's possible to derive erythroid cells. This is part of the hematopoietic lineage or macrophage out of these, but it's at a very low frequency at this point. We don't know, to be honest with you, whether you are, as I say, enhancing or nudging, whatever the proper term is. And as Dr. Varmus pointed out, the key now is to work out those conditions where we can get all of our cultures to form myocardiocytes and neuronal cells, specific neuronal cells, hematopoietic lineage, etc. to make this work.

Now let me go back, if I may here, to where we see or where I see, this going. Initially, we're very interested in studying aspects of early embryogenesis. We're interested in deriving lineage-restricted stem cells. Now part of this, and you have to think conceptually, is if you want to transplant something, there are certain tissues you can do it as a differentiated state. There are other ones that you'd like to have a lineage-restricted stem cell so that it could continue to divide, integrate, etc. There is evidence in doing it both ways. And then to the issue that if we get into that, what do we look to do with transplantation therapies? We had a discussion already on the issue of how you would manipulate those cells, if possible, to generate the universal donor, which I

certainly feel is absolutely possible. We can talk about some of those issues, and I'll do that right now.

PROF. CAPRON: What about PSCs - primordial stem cells?

DR. GEARHART: Yes, one of the evolutions here is in terminology. Unfortunately, over several years different terms have been used to specify the same thing. It obviously reflects an old slide. Not old thinking, but an old slide. What we would envision would be to have ES or, slash, EG cells banked that could then, under specific conditions, undergo differentiation to myocardiocytes neural precursors, hematopoietic cells, and others that could then be collected and used in transplantation therapies. Now I mentioned to you one important aspect here is to get all these cells to go in that direction. I would tell you that in experiments that have been to date on the mouse, even when you have purities of 95 or 98 percent, if you transfer cells, you do run the risk of developing teratocarcinomas in situ. Cells that haven't been influenced are going to form small tumors and this has occurred in the nervous system and heart, cardiac system, etc. So we're going to have to get very good at this if we want to do the transplantation. The second is to get enough cells to do this. To really get a robust growth of cells, you're not going to be transplanting a few cells; you'd like to transplant millions. That's another issue. Up here we are suggesting that at this point, one could alter these stem cells to make them more like a potential patient. Or, as an example, to try to establish cell lines that would be universal donors that would not be rejected. And I thought, what Dr. Varmus brought up, was then introducing nuclear transfer into this idea to generate a cell line that would be a perfect match for a potential person requiring, or a patient that would require, transplantation therapy through nuclear transfer into nucleated adult oocytes and then generating embryonic stem cells from those. One other aspect that we could mention, and Dr. Varmus alluded to this, is that there may be properties of these embryonic stem cells themselves that we can take advantage of, and there is some evidence for this. At the cytoplasm within embryonic germ cells or EG cells, they have the capacity to reprogram nuclei. If that is the case,

then we can begin to think about generating cytoplasms and then fusing those with a cell of interest to see if we could then revert that back to an embryonic state. In my few minutes I just wanted to give you an update on this and I'd be happy to answer any questions on the technical aspects of our work.

DR. SHAPIRO: Dr. Gearhart, thank you very much. If it is at all possible or convenient to have a copy, not of the slides themselves but perhaps the printed version, we could distribute it to the Commission.

DR. GEARHART: I will provide that.

DR. SHAPIRO: Thank you very much. And if the Commission will indulge, I think we=ll hold our questions until we've heard from all three panelists and then go to questions. So let me now introduce once again Dr. Thomson of the University of Wisconsin.

DR. JAMES THOMSON: I'd like to spend several minutes just on this first slide. This is an example of the [INAUDIBLE] preimplantation development and I want to focus in on these kind of off-red, orange cells. I want to talk about the word "totipotent"; you've heard it used a lot. You've got to be very careful how you use the word. I think there's an important ethical distinction to draw between an entity that has the ability to form a child and an entity that doesn't. What I would caution against is the word "totipotency" to draw this distinction, because the word is simply not up to it, because it's used in different ways in different contexts and it means different things to different people. I'd like to illustrate this just by going through these stages in mammalian development and offer some definitions of totipotency. And you'll see that it has to be changed in significant ways so that you don't end up at the same place you started.

So let's start at the one cell. Clearly the one cell is totipotent because it

gives rise to a child and adult. Everybody accepts that definition. But even with using that, you slip something in that you haven't thought about very much, in that in a sense, a one-cell frog embryo is more totipotent than a one-cell human embryo, because if you put a one-cell frog embryo into some pond water it has complete ability to develop into a tadpole all by itself, whereas with a one-cell human embryo, you have to put it in a very specialized environment for this property of totipotency to become manifest. So let's modify it a little bit and say that for mammals, totipotency is a cell that, if you put it in an appropriate maternal environment, has the ability to form a child. So that's fine. Let's go to the two-cell stage. If you take these two cells and you separate them and you transfer them to a woman's reproductive tract, they do have the ability to form individual children. So these individual two cells are indeed, by this definition, totipotent.

I'd like to skip the four-cell stage and go to the eight-cell stage, which actually is not drawn here. At the eight-cell stage, each of the blastomeres is undifferentiated. That means they don't look or act like the cells in the adult body. They are uncommitted; that means they haven't even decided what they're going to be. And they do maintain the potential to form everything in the whole body. So they can form placenta, extra embryonic membranes, and all the cells that make up the body. Are they totipotent? Well, by the definition I just gave you, they're not. If you take an individual cell from the eight-cell stage and transfer it to a woman's reproductive tract, they're physically incapable of forming a child. It's a distinction that is not made very often, but I think it's a fairly important one. And the reason is that at the eight-cell stage, a single blastomere doesn't have a physical enough mass of embryonic stuff to get to its very first differentiation event, called a blastocyst. And if you culture one of these individual blastomeres, either in tissue culture or you transfer it, it makes an abnormal blastocyst, which cannot implant and cannot form a child. So I think this is an important distinction and I'd be very, very wary about using the word "totipotency" to make this ethical distinction about something that can form a child.

So let's go to the first differentiation event. All these events in human development occur in less than a week. And as these events are occurring, the embryo is traveling down the ova ducts and into the uterus. So by this stage called the blastocyst stage, the embryo is in the uterus. All of these orange-red cells are cells that have the ability to form any of the cells in the body, including the cells at the inner cell mass. However, at least in the mouse, the cells in the inner cell mass by the late blastocyst stage no longer have the ability to form this outer layer of cells, called the trophoblasts. They've lost that ability. If you take an individual cell of the inner cell mass or a whole clump of cells from the inner cell mass and transfer it to a uterus, they will not implant and they will not form an embryo. So they're not functioning by themselves in embryo. So the cells that we derived are from this inner cell mass. And what embryonic stem cells are, are cells that maintain this unique embryonic property of the ability to form all of the cells of the body. But they have another property that is not inherent in inner cell mass itself. One of the important things about these orange-red cells is that they are transient. At the blastocyst stage, within a couple of days these inner cell mass cells will be committed to very specific cell types, so they're not actually replacing themselves over a long period of time. They are an ephemeral population of cells. And because at least in the way we use the word "stem cell" in mammals, they have to replace themselves for long periods of time. In reality, these cells in the intact embryo do not act as stem cells. However, if you take this inner cell mass physically out of the embryo and you put it into appropriate conditions, it will self-replicate and maintain itself for very prolonged periods of time, and it maintains the ability to form all these other cells. It defines what a stem cell is. So to define a little terminology, at least for what I consider embryonic stem cells, the first derivation is from the preimplantation embryo.

When mouse embryonic stem cells were derived in the early '80s, there had been another kind of cell type, called embryonal carcinoma cells, that had been used for a couple of decades as a model to understand in vitro differentiation. These were cell lines derived from germ cell tumors. And at the time that these blastocyst-derived cell lines were derived, it wasn't really known how different they were from embryonal

carcinoma cell lines. So people coined a new term, primarily saying "embryonic derivation." So the source of the cells was important. Later, when people derived embryonic germ cells, they took the same line of naming and they called them embryonic germ cells primarily to distinguish the source, even though the cells might be indeed quite similar between embryonic germ cells and embryonic stem cells. Embryonic stem cells should be capable of prolonged proliferation, self-maintenance- and indeed we feel they're probably capable of doing this indefinitely - and should be able to derive derivatives of all three embryonic germ layers. These are the basic three parts of the body plan. And they should be able to maintain this developmental potential over prolonged periods in culture.

The reason we were successful in deriving these cell lines in the human is we started with an animal model that was closer than what other people had used previously. And actually, one specifically, at the University of Wisconsin, derived these cell lines in primate species because they had a good reproduction and development department there. In 1995 we reported very similar cell lines from the rhesus monkey and in 1996 from the common marmoset. And primates are divided between old world and new world species. It's the basic divide between higher primates. And the evolutionary distance between the rhesus monkey and the human is actually much less than between the marmoset and the rhesus monkey. For this reason, we thought that because we were successful both in the old world species and the new world species that the same techniques would likely be working for the human. It turned out to be the case. The reasons we moved to the human were several-fold. One is that although these primate stem cells do offer a fairly accurate model for understanding human development, they are imperfect because there are differences between monkeys and people. And second, it was obvious that there were therapeutic applications that we could do with the human cells that we physically can't do with the primate species. At the time we started moving into considering doing the human work, we tried to look for some kind of guidelines or oversight of what was ethically acceptable to do with this. And the best thing at the time was the 1994 NIH Embryo Report. We followed all the

guidelines with respect to deriving embryonic stem cells that were suggested in that report. The important one was that the embryos that were used in the study were derived from in vitro fertilization. They were left over for clinical purposes. They were not specifically made to derive cell lines. The embryos were not wanted by the couples any longer and consent was obtained specifically for deriving embryonic stem cells - a very detailed informed consent process, the protocols reviewed by the IRB prior to us doing this work.

This shows a schematic of how the cell lines are derived [INAUDIBLE] from the inner cell mass specifically isolated from the embryo. Once the trophectoderm is taken off the blastocyst it's no longer an embryo.

The inner cell mass does not develop into an individual. The inner cell mass is cultured on feeder layers that produce factors that have not been identified [INAUDIBLE] and periodically the cells will split in two.

This simply shows the morphology of our cell lines. This is an already established cell line [INAUDIBLE]. As John [Gearhart] mentioned, there are a series of markers that historically have been used on human embryonic teratoma cells that have been used for the last 15 years or so. And without going into the details of the markers, one thing I will point out is that the markers' position in human ES cells and mouse ES cells are vastly different, [INAUDIBLE].

The karyotypes in the [INAUDIBLE] cell lines can be divided into all muscles [INAUDIBLE]. We have one cell line that is in culture now that continues at the [INAUDIBLE]. It's a remarkable new development.

Without going into detail, the [INAUDIBLE] cells express extremely high levels of telomerase, and what's good in this as a marker that mortality will improve [INAUDIBLE].

Now John mentioned that there are other ways to induce cells to differentiate. One is to just culture madly; if you just let them pile up over each other they'll spontaneously differentiate, all [INAUDIBLE]. But one way to demonstrate it is [INAUDIBLE] into a mollusk that doesn't have an immune system, and they form a disorganized mass called a teratoma. And within the teratoma there are examples of [INAUDIBLE]. I'll just take you through a few of those.

These are examples of mesoderm. The mesoderm examples include bone, and associated with this [INAUDIBLE] bone are hermatopoietic bone marrow elements. Kidney - these are fetal glomerular tubules and nephrogenic mesenchyme. Striated muscle - there's striated muscles, smooth muscle, cardiac muscles, cartilage. Embryonic ectodermCthis is neural precursor cells. It's actually a very primitive state, but these will give rise to neurons, glial cells, later in development. We also have examples of skin and hair, which I don't have a picture of. And endoderm - there is good gut structure, which is the third basic of the germ layers.

So why are these cells important? It's also been alluded to by the other speakers, so I won't go into detail. But I think in the long scheme of things, the real reason is because it gives us this wonderful new model to understand human development. Basically, everything we know in the early postimplantation period is based on analogy to the mouse, because you can't actively, directly study the embryo in this period. And the mouse is simply quite different. If you're not an embryologist and you simply look at this diagram, these represent similar developmental stages in the human and the mouse. As you go back and forth between, say, the yellow tissue and the yellow tissue, they look dramatically different. That's part of the yolk sac. It turns out that some of these differences are clinically relevant. So if you're interested in implantation, infertility, birth defects, it makes a lot of sense to have a human model. These cells give us an in vitro model to understand these events, for the first time in some cases. As has also been alluded to, these cells give people an ability to screen for

new drugs. You can imagine making purified populations of heart muscle cells, for example, and screening tens of thousands of potential drugs. Look for a very specific effect and just pick up the two or three that look interesting for further study. It will certainly speed up drug discovery. Also, you can use these cells for looking for toxic compounds or compounds that interfere with normal development: teratogenic compounds. And we can find new genes that could be potentially useful for regeneration therapies. And finally, where there's more interest but it's more of a long-term goal, is that these cells potentially can be used for transplantation therapies.

Basically, all human disease is based on the death or dysfunction of cells. And if the death or dysfunction of cells is based on just one or a few cell types, it's at least possible to envision deriving those cell types from human embryonic stem cells and using them for transplantation therapies. Examples that are usually noted include Parkinson's disease, where a very specific neuron is defective; juvenile-onset diabetes, with a specific cell in the pancreas, and leukemia, where there is a specific malignant cell that has to be replaced. I think I'll end on that note and open it to questions from the Commission.

DR. SHAPIRO: Thank you very much. Let me also request if we could have a copy of some of the slides on paper; that would be very helpful to send to all of the Commissioners. Now, let's turn to our final person on this panel, Professor Smith. And let me once again thank you for coming such a long distance to be with us today.

DR. AUSTIN SMITH: I'm not actually going to talk directly in detail about the work that my lab has been doing on trying to develop human stem cells because I think it would be redundant, really, in light of what we've heard from Jamie [Thomson] and John [Gearhart]. I'll simply say that for the last few years we've been pursuing exactly the protocol that Jamie has described with the same kinds of analogous ethical and legislative procedures, which I'll talk about in the end: the rules that apply in the [United Kingdom] (U.K.). I think that the achievements that John and Jamie have

made in deriving pluripotent stem cells in humans open up an unparalleled opportunity in human medicine, which is to develop therapies based on tissue regeneration using, ultimately, our own cells. So what I'd like to do for you now is just kind of overview and also present some of the challenges that we're going to be faced with, which ultimately is, to my mind, the justification for why this area of research needs major funding and public funding and public accountability. Pluripotent stem cells and cell therapy: the potential of this area is, first, that a stem cell source gives us an unlimited source of cells - numbers of cells. Transplants, in most cases, mean billions of cells. So we would have a renewable source of cells. Pluripotent stem cells can generate multiple cell types, so this principle is a broadly applicable technology. Something that hasn't been mentioned so far today is the potential of stem cell transfer to act as a method for delivering gene therapy. One of the major problems in gene therapy is: How do we get the genes, the corrective genes, into the dysfunctional tissue? Stem cells provide a source we can use to deliver corrective genes. Ultimately, the way to deliver cellular therapy is to have an autologous system where we use our own cells. And the ideal way to do this, although one can think of ways of approaching this by genetic manipulation, ideally we want to derive the stem cells from the patients themselves by somatic cell nuclear transfer. So in the mouse system we can think all of these things as really being achievable, and we can do experiments to test all of these things. The issue is how near are we to doing that in the human, and will it be straightforward to transfer what we can do in the mouse to the human situation?

So this is the scenario that we're aiming at: we have a patient who needs a transplant, say for Parkinson's disease. We could take a skin biopsy from that patient, take the nuclei or nucleus from out of the skin cells, transfer that into an oocyte, reprogram it, and develop it to the blastocyst stage that Jamie has shown you, from which we could isolate and propagate stem cells, differentiate those cells in vitro to derive the new neuronal cells, the nerve cells - in the case of Parkinson's, particular nerve cells, dopaminergic neurons. We could then transplant the patient. We should have no immune rejection problem. So the challenge that's facing us then is to make

this real. How long will it take? How much will it cost?

Just to give you a quick overview of the types of areas in which this technology could be applied. In principle, there are many areas where we could think of cell-based therapies playing a major role: tissue reconstitution and cardiovascular repair. As an alternative to having to do organ transplants, one can think of repairing damaged or diseased tissues in situ by introducing cells by keyhole surgery, for example, fracture repair to regenerate new bone. Arthritis - a major disease imposing a major economic burden. We have a tissue source to generate new cartilage, then we can think about ways of alleviating arthritis. liver damage. leukemias, and cancers. All through hematopoietic stem cell transfer, which is already used clinically. But one of the problems with the hematopoietic stem cell field is that despite 20 years or so of research and major funding, we still cannot grow hematopoietic stem cells. We can isolate them; we can't grow them. We cannot genetically manipulate them. The ES cell roots may provide the opportunity to do that. Some areas where gene correction and gene therapy could be combined with cell therapy: muscular dystrophies, wasting diseases of muscle. Diabetes we've already heard about. Thalassemia is another congenital disease of the blood system. [Acquired immunodeficiency syndrome] (AIDS) - one could think about the possibility of reconstituting the hematopoietic system with cells that are engineered to be resistant to the AIDS virus. Liver functionCthe liver is a potentially major target for delivering gene therapy for products that can even be secreted. And so if one can introduce liver cells that have been genetically engineered, again, this could be used to treat a variety of conditions.

Probably the area in which one might want to - certainly I would envisage that we would first see the application of stem cell therapies - is in the nervous system, and in the area of neurodegenerative disease in particular. Parkinson's and Huntington's diseases - certainly in the case of Huntington's disease, there really is no available therapy at present. There are trials in Europe that indicate that transplantation of fetal neurons derived from elective terminations can have some therapeutic benefit in

these patients. But the problem there is that one requires a large number of fetuses to get enough cells for transplant. The cells that you transplant are a mixture; they are an undefined population. We have a renewable stem cell source, then we can generate millions of cells that we need for transplant and we can, in principle, know exactly what they are, what stage they are, and that they are the appropriate cells to transfer. And one could extend that, then, to think about how one might treat other diseases, perhaps again with a combination of gene therapy to introduce protective factors that would limit the ongoing cell death to treat things like Alzheimer's. We could think about replacing cells following ischemic lesions in strokes. And one can also think about the possibilities of treating spinal cord injury. So these are our dreams, if you like. But if we are to make any progress here, then there are some major scientific issues that need to be addressed. If we're to produce the large number of cells that we need for transplants, then we have to have a robust system for growing human stem cells and maintaining them in a non-transformed state. We have to think then about how are we going to measure that state. In the mouse system, that's relatively straightforward because we can test the potential of the cells by making chimeras of them and introducing them into embryos. That's not something one would consider in the case of human cells. We need, as has been alluded to, to understand how to control the differentiation of these cells, how to get them to make the cells that we want to use. We need to understand how to genetically manipulate them. Now in many ways this is the area where we're most advanced. [Deoxyribonucleic acid] (DNA) engineering is now relatively straightforward, but there are still some issues about whether the human stem cells will be as manipulatable, as permissive for homologous recombination as mouse stem cells are. Actually, we don't know anything about them at present - and nuclear reprogramming, which is the ultimate way to deliver this medicine. My view on nuclear reprogramming is that we know from Dolly the sheep and Cumuli the mouse that it can be done. But actually we don't know anything really about how or why. This is just a complete black box in current science.

So I'm just going to talk very briefly about these first two issues: stem cell amplification and direct differentiation, to the issue of amplifying and expanding the

stem cells, growing them in large numbers. This basically involves maintaining the cycle of self-renewal, propagating the stem cells in an undifferentiated state where they remain pluripotent so that every division produces exactly the same cell again. I do believe that we have to be doing two things. We have to be preventing the cells from differentiating, in this case; we don't want to lose them through differentiation. And we also have to be keeping the cells alive, preventing them from entering the programmed cell death that Dr. Varmus mentioned. Now what we know from the mouse ES cells is that we can maintain a self-renewal cycle using a growth factor that's called LIF. And there's a small family of growth factors that act in the same way. We know from work in my laboratory and several other laboratories how this works. It acts through a particular cell surface receptor and a signal transduction pathway and there's a particular transcription factor at the end of that. What we don't yet know is quite how activation of that pathway and that transcription factor determines that this remains a stem cell. More significant, in the context of the work from Jamie's lab in particular, we don't know. The suggestions from Jamie's work is that in the human stem cells this pathway may not be operating. So the question then is, for the human cells, are they using some alternative pathway? And if so, what is it? Or are they using this pathway, but in a cryptic way that we haven't yet identified? This illustrates, I think, that the basic issue here is whether human stem cells are really going to be the same as the mouse stem cells. And if they're not exactly the same, can we make them the same by understanding more what the mouse cells are? Because it's the model-everything I've told you up until now is based on what we know and what we can do with the mouse cells. The issue is, Will we be able to do the same in the human cells? Even at this very basic level of what makes them grow there seem to be some differences. The second issue that I'm just going to touch on is the issue of directed differentiation. What we show here is that we can make blood cells, nerve cells, lymphatic cells, myogenic cells, cardiac cells, endothelial cells-a whole range of cells from mouse ES cells. What's masked in this little diagram is that the way we do that is through making the embryo body structures that John mentioned. And in that we get a mixture of everything and they're all mixed up together. So we don't get just the cell type that we want and, as

John also alluded to, within that we still have some undifferentiated stem cells. This is a major problem, because if we're wanting to transplant neurons into a patient to treat Parkinson's, we don't want to stick in blood cells and cardiac cells. Most important, we don't want to be introducing any more stem cells, which could start to grow and generate teratomas, even malignant teratocarcinomas. So we need to understand the basic embryology, the inductive signals that are used in the embryo that instruct the development of different lineages and cell types. And we also need methods that will enable us both to reproduce that in culture and also, since that's probably never going to work 100 percent efficiently, other methods that will enable us to pull out just the cells that we want.

I'm just going to briefly illustrate a technique that we've been working on for isolating a particular cell that you want, a method that's probably generally applicable. We have been interested in isolating from mouse ES cells neural precursors - precursors of the nervous system with the aim of then using those cells to investigate their potential in mouse models of Parkinson's disease. As I've said, the problem is that you generate a mixture of different cell types when you make the ES cell differentiate. So that's what's shown on the bottom here; we can ignore the top part of this. In blue is the neural stem cell, the neural precursor cell that we're after. And there are other cell types present. Basically, because we don't know how to make, how to significantly increase the proportion of these cells in the culture, we don't know what the real signals are that tell the stem cells to become nerve cells. All we can do is make the mixture of cells. But then, if we could genetically tag a gene that is expressed only in a neural stem cell - say a gene that has been identified from work on early mouse development that we know is expressed only in cells of the early developing nervous system and not elsewhere. We can, by genetic manipulation, by homologous recombination in the ES cells, introduce into that a marker gene that subsequently allows us either to physically separate using a cell sorter or to select with an antibiotic to remove all of the other cell types so that we end up with a pure population of neural

stem cells. And this is important for a couple of reasons. First, most cell types actually will grow - many cell types will grow better in the absence of different cell types. They'll grow better on their own provided you've got the right cocktail of factors around. And this provides a basis, also, for expanding them, for getting a pure population of cells for applications such as drug screening or understanding how genes function and develop. But it also then gives us a pure population of cells that no longer contains stem cells or other cell types that we could use for transplantation.

And this is just to show you that you do get a pure population, initially of neural precursor cells that we can expand as precursor cells. But we also then allow those cells to differentiate. What we see here, what is shown in green, is immunostaining for a marker that's expressed only in neurons. And the yellow staining here is DNA staining, so that will stain also. So what you can see is that every single cell here is differentiated into a neuron, and we've got rid of any of the other cell types contaminating the dish. So there is, if you like, a demonstrated method, then, for purifying populations of cells from mixed cultures. However, there are still many questions remaining. We have some evidence now that these cells are all transplantable and that we don't get tumors arising. But this is still a mixed population of neurons. We don't really know what type of neuron would generate. We don't yet know whether we can generate the dopaminergic neurons that you specifically want to treat Parkinson's disease. We don't actually know whether the best way to do that is to transplant the cells and let the host's nervous system direct them or whether we should be doing it in culture first. There are important issues to continue to address here.

Finally, I thought I would just touch on the situation in the U.K., which might be of interest to this Commission. In the United Kingdom, work and clinical practice with human embryos is covered by the Human Fertilization Embryology Act that was passed in 1990 in response to the development of in vitro fertilization. And Parliament recognized the benefits of medical and scientific research and therefore permitted licensed research up to 14 days. So you can work with an intact embryo up to

14 days from fertilization. These embryos that are donated with informed consent are not created for research, but are surplus embryos from IVF programs then, the same way that Jamie has described. To be able to conduct such research you require a license. It's a legal obligation that you have a license from the authorities. You have to have an agreement with a licensed clinic in the U.K. You have to have ethical approval from your local health board and the process of granting a license includes a scientific peer review. The Medical Research Council and other government funding bodies that could be considered analogous to the NIH can induce support for research projects that have appropriate IRB approval. So all the work that I do on human embryo research is supported by the Medical Research Council in the U.K. The situation on human cloning in the U.K.-there's been a major consultation exercise going on in these last 12 months, which has now been completed. A report has gone to the government that recommends that reproductive cloning, cloning to make a human child, should be expressly outlawed. The current situation in the U.K. is such that it would never be licensed anyway, but the recommendation is that it should be specifically prohibited in law-but that research into the therapeutic applications of cloning, specifically the use of somatic cell nuclear transfer to generate cells for transplantation and other biomedical research applications, should be approved. So this is currently being considered by the government, and the scientific community certainly is hopeful that this will be approved.

I think finally I would just like to say that in my view the potential of this area makes it unthinkable not to proceed. I've tried to indicate that there are some really major scientific challenges here. The implication of this is that this is going to require a major multidisciplinary and multinational effort. And in my view of the funding, therefore, there will be private funding in this and that should be welcome. But the major funding should be public. We need to bring the most talented people into this area as quickly as possible, and I think we also need toCthe research has to be seen to be publicly accountable and conducted in a publicly responsible manner.

PROF. CHARO: Thank you very much, Dr. Smith. It's five until 11:00,

which means that we're running about 25 minutes behind schedule. Why don't we take roughly 15 minutes or so to have a discussion and we'll take our break a little bit late, okay? Questions from the Commissioners? Bernie, then Alex?

DR. BERNARD LO: I want to thank our three guests for their presentations, but I want to ask each of them to comment not on the scientific issues, which you laid out so nicely for us, but on the policy implications. Could each of you say what in your view is currently lost by the absence of NIH funding for stem cell research, and the converse way of asking the question is, What would we gain by having public NIH funding for this line of research?

DR. GEARHART: This is certainly something we've talked about a great deal. Our research, as you know, our research approach has always been eligible for Federal funding; we just didn't seek it. [INAUDIBLE.] We proceeded on endowment funds and then in the last year we've had a corporate sponsor. Corporate sponsors bring with them licensing agreements in which the material is [INAUDIBLE]. I think my understanding of some of the variables we're addressing is [INAUDIBLE], but I think it is one of the issues already. Also, I think it constitutes a perception that by not having public funds that something is wrong. If we can demonstrate that there are clear benefits of this, why can't we have public funding for it? [INAUDIBLE.] And I'd like to build immediately on the final comment that Dr. Smith made, which was that with public funding, you can bring very good investigators very rapidly into this arena, and they can use NIH-sponsored research labs to conduct experiments. I believe we should have those people who are looking at neural differentiation in the dish - they should be doing this. [INAUDIBLE.] So I think for all those reasons [INAUDIBLE].

PROF. CHARO: Would either of the other two of you like to comment on that?

DR. THOMSON: I think NIH oversight is terribly important.

[INAUDIBLE.]

PROF. CHARO: Alex Capron, your question?

PROF. CAPRON: I have a question for Dr. Gearhart I wanted to ask. At the end of your presentation, I believe, if I was following you, that you alluded to the potential for transfer of nuclear material into embryonic stem cells as opposed to into an egg itself. [INAUDIBLE.] I thought that you hadn't gotten to that point in your description of what might happen. In that case, what is the potential? Do we have either mouse research indicating the ability [INAUDIBLE] a cell that functions as an embryonic stem cell with new nuclear information?

DR. GEARHART: That's certainly the hope. The information does come from the mouse side. And to be able during cell fusion [INAUDIBLE]. There are some problems here, including some technical ones. The various cytoplasms associated with EG cells [INAUDIBLE].

PROF. CAPRON: When you speak of fusion, is this fusion in which the nucleus [INAUDIBLE] the embryonic stem cell remains pluripotent?

DR. GEARHART: That's correct. In these experiments it remains.

