27th MEETING
NATIONAL BIOETHICS ADVISORY COMMISSION
February 2-3, 1999
Whig Hall-Senate Chamber
Princeton University
Princeton, New Jersey

DAY TWO - Wednesday, February 3, 1999

OPENING REMARKS

DR. SHAPIRO: Let me just outline very briefly our agenda today; we=ll begin, of course, hearing from Professor [Brigid] Hogan. We will then have some discussion that will follow up on that. We will pursue some further issues surrounding our stem cell issue. We want to reserve perhaps a half an hour this morning for revisiting the Human Biological Materials Report and some of the issues that came up yesterday

just to make sure we have a coherent notion of what we=re going to try to accomplish between now and our March meeting, which is only roughly four weeks, maybe exactly four weeks from now. So we=ll get to that later in the morning. We want to adjourn no later than 12 o=clock. I don=t know what the various schedules are, but it seems no matter when we schedule a meeting people will start leaving as we approach the end in any case. So we=ll just see how that goes.

But I want to turn our attention first of all to the presentation and to the welcome of Professor Hogan. Thank you very much for coming up here today. As everyone knows who traveled, yesterday was a hard day with delays just about everywhere because of the fog and rain and so on.

Professor Hogan is a professor of molecular oncology at Vanderbilt Medical Center, a Howard Hughes investigator, and really a very distinguished scientist. We are very honored to have you here on this campus and here before the committee. And as all the committee members have received a copy of Professor Hogan=s paper addressed to us, let me now turn to Professor Hogan. This is sort of set up physically like a hearing; I hope you don=t think of it this way. We=re really anxious to learn and we=ll have lots of questions. We are very grateful for you to be here to help us out. So thank you very much, and welcome.

STEM CELL SCIENCE

DR. BRIGID HOGAN: Well, thank you very much indeed. Having actually been on your side of the table in 1994, I realize what a tremendous amount of work and effort and other things it requires to do these sort of investigations, which I think are really, really important. So I have prepared this statement. I thought maybe I=ll try and just summarize some of the issues that I wanted to draw to your attention rather than just reading it. I=ll try and do my best to sort of summarize some of the things for speed to get through to your questions.

So the first issue that I wanted to really discuss was this question of patenting, and in particular the material transfer agreements. Because as you know, the methods for deriving embryonic stem cells from blastocysts and from primordial germ cellsXthose methods will have been patented by the investigators and their universities. And this also then covers the cells derived by that method. And these patents will then

have been licensed to Geron, either licensed, probablyXI don=t knowXbut licensed exclusively to Geron. So that any investigator, even with NIH funding, who wants to do some studies with those cells will have to have a material transfer agreement with Geron. And almost certainly, these cells will then come with strings attached to them.

And I think that this issue of accessibility is particularly important if NIH funding continues to be denied for the process of deriving pluripotent stem cell lines from extra embryos generated from IVF programs. Because as I said, in this case the only source of these cells for basic research will be from labs that are tied to Geron. Inevitably, as I said, the cells will come with strings attached. And I wonder if this monopoly really is in everyone=s best interests.

Will scientists be discouraged from working with the cells if the material transfer agreements are too stringent and do not meet the approval of the institutes by whom these scientists are employed? It might not be clear to you, but sometimes, if a scientist wants to obtain a materialXa chemical or a cell line or a clone that has been derived by another group but is patented and licensed to some other groupXthen it comes with a material transfer agreement. It might be that anything that=s subsequently discovered using that has to be the property of the licensee, or that they have to have first rights of refusal to that discovery.

And sometimes with these material transfer agreements, the scientists will be very happy to sign them. I mean, they just want to know the answer to their problem; they=re just interested in some research to answer a question that they are concerned with. But this material transfer agreement has to be signed by the employers of the scientists. In my case, I have to give that material transfer agreement to the Howard Hughes Medical Institute. Other people would have to show it to their universities. And it=s looked at by lawyers and people in the university, and they can turn around and say, ANo, you can=t sign this. We won=t sign it. You cannot have this material.≅ It has actually happened to me with a clone or something. And it could well be that a scientist will not be allowed to use these cells and willX

So I mean these are issues that have to be considered, and personally, I think that universities that enter into licensing agreements with companies have to be aware of the long-term implications of these kinds of agreements. In the particular case of the pluripotential stem cells, they have to realize the full societal implications of perhaps restricting availability of these cells to people who=ve got really strong scientific arguments for wanting to study them.

And I feel here, as I said, I feel that the couples who will donate their excess embryos from IVF programs, or women who with a great deal of heart-searching and genuine wishes to help other people will donate their aborted fetuses, then I think that these people are doing it in the spirit that they=re benefiting the general population and in the belief that their cells will be readily available. And I think their altruism has to be respected. But obviously these are broad issues and probably ones that are beyond your purview, but I wanted to bring that to your attention.