PROF. CAPRON: So you wait it out.

DR. GEARHART: [INAUDIBLE.]

PROF. CAPRON: They're binuclear?

DR. GEARHART: Binuclear. [INAUDIBLE.]

PROF. CAPRON: I don't know if anybody else wants to comment on

[INAUDIBLE] Dr. Gearhart.

DR. THOMSON: [INAUDIBLE] in the research; the cytoplasms [INAUDIBLE]. These cell fusion studies have suggested [INAUDIBLE].

PROF. CAPRON: Obviously, part of the reason goes to the point that you have gone over with your slide of the yellow-orange cells. And you skipped over the [INAUDIBLE] to turn to the four-cell stage. Obviously, part of what you said about totipotency was that it depends on what you mean by the term - and the differentiation between a cell being able immediately, on its own like a frog, to generate the organism versus the correct environment.

Going back to the four-cell stage, were a four-cell embryo - the wrong term for it, but a precursor - split apart, is there research indicating that in humans you could then get the cycle going again and begin cell division to the point that you can get the blastocysts, etcetera?

DR. THOMSON: I'm not aware of any reports that it works in human cell division.

PROF. CAPRON: And when you go to the eight-cell stage, this is the point at which you said that you thought we ought not to seek a totipotencyC

DR. THOMSON: Let me just play out that embryologists seek totipotency [INAUDIBLE]. They need something very different with that in a single cell [INAUDIBLE].

PROF. CAPRON: Well, do they mean that a single cell could not be implanted to become a human child, or do they mean that a single cell could not go through the process that we were just discussing with the mouse? Obviously, as you

say, it hasn't been done with humans.

DR. THOMSON: There's no direct way to make embryonic stem cells become an embryo.

DR. CAPRON: Even with a mouse?

DR. THOMSON: Yes.

DR. CAPRON: So that the line that you would be drawing would then be between four- and eight-cell?

DR. THOMSON: That would be correct in the mouse.

DR. CAPRON: Why is it that the term totipotency is used rather than pluripotency for those eight-cell?

DR. THOMSON: Well, it's an inexact term, but embryologists tend to use it in a way that—if a cell can become another cell [INAUDIBLE]. Some people don't think that's an appropriate condition, so that's [INAUDIBLE].

DR. CAPRON: Then how is "pluripotent" being used?

DR. THOMSON: As something less than that.

[Laughter.]

PROF. CHARO: Carol?

DR. CAROL W. GREIDER: Just a little follow-up on Bernie's question about public versus private funding. And you both, Dr. Gearhart and Dr. Thomson,

were saying that they were funded through private sources. And there seems some discussion here today about the possible future use of ES cells, one of them being directly making use of only those cells that are already derived as opposed to deriving new ones. So one of my questions is about the actual accessibility in the specific but also in the general area. I know that in my own work I've run into a number of cases [INAUDIBLE] that usually come with private funding, and I [INAUDIBLE]. I don't want to say anything negative here. But there are various vast interests among material transfer agreements some of which actually make it impossible for some of the investigators to use materials because their institution will not sign a particular material transfer permit.

So one of my questions is, Have people asked you for your cells and what is the success rate for people to be able to obtain and get their universities to sign the material transfer permits?

DR. THOMSON: We sent out a [INAUDIBLE] about three or four years now and we've had quite a wide range of investigators asking the same company that funded [INAUDIBLE] commercial leases [INAUDIBLE] that we didn't agree with all [INAUDIBLE]. They're not registered for human embryonic stem cell [INAUDIBLE] funding situation, and we have a very large staff of investigators wanting to make sure that [INAUDIBLE]. The licensing agreements announced [INAUDIBLE].

PROF. CHARO: Tom, then Steve.

DR. THOMAS H. MURRAY: Thanks for coming. Forgive me if the question turns out to be based on faulty premises, but I understand that in the human body there are a variety - in our bodies there are a variety of stem cells that one can find: hematopoietic stem cells, and just recently it was announced, stem cells in the brain. Is that correct?

DR. THOMSON: That's correct.

DR. MURRAY: Would it be a viable, at least in principle, a viable therapeutic strategy to find ways to isolate those stem cells from the individual, say in need of a transplant, then perhaps - building on the sort of work that you're doing - learn how to in fact grow those stem cells in such a quantity that they could then be useful for retransplantation to the individual? So I guess the question is: (a) Is that a plausible - granted it's quite farfetched - but a plausible strategy, and (b) In what ways might your research, the kind of basic research that you - re doing, provide some foundation for that?

DR. GEARHART: The question is well taken, Dr. Murray. We are not proposing this as a single approach for using embryonic stem cells. And it is exciting to see that more stem cells are being found in, for example, the central nervous system. And we can clearly find ways of isolating them, of stimulating them specifically to grow and to differentiate in certain cultures, research that should be pursued. Nor am I saying we shouldn't worry about the [INAUDIBLE], certainly. There are a number of options, and we should pursue them all.

How does our work feed into this? Most of our work is dealing with much earlier stages of cell development or differentiation. We would like to know how we would get, for example, from embryonic stem cells or many different cell types to those that are present in the central nervous system. So I see a value there and I see an interplay in many of these areas that we talked about with stem cells. I showed you examples of hematapoietic stem cells. Yes, they can be isolated in marrow. There are very, very few in the present. Here our argument would be that we can generate a lot more of them in an altered condition than we could isolate [INAUDIBLE] in the individual.

So I think there are issues of some number here, and there are targets -

therapeutic targets - so that each of the alternatives may be better than none. That would be my answer to your question.

PROF. CHARO: Dr. Smith, you have been shaking your head as Dr. Murray was talking. Did you have anything to add?

DR. SMITH: No, no. I think it's a very good question. The only point I would add is that, and I think Dr. Thomson did very well on this issue, is that the absolute approach isn't very complementary. There is one biological stem cell reality, and there seems to be increasingly a notion that there are stem cells in many other tissues. But it is not yet clear at all whether those cells really [INAUDIBLE] function. People have been pursuing the human embryonic stem cell for a long time [INAUDIBLE]

But it is possible that there's something fundamentally different about the biology of stem cells in the early embryo. Its primary function is to grow to generate tissue as opposed to [INAUDIBLE] in the stem cells, which is very tightly constrained. Essentially, it doesn't want those cells growing to any significant expansion. And that may be a situation that's not easy for us to overcome. So it may be the best we can conceivably do is to start out on the early embryonic stem cells and then generate the cells [INAUDIBLE].

PROF. CHARO: I have Steve and Eric on my list, and then Rhetaugh, then Patricia. And that, I'm afraid, will have to be it because we're running so late. Steve?

MR. HOLTZMAN: I wanted to follow up on Alex's question about the [INAUDIBLE] sources were stretched. To the best of my recollection, the nonhuman primate work was NIH-sponsored?

DR. THOMSON: Yes, it's licensed.

MR. HOLTZMAN: Was NIH sponsored. In terms of the license, the University of Wisconsin's with Geron is identical to that which also is associated essentially with that associated with [INAUDIBLE] sponsor on the nonhuman primate.

DR. THOMSON: I believe that's correct.

MR. HOLTZMAN: And that the patent application that was filed in the nonprimate study would include [INAUDIBLE] primate, including almost all primate ES cells.

DR. THOMSON: Yes.

MR. HOLTZMAN: So, importantly, any restrictions intervening in the way of the research, if any, are with patents or MTAs not publishing the source of the funding.

DR. THOMSON: But it could be.

MR. HOLTZMAN: It's not.

PROF. CHARO: Eric?

DR. ERIC J. CASSEL: As to the advantage of public funding, several of you have mentioned the oversight function of the NIH. Could you expand on that, please-what you mean by the oversight function and what you think it would do, or does do, or could do that is not present otherwise?

DR. GEARHART: I think a few issues are important. One is to assure

that the cells are available to the investigators who can use them. Importantly, Dr. Varmus brought up an issue that we are concerned about, and that is, Will this type of work lead to a greater demand for either spare embryos for investigators to pursue, or greater demands on fetal tissue for therapeutic transplanation. And perhaps when is enough? Because in a tissue bank, if this turns out to be a viable alternative to doing transplantation therapies, how much tissue actually has to be provided? I'm not so sure that we gain any mandate from the research side. But I think these rules the NIH can certainly handle by oversight.

There's also purely clearly a concern about human tissue that has the geneticists offering the potential. What ways are being looked at to make sure that we're not trying to turn this into human beings in a way where it is possible. But by having this open forum at the NIH in development of policy and carrying out and reviewing this work, I think a lot of these concerns would be addressed, and I would hope a lot of people would raise those issues.

DR. CASSELL: Dr. Thomson, Dr. Smith, do you want to comment, too?

DR. THOMSON: I guess from the investigator's point of view, we just want a set of rules for what's appropriate and not appropriate, what's ethical and what isn't ethical. Right now, it's [INAUDIBLE] and my guess is you're right to associate it with a university. You can do basically what you want to do at a university but I don't think that's appropriate. The NIH is involved in funding [INAUDIBLE] research and they have very is specific guidelines. Even if they don't [INAUDIBLE] theyre still under pressure to use the same guidelines.

DR. SMITH: I think there's actually [INAUDIBLE] In my position in the U.K., that would be the Medical Research Council's primary responsibility because it's very important. First, it makes it clear that this is a legitimate scientific endeavor, which means that it's really open to the rest of the scientific community. And what goes with

that, they say in the Research Council, and I presume it's the same at the NIH, is you have to prove that [INAUDIBLE]. You're also perfectly accountable. So we're saying you're protected as an individual because you've gotten the endorsement or approval for the science that you're doing. But it really is critical for this [INAUDIBLE] because it will be enormously challenged [INAUDIBLE].

PROF. CHARO: Rhetaugh, and then Trish.

DR. DUMAS: I'm really very impressed by the value and the potential benefits of this type of research. Would you say something about the downside? What do you foresee the potential risks and harms that might be anticipated were the Federal support significantly expanded and committed?

DR. SMITH: The downside if Federal support is increased?

DR. DUMAS: Yes.

[Laughter.]

DR. CHILDRESS: Let the record show that he's staring.

DR. DUMAS: Is that an unreasonable question?

DR. SMITH: Well, the only downside I can see is that [INAUDIBLE] will increase and it might do all kinds of [INAUDIBLE].

[Laughter.]

DR. DUMAS: Would you not concede that there are any potential risks or harms that could result for the research enterprise or the society in general from wide-scale expansion of this type of research with public support?

DR. SMITH: I guess there are two. One is the risk of developing inappropriate regulations [INAUDIBLE]. But really I don't see any. There seems to be a kind of [INAUDIBLE] on the goals, but I don't see a downside except for the possibility of raising people's expectations, which we can't deliver on because we are quite a long way off. There are big question marks that we need to solve. So there is a possibility of unduly raising people's expectations. And, also we at some stage, again, if there aren't appropriate regimes in place, maybe where we might [INAUDIBLE].

PROF. CHARO: Trish, you have the final question.

PROF. PATRICIA BACKLAR: I'm wondering if Federal funding does not become available for this research, or even now, if there might be a sort of reverse brain drain and people from America will be going to do research in England. Is that true now?

DR. THOMSON: I don't think it's true now, but it could happen.

PROF. CHARO: Okay. I'd like to thank you very much for having come all this way and taking so much time. It's very helpful.

It's now 11:15. We're about half an hour behind, so I would like to suggest we make the break 10 minutes instead of 15 to try to make up a little bit of time. We'll start promptly at 11:25.

Two quick announcements. If you haven't handed in your lunch form and you're here at the table, please do so at registration. And if you're a member of the public who would like to testify, please sign up with Pat [Norris] at the registration desk. I'll see you in 10 minutes. Thank you.

MEDICAL APPLICATIONS AND CLINICAL ISSUES

PROF. CHARO: May I have your attention, please? Unfortunately, our microphone system is not working. I'd like to start now with our next panel. Dr. [Gary] Hodgen seems to have been delayed, so we'll begin first with Mr. Perry, who is executive director of the nonprofit Alliance for Aging Research. Mr. Perry, thank you very much for coming. Please.

MR. DANIEL PERRY: Thank you very much, Madam Chairwoman and members of the Commission, I appreciate the opportunity to be here today to discuss the discoveries involving human embryonic stem cells. I'm here to provide a view of some of the clinical and ethical issues on human stem cells that reflect the thinking of my organization and that of many other groups of health care consumers and patients who may one day benefit from this research.

I wish to begin by applauding the important and historic statement made here today by Dr. Harold Varmus. The director of the National Institutes of Health has conveyed the opinion of the Clinton administration that research on pluripotent stem cell lines is clinically and ethically a different proposition than currently prohibited direct experiments on human embryos. It's vitally important that the view expressed by Dr. Varmus today prevail in Federal policy. If that view does prevail, it is likely that many of the best prepared and best equipped research scientists in the nation will move quickly to begin revealing new insights into human cellular biology made possible by some of the most important studies of our time. Americans and people everywhere will be well served if public as well as private funding becomes available to advance understanding of fundamental biological mechanisms by looking through the window opened by human stem cells that rejuvenate and retain the ability to become any cell in the human body. As the head of a not-for-profit group that is eager to find cures and preventions for the diseases related to the aging process and that is committed to overall better health and vitality for people as they age, my views are formed by the recognition of the

medical needs of the growing populations of older people.

The Alliance for Aging Research, which I support and represent, works to stimulate academic, governmental, and privately sponsored research into the chronic diseases of human aging. We anticipate that there will be concerns in some quarters regarding embryonic stem cells, which to date have been derived either from fetal tissue or from portions of donated in vitro-fertilized reproductive cells. However, it is the position of the Alliance, which I hope this Commission will share, that this research is too momentous, too large in its potential benefits, to impede, to stop, or to slow the thrust of current scientific inquiry.

The United States, along with much of the world, is experiencing a profound and wholly unprecedented demographic shift toward greater longevity for human beings. Every day in the United States another 6,000 people celebrate their 65th birthday. Meanwhile, America's baby boomers are entering their 50s in even greater numbers, about 10,000 a day.

In the decade between the ages of 50 and 60, the risks to the average person of being diagnosed with hypertension, arthritis, [microphone screech]-hearing disorders-

[Laughter.]

The risks of being diagnosed with aging-related diseases will triple between the ages of 50 and 60. In the next decade, the United States population over age 65 will double to more than 70 million people. As of today, the risks to those over 65 of being diagnosed with a chronic age-related disease doubles every five to seven years. If you add up the cost of just eight major diseases of aging-osteoporosis, stroke, depression, arthritis, diabetes, Alzheimer's disease, cancer, and heart disease-it approaches $600 billion in the United States every year. The incidence of these diseases

of aging and the costs of treating these diseases will not decrease unless new discoveries from biomedical research allow us to delay or prevent these debilitating conditions. Without making such discoveries and putting them to work for people as they age, the burden on Medicare and private insurance will be crushing as the baby boom moves into its high-risk years.

The alternative to aggressive pursuit of biomedical research is to let the population age under the same conditions as now exist and sit back and watch the diseases of aging and their associated costs grow exponentially. If in the absence of real breakthroughs from research we are left to rely on nursing homes and today's medications that treat only the outward manifestations of disease, we will surely overwhelm our financial and social resources in caring for a burgeoning population of disabled elders.

Fortunately, there is a wiser, less expensive, and more humane alternative to the path we are on. The alternative, and I believe proper course, is to encourage rapid advances and applications from our medical research infrastructure to hasten the discovery of the means to forestall the declining health status that we now commonly associate with old age. Even a brief delay in the onset of age-related disability translates into dramatic savings for our economy: We calculate that postponing physical dependency among older Americans by just one month would save the United States at least $5 billion in health costs and nursing costs. Postponing the average onset of Alzheimer's disease by five years would, over time, save $50 billion a year in health care costs. A five-year delay in the beginnings of cardiovascular disease would save $69 billion. These are just a few examples from a long list of potential savings.

But then we must ask: What kind of magic will it take to fine-tune the aging process so that we can eventually delay the ravages of age-related diseases by months or even years? Can people actually hope that diseases of aging might be put on hold? Is it reasonable to think that scientific understanding of aging at the level of cells

and genes might buy people several additional years of active life expectancy, with overall time of sickness and disability at the end of life reduced to a bare minimum? This is, indeed, the promise that is raised by the advances that are now emerging from many scientific disciplines in the field of human aging.

This research is being supported by universities, by government, by the pharmaceutical industry, by biotechnology companies, large and small, and by private philanthropy. Combined with better geriatric health management from the behavioral sciences and medical effectiveness research and better training of doctors and nurses in geriatrics, the benefits for today's aging population could be enormous.

Understandably, there was great excitement in recent months when the first reports of long-lived cultures of human stem cells were reported. These cells have the potential to become a full array of transplant material for people who cannot find suitable donors. This Commission has already heard the details of that research from the scientists involved, presented with great detail and authority. We understand that before the full payoff of stem cell technology is ready for patients it could take many years of further research and major technical hurdles must be overcome. It also will likely take millions, if not billions, of dollars to realize the full therapeutic potential. However, from the perspective of health advocates and patients, here's what we believe is in the offing.

First, we believe that stem cell technology will bring a deeper understanding by scientists as to how and why cells multiply, divide, grow, age, and die. Unraveling the processes by which cells form into different cell types with different functions offers a unique platform to understand and harness nature's mechanisms of cell development, tissue growth, and repair. This will advance the critical field of developmental biology and could be the basis of innovative new medical therapies.

Second, this technology could allow some to produce unlimited quantities of normal human differentiated cells in vitro. These laboratory cultures of

human cells then could be used for highly specific drug screening and testing for drug toxicology studies. This would be far more efficient and accurate than current testing and extrapolations taken from testing on animal tissues. Greater efficiencies in new drug development will mean more effective new medicines getting to patients faster.

Most promising of all from the vantage point of the patient is the advances that are likely to come in transplantation medicine. The potential therapeutic impact of human embryonic stem cells in replacing cells and tissues damaged by disease or aging is enormous.

We have heard from scientists close to this field that self-renewing cells and tissues derived from stem cells could conceivably replace damaged heart muscle cells that normally do not proliferate during adult life. Congestive heart failure is the single greatest cause of hospitalization among America's after-age 65 population, affecting some five million people. Another 1.5 million people in the United States each year experience a heart attack with damage to the heart muscle. About one-third of heart attack victims die immediately. Of those who survive, damaged heart muscle cells from an ischemic attack raise risk for later attacks and premature death. Transplants of cell-derived heart muscle tissue have already been performed on mice and dogs, showing exciting potential for replacing damaged tissue. Similar uses of stem cells and tissues for therapy for heart disease in humans seem very promising for the future.

Increasingly, medical researchers tell us that stem cells one day will be able to produce youthful cells that won't be rejected by the host and that could produce, for instance, dopamine - the brain chemical that is not produced in Parkinson's sufferers. Stem cells could be used to replicate healthy islet cells in the pancreas, and thus produce insulin needed by diabetics. Further speculation suggests applications of this technology to the relief of age-related blindness, atherosclerosis, cancer, spinal cord injury, Alzheimer's disease, and for the promotion of healing among many others. Despite the time and the money that it will take to realize some or all of these

applications, it is understandable that there is so much hope among patients and their families that there is such urgency that the research move ahead with all appropriate speed and support. To deny the opportunity for the benefit of this research to reach our older citizens as well as younger people with chronic diseases would be a tragic reversal of the dramatic recent biomedical progress and a great frustration of public expectations.

While some may oppose Federal participation in and financing of stem cell research, they must know that they cannot stop it altogether from going forward. A lack of Federal funding would affect only a segment of the overall research effort, albeit a significant portion of the total U.S. research initiative. Stem cell research will go forward in the United States using nongovernmental funding, and in other countries using both public and private funding.

The effect of a denial of Federal funding would be to deny government agencies, especially the NIH, the oversight we believe they should have. The bell of stem cell research cannot be unrung. It will continue apace in the private sector and will produce remarkable discoveries for the foreseeable future. If Federal government funding is available, then appropriate Federal oversight and review will be available, and this will serve to better manage the research while assuring that appropriate ethical guidelines are followed.

With increasing understanding of the mechanisms of aging and increasing interest in aging, continued support of this type of research is vital to the effort to uncover new discoveries that will increase the health and independence of the growing number of older Americans. If stem cell research is allowed to proceed with the guidance and oversight of the NIH and other appropriate governmental and scientific organizations, our society will be better able to develop much-needed cures for age-related diseases and conditions.

The vast majority of Americans strongly support the advancement of

biomedical research through the application of their tax dollars. Surveys consistently show Americans want to see greater efforts against serious and life-threatening diseases. That public support helped biomedical research advocates in Congress substantially increase this year's appropriated budget for the NIH. Many in Congress and many of us in the public are eager to see the NIH budget doubled over a period of five years. This is surely an audacious but vitally important national goal. These increases in medical research funding should be used wisely and without arbitrary restrictions.

Heightened opportunities to find new preventive and curative measures will be seriously undercut if inappropriate obstacles are placed against this enterprise for political or ideological purposes. And this is truly the answer to Commissioner Kramer's question earlier of what will be lost if this does not include Federal participation. We agree that policymakers, ethicists, scientists, and patient groups must continue to discuss and evaluate advances in science that increasingly will touch upon the fundamental mechanisms that create and define human life.

In the end, it is imperative that promising biomedical research go forward without inappropriate bars. The present dramatic breakthroughs in the life sciences and the profound implications of what we are learning will inevitably raise public concerns. But we are confident that most Americans will recognize that there could be nothing more unethical than impeding the effort to find help for those patients and their families in greatest need.

On behalf of the Alliance for Aging Research, I thank the Commission for this opportunity to present their views at this hearing, and I would be glad to respond to any questions you may have.

PROF. CHARO: Thank you very much, Mr. Perry. Would people like to ask some questions? Diane?

DR. DIANE SCOTT-JONES: Thank you very much for these comments. I have one concern about your testimony, and I looked over the list of diseases that you're concerned about, beginning with osteoporosis, and I understand your concern that there be research that would allow us to have, I guess, fairly easy ways to combat these. But aren't many of the diseases that you mentioned here ones that can be prevented by measures that people could take - lifestyle choices such as nutrition, exercise, and not smoking? Aren't there ways to prevent many of the diseases that you're saying we need this new technology for?

MR. PERRY: The increasing research is allowing us to understand the way bone is modeled and reabsorbed. It is teaching us how nutrition and exercise and other lifestyle interventions may help slow the loss of bone mass in postmenopausal women who are at greatest risk. However, we do currently experience some quarter of a million hip fractures in this country a year, at great cost. A quarter of those who suffer a hip fracture will not survive for more than six months. And half of those that do survive will not be mobile for the rest of their lives. It is a tremendous cost.

This research, as was stated in earlier testimony, holds the possibility of being able to create bone cells, bone growth factor cells, from stem cell research. So we both have to work on prevention as well as interventions when the disease or the event does occur.

PROF. CHARO: Alex, and then Steve, then Trish. Then that will have to be it. I'm sorry.

PROF. CAPRON: Is the Alliance for Aging Research independently or as part of a coalition now lobbying for either the removal of Section 511 from the public law that restricts the use of human embryos or the creation of human embryos for research purposes so that the kind of research we've heard about could go forward?

MR. PERRY: We have not taken that position as yet to remove the ban.

PROF. CAPRON: Could you tell us why you haven't?

MR. PERRY: We have not been asked to as yet. We have not—this testimony today represents our current thinking. We're applauding the statement today that stem cell research will be able to go forward in spite of the ban. We have not concluded that we will be taking an active position on removing the ban altogether. That is an option, but we have not made that decision as yet.

PROF. CHARO: Steve?

MR. HOLTZMAN: Well, it is effectively the same question. At the top of your statement you said that research on pluripotent stem cell lines is clinically and ethically a different proposition from currently prohibited direct experiments on human embryos. You advocate that we support Federal funding for it. But the fact of the matter is, and I think we all know it, is you're going to need embryos in order to make the embryonic stem cells.

Would your group be satisfied if this body came forward with a recommendation supporting Federal funding of embryonic stem cell research but not Federal funding of the derivation of embryonic stem cells?

MR. PERRY: We would be satisfied with that for the time being.

PROF. CHARO: Trish?

PROF. BACKLAR: I have nothing. I'm withdrawing my question.

PROF. CHARO: Then there's room for somebody to take her place.

Yes, Laurie?

MS. LAURIE M. FLYNN: As the executive director of a group of laypersons as well as others, can you comment a little bit about the challenges of accountability that this kind of research might bring? We've heard a lot about the oversight procedures at the NIH, and we have from time to time, and most recently, seen some gaps in those oversight procedures. And it appears that this research might be well spread among many institutes. There is at the same time a rising interest among many lay organizations in having a greater role and greater participation at the NIH and its institutes. What do you see in terms of the challenges of oversight for this research, and do you have any thoughts about the accountability that is particularly significant in an area such as this?

MR. PERRY: I think that the organizations that represent the lay public and patient and consumer groups, it goes without saying, are a significant part of the overall research infrastructure in this country, in that they provide the view of those that are the ultimate beneficiaries. Dr. Varmus has recently taken steps to increase the NIH's ability to draw upon such organizations and public to better inform their view.

Clearly, this research has the potential, as I said in my statement, to raise public debate and public concerns. And I think that by bringing it under the roof of the National Institutes of Health and having the NIH actively participating and funding this research and creating processes for appropriate review of applications for this research is the appropriate way to both satisfy public sensibilities and ethical concerns and to allow the research to go forward without delay. Does that answer your question?

MS. FLYNN: Yes. Thank you.

PROF. CHARO: Mr. Perry, I'd like to thank you very much for taking the time to prepare the testimony and come to speak with us. You'll certainly have left a

copy of that with the staff, I hope.

MR. PERRY: Yes. Thank you.

PROF. CHARO: Thank you.

PUBLIC TESTIMONY

Because Dr. Hodgen has been delayed, we're going to move directly to public testimony. I have six names. If your name is not on this list, please make yourself known to Pat [Norris] at the registration desk. Mr. Price, Dr. Sobel, Ms. Suh, Mr. Ewing, Dr. Fairfax, and Mr. Goodman.

As has always been our practice, we're going to limit comments to five minutes apiece, strictly enforced today because we're running late, but we encourage any of you who have more material than that to please give it to the staff and it will be made available to the Commissioners and it will be placed on the website so that members of the public can share it as well.

Mr. Price, if you'd like to come to the table to a microphone. Thank you for joining us.

MR. JOHN PRICE: Thank you. Good morning, Madam Chairwoman, Dr. Meslin, and distinguished members of the Commission. My name is John Price. I'm a former recruiter for Job Corps who served as a research proctor for the national Job Corps study. Presently, I'm a freelance writer who has completed a year-long investigation of the study. I'm also investigating other federally funded social experiments that are underway involving Department of Health and Human Services - Early Head Start program and Department of Education's Upward Bound program. All three of these studies, which experimentally withhold public services to the poor, are

conducted by a single researcher, Mathematica Policy Research, Inc.

These studies indeed shed light on the troubling state of federally funded social experimentation in America. For example, in 1994 the national Job Corps study pushed a new threshold in social experimentation by eliminating treatment alternatives and then withholding basic education, job training, and other critical services for three years from 6,000 at-risk youth in order to settle a longstanding dispute on Capitol Hill over the effectiveness of the Job Corps program. Researchers anticipating a higher level of crime among the study's control subjects tracked dire human outcomes ranging from joblessness to drug use to homicide.

Though it surely does not stand alone in America's dark alley of social experimentation, the national Job Corps study holds the dubious distinction of being the only human experiment in U.S. history where the anticipated outcomes include murder. Here are some of the ignored headlines: The *Tennessee Tribune* shows that "U.S. Study Withheld Critical Services From 6,000 Poor Youth"; one in the *Missoulian* newspaper in Montana, "Study Takes a Human Toll." The *Mother Jones* issue for this month also talks about the Job Corps study.

Madam Chairwoman, I'm here today because I'm gravely concerned that existing Federal laws do not adequately protect human subjects who are engaged in government research involving public service or benefit programs, or, more simply, social experiments. The exemption of these studies from common rule and the disqualification of these projects from the oversight of the Office for Protection from Research Risk leaves this genre of human research completely unchecked. Consequently, these subjects, who are typically poor, uneducated, and members of a minority group, are left unprotected.

In the absence of checks and balances, these highly vulnerable subjects often become political guinea pigs. They become human ammunition in data wars

waged on Capitol Hill by bureaucrats who need to prove their program's effectiveness, or to substantiate the program's funding, or to retain political control of their program.

The recent introduction of welfare reform programs and the passage of the Government Performance and Results Act of 1993 has increased the pressure on Federal agencies to prove the worthiness of social programs. Now, draconian study designs push new thresholds that permit duress-influenced informed consent, cursory risk assessment, the elimination of alternative treatments, the withholding of public benefits without appeal, and the abrogation of the right to decline or withdraw from research without penalty.

Madam Chairwoman, the untold ramifications of zealous and unchecked social experimentation are as disturbing as the silence that surrounds much of the research. There are noble voices in the wilderness who have spoken out strongly for the protection of human subjects but, tragically, when it comes to social experiments their voices go unheard. On January 22, 1997, Senator and astronaut John Glenn, perhaps the world's most famous human subject, introduced the Human Research Subject Protection Act, which if passed would have made the common rule mandatory. Forewarning that there's a gap in our legal system, Glenn's bill never received a single congressional hearing or the audible support of the NBAC or the U.S. President. The bill died at the end of the session.

On May 16, 1997, the President issued an offensively overdue apology to the handful of survivors of the Tuskegee study, and even extended the term of the NBAC to October 3, 1999. The following day, perhaps ceremoniously, the NBAC passed a key resolution: "No person in the United States should be enrolled in research without the twin protections of informed consent and independent review of the risks and benefits of the research." But despite this noble declaration, the NBAC failed to specifically address the ethical crisis of social experimentation.

Madam Chairwoman, on April 18, 1979, the National Commission for the Protection of Human Subjects, the NBAC's predecessor, released the Belmont Report, which raised concerns about the burden of research on the poor. It also raised concerns about the risks of psychological harm, physical harm, legal harm, social harm, and economic harm. The Commission recommended an important conclusion: that the problem of social experimentation be addressed by a successor body, of which the NBAC is the third successor body. Yet here we are on January 19, 1999, two decades later, and still there is no review of social experimentation.

Madam Chairwoman, quite simply, to disregard these imperatives and to allow unchecked human experimentation is a desecration of the fundamental human right to life, liberty, and the pursuit of happiness. It is a callous manipulation of those Americans who are trying to improve their lives who happen to be poor, who happen to be illiterate, and who usually happen not to be white.

Let there be no mistake with holding the cold, critical, publicly-funded services from this highly vulnerable group without checks and balances for the purpose of furthering the agency's political agenda is an American atrocity and it is a moral deficit that carries the stench of racism and bureaucratic indifference to human suffering.

Madam Chairwoman, all research subjects deserve the same rights of protection as Senator John Glenn; why would they not? Anything less is unconscionable and discriminatory. And let me be clear, whether they are the guinea pigs of political conflict or the hot commodity of the fat-cat contractors masquerading as America's leading researchers, the 6,000 Job Corps control subjects who can now be found in unemployment lines, jails, and cemeteries are a textbook example of America's dark crisis of social experimentation.

In closing, I ask the NBAC as the Commission enters a new millennium of unregulated social experimentation, when exactly will the U.S. President and the

Commission take on the mandate of Order 12975 and consider the protection of the rights and welfare of human subjects, including the human subjects of social experimentation?

And finally, if I may inversely paraphrase Dr. Varmus of the NIH, every time a control subject of a social experimentation kills or dies, the NBAC should be wearing black. Thank you for your time.

PROF. CHARO: Thank you, Mr. Price. Questions from members of the Commission? [No response.]

Let me ask you one question then. Could you help me to understand the source of the exemption from review for the programs you described? Is it the nature of the activity that's not covered by the current regulations, the source of funding that means it's not covered, or is it some other factor that has it falling through the gaps in the law that you've identified?

MR. PRICE: Yes, indeed, there's a gap in the law. The common rule, 45 CFR 46.101, Section B, Subsection 5, indicates that all public service and benefit programs that conduct research are exempt from the common rule. That is, they do not have to comply with the IRB requirements, all of the other requirements stipulated by the common rule. So that is the gap where they fall through the cracks.

PROF. CHARO: Thank you very much.

MR. PRICE: Thank you.

PROF. CHARO: Okay. Our next witness is Dr. Mark Sobel from the American Society of Investigative Pathology [(ASIP)].

DR. MARK SOBEL: Good afternoon. I'm representing the American

Society of Investigative Pathology, and I'll present to you a brief summary of things that have been submitted before the January 17 deadline for response to the NBAC Report on the Use of Human Biological Materials in Research. ASIP is an organization of 1,600 research scientists whose studies [INAUDIBLE], including-clinically based studies on the expression of the need for tissue samples that fulfill the conditions provided by research that may well lead to advances in the prognosis of certain conditions [INAUDIBLE]. ASIP has taken a leadership role in the pathology community, educating its members about the potential applications of human stem cell research and the Federal regulations that govern its use in federally-funded institutions.

We have been following the NBAC's deliberations with great interest. We're gratified that the draft report recognizes the research value of human biological materials in improving public health, and we're pleased with the town meetings that have been held under the auspices of the NIH and demonstrated overwhelming support for [INAUDIBLE] research. Although ASIP agrees with the necessity of protecting human subjects and their privacy and appreciates [INAUDIBLE], were disappointed with some of the draft recommendations. We understand that the charge of the Commission is a very important one, coming at a critical time as researchers and IRBs are looking for guidance to correctly make use of human biological materials in research.

My colleagues and I are dedicated to elucidating causes of human diseases, discovering better diagnostic and prognostic methodologies, and developing more effective therapies to help the public. In those pursuits, the use of human tissues, and particularly coded samples, is critical because it permits follow-up in the study of other specimens from the same individual over a period of time. The Commission has tried to balance protecting the rights of human subjects with the desire to not impede research that can benefit the public. This is, of course, a very difficult task, and everyone who has tackled the problem realizes that there are not absolute solutions and easy answers. It is fair to say that a flexible approach that can accommodate the variety of research approaches to studying human disease with human biological materials is

required, and that it will inevitably lead to a heavy burden placed on local institutional review boards. ASIP is gravely concerned that the Commission has grossly overestimated the potential dangers inherent in the use of coded samples, and in so doing has come up with a series of recommendations that will place obstacles to worthy pursuits in the biomedical research community to gain a better understanding of patients' diseases and to treat them. More important, it is not clear to us that the approach that the Commission has proposed will be effective in safeguarding human subjects. We believe that the emphasis should be on prevention of misuse of information rather than on the gathering of information. In general, we found the recommendations of the report to be diffuse and to lack clarity, and we believe that they require rewriting before they can be well understood by the biomedical research community and by institutional review boards. We appreciate the opportunity to speak to the Commission at this time to stress the following points.

One, that risk to human subjects occurs not in the gathering of information by researchers but in the misuse of such information, and that obtaining informed consent from human subjects, however worthy and respectful of their personal rights and autonomy, is not an adequate protection. It is critical that confidentiality and security measures be proposed by departments and institutions and that those policies be approved by IRBs, as in that way information gathered in research studies can be more secure and safe. We believe that researchers should be expected to respect the confidentiality of their results, just as health care professionals are honor-bound to protect medical information. Furthermore, research findings that are not validated and peer-reviewed we believe should not affect quality of care and should not be entered into the medical record unless they meet Federal standards. These standards were designed to protect the public from poor quality control tests and misdiagnoses. Two, we believe that there is a far greater danger to the public from the release of inappropriately validated research than from withholding such information - just as it is best to present patients and families with the results of genetic tests and pedigree analyses by a trained genetic counselor. The release of unvalidated research data to a

human subject should require counseling by a trained researcher who would have to explain statistical significance and different types of interpretations of the data, and we believe that the latter would be an unrealistic and herculean task. Three, oversight over human subject research is of course necessary to protect the public from inadvertent harms.

It is important to consider, however, that there is a fundamental difference between interventional therapeutic research on human subjects that directly affects clinical well-being and research on excess human biological materials. We support a simple consent process that authorizes the future use of excess human tissues for studies that follow IRB-approved confidentiality and security policies. And we believe that this should be sufficient to respect the personal rights of human subjects when their coded samples are used in that manner. Such a consent should preferably present participation separately from their clinical care consent document and should guarantee that failure to agree to participate in such research should not have an impact on clinical care provided by the institution. The Commission does not appear to appreciate how difficult it is for a researcher or a staff member of a repository to break the key to a code. The fears of the Commissioners do not seem to be backed up by the evidence of harm to human subjects despite decades of use of archived human tissues by the biomedical research community. Again, we believe that confidentiality and security procedures should be effective measures to prevent harm.

We'd like to comment on the wording of the draft report. We believe it does not provide adequate guidance to the biomedical research community or to IRBs concerning assessment of what should be considered as minimal risk and respect for personal rights and welfare. We believe that IRBs should be provided with guidance from the Commission. The use of coded samples in situations where there is no intent to establish the identity of the samples during the course of the research, or no reasonable probability that a break of the code can occur, should not constitute more than minimal risk.

We'd also like to comment that the Commission has failed to make direct recommendations concerning the use of the already archived millions of human biological materials that are in various repositories throughout the country. Some of those samples were obtained within an inadequate consent process by today's standards, and we would welcome your advice on how to use those samples.

Finally, quality control studies are usually considered part of the clinical care testing procedure. To avoid confusion, we request that the Commission clarify the use of human biological materials in such quality control studies as well as the use of human biological materials and education of public health professionals, which we do not believe were directly discussed in the report.

We thank you for your time.

PROF. CHARO: We thank you. Comments or questions from members of the Commission? One very quick one, if I may. In August 1998 the Medical Research Council of Canada said that it would now condition funding for this kind of research using existing collections on the requirement that consent be sought if the materials were what they called "traceable," which is roughly pretty much what we've called - I'm not sure what we've called them anymore - but that you called "coded." Does your organization have any contacts with its counterparts in Canada that could shed some light on reactions and experiences in the few months since then, in Canada, with that regime?

DR. SOBEL: Actually, the American Society of Investigative Pathology is an international organization, so some of our members are Canadian.

PROF. CHARO: I stand corrected.

DR. SOBEL: We have no specific information from our Canadian

members, but our members, although the majority are Americans, span all the countries of the world.

PROF. CHARO: Okay. Thank you.

DR. COX: Alta, I do have one question; it's sort of a point of clarification. So that it would be your position, then, that as long as information was coded and the researcher wouldn't break that code, that if a person's entire medical record for 50 years or however long the researcher wanted information to get the ongoing information, that that would be minimal risk?

DR. SOBEL: I think it would depend on the situation, and we're certainly not recommending that there not be any oversight. We believe that these proposals should be presented for oversight and review, either expedited review or IRB review. We seek clarification in the report as to what is minimal risk so that IRBs can better establish under what circumstances and in which cases a waiver of consent could reasonably be granted.

DR. COX: Well, I refer to Number 6, where you're asking the Commission to provide clarification that in situations where there's no intent to establish the identity of samples, okay, during the course of the research and with no reasonable probability to break the code, that that doesn't constitute more than minimal risk. That sounds like the situation I just described.

DR. SOBEL: Yes, of course, this has to be examined on a case-by-case basis, but we feel that the wording of the recommendations in the report, the examples that are given, represent worst-case scenarios and you're not giving guidance to IRBs as to how to better establish minimal risk situations.

PROF. CHARO: Jim Childress?

DR. CHILDRESS: In Number 7 you indicate we failed to make direct recommendations about the use of materials that are already present. What is - does your group have any recommendation as to what our recommendation ought to be in that regard?

DR. SOBEL: We have considered two options. One is the grandfathering of samples that have been collected prior to a certain date, which can be established based on the content of your report. With the understanding that we don - t believe that any research on human biological material should be done without some oversight, we have submitted a full statement in addition to this three-page summary, and I think that clarifies our position that even research on anonymized samples requires some oversight - at least some institutional official to certify that the proposal is consistent with human rights and welfare, or buck it up to a full IRB review.

PROF. CHARO: Any further comments or questions? Larry?

DR. MIIKE: I think, contrary to your statement, we do address the issue of existing tissue samples. And I think that in our recommendations we are not rigid. For example, unlike the Canadian system that says you must get informed consent, I think that ours is a much more flexible recommendation than what they ′ ve offered up. So I ′ m a little puzzled by some of your comments.

DR SOBEL: I think the confusion on our part reflects our belief that a lot of the recommendations as currently written - just the wording of them is a bit unclear and ambiguous. And I think that they need tightening up and/or better organization.

DR. MIIKE: You ′ ve made some specific comments?

DR. SOBEL: We ′ ve made specific comments on that in the full statement that has been submitted, yes.

PROF. CHARO: Thank you very much. Our next member of the public to testify is Ms. E.J. Suh from Collegians Activated To Liberate Life. Ms. Suh?

MS. E.J. SUH: Good afternoon, members of the Commission. I am E.J. Suh, director of operations of Collegians Activated To Liberate Life, a network of college students in more than 300 colleges and universities across the nation. I am not a distinguished scientist; I do not have a doctorate in philosophy or ethics, but I do study and was awarded a Bachelor of Science degree in biochemistry from the University of Illinois. In all my years of middle school, high school, and four years of undergraduate study in the sciences, the one thing I was always taught was that when a live human sperm unites with a live human egg at fertilization, the result is always a living human being. This human being does not have the same appearance as we do, but we all looked like him at one point. This is a basic fact of life that anyone who has studied any basic biology knows. One need only glance at a high school biology book or medical text to learn that the beginning of human life has been determined by science to begin at the moment of fertilization. These embryos are human beings with unique genetic codes. Why are some of them considered valuable human beings worthy of life while the rest of them are stored in freezers or used as objects of inhumane research?

One of the most revered of museums in Washington, D.C. is the U.S. National Holocaust Museum. Throughout the tour, the museum pleads and begs people to learn from the past so that we may not repeat history. After the horrors of Nazi medical experiments, medical professionals wrote a code of medical ethics in 1947: the Nuremberg Code. The first point of the statement says that in regard to medical experimentation on human beings, voluntary consent of the human subject is absolutely essential. We know that the embryos involved in embryonic stem cell research are human subjects. It is obvious that a preborn child cannot give voluntary consent. We have no right to destroy and experiment on human beings who cannot defend themselves. The dignity and human rights of these preborn children should not be disregarded because their parents have rejected them and donated them to science.

Would a scientist be allowed to do research that took apart the body parts of a six-year-old because the six-year-old's parents gave them consent?

Another point of the Nuremberg Code states, and I quote, "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur, except perhaps in those experiments where the experimental physicians serve as subjects." In the case of Dr. Thomson's research, scientists knowingly mutilate the embryos so that the embryos have no chance of survival. Human history, unfortunately, provides numerous examples of medical abuses. Today, we recognize the immorality of the Nazi experiments, the Tuskegee syphilis experiments, radiation experiments conducted by the military, and experiments on prisoners. When they were conducted, however, researchers rationalized these experiments because scientific progress was elevated above the human rights of human beings.

I come before you not only for myself but also as a representative of college students in more than 300 colleges and universities across the nation, many who are studying to be tomorrow's leaders in scientific and medical research. On their behalf, I make this plea now: Please ban all research on human embryos.

The outcome of Dr. Thomson's research is great, but we must look at the methodology. Please do not demean the dignity of human life to the same level as laboratory mice. Please reevaluate what we are doing to the smallest and most valuable members of the human family. Thank you.

PROF. CHARO: Thank you very much for coming and for taking the time. Comments or questions, please?

PROF. CAPRON: What is your organization's position on Dr. Gearhart's work?

MS. SUH: We also believe that abortion demeans human life, that human life begins at fertilization, that no one has the right to take that away. That is a born, innate right for all human beings: to live. And so we believe that abortion to begin with is infringing on the right to live. And because of that, those human beings should not be used for fetal research.

PROF. BACKLAR: And what about spontaneous abortion that's not planned? Would you permit that kind of research?

MS. SUH: I really couldn't give you a specific answer to that. That's something that everyone has different philosophies and different viewpoints on. I, personally, would not see a problem with that, but I could not speak on behalf on the entire network of college students.

PROF. CHARO: Thank you very much. Next we have Mr. Kneale Ewing, also from Collegians Activated To Liberate Life. Mr. Ewing, welcome. Thank you for coming.

MR. KNEALE EWING: Thank you. I would like to respond to the question that you just posed. First of all, I'm the Network Director of Collegians Activated To Liberate Life. And as E.J. [Suh] has already mentioned, we represent students from more than 300 colleges and universities from across the nation. Our group would have no problems with research done on spontaneous abortion. That would be like doing research on a cadaver.

Many people believe with good scientific and philosophical reason that all human life is sacred from fertilization to natural death. As you have heard before, human life is defined to begin at fertilization. We have to leave behind the idea that human life does not begin at fertilization. We act as though the embryo is something to be experimented with up until a certain time when it evolves into a human person. Many

scientific researchers demean the dignity of human life by destroying human embryos, by exploiting human beings. Human beings are scientifically created in laboratories via in vitro fertilization to be exploited in research. Scientists create excess human embryos in fertility clinics. Not all these human beings are created with the intention to be allowed to grow. Scientists eugenically select only those human beings with the best probability for implantation while the rest are kept frozen in freezers or they're used for research. I plead with you not to discriminate against human beings by age. We were all human embryos at one point. Science has defined time and time again that human life begins at fertilization. We have already allowed medical doctors to go against the Hippocratic oath to serve and to protect all human life. *Roe v. Wade* has already made our society barbaric. Please do not let the scientific world go down the same path.

In conclusion, it is our highest intention and hope that the scientific community harness the therapeutic benefits of stem cell research without violating the dignity of embryonic human life. Researchers, please focus on obtaining stem cells from alternate sources such as the aforementioned possibility of hematopoietic and neurological stem cell sources. Commission members, the ethics of stem cell research and public funding cannot be limited to human cloning. It must respect the uniqueness and sanctity, the right to live, for all human beings. Thank you.

PROF. CHARO: Thank you very much. Arturo?

DR. ARTURO BRITO: How does your organization see - since you're defining human life to begin at fertilization, how about production of embryos through somatic cell nuclear transfer?

MR. EWING: We would also be against that.

DR. MURRAY: Does your organization have a position on in vitro fertilization followed by implantation? That is, IVF to make a child?

MR. EWING: We are also against that.

DR. MURRAY: On what grounds?

MR. EWING: Well, our organization is also a Christian organization, and we believe that the unification of the sperm and the egg should be through the natural process of human sexual intercourse between the mother and father and God. That's one aspect. Another aspect is that the technique doesn't always take. The zygote doesn't always implant or the-

DR. MURRAY: That also happens in the old-fashioned way. Do you have a position...does your organization have the position that there should be laws to prohibit any in vitro fertilization in the United States, even if it's intended for implantation?

MR. EWING: Could you repeat the last part, please?

DR. MURRAY: Yeah. The same phenomenon-that is, IVF followed by implantation. Does your organization have a position about whether or not there ought to be any laws to prohibit the practice of IVF generally?

MR. EWING: Yes, we would believe that there should be laws prohibiting that.

PROF. CHARO: Any other comments, questions? Thank you very much, Mr. Ewing, we appreciate it.

MR. EWING: Thank you.

PROF. CHARO: Next, Dr. Olga Fairfax.

DR. FAIRFAX: May I stand up, please?

PROF. CHARO: As you wish.

DR. FAIRFAX: I'm a little more comfortable that way, thank you very much. Thank you for letting me testify. This is called "In Defense of Choice," by Dr. Lieberman: "A female's body is her own. She is free to do with it what she will. No one has a right to force her to give up anything. And even though in pregnancy she is connected to the womb, her body is still her own. She is her own self. She has her right to choose. She has yet to be born."

I was shocked while in Australia: you can buy fetus earrings, very cheap. Right here in Chicago you can buy paperweights made out of fetuses; there's an address here and a price list, if you're interested. What did our foremothers say about abortion? And why do I even mention abortion? Because I've been sitting here for three hours hearing very cavalier treatment of the word "abortion." There are now 40 million innocent preborn babies dead from abortion through the first nine months of his or her life. Here's what [Elizabeth] Cady Stanton said about abortion: "It is degrading to women that we should treat our children as property, to be disposed of as we see fit." Susan B. Anthony: "I deplore the horrible crime of child murder." Matilda Gage: "The crime of abortion is child murder and infanticide." And Victoria Woodhull: "Every woman knows that if she were free she would never, ever think of murdering a child before his or her birth."

On January 22, 1973, I was pro-abortion. I thought it was the greatest liberation that women could ever have. And then somebody very close to me had an abortion, and suffered a complete mental and physical breakdown as a result. Dr. Hurd and Dr. Bending, a psychiatrist and a medical doctor in 1920 in Germany, wrote a book called *The Evaluation of Life Devoid of Value*. They said there were many people that had no value: elderly, handicapped, senile, preborn babies, orphans, even widows. So

might does not always make right. At the Nuremberg trial where one guard said, "Well, we never knew it would come to six million Jews," the judge looked him right in the eye and said, "You knew with the first death."

Life should dance on the grave of death, and not death dance on the grave of life. Martin Niemöller, and he was a martyr, as you know, said, "First they came for the labor unionists, but I wasn't a labor unionist so I didn't have anything to worry about. Then they came for the senile; I wasn't senile so I didn't worry. They came for the handicapped; I was healthy. Then they came for the orphans; I wasn't an orphan. Then they came for the Jews, but I wasn't a Jew. And then lastly they came for Christians. I was a pastor. But there was no one left to speak up for me."

This is what we're talking about: innocent, preborn, dead babies, slaughtered. I pass the "abortuary" right across the street. They brag they've killed over a half a million babies - a half a million. One abortionist there told me over the phone - I wish I'd had a tape - he said, "I've done thousands of babies that are big enough to hold in my arms, up to seven months." Washington, D.C. has a distinction: we are the abortion capital of the world, more than any other state, city, county, or nation on the face of the earth. We do abortions here. Look at your yellow pages; you might be shocked. Look under the word "clinic." There are four full pages of "abortuaries." I'm talking about twilight anesthetics if you're seven months pregnant; no consent for minors under 18. My 11-year-old daughter could get an abortion today without my husband and my even knowing it, and yet we had to take her last Christmas to get her ears pierced. So here's partial-birth abortion that's legal for all nine months of pregnancy, as you know. The ban twice has been passed by the Congress, but our pro-abortion President - who as you know, according to Geraldo Rivera and mistress Gennifer Flowers both - Bill Clinton paid his mistress $200 to abort his own son or daughter in Little Rock in 1976. And then there's the connection between abortion and breast cancer. Yes, I guess you can argue we needed aborted babies to find this out. Not really, just look at the statistics. Why are breast cancers proliferating at such an

astonishing, skyrocketing rate? Because the women have been aborted.

PROF. CHARO: I apologize, Dr. Fairfax. I'm going to have to ask that you make sure you get the essence of your remarks in in the next minute or two.

DR. FAIRFAX: Right. I will end on this.

PROF. CHARO: Okay.

DR. FAIRFAX: This is a picture of you. It's a picture of me. It's a photograph, a sonogram, at two months, eight weeks. We've been talking about embryos, fetuses, I don't know, call them what you want. We devalued the Jews so much and others in Nazi Germany by calling them something else, [INAUDIBLE]. So it's just a lot easier to kill when we talk about embryos and even the unscientific term, pre-embryos. So let's consider ourselves friends. We have the backbone, we have the courage, we have the guts, we have the bravery to say no to this horrid research. I don't want you to be on trial someday, and I don't want me to be on trial someday. I don't want to be on trial asking, What were you doing? Where were you when they were doing these grisly experiments on our little brothers and sisters? Thank you very much.

PROF. CHARO: Thank you very much, and I apologize again for interrupting you. Questions or comments? Our last witness is Will Goodman, who is a member of the organization, Civil Rights and Antidefamation League of Embryonic Life. Welcome, Mr. Goodman.

MR. WILL GOODMAN: Thank you. Good afternoon. My sincere greetings to the distinguished members of this presidential Commission and assembled guests and friends. As a practicing Catholic living in the United States in the final moments of the second Christian millennium, I would like to express my personal concerns and voice universal opinions I hold in common with millions of other

Catholics, non-Catholic Christians, practitioners of other world religions, members of the pro-life community, and other human rights activists who are unable to attend today's meeting. Although many wonderful discoveries in the diverse biological field bring profound hope to the world, especially to those who will genuinely benefit from the recent medical breakthroughs, many Americans are nevertheless distressed by the disturbing advances currently being made in the human sciences at the expense of living human beings. For the sake of charity, justice, and simple, common-sense clarity, I would like to propose the following standard to be adopted by this Commission: a complete and absolute ban on all scientific experiments and methods, whether by private or public funding, that may directly ignore, contravene, and/or unnecessarily risk the fundamental right to life of any human person [INAUDIBLE] from fertilization through birth.

It is the hope of many that the decisions and proposals of this Commission will ensure equal and adequate protection for all preborn human beings without discrimination, just as the international community already recognizes such protection for human beings after the time of birth. This means, of course, that all human zygotes, human blastocysts, human embryos, human fetuses, whichever term you prefer - that all human persons, from the single-cell beginning of their organic life, be protected and respected in their special uniqueness and individual sovereignty. By utilizing such a ban as a common standard, many of the cloudy ethical dimensions surrounding human stem cell research and human cloning, for example, could be more [INAUDIBLE] with scientific exploration avoiding all possible exploitation while directing our intellectual and monetary resources toward endeavors that will work with [INAUDIBLE] of all persons regardless of their state of natural development.

As you are all well aware, one [INAUDIBLE] human beings [INAUDIBLE]. One should never use another person for a test in the [INAUDIBLE] research. One must never use another human person as a mere research source of tissue or another reason, especially if they [INAUDIBLE] tissue from a donor [INAUDIBLE].

Such obvious and simple examples illustrate why we must show the same considerations for human persons in embryonic or fetal stages of growth. What is needed most from the NIH is [INAUDIBLE] of a human person and an appreciation of the inviolability of every human being's right to life. Tantamount with these, there is also a profound need to [INAUDIBLE] the youngest and most vulnerable and defenseless humans, and the awareness to demonstrate a true sense of consistency with regard to the way we treat those who differ from us in size and in appearance. Satisfying the basic need of this society to recognize, accept, and work for the common good of all people, science can do its part to advance interpersonal solidarity. If such a consensus cannot be reached by this Commission, or the scientific community at large, our country will be adding to the already devastating number of innocent human beings killed in the name of progress. The standard of universal human rights must be the principle for guiding ethical decisionmaking into the new millennium. History, particularly from the past century, reveals the risks and atrocities engendered when these rights are not accorded to all human persons. The progression of science must be matched with the common understanding that human rights begin when the human life begins, namely at their natural beginning: the unification of sperm and egg. Any other subjective or arbitrary rendering of the human person or rights applicable to the person because he or she is a human is absolutely criminal. The trials at Nuremberg serve as condemning evidence against merely unilateral bans on the testing and manipulation of certain human subjects. Your responsibility as members of this panel of experts is to ensure the protection of genuine scientific progress. Your work, however, will be in vain if innocent human lives are lost in the search for knowledge and understanding. Science must be at the service of the person, never the opposite. As many members of our human family are dying today because their lives go unrecognized and unappreciated, I add my voice to the many concerned Americans who are calling for a permanent moratorium on all work that will jeopardize the rights to life and health of human beings in the first hours and days of life.

As a welcoming people, the United States should be leaders in the

promotion of human rights, not only throughout the world but also throughout the diversity of organic human development. Therefore, I entrust to each of you the serious consideration of this proposed ban and the promotion of just definitions of human life concomitant with all human rights from the beginning, namely at fertilization. And furthermore, it is my hope that any alternative method of synthesizing single-cell human life would be met with complete disapproval as an offense against the dignity of the human person who has the God-given right to be conceived from a natural act between husband and wife. As the great blessings of scientific achievement increase, may they be coupled with the appreciation of the sacredness and fragility of the human condition. Compassion and love for persons is the best weapon in the fight against repression. But only justice can prevent any discipline, whether science, philosophy, politics, or religion, from infringing on the rights of others. And unconditional respect of human life from the beginning to the end of life is the only solution for preventing crimes against human rights. It is the grave duty of this Commission to work to ensure the protection of human life from any injustice and the elements within the proposed ban stated in the [INAUDIBLE] will certainly be instrumental toward that task. Thank you, and God bless you.

PROF. CHARO: Thank you very much, Mr. Goodman. Comments or questions? Larry?

DR. MIIKE: I just want to get clarification. You mentioned the beginning of human life being a union of sperm and egg.

MR. GOODMAN: Right.

DR. MIIKE: If that is...if the union is through a nonsperm source, such as nuclear transfer-

MR. GOODMAN: Somatic cell nuclear transfer?

DR. MIIKE: Right. What do you consider the product to be?

MR. GOODMAN: Well, it is a human person. I mean, the beginning of human life, I'm saying, is we're asking for a moratorium-

DR. MIIKE: But you call that an abnormal way of arriving at something.

MR. GOODMAN: An unnatural way of arriving at a human person, that is correct. And with the proposed ban, such artificial ways of synthesizing human life...it isn't any different because of the genetic code. I mean, that's the single-cell beginning.

DR. MIIKE: But then I guess the follow-up question would be that since there is not a potential for multiple mature cells in your body and mine to become a human all by itself, with the union of - with an egg, what's your attitude? What's your stance toward those cells?

MR. GOODMAN: Just the somatic cells that you and I both have? Well, I mean they are cells, just like the germ cells. What I said here was that this Commission must recognize that human life begins at fertilization, and I used the example of the union of sperm and egg. I didn't say that's the only way by which a human person can come about in the beginning.

DR. MIIKE: That's why I asked the question then. You've answered it saying that whatever - some methods may be reprehensible to you -

MR. GOODMAN: Precisely.

DR. MIIKE: But once that union has happened, then you consider -

MR. GOODMAN: Once the single-cell beginning is there, it is a human

person, correct.

PROF. CHARO: Alex?

PROF. CAPRON: I wanted to find out whether you shared the view of the Collegians group; Mr. Ewing answered the question about the use of spontaneous abortuses, and his answer was that legitimate medical or scientific research was all right there as it would be on any other cadaver. Is that your view?

MR. GOODMAN: Yes, I believe that would be true. And I think that the parents of the child being used through the spontaneous abortion should be given the proper...understand...in the same way that a child just after birth, let's say dying within the first two weeks, the way that we would treat that. I would say, of course, yes, for medical research.

PROF. CAPRON: As you are probably aware, sometimes organ or tissue transplantation is done from a cadaver that resulted from a criminal act, and there's no taint through the use by the physician or the patient recipient of the material simply because someone else has engaged in a criminal act. Do you think that that analogy would apply to an abortus that had been produced through an induced abortion, but where the physician or researcher doing the research had nothing to do with that process?

MR. GOODMAN: I think I understand the question, and I believe I would probably side with some of the recommendations made from the Nuremberg tribunal, in which those who were victimized, the individuals who were the victims of certain crimes perpetrated against them, I believe that those decisions were made that it would not be appropriate, if I understand correctly. I have to admit I'm not an expert in the area of what happened, but I believe that at Nuremberg it was decided that for those who were victimized, it would not be appropriate to do further research. Is that correct?

PROF. CAPRON: I don't think that at Nuremberg the people doing the research were doing it on unconsenting people at the time.

MR. GOODMAN: And you're talking about-

PROF. CAPRON: And I'm talking about a situation in which, as with Dr. Gearhart's work, the researcher producing the line of embryonic stem cells does not operate in any way to produce the abortion, just as the transplant doctor does not go out and find a transplant donor and become involved in that person's demise. But sometimes someone else's criminal act has produced a dead body that then becomes a source of organs or tissues.

MR. GOODMAN: I think we have to realize, in these cases of the researchers during the time of the Nazi holocaust, that in many cases the doctors were not the ones killing the Jews. And I agree with you - they were unconsenting parties and it was a tragedy that their lives were taken. But you can't absolve, then, the scientists who take a body that they themselves did not kill and continue to do science and say, "Well, I'm absolved." In the same way, with procured surgical abortions, these are done against the will of the human embryo, the human person. And for the scientist to say, "We're taking these and there's a wall between us and the crime," I think that would be a great mistake.

PROF. CHARO: Thank you very much, Mr. Goodman. It's now 12:45; we're scheduled to return at 1:15, and we will in fact return at 1:15, so there will be an abbreviated 30-minute lunch, and we'll return to hear from Professors [Patricia] King and [John] Robertson. Thank you to all the witnesses.

HISTORY AND PUBLIC POLICY

DR. SHAPIRO: I'd like to have your attention, please. First of all, in line

with the well-known theorem that there are an infinite number of non-recurring mistakes that occur in all projets, in reviewing our Capacity Report with Secretary Shalala this morning, I realized that in Appendix 2 the titles of the second-to-last and last flow diagrams are reversed.

PROF. CHARO: Oh, Lord.

DR. SHAPIRO: So we will have to issue an errata sheet and we'll get it on...but I was taken to that spot as a quick way to sort of summarize what we were doing, and I realized that error had crept in somehow. So you can correct it on your own sheets; we'll of course correct it on the web and on subsequent printed copies.

We now have a panel with, once again, two very distinguished panelists, I think well known to all of you: Patricia King from the Georgetown University School of Law and John Robertson, University of Texas School of Law. Welcome to both of you. Both Patricia King and John Robertson have a long association with the issues that swirl around our issues of concern here over a long period of time, and we are very grateful to both of you for being here today. Let me turn first of all to Patricia King. Welcome, and we look forward to your remarks.

PROF. PATRICIA KING: Thank you, and thank you for the opportunity to participate in this discussion of human embryonic stem cell research. What I'll try to do in this brief time allotted, because I'm sure you'll get more from me by my answering questions, is to give a brief history of my experience with public policy development in the areas of fetal and embryo research. I served on three bodies: the National Commission, the Fetal Tissue Transplantation Panel, and I was co-chair of the Embryo Research Panel [(ERP)]. I'd like to give you the lessons that I've drawn from those experiences and to offer reasons for believing that it is feasible to develop an acceptable public policy for human embryonic stem cell research.

I believe that it is important for government to fund such research, and I believe that while government neutrality may have merit in other contexts, I have never been convinced that it has merit in this one. From my perspective, to not act is to make a decision, and to act is to make a decision. Both require justification in the same way. In each consideration of fetal tissue, fetal research, or embryo research, the abortion controversy has framed the discussion of the issues to a significant degree. This is, of course, expected, and I don't quarrel with that. But I would point out that because the discussion was framed that way, the discussion tended to ignore, in my view, other important moral and value issues that were at work in the debate under discussion. There will not be consensus on the morality of abortion, I am convinced of that. However, I am equally or also convinced that it is possible, if we work hard enough, to develop what some have referred to as overlapping consensus, and that is that persons can proceed to arrive at a common overlay, moving from diverse religious, political, personal, etc., views to achieve a consensus that might not permit everything but would not preclude everything either-that it is possible to do some embryonic stem cell research. This type of consensus clearly has instrumental value, but I have long believed that, if reached, carries with it a weight of its own. The fact that a person's coming from diverse perspectives can lead to any consensus carries with it weight that must be attended to.

My second point about the panels that I've served on is that I have often thought that we did not appreciate sufficiently that while we were attempting to work with ethical principles, we were essentially an old-fashioned public policy body. And this is critical. You cannot reach guidelines that are workable by starting at the level of principle and debating principle only. You must at some point recognize that you want to have a public policy that rests on moral and ethical premises, but rests on moral and ethical premises rather than trying to find a policy that we would label an ethical policy as distinct from an acceptable public policy. And indeed, this language appears in the history. The ERP, for example, stated that its report was acceptable public policy. The Fetal Tissue Transplantation Commission panel said that its work was acceptable public

policy. So we need to be clear about what goals are when we're working in very controversial areas when you're trying to set out guides that have to be practically applied in multiple situations.

So let me go briefly through, since I was asked to do some history, these three bodies. The fetal research controversy erupted in 1973 and was the subject of some debate in the Congress. The issue that was of immediate concern was two types of research but one type in particular: research that was conducted on what we then called the nonviable fetus *ex utero*. And by that I mean a living fetus, following abortion, who was not viable and could not, nor was expected to, live longer than a day or two. There had been research that was conducted on such fetuses; some believed that that research shocked the conscience and became the subject of congressional concern. Senator [James] Buckley, in offering his amendment in the Congress, made it clear, however, that the subject of concern was the voluntarily aborted fetus and not a spontaneously aborted fetus. The other type of research that proved to be controversial was of the following sort. In an effort to find out what drugs crossed the placenta and might injure a fetus, there was research that involved giving drugs to women prior to research so that we could examine after the abortion whether the drug had crossed the placenta and was harmful to the fetus. The object of such research, of course, was to see what drugs could be safely given to pregnant women. There were other types of research, but I think that this was the type that predominated.

The Commission's work applied only to postimplantation fetuses and embryos. The Commission did not make a determination of moral status; the Commission did say that in its deliberations it affirmed that the fetus, as a human subject, is deserving of care and respect. Members are convinced that moral concerns should extend to all who share human genetic heritage. The fetus should be treated respectfully and with dignity. The Commission debated at length something they called the "equality principle," and that is that fetuses aborted should be treated the same way as fetuses going to term for purposes of research. Recognizing that there would be

differences in the interpretation of the equality principle, among other things the Commission recommended that a review body be established, and that review body was going to deal with questions of interpretation and examine issues for scientific and public merit. The Commission also believed that such a continuing review body would facilitate public discussion. I call attention to that because I'm going to return to that when I talk about review bodies later.

The Commission's work was important, I think, in several respects. One, that it recognized that although fetal status or embryo status was an issue in abortion and an issue in fetal research, it recognized that the two contexts were not the same. That is, that the research context introduced an additional factor that should be considered, and that is the value of the research and what the research promised for the health and well-being, to give an example, of persons who suffer from diseases that might be helped. Indeed, given the fact that the Commission was started in 1974, a year after *Roe v. Wade*, I think there was shock in many quarters that the Commission had not taken the *Roe* decision and decided that you could do any research on a fetus prior to viability without constraints. The Commission's view was we were in a context and we would have to work out rules for that context. And I think that that's very important.

Two, the Commission recognized the need and value of continuing oversight and review. You cannot resolve every issue in the research all at once. And three, it just really recognized that we were not going to be able to resolve the question of the moral status of the fetus.

Now this group that the Commission recommended was in fact established—I was not a member of it—but it was called the Ethics Advisory Board [(EAB)]. And it was not only charged with referrals from the Commission with respect to research, but had to look into the issue of in vitro fertilization and fertilization outside of the human body. It issued a report in 1977 on [Health, Education, and Welfare]

(HEW) support of research involving human in vitro fertilization and embryos. And the report sat on the Secretary's desk and promptly - well, not promptly - just died a slow death. It was ignored; it had no impact. Subsequent to that time the EAB was disbanded, members were not appointed to it, and because it did not exist in any real way, all research involving embryos, for the Federal government, could not be funded because it could not go through this mechanism that it was required to go through because it did not exist.

I mentioned the EAB because it seemed to me that two things happened there. One, we had become fearful of oversight and review bodies, and I think we may have learned the wrong lesson. I think that there are ways to deal with that experience. And two, I think something happened at this stage of the debate that we didn't pay enough attention to. And that is that we had always known about the controversy about abortion in these issues, but a newer controversy actually emerged in the EAB report; the ability to fertilize a human egg outside of the womb gave a new dimension to the controversy. It was not just human status, it was also a concern that science was proceeding faster than the human mind was capable of following. There was fear even then, if you look at the literature about cloning. It seems crazy now, but that's the other time when everybody wrote articles about cloning and everybody was very upset about cloning, even though we were really far away from being able to contemplate it realistically. And the other fear and concern was genetic engineering. And that is, if you can manipulate the human embryo, then you had to worry about engineering as well.

That brings me to the Human Fetal Tissue Transplantation Research Panel, which was established in 1988. First of all, I'm going to say that I could not say anything better than Jim Childress said already about this panel when he wrote a report for an Institute of Medicine book titled *Biomedical Politics*. And so I urge that the panel, if you don't have it already, be given that article, in which he describes the origin of the controversy and also makes quite clear how the abortion context dominated and controlled the discussion of those issues, even though it was clear that there was at least

one competing model for discussion, namely transplantation, that the panel was rarely permitted to engage in at any depth. From my point of view, it would have been a preferred route to discuss both the abortion issues and also be able to discuss how much fetal tissue transplantation issues resembled transplantation issues in general, to give the public a fuller appreciation of the issues at stake. It would also have been better if we could have had a fuller discussion, because we might have outlined in a careful way, if we had been permitted more time, the other moral issues at stake and the value issues at stake in fetal tissue transplantation other than just the morality of the embryo.

For example, we could have discussed at length the vulnerability and protection needed as an ethical issue for women who are about to undergo abortion. We could have discussed the moral and ethical issues in more detail with respect to trying to ameliorate Parkinson's disease. Although all of this lurked in the background, it just was always overshadowed - the importance, from an ethical or moral perspective, of trying to heal, cure, or ameliorate disease for others. They too, it seems to me, are compelling interests. And notice I distinguish these issues from the imperative of science, which is the more we know the better we are. I'm going to stay very carefully away from that, because I think if we get too far into that it would justify anything. What I'm trying to suggest is developing the other issues that are at stake in these debates.

It's very hard to discuss the Human Embryo Research Panel because one never likes to point out one's own mistakes. But I will take a shot at doing that. The Human Embryo Research Panel was created in 1994, and it was created as a result of a provision that Congress placed in the 1993 NIH Revitalization Act, which rendered EAB review legally ineffective - thus opening up the possibility of being able to do embryo research. First of all, I want to make clear that I think the NIH behaved incredibly responsibly in the way it chose to deal with that congressional provision. There was no requirement that it hold public hearings, consult experts, consult the public, and try to develop guidelines for that method of conducting this research. And I think that often

that fact is forgotten - that the NIH itself understood the need to have guidelines that were developed outside of the department. I do continue to believe that the panel's recommendations are sensible and defensible. And as you know, with respect to embryonic stem cell research we recommended that such research proceed as long as an embryo resulting from IVF or infertility treatment or clinical research that had been donated with the consent of the progenitors was used. The panel was quite divided on whether such research should be permitted where the research was done with embryos that had been created for that purpose, and recommended not that it be permissible research but that it await further study. There was one dissent, one person who argued that it was unacceptable research and should never be done.

How do I assess what the panel did? First of all - and there are lessons for the future here - I continue to believe, and I dissented on this point, that the panel seriously underestimated the concern of the public about science getting too far ahead of the rest of us, in terms of our values, to keep up with. There were real problems with whether humans should create and try to control human life. I might add that this concern has been fueled even more since then by the cloning research and the discussions of cloning and genetic engineering that have followed. I agree with the critics who say that the panel should have avoided looking in any way as though we had adopted our own view of the moral status of the fetus. As I said before, I don't think that's going to be resolved in our lifetime. And I certainly agree with the critics who say that the panel could have done a better job of justifying its conclusions. I believe that I understand that the pressures we were under made it much more difficult for us to do that, and we, too, were operating within this abortion framework. If I had it to do over again, I would do what I was suggesting here, and that is that the panel give extensive time to considering the other moral issues that are involved - for example, that the vulnerability of infertile persons who contributed embryos and gametes be addressed by looking at issues of informed consent. I believe that to be insufficient, that we really needed to go much beyond that. Protection of vulnerable people, for example, may also involve careful scrutiny of the research that you're asking them to make their

contributions of embryos and gametes to. It may be of concern to them what kind of research they participate in. We may have to do more in terms of isolating them from some of the pressures that operate within the infertility centers where they are found. So I would hope, if we did it again, that we be more careful in developing our rationale for these other moral issues.

What are the prospects today of stem cell research? I think that the prospects, and I hope you will indeed do this, of government being able to fund this form of research are better than they were in 1994. And there are several reasons for that. One, I think that the potential benefits of the research are clearer, and clearer in two ways. One, they are clearer in the sense that what is possible seems closer at hand today than it did in 1994, when we were certainly doing a lot of speculating about what the benefits would be. And two, the prospect of clear benefit is clearer today because in 1994, what was clearest was that we might be able to benefit infertile couples who were seeking to have a child. Today I think it is the case that we not only have the prospect of helping such couples but we also have the prospect of helping a much wider array of diseases and persons with diseases. This I believe is really important because even though the suffering of infertile couples is real, not all are convinced that research to assist persons to have children is a sufficiently weighty research to justify or outbalance other kinds of concerns that they might have. So I think the prospect of what we can offer is clearer. Two, I think that the prospect or the need for national Federal oversight is clearer. As I said before, there's always been controversy about whether we want to have continuing bodies. The EAB's existence and the controversy ought to give us pause, but I think that the reasons for having national Federal oversight are important. First of all, we are clearer since 1994 that the regular review and oversight process for human subject research in general is not as satisfactory as we would like it to be. To take a really controversial area and argue that much or some of this research can be reviewed at a local level I believe would be a serious mistake. The last thing we need is something passed in Massachusetts and held up in California in a very controversial area of research in terms of difference in local review.

Second, I think we need a national body to oversee the science. We need this for several reasons. This is a way of making sure that guidelines are adhered to. Two, it's a way of making sure or of assuring the public that nothing is going to go further than we have promised them that it would. And this is very important, because some of the research that we're talking about that has these possibly good benefits is also the kind of research that may lead to other consequences that are frightening or unwanted. So we need some assurance of that. We need a public body to do interpretation and application of guidelines, a body to let us know that the research is worth doing. You at least want those factors in place when you're dealing with this kind of controversial research. I think we can get there with the consensus is my final thought, because unlike others I do not believe that abortion resolves these issues. One can be pro-choice and be against some embryo research, as I was. And some people are pro-life and can vote for Federal funding and oversight of research.

I want to quote to you from the chair of the HIFFRA panel: "At least for me, the problem has been weighing one major concern, my objections to abortion, against another major concern, making it possible to do medical research that can improve the lot of thousands of our citizens in a sensible and rational way." He says he was able to concur in the report of the HIFFRA panel because he wanted to prevent commercialization of fetal tissue use. He liked the separation of the procedure of acquiring tissue from the use of tissue. He thought that with Federal funding we would employ more careful scientific approaches as well as utilize the highest professional standards, and finally, he thought that without government funding research would be unsupervised and not governed by guidelines. It seems to me that his arguments, made by a person who considers himself in no way in favor of abortion, is at least some evidence that persons who set out to try to reach consensus or try to work together may end up doing so. Thank you.

PROF. CHARO: Thank you, and let me extend Dr. Shapiro's apologies; he was just called out of the room for a moment. Because I have a feeling some of the

questions may relate to both of your comments, I'm going to suggest that Professor Robertson go directly on and we save the discussion for after the second presentation.

PROF. JOHN ROBERTSON: I have some overheads.

PROF. CHARO: Sure.

PROF. ROBERTSON: May I approach the bench?

PROF. CHARO: Yes, you may approach the bench. Did you get a mobile mic? Ah, there you go.

PROF. ROBERTSON: First, let me thank you very much for the opportunity to come and present on this topic. As we know, this is a very promising area of research, but there are ethical issues primarily because the source of the stem cells is either from aborted fetuses or from preimplantation embryos. With regard to stem cells from aborted fetuses, a couple of words about that. We do have some prior experience with that. Obviously the cells are retrieved after the death of the fetus and there's no question of them being totipotent or embryonic in themselves. The main ethical issue here that has evolved in the debate is a distinction between abortions occurring anyway, and fetal tissue derived, versus having abortions to get fetal tissue. And it was that main distinction that drove the conclusions of the 1988 NIH Fetal Tissue Transplantation Research panel that Pat King just talked about, which I was a member of as well. And that panel was appointed to assess whether a moratorium on fetal tissue transplantation research should continue or not. It examined the issues and came down on the side that the key issue here is whether the tissue is being obtained from abortions that are occurring anyway. If so, it may ethically be used as long as the consent or the use of the tissue was arrived at after the consent to the abortion itself - a wall between the two decisions - and as long as there was no financial reward to those donating tissues or any change in abortion procedure. And eventually Congress, even though HHS

Secretary Sullivan at that time refused to lift the moratorium on the basis of that report, in 1993 Congress enacted legislation that banned moratoria on fetal tissue transplantation funding and incorporated it into law with some conditions under which that should occur, which we heard about this morning, essentially taking over the recommendations of the panel.

Now with regard to stem cells from still-preimplantation embryos, again, the first issue here is the impact on embryos, and I think we're aware that embryonic stem cells would be removed from the inner cell mass of the blastocyst and essentially destroy the embryo. However, the retrieved cells are not themselves embryos - are not themselves totipotent - as was explained this morning. So therefore the research that is occurring on the retrieved stem cells is no longer itself research with embryos. And as general counsel to HHS Harriett Rabb ruled in their ruling memo, which was handed out this mornings, she came to that conclusion as well. So it should now be clear that there could be federal funding of embryonic stem cell research with the stem cells themselves after they have been derived from embryos. And as many of you are aware, Senator Specter is talking about a bill to that effect as well. And so with that clarification there is a great deal of room for research with embryonic stem cells to occur that does not involve research with embryos. But it is inevitable that at some point it will be necessary to have research that involves derivation from the embryos themselves, either because the existing lines or panels of embryonic stem cells will not serve all purposes or there will be new needs as our scientific panel this morning commented on. And at that point we face the issue of the ethics of embryo research for the purpose of obtaining and then studying embryonic stem cells.

This takes us to the key ethical issue of the moral status of spare embryos and the moral acceptability of research with spare embryos from IVF. And here it's important to distinguish those who take a strict right-to-life view and view the fertilized egg itself as a person or human subject - they of course would be against this, whatever the purpose, as we heard in some of the public comment this morning. However, it

appears that that is not a dominant view. Every ethics commission, at least in the United States, Canada, the U.K., and other places that have reviewed the matter, has come to a consensus - which is reflected in law in Anglo-American jurisdictions as well - that the early embryo, the preimplantation embryo, is too rudimentary in development to have interests or rights in itself. It's still not committed as an individual because spontaneous twinning could occur. There's no neurological development yet; there are no differentiated cells or organ systems as yet. So as a result, the dominant conclusion has been that the preimplantation embryo is not itself a person or individual. It lacks the capacity to be harmed because it is too rudimentary in development to have that capacity. However, that is not to say that it should be treated like any other tissue. Special respect is owing it because it is a potentially developing form of human life. And that special respect is especially important if transfer to the uterus were to occur, because then preimplantation activities could harm the resulting child. However, even in cases where no transfer is intended, still a special respect is important here because it's a symbol, or it denotes human life, or it's a form of human life. So therefore it's not to be treated like any other tissue.

However, the conclusion that's drawn from that is that it is ethically acceptable to do things with discarded spare embryos, as long as it's not trivial or not serving a good scientific purpose. So, for example, it's widely accepted that couples may fertilize many more oocytes than they will ever transfer to the uterus in the hope of overcoming infertility. And it's also accepted by the commissions that have looked at this that it's acceptable to use discarded embryos in legitimate medical research. And if that's so, it would follow, then, that the use in acceptable medical research would include embryonic stem cells as well. And I might just note in passing how previous commissions that have looked at this, both in the U.K. and the U.S., have arrived at exactly the position that I've just talked about. The Warnock Committee in 1984 in Great Britain, where as you know IVF was very successfully achieved in 1978, held up essentially what I just summarized: an embryo is not itself a person but deserves special

respect - yet embryo research would be acceptable. And the legislation passed on the basis of the recommendations of 1990 took that position as well. And it had a list of acceptable purposes for embryo research. Those purposes related to overcoming infertility and preventing congenital abnormalities. Now under that schedule embryonic stem cell research was not one of the listed purposes, but the secretary of health in Britain could certainly add it, and indeed there's recently been a Human Genetic Advisory Committee that has recommended exactly that - that the schedule be changed to permit embryonic stem cell research. And in the United States, as Pat King has reviewed and as several members of the embryo research panel on this Commission know, the Ethics Advisory Board in 1978 found it acceptable to use spare embryos in research, again on the theory that the embryo was not itself a person because it had too rudimentary a development at that stage.

The Human Embryo Research Panel essentially found the same thing and came out in favor of many kinds of embryo research acceptable for Federal funding, including embryonic stem cell research. Now the hot issue; excuse me - as you know as well, the political reactions to the Embryo Research Panel. The President accepted the recommendations with regard to spare embryos. However, Congress soon added an appropriation rider to ban any Federal funding or embryo research and that ban, through a series of other riders, continues in effect today and is a major limitation on embryo research. I just point out that's what the basis of that ban is. And it's unclear. It seems to me that it really reflects - I guess I should cross out "minority" because the majority of Congress voted for it - but it seems to reflect either the view that embryos themselves are persons and can't be used in research at all - which all the commissions that have looked at this, including the Human Embryo Research Panel, disagreed with - or it reflects the judgment that, well, maybe they're not persons, but they still symbolize or are former human life, and it just isn't worth the benefits we would get from that.

One or two of those positions underlie the current ban. Obviously, if you disagree with that, if research with spare embryos is acceptable, then stem cell research

with spare embryos should be as well. Let me then just talk for a moment about what is the most difficult issue in this area, the issue of creating embryos for embryonic stem cell research. You're actually in a fortunate position. In a sense you don't really have to grapple with that as fully as the Embryo Research Panel did because that's not going to be an immediate area of research, I take it, for some years to come - at least three to five years, maybe more. The real needs of embryonic stem cell research are to get sufficient numbers of embryonic stem cells in a reliable way, and then after that to learn how to direct their differentiation into certain kinds of tissue. Only after that is done in a reliable way consistently would one have to face the issues of histocompatibility with the ultimate recipients of tissue transplantation, which would then raise the issue of creating embryos for research. But it's certainly possible, and as I say, that's likely not to happen in the next three to five years, so in a way you could put that aside if you want. But at some point, if the research develops the way it's expected to, that is going to be an issue. At some point the issue of histocompatibility between the tissue cells derived from embryonic stem cells and the immune system of the recipient is going to be a major issue, and at that point it may become necessary to create embryos solely for research to test out histocompatibility - as the Human Embryo Research Panel recognized, either to create libraries of stem cells compatible with many people in the community or to create histocompatible embryonic stem cells through nuclear transfer cloning so that they're compatible with the cells of the recipient. And at that point, one would have to face the issue, and I would argue that one should find it ethically acceptable, and indeed deserving of government funding, to go ahead with such research.

I'm just going to review for a moment the ethical ideas there, because you might have to face them. Obviously, in the ethical analysis of creating embryos solely for research, persons who view embryos as persons themselves and who are against all embryo research would be against doing this. So the real ethical debate arises with those persons who approve of embryonic stem cell research with spare embryos because they agree that embryos themselves are too rudimentary to have rights or

interests. It's that group that poses the challenge on this issue, because that group actually breaks down into two subgroups. One part of that group who say spare embryos may be used for research seems to me to approve creation of embryos for research purposes if there's a good purpose that could not otherwise be conducted, again because the embryo created would not be harmed, and again because this would not be inherently disrespectful to human life because it would be for a good purpose that could not be carried out in any other way. It's the other group - those who approve of research with spare embryos but who have difficulties with creating embryos for research—that is of interest ethically here, and I think Pat King said she was in that group for certain purposes at least. It seems to me very helpful in reviewing this debate to try to come to terms with what the objections of that group of people are. Now note: it can't be because creating embryos for research would harm the embryos, because people who are taking this position already agree that you may use spare embryos from IVF for research because they're too rudimentary to be harmed. So their argument really has to be based on other grounds, such as consequentialist grounds or deontological grounds, such as the consequentialist concerns that have been raised in the Human Embryo Research Panel report that it could imperil other research subjects.

Professors Annis and Kaplan have argued, in the *New England Journal of Medicine*, that it would demean procreation. Some people have argued it would be inherently disrespectful of human life, and yet people making that claim have never really shown how that effect occurs - what the precise mechanism is for creating embryos for research, how that is really going to affect our attitudes toward other human research subjects or toward procreation or toward people as a whole. And indeed, we're talking about such a small number of cases of creating embryos for research that it seems highly unlikely that those kinds of effects could occur. A second line of attack, then, has been deontologic, the old, important Kantian ethic: Don't use persons as mere means; use them as ends in themselves - a very important part of our ethical tradition. Well, the problem with applying that to creating embryos for research is that embryos are too rudimentary in development to be persons or to have interests in

themselves. So therefore the Kantian ethic would not apply to them. And indeed, people who make this claim often permit spare embryos to be used in research, but if you're using spare embryos in research, at that point you're using them as mere means as well. There's an apparent inconsistency there. And they sometimes say, "Well, it's inherently disrespectful of human life." But if the human life does not have the status of a person or an entity with interests, the question is, How is it inherently disrespectful of persons?

So it seems to me that some of the concern is what we may call symbolic or constitutive - that is to say, the idea that, well, it just denotes disrespect for human life if you're going to create embryos, even though they're at a very early stage of development, use them for research, and throw them away. And there's no real answer that one can have to that. People hold that view and it should be respected. But not everyone holds that view, and I don't think it's morally obligatory on us to hold it. Ultimately, what we're dealing with here is a judgment of how much disrespect for human life would occur from such procedures, given that we allow more embryos to be created for IVF than could ever be transferred, and given that we allow spare embryos to be used in research - how much more disrespect, if any, is created in light of the benefits that would be achieved? And if there would be very great benefits, such as might occur from stem cell research, and if indeed one views it as not a great deal of additional disrespect for human life, one could come out in favor of that. And it's interesting that the commissions that have looked at that have reached essentially that result. In the U.K., right from the beginning the Warnock Committee approved the creation of embryos for research. The Human Fertilization Embryology Act adopted that as well by even a greater margin. Of course, as I've said earlier, to do embryonic stem cell research with embryos in the U.K., whether spare embryos or created embryos, the schedule of acceptable purposes of research has to be changed, but if it were there would be no objection in the U.K. to creating embryos for research. In the United States, this question was not before the Ethics Advisory Board in 1978. It's interesting that the

Human Embryo Research Panel did in fact approve for Federal funding the creation of embryos for research when it was necessary to conduct the research, or when the validity of avowed research could not otherwise be conducted. Now, as Pat King said, they did not specifically say you could create embryos for embryonic stem cell research, but they recognized that that warranted further review at a point in the future when there was more evidence of the need to proceed. Indeed, they recognized that that might be a valid purpose, such as in cases of histocompatibility and even recognized nuclear cell transfer as a form of doing that, and it seemed to me they strongly implied that it would be acceptable for Federal funding in the future when the need could be shown.

In conclusion, then, let me offer, with your indulgence, some suggestions and recommendations for what the NBAC should do on this issue. And it seems to me that first of all, with regard to embryonic stem cells or stem cells from aborted fetuses, follow the 1989 NIH Fetal Tissue Transplantation Research Panel guidelines, which have now been incorporated into federal law, and support stem cell research with aborted fetuses when that's appropriate, in strict conformance with those guidelines. With regard to stem cells from embryos, clearly emphasize that the stem cells themselves are not embryos - are not totipotent. And second, that once the stem cells have been removed from embryos it's no longer embryo research, and therefore falls outside of the restrictions of Federal law on embryo research. General counsel Harriett Rabb agrees with that, and indeed Senator Specter has a bill that might make that clear as well. However, when it becomes necessary to derive the cells themselves as part of this research, it seems to me that the NBAC should follow the 1990 guidelines on this from the Human Embryo Research Panel report, which would be that it's acceptable for Federal funding with spare IVF embryos. And you might want to consider, or not, that if the need arises, which it may not for some time, but if it does arise, to create embryos for research for histocompatibility purposes, that that should be acceptable as well, as the Warnock Committee and as the Human Embryo Research Panel I think implied. Finally, then, the last pointCit was just made, I think, extremely well by Pat KingCis the importance of a Federal presence here, both because Federal funds will spur the

development of research and also for the additional reason that it will provide a greater regulatory oversight structure, which I think is long overdue in this area. Thank you very much.

DR. SHAPIRO: Thank you very much, and thank you both. Let's now open the floor for questions from Commissioners. I have some questions, but let's see - Tom?

DR. MURRAY: My question is actually for John [Robertson], who is I notice is still wrestling with something there. Microphones? My question is for you, John, but it's really based on some things that Pat said earlier. By the way, thank you both very much: very clear, very helpful, right-to-the-point presentations. Pat noted that, if I understood Pat correctly, that in an effort to achieve consensus one might end up proposing as public policy something that you don't think is or may not be strictly everything you'd want to get given your particular moral analysis of the situation, but it might be an acceptable kind of consensus. Now, would that, bearing Pat's comments in mind and bearing in mind also the response to the Human Embryo Research Panel's split over it - although in the end the majority voted to permit, under special circumstances and with lots of caveats, the creation of embryos for research. And that being the part of the report that probably provoked the strongest public reaction, and in fact was immediately stricken from it, the President immediately decided to disown that part of the report. Given all that background, what would you say was the wisdom, or lack of wisdom of a proposal from a panel such as this to permit embryonic stem cell research to go forward but not to recommend that the creation of embryonic stem cells be permitted? Not to permit the creation of embryos for the purpose of this research to be committed? Sorry for the length of that question.

PROF. ROBERTSON: I don't care; it's a good question. I would say that that's the minimum position you could take, would be my advice here: It's the minimum position to take [INAUDIBLE]. On these difficult and controversial

issuesCthe areas involving human embryonic stem cell researchCthat that itself could detract away from other aspects of your report, so it has to be handled in a very careful way. So the question would be how to handle that, and the way to handle it is to duck it by saying that that's not immediately before us. However, as an ethics commission-

DR. MURRAY: I might phrase it differently than "duck it." I might say-

PROF. ROBERTSON: Well, it's an area of public controversy. I'm sorry-perhaps that's not the best way of putting it, but to avoid expressing a definitive position on that point-I wasn't sure. We're in Washington: you don't speak quite as directly, but you find other ways of saying the same thing. You may not want to address that issue at this point. I mean that's one option. However, as an ethics commission that to some extent has a duty or role to recommend what, perhaps, should be acceptable public policy even if the public policy is not ready for it, I think you should also consider at least pointing out how previous commissions, despite the controversy in this area, have almost uniformly come down in favor of the creation of embryos for research in limited circumstances where there is a strong need that could not otherwise be accomplished.

DR. MURRAY: A quick follow-up, because in fact there was a nearly 50-50 split on the Embryo Research Panel. So you say, yes, they can. In the end the report came down that way. There was a lot of divisiveness, and quite frankly I'm not sure anyone around this table today could tell you how this Commission would come out on the issue because we have not had the chance to talk about it, and I suspect you would find a variety of views on these issues. But I'm not sure it's ducking it; it might just be an honest recognition that this is a sensitive area on which there is room for debate.

PROF. ROBERTSON: If I could just say one other thing about that, and that is, of course that certainly would be your prerogative, and that may be how it works out. I think it's important, though, however you come out on it if you address this

issue, to get some clarity about the kinds of concerns that motivate the different positions. I think we will come out in favor of doing it, at least try to consider, [INAUDIBLE], as I try to do, a bit of what the concerns are.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Thank you both very much for your clear and very illuminating presentations. I have a two-part question I'd like to address to both of you, in part to help us see as much as possible where you've both come out on the question of the acceptability of using different sources of material for this research. The first part would be: Did you rank the sources? Now your answers are in part implicit already in some of your comments, but I'd like to sort of tease them out, get them out on the table before us and compare them if we could. How would you rank the possible sources, and would you in terms of acceptability say for various reasons - it might be ethical reasons, it might be reasons of public concern, etc. - how would you rank the sources? And second, what kinds of - to use language now from the Human Fetal Tissue Transplantation Research Panel - what kinds of safeguards or guidelines would you feel are important if we were considering the use of those sources to be acceptable? I'd like to hear from both of you, if you would.

PROF. KING: I think I can rank them. It would be a tougher question if you asked me where I would draw the line between what was acceptable and unacceptable. Clearly, and easiest to justify, I think it would be in accord with the moral views of many more people, a range of views, to use fetal tissue as a source in part because we have been through that and because there is now an accepted regulatory scheme for that. So that's the easiest. The second, I think, would be to use spare embryos, although we made a qualitative leap. I'm doing this off the top of my head, Jim, and I can't - I won't get all of the factors in, but let me explain the similarities and differences. One, we are essentially talking about the same question about spareness, which has some ethical aspects to it in both fetal tissue and in fetal embryos that are

spare embryos. Two, this area of stem cell research, I think like no other area, is finally pushing us to grapple with how difficult this little point is between cell and embryo. We also thought it was a big leap. It turns out not to be as big a leap from different perspectives as we once thought, and I think that that has to be grappled with as well. But the fact that the stem cells can be taken from the embryo and one does not then need to continue to do so to use that embryo - if we are really successful in terms of being able to generate cells, we would be using very few embryos. This makes this a very close call indeed between one and two.

I, as you know, am one of those people who is very reluctant to go beyond the use of spare embryos in research, and so I would place it at the bottom of my priorities. I have never said "never" because I have learned over the years one never says "never." One has to think carefully about each new set of circumstances. One may still say "never," but you have to think carefully. But I can certainly imagine a time when we would need to use embryos that were created for research for some purposes. But I think if one is going to deal with that issue one ought not be speculative about it - that one needs to be right up on top of it. And unlike John [Robertson] - but I'm biased - I would say, "Stay away from it with a 10-foot pole and leave that to some later group."

But then you asked me about safeguards. I think that the Embryo Research Panel - I think it would be useful. My advice would be for you to review our guidelines. I think some of them can certainly be justified better - and carry it a little bit further. Maybe you will find some of it unnecessary, but I think we worked hard to try to come up with some guidelines. So that's certainly a source. What we were basically trying to do was no commercialization. It was a question of consent from those from whom we obtained the tissues. We were concerned about minimal risk, but I think not concerned enough, frankly. But we were concerned about the vulnerability of women in particular in being asked to give up their eggs for research. It's a very hazy area, where

somebody is treating you for infertility and you're using your ova, not to use some of those ova for other purposes when you're looking at the one person who offers you hope of being able to have a child of your own. So my own recommendation is that you might look more carefully at the guidelines in that area, because I think we just didn't have sufficient time in discussion for me in those areas. But finally I would say, and I won't repeat the reasons, that I think not trying to do all of this at once is a critical lesson to be learned. I'm from the old school. The nose under the tent is still the nose under the tent. We don't have to have it all, but you need to make the strongest cases you can make for what is there, what offers real hope and prospect, without trying to have it all, because I don't believe that anybody is going to have it all on any of these controversial issues, so my committee for me is critical. If you didn't have a continuing review body I think a lot of the safeguards would fall down. And certainly I think any kind of public trust would be undermined if we didn't have some sort of public body. I could talk about that public body in more detail, but not necessarily as a safeguard.

DR. SHAPIRO: John, do you have any response to that?

PROF. ROBERTSON: I'll just try to be brief on it. Obviously, on the hierarchy of how to rank the sources, creating embryos for research is the one that would pose the most problems. And I think it's the least necessary to address now, because the need for that research is still far off. As between the other two, and just as a practical approach, if there is a clear set of rules enacted in legislation after an advisory panel with regard to fetal tissue and the conditions under which it would be used seems to pose fewer issues. However, the research might show that it's more essential to get stem cells from embryos, and so that will have to be faced as well. As I said to Dr. Murray's question, I think at a minimum it would be helpful to the public, the community at large, and to researchers to address the issue of research on spare embryos. The only thing I'd say about the safeguards is that I, for one, think the Human Embryo Research Panel did a terrific job. I know it's been criticized and some of its own members have had second thoughts, but just as someone out there reading

about those who have been involved with the field, when you look at it again I think they did an excellent job. And I thought the provisions, the guidelines for protecting donors and such, are excellent as well, so they would serve as a useful start.

I just want to add one other aspect to that. When you start asking couples going through infertility treatment and have spare embryos to donate them for research, you have to be very careful about that. But in the reality of it, those couples are now facing storage charges to keep those embryos frozen, and it is inevitably going to affect their willingness to continue storage of their embryos. Indeed, the fact that they may be able to donate them for research may be helpful for some couples. So I think that's an aspect that you may want to explore further.

DR. SHAPIRO: Okay. There's a long list of Commissioners who want to speak, so long that unless you don't have any more questions like Jim, who managed to ask four questions at once to each of the panelists, we just won't have time for that with this long list here. So I'll ask people to try to ask one question, and our panelists to answer only one question also. Larry?

DR. MIIKE: My question goes more toward the assumption that we work under. If we take this out of the context of abortion and embryo research, to me it becomes a question of the NIH saying "scientific opportunity," and people like me saying "burden of disease." In other words, who sets the priorities? How wide a parameter do you deal with? So in the context of this discussion, when we talk about the three choices about aborting fetuses, excess embryos, and embryos created for research, I don't see why we need to take an all-or-nothing approach and say all of these. Because I think that over time, as we have seen, if one restricts an avenue one way it forces the researchers to find alternatives to get to the same place. And I'm struck by one of the comments that was either from the 1988 or 1994 report, where one of the senators said under no circumstances would she approve stem cell research. But if you look at that in the context of today, I wonder whether that same question would apply

and whether she would answer it the same way. So I guess - it's not so much a question, but I guess I'm agreeing with you, Patricia, that I've always been a pragmatist rather than an absolutist, so I am sort of encouraged by what you have seen as a lesson from working on those past commissions.

DR. SHAPIRO: Bernie?

DR. LO: I want to first thank both Professor King and Professor Robertson for giving us a lot to chew on. I want to follow up this line of thought having to do, really, with the tempo and pace of trying to forge what you called an overlapping consensus, Pat. A lot of the ways we're talking about it, it almost sounds like we're saying that we're going to get there eventually. Let's just go step by step and sort of do a little and make sure everyone kind of understands it and feels comfortable with it and demonstrate that we can do it responsibly, and then take the next step. I guess maybe it is a two-part question. But I guess one question is, Is that the wrong model? I mean, shouldn't we allow the possibility that we may say that this is the least morally problematic public policy, and start with that? And then if we try and we say we were wrong, we're going to stop there because we discovered some things we hadn't anticipated. Sometimes we talk as though we're going to get to allowing creation of embryos, but just how quickly?

But I want you to comment on is it all irreversible once we get that nose under the tent? Second, what else needs to happen to make - if we can reach consensus on anything, which we haven't yet as to public policy - what else do we need to do to try and keep enlarging that consensus into larger circles? Because I think we haven't really paid enough attention to what else has to happen to develop this kind of exceptional public policy, so primarily to [INAUDIBLE].

PROF. KING: I'm not wedded to a particular model. I am sort of wedded to a particular view of how to do public policy. I am wedded to it in this way,

based on experience, and that is that the issue is so controversial, as we all know, that the only way that one can reasonably proceed is not to be too speculative. We have essentially a real problem that you can air out and get some consensus on, and move on that as was done in fetal tissue transplantation, and then you do a little bit of the next one. I don't think that's necessarily the best way to make public policy. I think that's what works for this one. And the reason I am interested in that is I have always been surprised all these years that those who have a stake in the research have not been as active as those who don't have a stake in the research. That's not entirely true; I have participated in efforts of my own to work with disease groups to do advocacy work, etc. Maybe there are too many disease groups. Maybe, I think, we may not have explained adequately what is at stake. I pointed out that most of these panels had inadequate time. When the National Commission was there for four years, they would do it in four months in which they hit the ground running to do a policy on fetal research. The Fetal Tissue Transplantation Panel was expected to act in what was it-one or two or three meetings on an enormously controversial issue. The Embryo Research Panel started out, then we had to add meetings. We really had no staff. One of the problems is that we have never been able to take one of these most difficult issues and explain it in a coherent way so that something was available for others. So, in terms of having public support and public interest in this beyond fear, it's up to people who want the research to explain it more adequately and to be able to talk about it. That is why I'm advocating the way I'm going. I hope-I'm going to get shorter, I promise.

DR. SHAPIRO: Thank you. We have only 10 minutes left for this part of the question period. I'll go down the list as far as I can take it, but it's not going to get everybody on. I apologize. We can take some other questions perhaps later in the afternoon. Steve?

MR. HOLTZMAN: Thanks. If I understand the two of you, you are actually advocating very, very different ways of going about analyzing or approaching this. Dr. King's way is, you said, to build on the ethical base not in examination but in a

more policy kind of orientation. Prof. Robertson is really tackling head-on the moral analysis. So this is directed to Prof. Robertson: If I understand your position, it comes down to what you said: basically, there is no ontological basis for respect for the embryo. And so, therefore, if one is going to have certain kinds of measures, for example, that suggest you should not create research-purpose embryos, it would largely be in terms of symbolic or constitutive kinds of concerns. I don't think "constitutive" is the right word, because you then talk about it in terms of no precise mechanism or causation of harm and that this is not morally obligatory. It's almost a matter of opinion whether these things really are involved. If that's the position you take, then I don't understand - and I respect that position - but I don't understand, then, how you come to the conclusion advocating all of the apparatus in terms of review and control mechanisms. What's the basis for those? Is the question clear?

PROF. ROBERTSON: I think so. But, again, you have to keep in mind that there are people who have strong right-to-life views who are against any embryo research, whether creative or not. So if you're asking me about creating embryos now, or about -

MR. HOLTZMAN: If we go down that path and adopt the analysis you suggested and agree with it, then how do we come to the conclusion that we should then impose on top of it various kinds of control mechanisms? Why isn't it just okay to do it completely willy-nilly?

PROF. ROBERTSON: What I tried to make clear, and it might take more time to do it, is that the basis of concern here isn't - unless you hold a strict right-to-life view - based on grounds of what is morally owed embryos in their own right because they're entities with interests. It has to be based on some other grounds - consequentialist grounds or grounds that this still matters to us, even though this is not a moral entity that we have to respect. But it helps define who we are. It helps denote our

degree of commitment to giving life. So it's those kinds of concerns. Now those kinds of concerns are still very important to people. They constitute who we are. They help define who we are, so that would be the basis for the other kinds of restrictions as well as the interests of those who are the sources of the gametes or the embryos.

DR. SHAPIRO: Alta?

PROF. CHARO: I'd like to ask both of you to reflect on your experience, specifically with the fetal tissue panel, on the issue of complicity. Complicity is a matter of discussion here at two levels: one, the degree to which the use of stem cells is tainted by their manner of derivation, so that anybody using the stem cells is somehow complicit with the underlying act, which many people object to; and second, that the use of public monies to support such research makes taxpayers who oppose it complicit with the research in a way that is fundamentally inappropriate. And this is a topic on which I would appreciate your reflections on the best discussion about what does or does not make people complicit with acts that were not their own directly, as it was certainly a matter of discussion in your panel. We see it in very routine ways when our IRB refuses to let PIs in our university work simply at analyzing data that was derived from people at universities who didn't follow rules that we think of as being ethically required. So we routinely take seriously the notion of complicity, and I was wondering how you answer that objection with regard to fetal tissue.

PROF. KING: I never try to speak in ethical terms; I like to just speak in common sense. The complicity argument to me was one that said, if we took it far enough, that everything was complicit with everything else. I mean, this is an act and a causal sequence that you can make into everything. The key is, can it be broken and where can it be broken? And that was the question for me, so that if a researcher-the other side of the complicity was encouraging women to have abortions. If the decision to have an abortion and the decision to make that tissue-available for science were totally removed from the decision to use any particular tissue, I thought we were going

down the right path, that they were getting a good separation. And there are lots of details about how you can enforce that separation, or make that separation apparent. But I think that there is no magical way, except to make carefully crafted arguments about what's at stake on each side to draw the line. It's like a spectrum argument. You've got to draw the line somewhere, and you can just as easily, sometimes, make the argument on both sides. But that's the approach I use. Complicity, in terms of taxpayers, is again one of these difficult arguments - I mean taxpayers pay for a lot of things that they don't approve of. I pay for a lot of things I don't approve of, and the issue is - that's why the wave on consensus is so critical, and that is if you can take people who start from diverse beliefs and get them to agree to a range of rules, you've gone far in saying, "I cannot satisfy your moral view about this, but I have tried to take it into account. I have tried to make it as less onerous as I can consistent with some of these other good and moral issues that I have identified." And I think you have to leave at that the more difficult questions of whether we should ever treat anybody who has moral objections to abortion with therapies that are derived from stem cell research. And I think you handle that by making it clear to them what has happened; let people choose whether they wish to receive the therapy or not.

PROF. ROBERTSON: I have two quick comments on this. I agree with everything that Pat King said in her last point on how to actually operate such a system. I think it's very important. If you look at the Federal legislation on fetal tissue transplantation research that was passed after the panel, they go a long way in that direction by requiring notification, not only of recipients of such tissue of its source to let them [INAUDIBLE], but of researchers as well, because some researchers may not want to use material from the research source. So that would be a way practically of handling your more basic ethical or moral issue about complicity.

You raise a key point that was at the center of the fetal tissue panel's work, and I just want to make two quick points about that. One is that you have to ask if it's something that happens after an act occurs for that to be complicit with the act

itself; assuming that the act itself is wrong or immoral, you'd have to show that the later use somehow encouraged or brought it about. It seems to me it's very difficult to show that with abortions that are occurring anyway, just as Alex Capron's example earlier that the murder is occurring anyway, so then to use the organs doesn't make you complicit in the murder. Well, in the embryo research area, even if someone who is not funded is deriving the stem cells you could say, "Well, the reason that they're deriving the stem cells is because they think it's going to be used later in research," and that might be a case where the later use is influencing the first. On that issue you have to address the morality of the first act and question whether it is indeed wrong or unethical. Because if it is wrong or unethical and it's done because the later use will then take place, then that's an argument against the later use if you can show that actually. If there is that connection, you have to ask whether the earlier act is itself wrong or immoral.

DR. SHAPIRO: Well, with apologies to Trish and Bette and Carol, Alex, you get the last question. You're the next on the list.

PROF. CAPRON: I hope that we will get a copy of your remarks, your statement, and your overheads. And I wanted to focus in on something that Steve Holtzman had begun to raise, or had raised very nicely, and this is just a follow-up. Your phraseology about that was interesting to me, John, on the symbolic. You said that symbolic harm is minimal because there is no other way to conduct important research. And I would have thought that one might say the symbolic harm is justified because there is no other way to conduct research. Your suggestion was that the symbolic harm itself was lessened, and I'd just like a sense or two of elaboration on what your meaning of symbolic harm is. I'd just like a follow-up.

PROF. ROBERTSON: Well, let me say that the use of the term "symbolic harm" is a way to try to get at the concerns of people who otherwise accept

embryo research on spare embryos. It's a way to try to describe a strong feeling that a lot of people have. I'm not sure it's been adequately elaborated in the ethical literature, and the "symbolic" talk is a way of getting at that. It seems to me that I used it the way I did because if you're creating the embryos for research for a very good reason, then you are not really showing disrespect for human life as much as if you used it for a less compelling reason. Now you can put that in justification terms, but given the inarticulate nature of this response in people, I find it equally accurate to talk about it as the symbolic harm is minimal in that case. Because you're not doing something in a trivial or disrespectful way, you're doing something for a good reason and, indeed, you're doing something that's not all that different than other things that we do with embryos. I'm not sure there is this clear and analytic distinction here as your question raises, but I think it's worth thinking along those lines and the basic inarticulated nature of what the underlying symbolic concern really is.

DR. SHAPIRO: Just to clarify, because I was interested in the same question - the question focuses, I thought, on the question of minimal symbolic harm. Where did that evaluation come from - minimal as opposed to some other measure?

PROF. ROBERTSON: Well, it's more an inductive statement, if you will, given that when you go back to all of the commissions in this area, they are willing to use their embryos for research. While this is still an early form of human life and it's still alive, why are you willing to do it, and the Warnock Committee and then the Human Embryo Research Panel, even willing to go forward and create embryos for research? Again, it just seems to me that that's an accurate way to describe what they have not attempted to really ground in a very new way.

MR. HOLTZMAN: You can get your way by formulating it by saying that you're reformulating the description of the act to include it.

PROF. ROBERTSON: Yes.

MR HOLTZMAN: I mean, therefore, that's why it changes, okay? The problem that we are having from this is by calling it symbolic as opposed to constitutive, where constitutive is built into the grammar of the concepts and how we live by them. It's not a matter of opinions. Where you're going to have problems is, then, at the back end of it, where you responded by saying you have these feelings. It is built into our response, and that's why we need to erect certain symbols in institutions to treat them in certain kinds of ways - a real long discussion.

PROF. ROBERTSON: It is.

DR. SHAPIRO: I have a response, but it's too late, as I said a moment ago. So let me thank you all very much for participating.

ETHICAL AND RELIGIOUS CONSIDERATIONS

DR. SHAPIRO: Now we have a panel on ethical and religious considerations. If our colleagues would please come and sit at the end of the table we'll get that started as soon as possible.

I know that some of you have deadlines, and we'll certainly respect those as best we can; I understand that some of you have to leave before the questions here. So just let me one final time apologize for keeping you waiting. We have, once again, a distinguished panel. I'm never quite sure what the order we put in our agenda comes from, but the order that we have is that we hear first from Dr. Parens of the Hastings Center, Dr. Baylis from Dalhousie, then Dr. Peters from the Center for Theology and the Natural Sciences, and Dr. Karen Lebacqz from the Pacific School of Religion. Obviously, the more concise and forceful your testimony, the more we'll like it. So let me start off with Dr. Parens.

DR. ERIK PARENS: Thank you. It's an honor to be here. Like Pat King, I'm going to try to put this issue of ES cells and embryonic research into historical context. However, I'm going to reach a very different conclusion than she did. I'd like to propose that the NBAC should address two issues that were not addressed in two reports that are, of course, quite relevant to embryonic stem cell research. First, NBAC's report on "Cloning Human Beings" did not address the issue of research on embryos created by means of somatic cell nuclear transfer. Second, the 1994 Embryo Panel Report did not address the issue of altering embryos by means of germ line gene transfer, exactly the opposite direction from that Pat [King] wants us to go in. In light of the creation of hybrid human embryos and the isolation of embryonic stem cells, the NBAC, in my view, has an excellent opportunity to grapple with those issues at one time in one report. If the NBAC avails itself of that opportunity it will be taking an important step toward looking at what I am calling "the bigger picture." As I will try to suggest a little later, the bigger picture is - hold onto your hats - the bigger picture is of us genetically shaping our children. I'm sure you'll be relieved to know I'm not suggesting that by spring the NBAC should tell us how far we should go in that shaping. But I am suggesting that that is the bigger picture and that an excellent report on hybrid embryos and embryonic stem cells will acknowledge their place in that bigger picture.

So now to the first issue that I just asserted the Cloning Report did not address: the acceptability of using somatic cell nuclear transfer to produce embryos for research. It might seem that despite the Cloning Report's silence on that question, the answer is clear if one just puts the results of that report together with the results of the Embryo Panel Report. According to the Embryo Panel Report, one may do research only on embryos that were originally intended for the purpose of reproduction unless the research meets one of those two conditions the ES cell research doesn't meet. According to the Cloning Report, it's not now acceptable to use somatic cell nuclear transfer to produce embryos for the purpose of reproduction. It might well seem to follow from those two results that it would never be acceptable to do research on embryos created by means of somatic cell nuclear transfer, at least not ES cell transfer.

In slightly different words, one might think of it this way: In doing embryonic stem cell research, you may only use embryos initially intended for reproduction. No embryos intended for reproduction may be created by somatic cell nuclear transfer. Therefore, you may not do research on embryos created by somatic cell nuclear transfer. That might be the conclusion that the NBAC would reach if it were to take up the question. But I want to suggest that that's not necessarily the conclusion it should reach. That's because, as a comparison of the Embryo Panel Report and the Cloning Report makes clear, means matter morally. Whereas it is acceptable to use IVF as a means of producing an embryo for the purpose of reproduction, it is not acceptable to use somatic cell nuclear transfer for the same purpose. And we've been told already, indeed Britain's Human Genetics Advisory Commission and their human fertilization and embryo authority have jointly suggested, that it's not acceptable to use somatic cell nuclear transfer for reproduction, but it is acceptable to use the same means to produce embryos for research. I can chart that out for you later if you want-it's an interesting chart for those of you who like graphs better than words.

Although I admit I don't quite envy you, the NBAC needs to return to the "creation of embryos for research" debate. When it does, it will need not only to revisit the significance of the intention of the maker of the embryo, it also will have to begin to ask what moral difference the means make. And as I want to suggest when I take up the nature issue that the Embryo Panel set aside, the NBAC, more than any earlier groups, will have to begin to consider a wider range of purposes to which those embryos can be put. Before I turn to the Embryo Panel Report and the second major issue I think the NBAC should address, I want to acknowledge why the issue of using somatic cell nuclear transfer to produce embryos for research might seem irrelevant to a discussion of the entities created by Advanced Cell Technologies [(ACT)]. By the way, that work has come up hardly at all today-I'm not exactly sure why. After all, should we even call ACT's entities hybrid embryos? One reason not to call them embryos is clear: if they can't become organisms, they lack a crucial property of embryos and may seem unworthy of the name. It strikes me, however, that there are at least two reasons

why we should call ACT's entities embryos. First ACT's entities possess a crucial property of embryos: They conserve the source of embryonic stem cells. The second reason to call them embryos is, to my mind, more important. It has to do with what we might call the rules of engagement in public conversation. In my view, the research community has an obligation to speak openly and clearly to the public about what they're doing. Even if a given line of research is funded privately, that research could never have gotten underway if it weren't for this country's extraordinary publicly funded scientific infrastructure. Indeed, the aspiration to openness and clarity seems to be one of the primary things that moved Michael West to make ACT's work public. But I think if we aspire to openness and clarity we ought to go all the way. We even ought to risk incurring the anger and/or anxiety of some of our fellow citizens. Let us call things by the same names as would most speakers of the English language. To most speakers of English, if you take a human somatic cell and use it to enucleate a human egg, you get a human embryo. If for some reason that embryo is not viable, you would call it a nonviable human embryo. If you take a human somatic cell and fuse it to an enucleated cow egg, you get a hybrid embryo. If for some reason that hybrid embryo is not viable, I think most of us would call it a nonviable hybrid embryo. Because of the confusing ways in which ACT's entities were described in some places, many people seem to be under the impression that ACT's use of somatic cell nuclear transfer is a direct route to hybrid embryonic stem cells. But of course it's not. ACT's technique, somatic cell nuclear transfer, is a direct route to perhaps nonviable hybrid embryos, which in turn can be a source of human embryonic stem cells.

Thus I would suggest that the results of an inquiry into the appropriateness of creating embryos for research by means of somatic cell nuclear transfer would indeed be relevant to a discussion of ACT's work. Even if the NBAC could not agree that we should consider ACT's entities hybrid embryos, given how much reasonable enthusiasm there is, it seems to me that there's a public need for the NBAC to speak directly to that issue-that is, given how much reasonable enthusiasm there is for using somatic cell nuclear transfer to produce embryos for research. From

the easy issue - the issue that the Cloning Report set aside - now I want to turn to the issue that the Embryo Panel Report set aside: altering embryos by means of germ line gene transfer. Before I suggest how embryonic stem cells facilitate germ line gene transfer I need to underscore a point: the scientists and companies doing the research we're discussing today have no intention of using ES cells to facilitate germ line alterations. Nonetheless, there is an important reason to think that ES cells could, in principle, be used to facilitate germ line gene transfer in humans. All of you well know that one of the remarkable properties of ES cells is their so-called immortality. As Antonio Regolato put it in *Technology Review*, "Because ES cells grow tirelessly in culture, they give researchers ample time to add or delete DNA precisely." That is, because of their so-called immortality, ES cells are potentially a powerful tool with which to facilitate germ line interventions.

As we heard this morning, long before ES cells were isolated from humans, they were isolated and used in mice to facilitate germ line alterations. The strategies used to achieve those alterations, however, were complicated, and for reasons that would be evident to everyone if we had time to go into them, could not be undertaken with humans. But one strategy that the non-scientist can easily imagine, a strategy that would not be equally repugnant to everyone and that could be undertaken in humans, is as follows: You isolate an ES cell, taking advantage of its immortality, perform on it a precise germ line alteration, and then use somatic cell nuclear transfer to create an embryo. There are, of course, ethical reasons not to attempt such a strategy. There are surely technical obstacles in the way of successfully implementing such a strategy. And there may be other equally, if not more, efficient ways of producing germ line interventions. Nonetheless, it seems to me that it would be a serious mistake to set aside the germ line alteration issue and thus ignore one of the purposes to which embryonic stem cells could, in principle, be put.

Much has changed since the Embryo Panel set aside that issue in 1994. First, many researchers are increasingly eager to undertake germ line gene alterations. As

someone pronounced at the recent [University of California at Los Angeles] (UCLA) conference on germ line gene alternations, it's not a matter of if, but when. Second, as all of you know all too well, there was Dolly. Even though many people in this country have grown comfortable with the idea that somatic cell nuclear transfer would be just one more way to help infertile couples, that strikes me as naive. Ian Wilmut was not trying to help infertile sheep. He was trying to help a pharmaceutical company to more efficiently genetically shape animals—animals that would result from an ingenious combination of somatic cell nuclear transfer and germ line gene transfer. And in so far as we already are using somatic cell nuclear transfer and germ line gene transfer in the world of animal biotech to genetically shape nonhuman animals, it seems to me that it is incumbent upon us to begin thinking hard about using the same techniques in the world of human reproduction to genetically shape children. Now there's a simple reason why the NBAC may be tempted to conclude that it cannot take up the two issues I discussed: Using somatic cell nuclear transfer for fusing embryos for research and using embryonic stem cells for the purpose of germ line alterations are exceedingly complicated issues. Analyzing them fruitfully will require considerable time. I appreciate the power of that reason not to take up these issues, but I urge you to reject it. Easy for me to say, I know. There also is a simple reason why the NBAC might conclude that it should not take up the germ line issue. That issue is, after all, within the domain of the Recombinant DNA Advisory Committee [(RAC)]. Moreover, the NBAC charter explicitly states that it is to consider those bioethical issues where there is not another entity able to deliberate appropriately on it. But the RAC, too, has a carefully circumscribed mandate: It is to concern itself with issues involving recombinant DNA. Thus, insofar as, for example, somatic cell nuclear transfer does not involve recombinant DNA, somatic cell nuclear transfer is outside the RAC's mandate. Notice you've got two techniques - germ line gene transfer and somatic cell nuclear transfer - that are already being used in the world of animal biotech and could, in principle, be used together in the world of human reproduction. But as of today, our public policy conversations about those techniques that could in principle be used together are completely segregated.

To someone like myself who believes that bodies like the NBAC have a public responsibility to keep an eye on the bigger picture, this current situation is untenable. We cannot afford to keep looking at one brush stroke at a time. If we keep setting aside crucially important and immediately relevant issues, we will keep missing the bigger picture. If we keep doing that, every time there are research advances like ACT′s, the NBAC or its successor is going to have to scramble to put together a report on that aspect of the bigger picture that an earlier report set aside. More important, if we keep setting aside crucially important and immediately relevant issues, we′re going to miss an opportunity to engage in an open and clear public conversation about where we are going with our ability to do things with embryos. In the most flat-footed of terms, we′re going to miss an opportunity to engage in an open and clear public conversation about the possibility of genetically shaping our children. The NBAC will be making an important contribution to that conversation if it takes up the issues that the Embryo and Cloning Reports set aside. Thank you.

DR. SHAPIRO: Thank you very much. Let me now turn to Dr. Baylis. Dr. Baylis?

DR. FRANÇOISE BAYLIS: I had a brief look in preparing for todays conversation, or presentation, I should say, at the draft outline that had been prepared. And there seem to be a few points in that outline that I might usefully be able to say something about for consideration by the Commissioners. And this is really what I′m going to try to cover today, obviously very quickly. The first is to insist upon a distinction between standard practice, and nonvalidated practice and research. And thats because of the comment to the effect that seems to suggest the recognition of two of those activities, so that I think we must pay sufficient attention to the third, the nonvalidated practice. I also want to talk very briefly about the moral permissibility of intervening in the genome and the moral status of developing human life. I will actually spend the bulk of my time looking at this question of embryological viability as I understand that; that′s largely the reason I was invited to come and speak to you.

The first point that I would like to put before you is the fact that it's really important to recognize the distinctions among the three types of interventions. I think it's particularly important to do this because we need to recognize that we're not just looking at embryonic cells, but that we may be looking at research that is going to involve either of the donors of that genetic material. Or, if we're looking at transplanting that material back into a woman, we're looking at other people as well. And it's really important to appreciate the context in which those interventions are going to be presented to those individuals. And so one of the things that I'm alluding to here is the fact that when we look at these histories and new reproductive technologies and fertility clinics, there's a clear history of interventions being presented to people as treatment, either innovative treatment or conventional treatment, when they're not. I think that's absolutely key. And particularly important in this regard is recognizing that having a therapeutic intention is not a sufficient condition for having a therapy. You can have a therapeutic intention and be involved in an innovative practice, but also still be involved in research.

So the thing that I'm wanting to put forward is a proposal that would be a recognition on the part of the NBAC about the need for clear guidelines that would actually distinguish among these various types of intervention. And the types of things one would need to look at in terms of guidelines would be issues such as peer review, monitoring, the perspective review of the decision-making process, and the scope of disclosure. And that's because I would argue that those who back change intentionally depending on the perspective they want to advocate for depends on which intervention you're actually looking at. Just to illustrate that I would take, for example, the last of those points, which is scope of disclosure. It's widely accepted, I would suggest, that when you look at the notion of informed choice it's important that the persons who are being asked to consider consenting to or refusing standard practice, nonvalidated practice, or research would actually understand the nature of what it is they are being asked to participate in. And that becomes really key. Then I think once they understand the nature of what they are participating in, they may or may not elect to do so. And I

think that becomes really important in the context of reproductive technology when people believe they are pursuing their own goals, hopes, and aspirations when in large part they may in fact be furthering the goals, hopes, and aspirations of the researcher.

That's not to say that that's a bad thing to participate in. It's a very important goal to want to pursue, but you have to understand that that's what you're in fact doing. The next point I want to make that I think is particularly important is that intervention should not move from the realm of nonvalidated practice to the realm of practice without validation. And that's despite the fact that many of you could say back to me that lots of contemporary health care and treatments are in fact nonvalidated. That doesn't justify continuing in that domain when we're in the process of developing potentially new and exciting interventions. The next point that I wanted to touch on very briefly is this notion of the moral permissibility of intervening in the genome. And I put there for you a series of questions: Is there a right for unique genetic comparisons? You'll appreciate that that's alluded to in the cloning type question. Is there a right for genetic comparison that has not been manipulated? And that's alluding to the germ line being transferred possibilities. And looking at those issues, perhaps in combination or separately, is there a right to be born healthy, whatever that might mean or what we might take it to mean? Is there a right to genetic enhancement?

I want to suggest to you that these are, in fact, common questions that we find in the literature and they are important questions. But I think one of the things that is interesting to think about is whether in fact these are the right questions or the appropriate questions. I think the level of the questioning is appropriate, but perhaps the orientation is wrong. What I'm wanting to suggest is that perhaps framing those questions in terms of the right language is ultimately problematic and not going to help us or effectively guide us, if you will, in the decisionmaking about the moral acceptability of human genetic engineering. So when we think about that question, controlling our destination or the destination of the species, I want to suggest that instead of looking at it in terms of the rights of this developing being or the rights of

other persons that we need a richer ethic of community and connectedness. And why is that to make sense of what I'm labeling, anyhow, the fundamental question, which is: What kind of world do we want to live in? Whether we as a very rich-the royal "we," if you will-I guess I can still say that in a Canadian context-the "we" is not limited to a population cohort, but ultimately includes future generations. I don't think that's the way in which we've traditionally thought about problems: how are "we" going to solve our problems, thinking about ourselves as part of the species and in a context where we might, in fact, totally control the definition of that species.

More generally, then, what I want to suggest when we look at this question about the moral permissibility of intervening in the genome is that we not parse the debate in terms of reproductive rights or procreative liberty. And I think there can be a tendency to do that based on the way some of the debates or discussions have been shaped thus far. The questions that I think we really need to struggle with are questions of transgenerational justice. And they are the sorts of questions where what we're asking is, What is it that we owe to future generations? Notice I'm using the language of obligation, not right. Some of you philosophers are going to say, "Well, it kind of finesses the question because we have rights and relative duties." I don't think that's what I'm doing, and I'll tell you a little bit more about that in a minute. But I think we really do need to grapple with the question about what we owe to subsequent generations in a context where those subsequent generations may be subject to an unprecedented amount of control from us in some sense.

Picking up the pace, the third question I wanted to just briefly touch on is this notion of the moral status of developing human life. The question typically is framed in terms of when does the potential human or the developing human gain moral status? I'm using the terms "human" and "person" here distinct from "human being," the biological term that is not up for being contested, "person" being the moral term. One of the things that's interesting about this question is that it seems to be

widely believed that the answer to this question is going to solve all of our moral problems. Because if we just knew if this genetic material or this developing being was a person, we would then know what we needed to do or not do. And what I want to say very clearly is that this question is not amenable to factual resolution, despite the fact that many will continue to look to biology and continue to parse the embryo hoping that somehow the answer will be there.

I think one of the real risks is what I've put in the overhead there - that there's a real risk of either overemphasizing or ignoring important aspects of the development process. I think that kind of argument can be made with respect to what is in fact an international consensus in around 14 days. It's choosing a particular part of that development process and giving it some weight - maybe deservedly, maybe not. And the last thing that I want to say about the moral status of developing human life is that I think we need to remind ourselves that personhood - the moral term here now as contrasted with the biological term "human" is an essentially contested concept. And that comes from the work of W.E. Galley - the concept, the proper use of which inevitably involves endless disputes about its proper usage. And so a word of caution: it's not worth spending a whole lot of time trying to solve this particular problem. People have been at it over the generations for some 2,000 years. It's unlikely that you'll be able to do it in the next six months. So instead what I'm suggesting is that rather than trying to wrestle with the legitimacy of the rights claims that are going to be made on behalf of embryos or potential persons, what we ought to do is focus on the duties of individuals whose personhood is not in doubt. And that's really getting you back to the question I was asking about, instead of looking at rights, looking at duties. The reason I think that that would be a useful thing to do is that what it does is it shifts the discussion. Instead of discussing the prospective right-bearer, we end up discussing ourselves, and therefore we end up getting to what I think is the fundamental question, which is: What kind of world do we want to live in? What kinds of obligations do we want to impose upon ourselves with regard to different types of entities?

I'd like to quote from what I think is a really fine paper called "The Entity Restriction of Rights" by Benjamin Freedman, which really looks at this notion of trying to move the conversation from one that's focused on rights to a conversation that's focused on duties. He wrote, "We need to determine what we ought to do, how we ought to behave, and then our statement of rights serves to formalize our commitment to this ethical way of thinking." So the crucial questions I'm suggesting are: What ought we to do, how ought we to behave, and not, Does this entity have any rights?

Now for the question that I was originally asked to address. Some of you will have had a chance to read the paper that I put forward several years back articulating the distinction between viable and nonviable embryos. I've put up here just a couple of sentences that are an effort to encapsulate the whole paper and obviously don't do it justice. What I'm trying to suggest is that the viable IVF human embryo embodies an imminent plan that includes the ongoing functioning of the organism as a whole. What I'm suggesting, then, is that there isn't an inherent defect in the embryo that would prevent it from producing a live infant, assuming, of course, that it's been in an appropriate environment with appropriate nutrients, etc., that would in principle be capable of postnatal survival. What I'm saying is that the embryo itself doesn't have some kind of a genetic or metabolic disorder that would cause it to die at either the preimplantation stage, the fetal stage, or the immediate postnatal stage. So I would capture all of that in my description of a nonviable embryo. Now just very briefly, so that this isn't seen just as an interesting conceptual distinction but not in fact all that useful, I'll put up here for you a couple of slides - examples of embryos that would fall within the category of nonviable embryos. So it's just to say that there are, in fact, embryos - and this is not a complete list, this is an illustrative list - to say that there are such beings out there. One of the things that I'm going to be suggesting is that if you buy the distinction that there is such a thing as a nonviable embryo, then it bears some thinking about policies, decisions, or ethical stances that have been taken that fail to

speak to this difference.

One of the things, then, that I would be suggesting in this particular context is that not all IVF human embryos are of equal value. So when we think about how we ought to behave with regard to human embryos, we could at least draw this distinction: We could say that those embryos that are nonviable and do not include an imminent plan for ongoing function of the organism as a whole are not of the same value as those that have some potential for that kind of ongoing development. And why we might make that distinction is because generally it's held that the human embryo's potential for continued growth is what gives it its moral value. At least that would be the perspective that would be advanced by some. And therefore the manipulation of the human embryo becomes problematic because it potentially hinders that potential. I'm suggesting - and some will not agree - that the nonviable IVF human embryo is morally equivalent to other cells and therefore could routinely be targeted for research. One of the implications of the view that I'm putting forward here is that it doesn't even make sense in this context to have any kind of a numerical limit on the time frame within which the research on this particular group of embryos could take place.

I want to say one thing, though, just before I go on. Let me put that back up there. The conclusion that I'm articulating is that it could be routinely targeted for research. And one of the things that I think it's really important for me to say is that doesn't go without some kind of a cautionary tale, if you will. What I want to say here is in the context of research, the identity of the research subjects, say that it's a nonviable embryo, is not sufficient to say that the research in and of itself is ethically defensible or acceptable. And I think I need to emphasize that, because Jerry Hall and his group at George Washington University, after they had done the initial blastomere separation, in some of their defense of that work attempted to say that that what they had done was ethical because they had used nonviable embryos. I don't know about the accuracy of that claim with respect to what research they did or did not do, but they did at some point try to defend what they had done on the grounds that they had used

nonviable embryos. And so that leads me to emphasize that the fact that the embryo is nonviable isn't sufficient to say that the research is ethically acceptable. There would be a number of other conditions that would also have to be met in order to say that this is noncontroversial from an ethical perspective. You would want to know that the research objectives are morally sound; you would want to know that the research itself had scientific merit. And I would draw the distinction and emphasize that it needs to have both value and validity.

You're asking a question that is worth pursuing, and it's structured in such a way that you can actually get an answer to the question that you are pursuing. You've got a proportionate harm/benefit ratio - some people argue a favorable harm/benefit ratio, and I won't defend my claim here. And you've got appropriate informed consent from the gamete donors. A number of people today have made that point about having appropriate consent from the gamete donors, but the one thing I want to emphasize, and I think it's absolutely crucial when you get to this issue that you address it: What's going to mean appropriate consent? And I would urge you to think not in terms of, do you consent to the research use of your embryos or embryonic material or spare embryos or whatever it is you're asking for consent for, but it's absolutely key that people understand, I think, what's the overall research objective, because certain research objectives will be morally objectionable to some people. So even though they'd be willing to consent to research or to having their embryonic material used for research, they might not be willing to help you further your particular research objectives. So yes, I'm happy for you to use my spare embryos to do research on Alzheimer's. I'm much less happy for you to use it for research on developing a new abortifacient. So I think it's absolutely key that that become part of what it's going to mean.

In the few minutes I have left I just want to very quickly, with respect to the issue of embryological viability, name for you what I think are the objections to the proposal that I have put forward and try very quickly to answer them. People will argue

that it's not helpful to have this distinction and to justify research on nonviable embryos for one of the following reasons: We have the problem of extrapolation, the problem of doctoring the nonviable embryos, the problem of adequate supply, the problem of slippery slopes, and the problem of foregone knowledge. The problem with extrapolation is that there have been concerns already raised about problems in extrapolating from research data from men to women and problems in extrapolating from research data from animals to humans. It's quite reasonable that people would say if you are doing research on nonviable embryos, we may not be able to extrapolate that data and apply it to viable embryos. Well, one point. Just to take one example of a nonviable embryo, a triploid embryo develops more or less normally in culture at the blastocyst stage. Yes, the nucleus is abnormal, but the embryo itself is metabolically normal. So there's at least a range of research that could happen with that. So the point there is to say that the nonviable IVF human embryo is still valuable research material, valuable research material that the IRB doesn't raise the kinds of ethical concerns or objections about that have been raised. As for the problem of doctoring the nonviable embryos, well, what happens when we have the knowledge to treat these embryos that we've already identified in vitro as being defective and not having moral status? Would we have an obligation to go in and to render these nonviable embryos viable? I'm arguing that there's no positive obligation to do so. I can't build that argument; maybe somebody else could. But at this point I'm willing to say that maybe you might have that kind of an obligation to the gamete providers. I could see how you might develop that argument. I don't know how you could ground the obligation in an obligation to the nonviable embryo.

The second point, which I think is really more a pragmatic point, is that it might be technologically possible that you could doctor the nonviable embryo, but why would you do it? The potential risks and harms in terms of actually going in and transferring that embryo would be significant. Whether you would do that and then use them for research purposes - well, why wouldn't you just use a viable embryo if that were going to be the alternative? The problem with adequate supply is going to raise the

question, Could researchers purposely create nonviable IVF human embryos? If that's going to be your source of research material and you argue you haven't got enough research subjects, could you go about doing that? There are two ways you might think about doing it. You might take a viable embryo and try to make it nonviable. But if that were ethically acceptable, then just work with your viable embryo or do the research on the viable embryo. So that raises a separate question: Could you create a nonviable embryo by manipulating the [INAUDIBLE] gametes? I actually don't see that as morally objectionable, and that might be a contentious claim.

The last two problems then, very quickly. The problem of slippery slopes: I think the argument can be made that if it's morally acceptable to use the nonviable embryo for research purposes, why can't we then use babies that are born dying? Why can't we use comatose patients who are also dying? I want to say very clearly that I think there are morally significant differences between those potential patient populations. The one I've put up there is just an example, and while both or all three that I gave as examples may not have much of a future, they have a very different past. And it's that past that creates certain kinds of obligations in terms of how they might or might not be used in the context of research.

The last objection that would be raised to this proposal is the problem of foregone knowledge, which is basically to say that look, if you have this kind of distinction it's going to restrict the scope of the kind of research that we can do. And it means there are things out there that we'll never learn about or know about. Well, one response is to say that there are still alternatives to research on the viable embryo - again, if you accept the distinction. We've all heard about taking tissue from aborted fetuses. But the last point, which is critical, is that up until this point I've actually tried only to say that there are two kinds of embryos, and that one of those embryos is at least morally nonproblematic. I haven't actually said what should or shouldn't happen with respect to the viable embryo. And I think what remains to be discussed is whether that

distinction should then serve as an absolute demarcation line meaning that=s all you can do, or whether it serves only as a preferential mechanism for saying first, or in certain instances, use the nonviable embryo. And so the last two overheadsCone proposal, then, is that it be used as an absolute demarcation line. And then I would say that if this were the proposal, the fact that some research could not be precluded would not be grounds in and of itself for criticizing the distinction. Why? Because the purpose of going through the exercise of making ethical distinctions and trying to find morally relevant differences is not to go about trying to find out a way to justify anything that anybody wants to do. It is, in fact, about trying to understand what is morally acceptable and then accordingly imposing certain kinds of ethical constraints. And so the fact that there might be things that you could not do or would not, in and of itself counts against the distinction. The alternative is instead of having it as an absolute demarcation line to still use the distinction and set it up in terms of what I've referred to as an ascending order of permissibility for research participation - somewhat taking and bastardizing a concept originally introduced by Hans Jonas.

Basically, what I'm proposing here is that one could require that research on nonviable embryos precede research on viable embryos for a certain area of research or interest. Alternatively, one could develop discrete categories for research and some would be done only on nonviable embryos. Others might be done on viable embryos. And again, one might actually go through some effort at distinguishing that. I just put up a couple of examples of how that might work. With respect to the last point, what I'm willing to put forward as a potential proposal is that there is a moral difference between at least two classes of embryos, the viable and the nonviable. It ought not to be seen to be problematic to do research on nonviable embryos, and there's no need to have either a complete ban on that kind of research or to introduce permission to do that research, but to introduce a time limit of 14 days. There just isn't grounding for that kind of claim. And then what still needs to be done is some work as to saying, How would that relate to any research that might or might not be done on viable embryos? Thank you.

DR. SHAPIRO: Thank you very much for covering a very broad territory very quickly. I really appreciate that very much. Let me now turn to Dr. Peters.

DR. TED PETERS: Thank you Dr. Shapiro. I feel a little bit like a can of Pepsi-Cola in a Coca-Cola machine: I didn't come here to tell the Commission what to do. I would like to share with you a little morphology of thinking and some items for your continued deliberation. Let me mention that the context is that of thinking through the theological and ethical implications of the work of James Thomson. We have not taken a look at the work of John Gearhart or Michael West. And when I say "we," I'm talking about the Ethics Advisory Board of the Geron Corporation. You should have received, I hope, one of these two-sided reports of our statement about that. And if you get bored with what I'm saying, go ahead and read this and then you'll be ready when my colleague, Professor Lebacqz, comes on to give more detail about that particular statement.

Let me just enumerate some items that I think are worthy of continued deliberation. The first is the moral status of the blastocyst, even though I was quite sympathetic with Dr. Varmus earlier this morning in drawing the distinction between a blastocyst that could become a human being and a stem cell that could not - and that certainly research could be permitted on the latter even with restrictions against the former. The issue that we're going to have to face in our culture and in our society really has to do with the source of these embryonic stem cells, and the Commission has seen that. I'm concerned, as a theologian, with what I call "the religious yuck factor" - that is to say, the explosion in culture whenever issues essential to human nature become matters of public debate. Biotech and pharmaceutical companies are appropriately nervous about the yuck factor, fearing that the amount of money raised for research would be put in jeopardy if there were to be a cultural or social uprising akin to that against fission nuclear power some decades ago that might shut down ongoing genetic research. So there is some reason to be concerned about it. And of course we were alarmed in 1995 by the gene patenting controversy and in 1997 by the cloning

controversy. And finding out what's going on in people's guts - our social and cultural guts - is worth some effort. So we had to take that up in deliberating over the use of the blastocyst in order to obtain human embryonic stem cells because there's no question - the blastocyst has to be destroyed, the cells separated, and put on the feeder tray in order to establish the cell line. Now if I were Pope John Paul II or Cardinal Rotsinger I think I would be able to have a clear position and say that no, that ought not to be done because regardless of the source - and in this case we're talking about fertilized ova from a reproductive technology clinic - regardless of the source, there's dignity there.

It's my own deliberation, as much as I respect that position, that I think is the better one, despite the warnings of Dr. Baylis a little bit ago about trying to rely too much on what science has discerned here. It just appears to me that the better place to look is the gastrulation, the arrival of the primitive streak. You see, there we have really an individual that has a certain status that is worthy of consideration. And even though we talked about it quite a bit, for the most part our committee came up with a developmentalist point of view, thinking that maybe that 14-day period in there has a certain amount of wisdom to it. Not all are going to approve of that, as we saw earlier, but that's where it is that we went. The second item continues to be the issue of human dignity that we heard about. One of the questions continually, of course, is whether or not that should be grounded in rights as Prof. Robertson would do, or in some other way of looking at it. For me, human dignity - I get this from Immanuel Kant - is to treat a person as an end and never merely as a means to something else. My New Testament version of it is that God loves each one of us regardless of our genetic makeup, so we should do likewise. Exactly when and where to apply that is a question that is unavoidable when it comes to these kinds of decisions.

In terms of mitigating factors, I'm finding that a little bit difficult. Items that have already come up today have to do with the viability or nonviability of these pre-embryos, these blastocysts. We were originally told by the Geron Corporation that they were going to take nonviable, that is to say low-grade fertilized ova, and then later

we found out no, no-these are ova that could, in principle, be implanted and become children. We had to, or we felt like, settling for the difference between "in principle" and "in practice." That just for practical reasons, these fertilized ova would never become children, and would that then make them more available for this kind of work? It was also important to us to think of the immortality of these cell lines, even if they're not completely immortal but just last a long time. In principle, one could use a fertilized ovum and get the cell lines going; you wouldn't necessarily have to go back to the source again and repeat that particular process.

Now Dr. Meslin asked if I would say a few things of a theological nature that might be relevant. I think that this has to do more really with the scientific community than with public policy and where people in the church ought to be in our society. And it has to do with human nature, what I call Christian anthropology. It's my belief that who we are as persons is determined more by our future than by our past. And that's rooted in my understanding of God, who comes to Abraham in Israel and promises that a new people will be created and this people will be given a promised land at some point in the future. Or in the New Testament, when God raises Jesus from the dead and promises that there will be a new creation coming. One of the things that this signifies is that the future will be different from the past and that we can't necessarily assume that the future ought to be the same as it was in the past. So when you hear a point of view like we heard a little while ago, that nature is intended to function in a certain way, that is the Christian view: that there has to be a mommy and a daddy and a sexual act in order to produce a child.

I am not necessarily concerned that the future will have to be exactly the way it was in the past. I think that we have a mandate to make this a better world. There is something inherent, theologically, about transformation and redemption and your and my ethical responsibility to make this a better world. And the scientists, in a sense, even though individually they may or may not be virtuous, are doing something on behalf of the entire human race when their research is aimed at improving human health and

increasing the quality of human life. And let me just say that that was very important in our deliberations in the Ethics Advisory Board, to be certain that despite what might be said about public policy and what might be said about profit in this kind of industry, will there be a long-range positive impact on the human race? We feel that there will be.

Okay, then that brings me to the final issue, and that is one of justice. That even if we were to salve our consciences with regard to the use of the pre-embryo and with regard to how it is that money is raised for this research and who gets the financial profits. In the long run, we have a responsibility that if there is going to be a gain for the human resource that it be distributed as justly and as widely as possible. In such issues as intergenerational justice, which Dr. Baylis raised here, it seems to me to be not just a kind of an extra, but something that ought to really hover around all of these deliberations. That's all.

DR. SHAPIRO: Thank you very much. Dr. Lebacqz?

DR. KAREN LEBACQZ: You have before you copies of this little buff piece of paper that lists on it six conditions that the Geron Ethics Advisory Board believes must be met in order for human embryonic stem cell research to be conducted ethically. I am not going to review all six of those. I hope that you will have time to read this document later. We apologize that you didn't receive it in advance - we thought that you had.

PROF. CAPRON: We did.

DR. LEBACQZ: WonderfulCthen you've seen it. That's excellent. Let me say just a few words about this Ethics Advisory Board. I was listening to Pat King plead for some board to have adequate time to look at these issues. I was smiling to myself because the Geron Ethics Advisory Board is a small board composed of five people. All of us are trained both in secular bioethics and in several religious traditions

of looking at bioethics. But we had at the time of developing this statement no staff and no time whatsoever. I drafted this document the night before our meeting and my colleagues on the board had approximately five hours in which to redraft it and get it into a shape where we could make it a public document. So there will be flaws in what you see before you. And we have since that time had some energy developing a more extensive statement of rationale for the principles that you have received. I'm not at liberty to give that to you today, as that rationale will be published, we hope very soon, in the Hastings Center Report. So you can look for that. And because of that, I cannot distribute it to you today. But I do want to share with you, with respect to three of our principles, a little bit of our more developed thinking. I want, however, to reiterate that we are not issuing a carte blanche approval, either of Dr. Thomson's research or of anybody else's research on human embryonic stem cells. Rather, our concern, as your concern, is to ask, Are there conditions under which this research could be conducted ethically? And, if so, what would those conditions be? You have some additional difficulties that come out of government regulations that, fortunately, we were not stuck with.

So let me turn very briefly - and I'm going to be very brief because I am racing for the airport at 4:15 and I do want to leave some time for at least one or two questions - I will turn briefly to three of the conditions that we have outlined here. First, the one that my good colleague, Ted Peters, has already mentioned: this very difficult question of the status of this early embryonic tissue that some people call a pre-embryo but that I think is best called an embryo. That's what we're talking about, the early blastocyst. Our board was unanimous in holding that this early human embryonic tissue is deserving of respect. In fact, in our developed statement, we say point blank that "We hold that a fundamental principle of respect for human life applies at all stages of human development." So we want to make clear from the outset this tissue is to be respected. The question then is, What does it mean to say this tissue must be respected? When we are doing research or medical intervention of any kind on a small child, we do not ask for the informed consent of that child because the child is not yet capable of giving

consent. So being respectful requires something different of adults than it does of young children. Similarly, we would hold that being respectful requires something different at different stages of embryonic development. Once there is the capacity for pain, being respectful means you are under a moral obligation to minimize pain. But it is our understanding that in this early blastocyst, there is not as yet the physical substrate that would provide for the capacity for pain. Therefore respect does not require the minimization of pain. We hold, then, that what respect requires at this stage is that the embryonic tissue not be used except for very serious, overridingly serious moral purposes such as the kind of research that we have spoken about today that we believe holds out the promise of some very important interventions and possible therapies in the future. But most important here is to understand that we were operating with a principle of respect and I think that one can do so and still allow some forms of fetal research. And in that I fully concur with Pat King.

The second principle or condition to which I would turn your attention is the requirement of consent on the part of the woman or couple. One thing that we did not resolve, and I know that you will struggle with it, is from whom must consent be gained? We put woman/couple. Must you get consent from both the woman and her partner, who may or may not be a man? Must you get consent only from the woman who has given the eggs from which the blastocyst is developed? These issues are not clear and you are going to have to struggle with them. But I would want to point out to you and to stress the vulnerability of the people who may be undergoing these procedures. This is true not only in cases of in vitro fertilization, but also when you talk about women undergoing abortion. But let me say a little bit about in vitro fertilization. A lot of people think of in vitro fertilization as a simple procedure that is done in the laboratory where you extract eggs, you fertilize them in vitro, develop them a little bit, and then reinsert them into the woman's body. I wish it were so simple, but in fact it is not. The in vitro fertilization process is often a very lengthy, very painful, very emotionally distressing process. You are dealing with people who are already very, very vulnerable. Hence, I think the consent issue needs particular care. That will also be true

when you start looking at issues of the use of aborted fetal tissue. If you are going to permit any research to be done with that tissue, the question of consent there also is very difficult. You cannot presume that just because a woman has chosen to have an abortion that she no longer has any interest in what will happen to the aborted fetus. You cannot presume that she does not care about that fetus simply because she has chosen to have an abortion. So issues of the special vulnerability of the subjects who would give consent, I think, are quite crucial.

Finally, I would point your attention to Principle Number Five, where we have suggested that all of this research needs to go on in the context of concern for global justice, and I would want to stress both of those terms, both the "global" and the "justice" terms. Those of you who know my earlier work know I have an overriding passion for issues of global justice, but I would say that I'm not the only person on our board who has that passion. And I quote to you from our longer statement of rationale, and we even put this sentence in italics to emphasize it: "The Ethics Advisory Board considers concerns about global justice in public health to be of overriding importance."

Part of the reason that we do this is that we have a concern: that we may develop, if we are not careful, exotic technologies that assist people in the First World, so-called, that help us to push back the boundaries of aging and the diseases of aging and so on, as you heard this morning, but that, if we are not careful, will never reach those beyond the boundaries of the First World - where most people are still struggling for adequate water supply, decent housing, and enough food to feed their families.

Two features of the current research make this concern for the global picture particularly problematic. The research that has been conducted to date that you heard about this morning is privately funded. It is undertaken in the context of market forces, of the patenting of products, of the interests of shareholders and investors, and of a bottom-line consideration of profits. I would say that's one of the primary reasons to move this research out of the private arena and into government-funded arenas, though I

will caution you that you will not avoid all of these problems if you do so, but you may at least be able to minimize or reduce some of those. And in all of your work, I hope that you will also attend to some of these very difficult justice issues.

So I offer you those very brief reflections, and will be glad to take any questions that you have before I slip out. Please don't take offense when I turn and go; it's nothing to do with you, it's to do with trying not to miss my airplane.

DR. SHAPIRO: Thank you very much, and I very much appreciate that. I know we're running late today, which has disturbed various schedules, and we take responsibility for that. So we're going to turn first to those Commissioners who got cut off last time and see if they have any questions and then go to others.

Eric?

DR CASSELL: Eric, I take it from what you're saying, if I understand your reasoning, is that in any decisions we make that we should not be looking at the smaller issue of stem cell production from human embryos without looking at the much farther-reaching issue of genetic change and its impact on populations. Is that what you're trying to say to us? I also take it that's what Dr. Baylis was telling us in her own way.

DR. PARENS: One of the purposes to which ES cells could in principle be put is germ line alteration. Insofar as that is the case, I do not see how you can, as did the Embryo Panel, bracket off that issue.

DR. CASSELL: I take it that's a way of saying yes.

[Laughter.]

DR. PARENS: It is, yes.

DR. CASSELL: It's a philosophy, basically.

DR. SHAPIRO: Okay. Carol, do you have any questions?

DR. GREIDER: I'd like to return to the issue that Dr. Baylis raised about nonviable versus viable embryos. And in the context we were talking about earlier, where we have the possibility of using somatic cell nuclear transfer into either an oocyte or potentially in the future into ES cells, let's say in the case of somatic nuclear cell transfer into an oocyte, when it's not clear whether this is a viable or nonviable embryo, what sort of context would you put that research in?

DR. BAYLIS: And so why is it not clear whether it's viable or nonviable?

DR. GREIDER: The experiment hasn't been done. It's not clear that if you take a human oocyte and do somatic cell nuclear transfer that it's going to develop normally into a human because nobody has been able to do the experiment.

DR. BAYLIS: No, but I guess what I would be saying is that, first of all, you'd be looking at the initial cell division. At that point, we'd be able to identify, for example, if it would be considered nonviable on morphological criteria, and I know that's a difficult one to establish as a firm demarcation line because we know that there are some embryos that look pretty darn bad and you put them back in, in an IVF context, and they give rise to a healthy human being. But it seems to me that there is some work that you could do in that domain. Probably also you could identify triploid embryos relatively easily, I would think, if that were the case.

So I think in part it's going to be a function of what you can or can't

identify, and that's a limitation of the proposal that I'm putting forward. Some of the techniques that I had put up there for nonviable embryos would require you to biopsy the embryo, which arguably would be questionable if it was potentially a viable embryo. I think what I would be putting forward there, at least on my understanding of the science, probably up until about the eight-cell embryo you can remove one of the blastomeres without hindering the potentially viable embryo, such that at that point you could identify it as viable and it could continue on whatever path it was originally intended for - for example, if it had been created in the context of an IVF program for transfer. If not, if at that point it were identified as nonviable, it could be streamlined into a path where it would be available for research or it could be destroyed or whatever had been arranged in advance.

I guess it is hard to answer the question without knowing in what context the embryo was developed and what the other options are for its use and what had been planned for it.

DR. GREIDER: The question was more to get at the issue of creating an embryo for the research purposes we had talked about using embryos. And you had suggested that using a nonviable embryo has a different moral status than using a viable one. And we had had earlier a discussion about the moral demarcation in creating embryos for research purposes. It has come up several times whether or not the technique of using somatic cell nuclear transfer would actually be creating a human embryo or not. So I just want to -

DR. BAYLIS: I think if you're creating a human embryo, and I think if you set out to purposely create a nonviable human embryo with the express purpose of having that available as research material, that I would not find it morally objectionable. I think that was one of the points I'd put up. You might have a problem in terms of numbers. What I haven't explored are what are the full obligations that you might choose to impose on yourselves as researchers, as members of the community, as the

NBAC, or as policymakers in terms of what could or could not be done with viable embryos.

DR. SHAPIRO: Bette, do you have any questions at this time?

MS. KRAMER: No, I'm sorry.

DR. SHAPIRO: Trish?

PROF. BACKLAR: No.

DR. SHAPIRO: Alta?

PROF. CHARO: Françoise, I'd like to ask you to return to a different aspect of your testimony, in which you suggested that a more fruitful avenue for discussion is to focus on the duties owed to those whose personhood is not in doubt rather than the rights that are held by those whose personhood is debated. Now I can understand this, and certainly there are analogies. The notion of animal rights has certainly never been resolved, yet there's a consensus about certain duties to treat animals certain ways, duties to preserve the natural environment, etc.

I wonder if you could expand a little bit, however, on the methodology that one uses in order to come to a consensus about what those duties might be. Is it exhortation followed by a referendum and a "majority rules" kind of straight political exercise, or is there something different, something that's more compelled by a certain kind of line of analysis that leads to certain duties falling out from some kind of particular discussion?

DR. BAYLIS: I have a sabbatical next year to study the question.

[Laughter.]

Actually, I can't give you a straightforward answer to that question. I think I can say that I don't think it's about majority rule, I don't think it's about a plebiscite, because I think that's exactly the kind of way in which you can end up with very discriminatory, negative policies because people don't necessarily want to impose certain duties upon themselves that might limit what they might or might not be able to pursue. But I think that the point that I was trying to make is much more along the lines that you are articulating in the question - that we recognize that we have certain rights, for example, to our pets. If you have a dog, you ought to feed it and you ought to take it for a walk periodically, and we don't go through this great exercise of figuring out if it's a person or not to say that you have those obligations. We also have obligations not to destroy the rain forest.

And we understand that, I think, in the terms that I'm trying to work toward, this sort of transgenerational justice. And I'm using "transgenerational" instead of "intergenerational," and I'm not sure yet that it's the right term, but it is because when I look at the literature it tends to be looking both backward and forward and it tends to be really almost always looking at, well, not environmental ethics, but almost looking at a population cohort. And so I'm trying to understand what it means to look at that literature in the context of genetics, and what does it mean to understand making this a better world for us, when "us" is subject to molding in a way that it has never been subject to before, so that we're not only controlling the environmental factors that contribute to who we are, but also the genetic factors.

DR. SHAPIRO: Thank you. Diane?

DR. SCOTT-JONES: I have a question for Karen and Ted. I like very much your assertion that all research on human embryonic stem cells must be done in a context of global justice. Would you say how, specifically, you've advised your own

corporation to exhibit a concern for global justice?

DR. LEBACQZ: I can answer that very briefly and say that as of this moment our Ethics Advisory Board has held only three meetings. Our first meeting was in July and it was for purposes of understanding the research that was being done. In our second meeting in September we crafted the statement that you have before you. Our third meeting was in December and what we did was to look at the larger statement of rationale that lies behind that statement. So we have not as yet undertaken to advise Geron about how they as a private corporation can be influential in seeking global justice.

I do need to say, and I'm sure you know this, that we're an advisory board only. And any teacher knows that you can give a lot of advice and most of it is not taken. So I'm under no illusions about the amount of power that we have to effect what we might like to have done. But I do think that one of our ongoing agenda issues will be to examine the global justice question. Thank you for asking that.

DR. PETERS: Geron knows we=re coming.

DR. LEBACQZ: Yes, they know. Thank you.

DR. SHAPIRO: Thank you. David?

DR COX: I have a question for Dr. Parens, and it's this interesting dialectic that I think was so nicely exemplified by your presentation of the contrast of [INAUDIBLE]. And so how do you deal with the bigger picture issues without knowing what the specifics are? Some people would say that that's like buying a pig in a poke. On the other hand, if you just have the specifics, you never look at the bigger picture issues. And so how do you address that, because it really pertains very specifically to what the NBAC is about?

DR. PARENS: Yes, it's much easier to be a critic than to make a positive suggestion, isn't it? I honestly do not know how you can, in the time given to you, do what I think you have to do if you're going to deal with this issue well. Again, let me repeat something. I don't see how you can talk about ES cells without talking about germ line transfer, and I don't see how you can do that in six months.

DR COX: But you believe that we can do it without dealing with the specific issues of germ line transfer or specific applications? That's really sort of my question.

DR. PARENS: Wait a second. You're pointing out that I am speculating about the prospect of germ line transfer. That is absolutely true. The scientists who spoke this morning are speculating about medical benefit. It's the nature of the game. We have to speculate.

My concern is that the speculation of public bodies like this one has been a bit too narrow of late. And I'm just asking for you to, if you cannot speak directly to the question, at least make known to us, the public, what the larger context is.

DR. COX: Great. Thanks very much.

DR. SHAPIRO: Thank you. Alex?

PROF. CAPRON: I guess the question I wanted to ask Karen and Ted was answered partly by the answer to Diane, which is that your process thus far has been a post hoc process - that is to say, the research has gone on by Dr. Thomson and been completed and then your statement was sought. You haven't looked at Dr. Gearhart's work, which is also sponsored by Geron. So I want to ask a factual question - unless you want to correct that impression, Ted.

DR. PETERS: No, that's correct. We were originally invited to serve not post hoc, but to actually integrate ourselves into the research process. What happened was the Thomson discovery came up really quickly and we were just kind of called into action on that at that particular point, kind of the way this Commission was when the cloning controversy broke out.

PROF. CAPRON: Now the question I wanted to ask Dr. Baylis is also just a question of clarification. Part of your definition of viability turned on what you call an "imminent plan for development." And I wanted to make sure that I was understanding you correctly about the word "plan" that there is a biological or genetic plan independent of human volition: Is that correct?

DR. BAYLIS: Yes, that's correct.

PROF. CAPRON: That's the simple question. It was actually just a clarification.

DR. SHAPIRO: Thank you. Eric?

DR. CASSELL: I want to follow up on what I asked Eric before, and there's some comment that's come since then. I think that because of the nature of the developments and how we got the charge we have and also the politics of the embryo, we're brought to this very narrow issue. And it seems to me it is in large part the politics of the embryo that keeps us focused on that because it's very thorny and difficult. And yet, I took it from Eric's and also Françoise's presentation that the issue of the longer term effect of this issue on human stem cell research is the responsibility that we have toward the future rather than the rather heuristic view that science wants a better world, because it has wanted a better world all this century, and judging from the results, it hasn't done all that hot.

So I would wonder how would you see us both solving the narrow-which, really, that's our charge, we really have to come up at the end with some recommendation-at the same time as we have a focus on the larger issues, that allows us to do that in an intelligent and intelligible way so that both paths are done without losing sight of either. And it's open to the three of you.

DR. BAYLIS: One comment I would make, I think, building on what Eric said earlier, is that there is still a job, for example, in just legitimizing that as a question. I will tell you, in terms of my own work and reading in the literature, it is not infrequent that talk about the technology being used in this domain is getting dismissed as stupid talk, right, so we don't actually have to address it; that that's stupid, we're never going to do that or we can't do that. Just reclaiming that conversation I think would be a huge step forward.

And I think that for myself, when the work was announced in 1993 when Jerry Hall had done the blastomere separation by splitting, colleagues and I wrote a letter to *Fertility* and *Sterility* saying that, look, there really needs to be attention to the ethical issues here. And we wrote that in response to an article by Edwards, Jones, and Sidel, whom many of you will recognize as pioneers in IVF, because in their article they dismissed the types of concerns that people were raising as "ethical hullabaloo," and that's a quote. And our letter back to *Fertility* and *Sterility* was about saying this is not ethical hullabaloo and went on to try and address that. And to this day, one of the things I find most interesting is that they published the letter under a new title called "The Best of Us."

DR. CASSELL: That's how we get rid of hullabaloo.

DR. BAYLIS: That's how we get rid of ethical hullabaloo. And I think that part of the problem is that naming this as a difficult ethical issue with huge

implications is either dismissed as stupid talk or as somehow calling into question the good intentions of scientists. And it's about neither of those things. It's about looking at what's conceivable, what's possible, and what may in fact be morally justifiable at some point were it to be possible.

And so I think I would definitely agree with Eric that it's important to have that as part of the focus in terms of what one's talking about. Even if you can't give a definitive position, you can validate that as an area of inquiry.

DR. PARENS: It's very difficult for me to add anything to that. I thought it was beautifully said. I think we have to reclaim the seriousness of the concerns that were articulated almost 20 years ago now about genetically designing our children. I mean, I can barely say those words because they've come to feel so unprofessional, so unsophisticated. We don't have those words at the very moment when we almost have the power to do exactly that. I mean, we're doing this sort of thing in the world of animal biotech. We are working to [INAUDIBLE] somatic cell nuclear transfer and gene transfer.

Again, see, the reason why I didn't like your original formulation of what I said was it was so grandiose. I don't want to sound grandiose. I don't want to sound alarmist. I just want to plead that you take this question seriously.

DR. SHAPIRO: We'll take two final questions. Diane, then Larry.

DR. SCOTT-JONES: My question is for Françoise. I wanted you to say just a little bit more about the distinction you made among standard practice, nonvalidated practice, and then research. Could you give an example to make that concrete?

DR. BAYLIS: I think, for example in the realm of new reproductive

technologies, typically somebody has a great idea, you subject it to research, you try to generate some data about safety and efficacy, you hope that it's not going to harm people, you hope that it'll actually do some good, and in that context one hopes you move it from the realm of research into the realm of treatment. Certainly in the context of a number of the new reproductive technologies that process does not appear to have been followed. Some of the women and the couples whom we've already heard a couple of speakers describe as very vulnerable have been approached in a context where it is my belief that it has been presented to them as an innovative practice, as an experimental therapy. And what you hear is that a therapy is new and innovative. I think that there is some good literature and I think I tried to excerpt some of that in a one-page handout that I circulated before, saying that if you look at those three areas of intervention, you can in fact draw distinctions among the objectives, the target population, the available data about safety and efficacy, the lack of or the existence of professional consensus, etc.

I think that what we're saying is that it's important to have informed decisionmaking by the people who are participating, who are giving permission to use their embryonic material. It's important that they understand what they are participating in and whether or not it is at a complete research phase or it's ideas and the goal here is to generate new knowledge and we need this material to do that and we would like you to help us. People aren't necessarily going to say no. I have reason to believe that if you had family members with Alzheimer's and someone approached you for research in that domain, you might be quite happy to do what you thought you could to contribute to that research. But you should understand that it's research as opposed to in six months you're going to get cells to be able to offer to your parent who has Alzheimer's, for example.

And I think that it's not necessarily that people are misrepresenting, it's just the whole context within which certain interventions are offered. If you actually

look at the literature, there are reasonably good guidelines for what you should do in a research context - there's prospective review and it's pretty clear, and there's a reasonable understanding of what happens in the realm of practice. There is, in fact, very little literature and very little guidance about what kind of review you do or don't need for innovative interventions.

And I'm not saying that they shouldn't be offered. Sometimes you try an innovative intervention before you get enough of an idea to formulate a research protocol, so it's not even that. It's a linear progression. You can have an innovation prior to research, you can have an innovation after research has been initiated and started, you can have an innovation with an existing therapy where you want to tweak something because you think it will be more effective. And we just don't have good guidelines for that. And a quick example of an innovative practice recently would be something like Eknol, and I don't know if you know about that, but that would be another example outside of the domain - just to say that this is not restricted to new reproductive technology, that it happens in all kinds of areas of health care.

DR. SHAPIRO: Thank you. Larry?

DR. MIIKE: I guess at the question that Eric Parens raised in the beginning my ears perked up, because that's my opening salvo in our discussion about how to go about doing our study, as some of you have seen in my e-mail. But I'm a little confused about what you're actually asking us, because you talked to a gamut of things. So let me try to respond and then tell you what I think we should do and see whether that meets what you want.

First of all, just to be a little funny - and I can be funny, right?

[Laughter.]

DR. CASSELL: You've got to watch out. What if you're not funny?

DR. MIIKE: One of my wisest mentors when I was much younger than now said when you're faced with a difficult problem, frame it as an even more difficult problem so you don't really have to address the difficult problem you had in the first place. And I think that's how I took your first recommendation. And then you told us you need to do this but you can't do it, but that's what you've got to do. So I'm at a loss.

But I think that the way we need to approach this is that I think first of all there is no once and for all study in this area. Second of all, I think why many of the problems have gone by in the past is because the issues are discussed and decided at a fairly abstract level. Embryo research may sound concrete, but it's not. So I think that what we need to do is that we need to make clear that we are doing a study on human stem cell research in the context, and unavoidably in the context, of embryo research in general. And that we should use, in my view, the old ways of doing things, where you do a large study and within the large study you do a case study to show how you would implement given concrete facts about the principles that you've agreed upon.

And I agree wholeheartedly with Patricia King, and I'm amazed to even discuss it, that I see our role as making public policy or recommending public policy based on ethical principles.

DR. PARENS: May I try once again? I do not think that in six months you're going to say all that needs to be said about the germ line question. You cannot do it in that sense. I do think, however, that in six months you can take up the question. Indeed, I think that if you don't take it up, you'll be making a mistake.

I think that even if you can't resolve the issue, you can help us - people

who pay for your service - understand the bigger picture. Just get us thinking about it. That doesn't seem to me contradictory. It seems to me one could hope that you would raise the question, acknowledge the question, and not hope to resolve it in six months. That doesn't seem to me contradictory.

DR. SHAPIRO: Thank you. I think we're going to have to call this part of our session at an end because we are, as I said before, still running behind. We will, however, take a 10-minute break. Let's reassemble at 20 minutes to 5 p.m. to go to our own discussion regarding what our next steps are. Thank you.

GENERAL COMMISSION DISCUSSION

DR. SHAPIRO: We have a few moments this afternoon, if not as long as I'd hoped, to discuss just how we're going to structure our report, with the aim not of making all the final decisions about the structure today, because we'll learn as we go how quickly we can put together satisfactory materials. So some aspects of this will evolve as in the next month or two we begin to put materials together for your consideration. And what we learn and decide may very well impact on the precise nature of the report. So I'm not trying to, and I don't think we should be trying to, settle all the details of that report at this particular time. However, because of the time constraints we do have to begin to make some decisions. And it was with that kind of idea in mind that I wrote my brief memo to the Commissioners a week or two ago trying to outline one possible way to think about this, at least in certain dimensions. And that is asking you whether we ought to make, in some sense, the narrowest possible response to the questions posed to us, which I would interpret as being to look at the issues involved in using existing human embryonic cells for research purposes. It seemed to me that was the least one could do to respond to the President's letter. The language of the President's letter, however, I think could easily be interpreted in a rather straightforward way to encourage us to do more than that. Although it's a brief letter, the letter itself mentions that new science is developing, that there are new ways of balancing these things. That seems to me almost automatically to refer to a somewhat broader subject, because otherwise the isolation of human embryonic cells themselves is a new development. I think myself, that that referred to some of the previous issues that were of concern in this area having to do either with embryo research itself or possibly even the creation of human embryos for research. So my own inclination was, as you know from the memo I sent you, to try to see if we're capable of writing something in somewhat broader terms, which at least in the initial suggestion I made did not deal with what I think was Category Four, if I remember that letter correctly, which was the creation of embryos specifically for research purposes. But I wanted to stop just short of that and take on in at least appropriate ways the embryo research issues that had an

impact on the things we were discussing.

I then asked the staff that if we did take that, because I had to start somewhere, could we produce an outline of how our report might look, recognizing of course that the Commission might decide to stop at a different place, in which case the report would have a different outlook. And I believe in your briefing books you have a working draft, which was the responsibility of the staff, to say all right, if we take what was, I believe, Category Three in my memo to you - that is, to focus the report on issues arising out of research using embryonic or fetal material, including issues raised by One and Two above. I'm not going to go through all this today, but that was the stopping point I suggested. And you've heard a variety of recommendations and observations today and have had the extra advantage of not only the briefing material, which was itself quite comprehensive, but the additional presentations made today by people working in the area.

So I'd like to just open the floor for discussion regarding whether the framework I've introduced in the memo is a useful framework to have our discussions with, or why not, or if there is an alternative. I have watched the e-mail traffic - I think you all have - that came after that. And my, at least, quick interpretation of it was that we should work on something like what I've interpreted as Number Three here, although people had different observations and suggestions regarding what it should, or should not, say. I'm sorry - I heard, Larry, that you had a different perspective, but I didn't see that in the e-mail traffic; that came somewhere else in the system. I didn't receive it but -

DR. MIIKE: That's right.

DR. SHAPIRO: Let's just, without any further conversation along those lines and whether I've adequately described the e-mail traffic or not - people who have

participated can speak for themselves - let's just open that issue for more discussion. One further thing: I think you've seen something like this that has just been passed around. This in some sense is a work plan, which looks at presuming what we were to do. Something like it was outlined here, with appropriate modifications pointing out where - and we have some lead Commissioners helping us do that - where we would have some Commission papers and so on, and you might just want to look at that. But that's in some sense trying to make a reality out of this outline here. So that's just for your information. Obviously, all these things are going to shift and change as we go along. So...the floor is open. David?

DR. COX: I wasn't part of the e-mail traffic, but I'm very much in favor of working on One, Two, and Three in terms of your proposal. I think that my personal position is one sort of like that espoused by Pat King. I think that trying to have a discussion broad enough to bring more people into the discussion to find some common ground is particularly the rationale why I'm interested in One, Two, and Three. But by doing that we can focus on specific examples of Number One, because I think that that's an immediate problem before us. But it's primarily by bringing in Two and Three: it's to broaden the discussion so we can have more people even considering Number One.

DR. SHAPIRO: Thank you. Larry?

DR. MIIKE: I guess for those of you who haven't read the e-mail, let me explain what I said. Harold's four propositions were: research with existing stem cell lines; Number Two was other sources, which would be fetal material and other sources for stem cell lines; Three was research on embryos per se, and Four was the creation of embryos for research purposes. And his recommendation was that we do a study on research on embryos per se with an emphasis on the first two.

I disagree. The reason I disagree is I think it's going to be sort of a hybrid

of what Harold proposes. Number One, let me just say that our charge, the way I read it, was human stem cell research. In order to do that - which I think should be the focus of our study - we inevitably have to deal with the issue of human embryo research, because it is the resource materials for the human stem cell lines. So we can get it that way. But not only that - if we do that we inevitably must address the fourth topic, which is creation of embryos for research, because that is another alternative source for stem cell lines whether one agrees with it or not. I'm just talking about the possibilities. If we focus our study on human embryo research per se, we are not going to be grounded in anything very concrete and we are going to be all over the place again, we are going to get into theoretical discussions, and we are going to end up in the same place that past commissions have. If we ground our study on the real reality, or at least the greater reality, of stem cell research, then we have something in which we can ground our analysis that we still have to do about embryo research in general. So what I'm suggesting is that our study should be on human stem cell lines, but the issues of human embryo research come in through that avenue because we've got to establish certain principles and reach certain public policy conclusions about what we believe about human embryo research in order to apply that to the concrete situation of human stem cell research. And so I would say that that's what I'm suggesting: that we focus on human stem cells, and then we would have to address all four of the areas that you mentioned in your memo.

DR. SHAPIRO: Thank you. Alex?

PROF. CAPRON: I also agree with the comments and suggestions of Pat King. And I think I take them more or less the way Larry is describing it. But just to be clear, my sense is that the present outline, if I can begin there, is much too extensive and tries to cover much too much ground. And if that's what Larry means by we=ll never get anywhere and we'll go all over the place, I agree with him. I don't think - with no disrespect to the staff - I don't think we have the staff to do that just in terms of person-hours, not speaking to the talent of both onboard staff and any contracts or consultants

who are writing for us. I would therefore look at page 3 of the present outline, where down under (d)6 the question is posed: Should the Federal regulations relating to research on the embryo and fetus and on pregnant women be amended in light of the new science? And take that as a version of the question that's before us. It's clear that that question can be answered no, they don't need amendment: What we heard from Dr. Varmus indicates that important research can go ahead and that's enough for today. What we heard from some of the witnesses is that they should be amended to close off this line of research. What we heard from others is that they should be amended to ensure that the research can be expanded and that there is not a barrier to the sorts of things that were under Harold's points One and Two and maybe under his point Four. I think it's point Three that generates a lot of the additional materials here, which is trying to be more encyclopedic about the whole world of embryo and fetal research, that is not going to be something we're likely to be able to do very successfully.

And so I'd like us very early in the process, if it's not question 6, (d)6 on page 3, then some other formulation of the question drawn from the President's letter and drawn from the present stance of things in light of the general counsel's report from HHS, to say what is the question we're trying to answer and what questions do we have to answer to provide an answer that is acceptable, that is to say that is responsive to that and that rests on good moral reasoning - again, as Pat emphasized, not trying to answer the question as a moral question but as policy that is defensible because it rests on a necessary consideration of the ethical considerations. I very much agree with her, and I would disagree with Erik Parens's suggestion, that we have to in any real sense address things that are further down the horizon. It is one thing to say, as Pat did, that this would be an appropriate area to have the kind of response that the Recombinant DNA Advisory Committee has, that is to say a group that is given a general framework and then asked to make serial decisions in light of the developing science. It would be one thing to say that one thing we could note is that in the future perhaps ES cells might be used or a way that doesn't yet have full Federal regulatory

oversight, say for manipulations of the human germ line. And although the first major example we have that I can think of after the cloning technology was developed, which is Dolly, which was the calf or sheep-sheep-it was modified without the use of stem cells to have an inheritable change. Two weeks ago the NIH had a genome, or genetic transfer, policy conference on prenatal or in utero modifications where the issue was the germ line transfers. So our suggestion could be, if this is an issue and if the RAC doesn't have purview over all the necessary technology, it would be good to have another body, and between the two of them they could work that out. Just mention to that as the kind of issue that cannot possibly be fully considered in the present state of knowledge, where the relative science is so undeveloped. At that conference two weeks ago, even as to the kind of in utero technologies that were being talked about, people gave "We don't know" answers to dozens of the scientific questions you'd have to answer even to understand which of the various means of intervention will be used first with human fetuses to try to make a genetic transfer for a therapeutic [INAUDIBLE]. I think it would be very premature, and we're likely to get the ethics and the policy wrong if we speculate too much. I would therefore narrow it and if we need to mention some future things, that would be something for the ongoing body to look at.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I agree that we need to narrow the scope of the report. And I'd like to suggest that we do this backwards, that we talk about and try to come to some agreement on what kind of recommendations we want to make and then move from there to find the justification for those recommendations, and then include whatever educational information we would want to include. So I like the idea of not having a long, drawn-out, wordy report for something that's going to be pointed and clear.

DR. SHAPIRO: Sounds good. Bernie?

DR. LO: I would also strongly second what a number of the other Commissioners have said about trying to keep this a focused report. In addition to the reasons others have articulated, it's easier to argue from specific cases rather than from abstract speculations. I think also, having been part of the 1994 commission, what's being proposed now by the NIH is to provide Federal funding and oversight of stem cell research deriving from fetal materials on the grounds that it would not require any changes in existing laws and regulations. I think to clarify the ethical underpinnings of that and the concerns would be a very important first step. I mean that really has not been done and the total privatization of the research is disturbing. And I think if we could clarify just that one issue, it would be a very, very substantial contribution.

I think there are going to be issues that come up in the future, but we're not going to be able to settle everything, and I would like to see us take a sort of very incremental approach and say that if we can resolve some things first and build some consensus, set up a procedure that allows for real, responsible oversight, that would be a big first step. And in the next discussion, in six months, a year, or two years, it may be a little easier for that having been forged - some agreement to do, you know, very narrow types of research. I think to readdress the issue of the public policy acceptability of Federal funding for human embryo research is a whole huge issue, so extremely contentious it's going to detract attention from work that probably can be done under existing Federal policies. And I think it may get us into more trouble without really allowing us to resolve issues in a concrete, practical way that provides guidance to scientists and Federal funding agencies.

DR. SHAPIRO: Bette?

MS. KRAMER: Well, just about everything I wanted to say has been said. I want to second the approach. Given the rate at which the science is exploding, the speed with which it's exploding, there's almost something arrogant about trying to answer all the potential questions that are out there. And it seems to me that we could

make a strong case for an incremental approach to it. I also would go along with a narrow approach.

DR. SHAPIRO: Thank you. Trish?

PROF. BACKLAR: I'm going to agree. I would like us to write a Belmont Report, in a sense, on this subject. And so I just want to add my voice to say keep it short and crisp.

DR. CASSELL: I agree: five clear principles.

DR. SHAPIRO: Carol?

DR. GREIDER: Well, I'm mostly going to agree, but I'm a little bit troubled that I'm hearing different things from people that are all agreeing with each other. The idea of having a report that is focused primarily on a particular issue and is grounded in the facts, I am all for. However, I'm not going to agree with the component that says this means we won't try and at least tackle some of the issues involving embryo research, which I think was in Harold's original memo. I would not agree with what Bernie just said because I heard him saying that we should essentially not get into that area at all. If we're going to tackle the area of embryonic stem cells, one by necessity has to tackle how they are derived; otherwise we will be seen as ducking the issue. So whatever I'm agreeing to, that's what it is. And then to second what Rhetaugh said about recommendations first, maybe not first but at least early in the process, because I think one of the problems that at least I felt a little bit frustrated with in some of the earlier work that we did was that we were writing things in concrete terms when we hadn't yet agreed to what it was we were going to say. I would like us to agree on what we want to say and then write the recommendations rather than the other way around.

DR. SHAPIRO: Alta?

PROF. CHARO: Well, in light of that I'd like to try out a somewhat different outline, somewhat concretely, and see how people react to it. To very clearly separate, perhaps, questions around what would be appropriate uses of stem cells in research and down the line in therapy from the question of variety of sources and the special problems associated with each source, because just focusing alone on the uses already opens up some avenues for discussion and for recommendation, such as in the context of their use in experiments that would ultimately involve a reproductive form of experimentation. We've got statements in the Cloning Report that have suggested that we're very chary of anything that is going to be reproductive in its outcomes. That's one of the things we might want to look at. And looking at some of-at least acknowledging some ofthe problems that exist in the system generally in the area of clinical trials and the way in which this would get into the clinical trials area. So there's in vitro drug testing, there's transplantation, there's genetic engineering done on the stem cell before transplantation as a vector, etc., there's its uses for dedifferentiation of somatic cells-all of which may be worth discussion on its own. And to then take the sources in a very reductionist fashion and in a very modular way, perhaps, to decide one by one which ones we're going to tackle, starting with what appears to be the least problematic and moving to the most. Then one can start with the neuronal and hematopoietic, etc., stem cells and then move on to the existing supplies, first in Gearhart's lab, which came from fetal sources, then from Thomson's lab, coming from embryonic sources where we have to deal with the problem of taint in those two cases. Only then moving on to new ones from miscarried fetuses, from induced abortions, from spare, so-called "surplus" embryos, and the last probably being the new created embryos. If we dealt with the sources in a modular fashion we could stop anywhere along the way, and that module of problems of source would fit nicely with an existing discussion about appropriate uses and be a kind of stand-alone set of discussions.

MS. KRAMER: Alta, do you mean stop anywhere along the way when

we reach disagreement?

PROF. CHARO: Or when we reach disagreement about whether or not it's important that we tackle the next module.

MS. KRAMER: Okay; all right.

PROF. CHARO: For example, the one that deals with new stem cells, not from nonviable embryos but new stem cells from viable embryos, which would necessarily get us right squarely back into the embryo research debate, might be the point at which everybody here fails to agree that we really want to go down that road and do that module and do that report.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Okay. I'm quite comfortable with the direction that Alta has just suggested. And I was struck in the discussion by actually how close Pat King and John Robertson were in the final analysis in at least a kind of tentative early ranking, and then by the kinds of safeguards and guidelines that they recommend. And then I think we'll end up with something like that ourselves when we get pretty concrete and keep a good, clear, sharp focus on exactly what we're asking-what we hope to accomplish. I would note, though, as we think about some kind of advisory group, there are some differences that have already emerged in today's discussion. For example, it seemed to me that Harold Varmus's presentation really was a kind of administrative approach that really didn't involve very much public input at the point of oversight, whereas I heard some others offering a much broader view of what the kind of oversight mechanism might actually involve. So I'm sure there will be a lot of room for disagreement and controversy, but I really think we'll be able to take several steps along the lines that have been suggested before we have to have dissenting reports.

DR. SHAPIRO: Larry?

DR. MIIKE: Just on Alta's top-of-the-head proposals, I think in terms of the uses it should be just a descriptive. I don't think there's much public policy issues for us to address on the actual uses. The main issues seem to be around the complicity issue, once you have the human stem cells, and the source issue about where do you get future ones. And so I think that should really be the focus of our policy debate and conclusions, whereas much of the other should be more a description of the technology and the possibilities, etc. Clearly, within the context of the stem cell uses themselves, we have to get into the oversight, the regulatory mechanisms, etc. But that's the way I would cut it.

DR. SHAPIRO: Other comments? Who has some comments? Eric?

DR. CASSELL: Well, I liked Alta's outline a lot because it does allow us to stop short of, I think, where we can get in a lot of trouble - because we enter the embryo research debate and die on those rocks. On the other hand, I do want us to keep the fact that as we see it this is part of our function, that this is a report that we have an interest in larger issues and that's made perfectly clear in the report. We're narrow because we know we have a responsibility to a science that's right on the line now, but we're broader because we know we have a larger responsibility to the people and to the President, and to ourselves.

DR. SHAPIRO: Bernie?

DR. LO: I'm very comfortable with what Alta suggested, and two additional comments. One, I think we can signal the importance of a lot of ethical dilemmas without necessarily feeling we have to resolve them. I think it may be better to say: Here are the issues, here are what some people believe, here are what other people believe, here are the problems trying to work that into a public policy. Second, I think in

light of this discussion, are there other kinds of witnesses we might want to invite to sort of help us through these kinds of issues? I mean some of the issues I heard come up during the course of discussions had to do with, first, the complicity issue that Alta raised, and second, the issue of trying to develop public policy on an issue where there are very deep divisions in society. I don't know if someone like Jamie Thomson, Harold, would be able to shed some light on that. We're going to be in Princeton next time. And third, we started to talk a little bit about different models that have been tried in the past providing some sort of ongoing oversight. And Jamie Gearhart - I'm sorry -

DR. SHAPIRO: Jamie is Thomson. You created a hybrid.

DR. LO: The association would have come.

DR. SHAPIRO: But I kind of like the name.

DR. LO: And a third topic would be to try to get some more experience. Jim and Alex, you said some things about the experience at the RAC and other bodies that have been charged with ongoing oversight. It seems to me one contribution we could really make is to think through how we might be able to do that effectively without being regarded as overly burdensome by the scientists or as having no teeth from the point of view of public input.

DR. SHAPIRO: Alex?

PROF. CAPRON: A procedural comment in that regard. I noticed that on the chart that Kathi prepared three or four weeks ago we have contracts and Commission papers that may relate in some ways to some of the testimony we are already getting. And I hope that our arrangements with the people with whom we have these contracted papers are flexible enough or we have the ability to bring in other people, because it may turn out that the questions we ask are not the ones that were

anticipated fully a few weeks ago. In fact, the point that Jim has borne down on twice today about the different sources of cells - the fetus, the created embryo, the existing embryos, and so forth - and ask people to rank them. It might be helpful to have someone both do a little bit of a sort of empirical analysis of are there position statements by all sorts of different groups on that subject. But it also would be helpful perhaps to have some thought by people specifically on that because it seemed to me that there's an interesting tension in the notion that the more developed fetus is a more acceptable source of cells than the blastocysts of a few dozen cells. And I understand part of that, which is in part not an inherent constitutive argument but is in part also a consequentialist argument in that the likelihood that people are going to undergo abortions simply to create tissue for someone may be seen as being smaller than if people could be persuaded to create embryos for this purpose. And so it may be that people think the risk's there. But I'd like to have that explored.

It may also be, from what Dr. Gearhart said, that there are some differences between the ES and what he calls the EG cells. And ironically, as I understood it, the EG cells may be less imprinted than the ES cells, that is to say they may become backwards in the developmental process to the point where they have characteristics that are desirable to have in the stem cells. Anyway, these are all the kinds of questions that we need to have [INAUDIBLE] so that we may debate the issues. [INAUDIBLE]. So I think the staff needs to respond by getting these additional papers and reading them.

DR. SHAPIRO: I think the answer is that there's still a lot of flexibility here. A lot of these have not really been done or contracted for. They're sort of people that we're thinking of or we've talked to preliminarily -

DR. MESLIN: In most cases.

DR. SHAPIRO: Good. Yeah. David?

DR. COX: I agree with Carol: I hear lots of people agreeing and saying different things. So if I go to Alta's suggestion which as I take it and hear you meets the focus criteria but also meets the idea that you would in specific contexts talk about them in the broader context. So I'm very in favor of that. I'm not very interested, though, in going out to try and answer scientific questions that there's not scientific data for. That's exactly where we could get that's one of many ways we could get quite sidetracked. So I think if we stick to your outline as our life raft, Alta, then it gives us enough berth where we can discuss things but then decide when we want to quit rowing, too.

DR. SHAPIRO: Arturo?

DR. BRITO: I, too, like Alta's modular idea or outline, and I want to touch on something David just said. One of the things that I have not heard anybody say that's a little bit different than when we did the Cloning Report is that I think here it's going to be very key to be very clear, and aside from making all the definitions about the science is making it very clear what we're currently capable of doing, or what science is currently capable of doing: what is potential and what's totally theoretical within the context of the outline that Alta's been proposing. So I think that's got to be clear, too. The purpose of doing that would be to defuse some of the hysteria that comes from doing this kind of work and some of the fears that the public may have.

DR. SHAPIRO: Alta?

PROF. CHARO: Yeah. Let me just clarify one small thing for Larry that relates to what you said, Arturo. When I suggested that part one, which would be kind of-if you think of it as a matrix of sources and uses-part one would be on uses. And Larry said there's not much public policy. It's not huge, but what we discovered at the University of Wisconsin because of Jamie Thomson's work taking place there is that there was a need for discussion about appropriate licensing restrictions, if any, to be

placed on licensees who would receive some of the stem cells he had generated. And we had discussions about whether or not there was any kind of particular experiment that we thought was so inappropriate that we would not permit a licensee to use the cells provided by Jamie Thomson's lab to perform that experiment. We also discovered that the views of the bioethics committee for the university - that's not the hospital IRB or the ethics committee for the hospital, it's a separate committee that just advises the chancellorCthat our views on acceptable experimentation were broader than the views of the actual university licensing office, which had political considerations in mind as well as ethical considerations in mind when it set out its own parameters for what the licensing agreement would look like. But that's where we got into questions about things like human and nonhuman cell combinations and various forms of genetic engineering, and began to focus again very, very much on the bright line of demarcation between reproductive versus nonreproductive uses of these cells. And that's the kind of thing I was talking about, which is an issue that is broad in the sense that it covers all stem cells regardless of their source, but focused because it's really on one particular aspect of the problem, which is: What kinds of experiments should or should not be done with Federal money with these particular cells?

DR. MIIKE: All right. We're not in disagreement. What I was focusing on is that when we have whatever the quasi-science or the science part about what these uses are, that that be a descriptive piece and that there's not really much policy around that. But when you get to the issue of oversight, then, that's where all of those issues come in.

DR. COX: Exactly. It's the oversight.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I like the idea of raising that last question you raised, Alta. First, you know, what will the Federal government support? What will we recommend,

what would we like to see the Federal research enterprise support? And then, if we could have that dialogue, I think we could move much faster to fill all the other gaps in the outline that you have.

You see, the outline that you're proposing is an outline for reporting, and I am suggesting a process of getting the work done to keep us from getting bogged down and to give us a direction. So I'd like to see us think about what is it we'd want to see happen here in relation to this research, and what will be necessary then to consider as we make recommendations for oversight and all of that.

DR. SHAPIRO: Yes, Kathi?

DR. HANNA: All right. I wanted to respond to a couple of things and to thank Alex for being concerned about our health and welfare. Just to clarify a few things, first of all the outline. The way that it's presented was to try to be as comprehensive as possible just to give you the full menu. You can choose from column A or column B. Also, as Rhetaugh just said, it doesn't have to be the way the final report would look. You might, in fact, want to organize it quite differently along the lines that Alta suggested. The contracts for Commission papers are just - we're just exploring with most people what issues they might be able to help us out on, so there's a lot of flexibility there, as there is in any future witnesses that you would want to invite.

The only one or two things I think you should be aware of is, one, that the outline was done without the knowledge of what the announcement was going to be today, and so the announcement from Dr. Varmus has slightly changed the universe. So I think we now have to make the outline accommodate that announcement of the direction the NIH is going to be going in. And then the last thing that I wanted to mention is that we are doing a somewhat mutated public comment process this time around. Next week, or actually this week, I would hope, letters are going out to probably 50 or 60 organizations that we've identified - that staff have identified, some of you have

given us the names of people - asking them to submit to us in advance any statements that they would like to make about embryonic stem cell research specifically or any other issues generally, to provide us with any guidelines, policy positions, or statements that they might have. So we will be collecting public comment in a sense as we go through the process. And as we get those responses in, we will circulate them to Commissioners. So we won't be waiting until you've issued your recommendations and then have it go out for public comment, although I think we need to consider doing that in a more abbreviated way, but we're going to try and get public input in a more formal way throughout the process. The invitation to comment will be-is-might even already be out. Not yet?

DR. MESLIN: No.

DR. HANNA: Well, it should go up on the website this morning.

PROF. CAPRON: In light of the kind of consensus that seems to be emerging, that the questions would be posed in terms of some rank ordering of difficulty of supporting particular steps. As a Commission device, the way Rhetaugh has said and I took Alta's list to be, in effect, these are the agenda items for February, do we agree what are the considerations in reaching a conclusion on this and then moving on instead of waiting until the circle, like a bubble, gets so big it fractures and then doesn't go any further? That those would also be the ways in which we would tell the public and these groups, rather than asking them for their kind of global comments on it, saying, AIs it justifiable to support this? Is it justifiable to support that?@

Is that correct? Is that how you would probably try to frame what you're going to ask people, if that's the consensus that comes out of today, that a kind of modular approach be used there? I mean, not to tell them we won't take other comments, but this is the way we're going to be talking about it. If you want to be helpful to us, why don't you try addressing the issues we think we're going to be

addressing?

DR. MESLIN: Well, our initial plan is to send out the first set of letters that Kathi just described. We do want to get descriptive information from those organizations that are likely to have specific interests in our work and to tell us any statements of policy that they may have and what their concerns might be on a particular question, and we wanted to do that to be ahead of the curve. We wanted to gather as much information for the Commission as quickly as we could given our relatively short timetable. The specific questions that you've asked, which we have only now begun to formulate and process, can also be supplemented and be sent out in addition. So we're not going to stop the process of sending out the letters that we're now in the process of doing to get statements. I think your point is to supplement that with specific, directed questions. And we can easily do that.

PROF. CAPRON: Well, you had the transcripts today, and Alta did a beautiful job of going through those, and from everything we've heard from Dr. Varmus and Dr. Gearhart and Dr. Thomson, we know the different questions that are there. And if I were executive director of one of these outfits you're going to be querying, I'd like to get it all at once: What statements have you done, we're talking about it, here's how we're going about it, could you comment in this context? If you want to be helpful. I mean, the whole purpose of this, as Rhetaugh first stated it, was that we move ourselves forward in this process rather than spending months having global discussions of all the possible ethical ideas and considerations that might come in. I would certainly hope that the February agenda is mostly the Commission going through that exercise and not, in a day and a half, hearing a lot of witnesses.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Actually, I think the two can be brought together if we ask for the broad statement of policy, etc., and please pay particular attention to this

set of concerns, for instance. And it seems we could ask them that.

PROF. CAPRON: Yeah. I don't mean to - I just, as a supplement adding onto the letter, that we do it now.

DR. MESLIN: Right.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: My thoughts about the letter are different. I think that if the letter is open-ended we are likely to get what are the critical issues on the minds of the people that we're contacting. If we structure it, we might get their reaction to something that later on may not turn out to be what they were really interested in. So I would be in favor of leaving the communication and the query open-ended so they can tell us what's uppermost in their minds and hopefully we'll have a feel for that before we come out with a report on the Internet that they would then barrage us with concerns about.

PROF. CAPRON: Good point. With all deference to what we heard from the Alliance for Aging [Research], if we were to write them this letter asking what's on their mind, we know that they, like many other disease-related groups, are going to say what's on it is great freedom for this research to go on, the great value of stem cell research. We started asking. I asked the gentleman, Mr. Perry, whether his group has now taken the view that the prohibition on the creation of embryos or the use of embryos that exist to create stem cells ought to be lifted. We haven't gotten there. Well, if we ask him to go back and think about it - would you get there, would you support it? - that's the question, that's one of the questions on Alta's list. I would like to know more than that they're in favor of progress, which I think is what we're going to hear from most of the groups.

DR. SHAPIRO: Well, let's just agree without trying to write the letter.

PROF. CAPRON: Yeah, I don't want to write the letter now. I agree there should be an open-ended point in there, too.

DR. SHAPIRO: We will get the opportunities to do both things in some appropriate way, and that will be done. Bernie?

PROF. CAPRON: You've persuaded me.

DR. LO: I think that in this discussion we've identified the rudiments of part of an outline. I mean, one topic that Alta has raised is from where do we get the materials on which we're going to do stem cell research? It's sort of a graded hierarchy and a plan to see how far down we're willing to go. There are other issues that people have raised that seem to be following the general rubric of what can you do once you're allowed to start doing this research? It has to do with reproductive research, sharing, and licensing agreements. Finally, it seems to me there is a big Roman numeral III in terms of ongoing oversight by somebody to make sure that people are actually doing what we think they ought to be doing: How to devise that and set it up? It seems to me that those are the three big issues we want to focus on at this point. It would be helpful, it seems to me, in planning our February meeting, also to try and stimulate some feedback in this letter that we're going to be circulating. It's going to be evolving, but the more explicit we can be about what are the big topics we want to address at this stage of our report maybe will help accelerate the process.

DR. SHAPIRO: Larry?

DR. MIIKE: In that vein, then, when I looked at the speakers list for the February meeting, just to broaden it I would suggest off the top of my head that if we do have speakers we have speakers knowledgeable about the regulatory and oversight

function and we focus in on that, because the other types of issues here about collaborative efforts, etc., I think are tangential to our immediate needs.

DR. SHAPIRO: Other comments? David, then Steve.

DR. COX: If we're going to make sort of personal statements about top priorities, I'm happy to do that. I think that—just thinking as a scientist, and particularly based on Dr. Varmus's presentation—to have some clearly thoughtful discussion about complicity is going to be extremely important, because the path the NIH is going down is going to be confusing the matters. But without having some really thoughtful discussion about what it means to do that, not having been involved with creating them, I think is really high on the list for me.

Almost equally high, sort of like the twin pillar, is then the issue of oversight. And those issues of oversight are both in terms of scientific quality and also in terms of protection of vulnerable people involved in this enterprise. And we heard that from several different individuals. And that vulnerability I think is something that never really gets discussed but is really critical in terms of our mandate. So those would be my twin pillars. Not to change the outline at all, I think that it could be dealt with operationally, but those were the things that at each of the steps I would be really interested personally in paying careful attention to.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: As we march through Alta's outline, we're going to be reaching conclusions with respect to recommendations that say the Federal government ought or ought not to do the following. I think I have a question here about how we're going to be grounding those recommendations. Dr. King came forward with a suggestion, which is highly consonant with a recommendation of Alta's in her article in this briefing book about their report, which was a very different kind of approach

than, for example, was manifest in the Embryo Panel Report, I think. And the question is, How are we going to think about how we're going to think about these things?

DR. SHAPIRO: Let me say a few words about my own understanding of what I'm hearing and how we might proceed. First of all, to go back to the beginning of our discussion, I already began by saying that he took a somewhat different view than I did regarding these elements I put forward, then he went on to describe his view and I couldn't distinguish it from my own. [Laughter] In my mind, I realize that the reason for it is that the way I've worded it makes it look different than I had intended, and I apologize for that, because in writing these down I had never meant to move away from item One as the most important aspect of it, no matter which one of these you chose. And you got to the others just exactly in the way that Larry described, be that as it may. So that obviously what was Number One in this in its various aspects, however we structure or look at it, will have to be the center of what we do. The second thing is, and I think this is one of the difficulties with the staff outlines that currently exist, I do think our report has to have more in it than simply recommendations. One, we have to justify the recommendations on some basis, whether it's "resting on" or "derived from." I think it has to be "resting on." Anyone who's been through any exercise like this knows that there's no choice here: it just has to be "resting on." And so we'll have to provide that. We also need to provide in the report, in my view - but perhaps not in the body of the report but in appendices of some kind or another, or a second volume or something - material that is in some sense educational in form. It's one of our responsibilities, I think, because a lot of the people who are making decisions on here don't know what even we know. And it seems to me that we have some responsibility to do that, but we don't have to do that right in the body of the report itself. We can do that in some kind of - whatever we think is appropriate. We can separate it out in some way and not make the report more complicated than it needs to be.

But to return to the more important issue of justifying what we

recommend, it's very hard for me to think about how we're going to make a series of recommendations in February, as attractive as it sounds, without understanding or reaching some agreement on what basis we do this. Now I'm in favor of going ahead in that form, actually, because I do think it will give us some discipline and get us to our target sooner. But we're going to have to do some careful thinking along the way here as to why we think this use or that source has this and that characteristic that makes us feel good or bad about it. You know, I can give you my own ranking right now, but on the other hand, if you'd asked me to give more than a two-minute impression of why I feel that way I might not be so ready to do that. So I think the general notion that's come up here that we ought to try to focus as much as possible on some issues and some recommendations without making it sort of encyclopedic in nature is one I find perfectly fine. And maybe the suggestion of Alta's might really be a very good framework around which to build. I just don't want us to think, walking away from here today, that we can do that by focusing on the recommendations alone, and by the way, we'll figure out just why we got there some other place down the road. I don't think anyone intended that. So it's not that I'm accusing anybody of thinking in that form. That's not what I mean at all. But I do think that we will find ourselves iterating back and forth on this as we get toward our agreement.

And there are other people who want to speak here, although I want to adjourn in a few moments. I want to say that what I will do is pull together a small group of Commissioners to review the transcript of what we said today and try to reformulate pretty quickly an outline for your response over the next few days. So I don't want to have to wait for our next meeting for us to reach some iterations on this. But let me now turn to Jim, then Tom.

DR. CHILDRESS: I very much agree with what you said. I'd assume in the context of trying to come up with some recommendations in a response to a very focused question that what we engage in here is a process of public justification. The

kind of reason-giving that necessarily involves a variety of considerations - ethical, legal, etc.Cand that in the course of doing that we may come to some greater clarity about whether we have what Professor King called an overlapping consensus on what exactly we have going on. So I would see it kind of moving back and forth between the particular and the general.

DR. SHAPIRO: Tom?

DR. MURRAY: Jim just made my point.

DR. SHAPIRO: Thank you very much; I appreciate that comment! Bernie?

DR. LO: Just to say I totally agree: We have to give justification. I just urge us to try and see if we can develop justifications that will appeal to people with widely differing views on the moral status of the embryo, and not to make our justifications contingent on a certain conception.

DR. SHAPIRO: Larry?

DR. MIIKE: Just in response to Bernie, and then I have another thought. That's what I meant by we have to have our reasoning, and then we see how our stem cell recommendations fit into that reasoning. I think by February we should be able to have a list of questions that we should answer, out of which come our conclusions and our recommendations. And that should be pretty straightforward.

DR. SHAPIRO: Other questions before we adjourn and take a deep breath? Do we have another? I don't know if we'll have more time to come back to this tomorrow or not. We have another major item on our agenda tomorrow, and that has to take as much time as it needs tomorrow.

DR. COX: So it's - to follow up - Steve asked a question and sort of no one bit.

MR. HOTLZMAN: I think Harold bit.

DR. COX: Okay. All right.

DR. SHAPIRO: If there are no pressing issues, we are adjourned.

[END OF DAY ONE]