The other issue that I wanted to talk about was also this issue of informed consent, which has some bearing indirectly on this question of accessibility and material transfer agreements and so on. In our 1994 NIH Human Embryo Research Panel we discussed this issue of informed consent. And we drew up the recommendation, and I quote here, that, AIf the physician and the researcher are one and the same, the IRB≅Xthat=s the institutional review boardX≅may require consent monitors to ensure that free and informed consent is obtained. In addition, the IRB should require consent to include financial disclosure by the investigator.≅ And obviously I think that these recommendations still hold for derivation of pluripotential embryonic stem cells.

Again, in the case of the women donating aborted fetuses, I think it=s also particularly important maybe that these safeguards of informed consent are adhered to and that everything is discussed with these women and that there is somebodyXagain a consent monitorXbetween them and the investigator. And really the issue here is that I think that maybe not many institutional review boards have had to deal with these issues. And one of the things that came up in our panel was that there=s a real need to educate institutional review boards in all of the issues that surround this kind of research.

Another issue that we discussed also in the 1994 panel was this one of how to respect the special status of human pluripotential stem cells. And in particular, here I mean that I just want to say that I know a tremendous amount of heart-searching, again, goes into the decisions to donate embryos or fetuses by the couples involved. And I think that, again, one of the feelings that they have is that the very, very best studies are going to be done with the very precious material that they are donating.

And so one of the ways to ensure that the special status of human preimplantation embryos is respected is to ensure that they are used only for research of outstanding scientific merit. And I just wanted to point out, as you all know, that in order for research proposals to obtain NIH funding, they must have passed very

stringent peer review for scientific merit and originality, most likely placing them in the top 20 to 25 percent of all proposals submitted for funding. Moreover, applicants for NIH funding have to show evidence of their expertise in carrying out proposed experiments, and evidence from preliminary studies using mouse or primate stem cells for the feasibility of their claims.

So it=s not that these cells are going to be just available to anybody or for NIH funding. They have to have shown that they have got the expertise, they have a really original proposal, and it=s going to pass very stringent peer review.

Also, by allowing NIH funding, scientists with a wide range of expertise will be able to derive maximum information from this really valuable resource. And again, with NIH funding, this information will be freely available to the scientific community so that discoveries made with these cells will be published and this information, because it=s been obtained with NIH funding, will be available.

Now I want to move on to some of the more scientific issues about pluripotential stem cells. As you know, these stem cells have been derived from two different sources. And actually, I have a slide; my first slide is just illustrating these two different sources. I know that you know this, but I thought I=d just sort of summarize it here, so can I have the first slide? All right.

This is just a slide to illustrate the two methods that have been used so far to derive the pluripotential stem cells. One of them is to take the blastocyst-stage embryo and to grow it in a culture dish in which these outside cells, the trophoblast cellsXand I=ll mention that again laterXthese outside trophoblast cells attach down onto the culture dish, and the inside cellsXthe undifferentiated inner cell mass cellsXcontinue to proliferate here. And they can then be subdivided and grown indefinitely in a culture dish. They can be frozen and thawed and will continue to maintain the correct chromosome number and will not age.

Another method, which is actually one that I developed from working with mouse embryosXand this is a depiction of a mouse embryo at about nine days of development. In the posterior of the mouse embryo there=s a group of maybe several hundred to 1,000 cells, which are called primordial germ cells. And these are cells that are set aside very early in development and are destined to give rise to the germ cells in the ovary or testes. And this is meant to be a little embryonic ovary or testes, the somatic cells here.

These cells, primordial germ cells, are actually fascinating. They undergo a migration down the posterior of the embryo and find their home here in the gonad. And when they get thereXduring this migration they=re actually proliferating, but when they get thereXthey will go into a resting state. And in the case of the female germ cells, they don=t divide any more. All the germ cells a woman has during her lifetime were made during this migration process. But in the case of the male, the cells will start to proliferate again around the time of puberty.

But the important thing here is that we found that if we took these germ cells, either primordial germ cells either on their migration route or when they had just got into the gonad, and put them into culture with a cocktail of growth factors that would stimulate their proliferation, we found that they would revert back to the cells, which are very, very similar to these stem cells or inner cell mass cells, in the blastocystXand that again, they would remain as undifferentiated cells indefinitely.

One point I wanted to make to you, because I know that it has come up in some of the discussions, an important point here is that when the germ cells reach the gonad they go into a state eventually in which they cannot be persuaded to proliferate again in response to this cocktail of growth factors. There=s only a very narrow window of time in embryonic development, which in the human, by analogy with the mouseXI don=t know experimentallyXbut obviously by analogy with the mouse it would be up to about eight weeks, or possibly even nine weeks of gestation. Only during that time in the mouse embryo, in that window of time, is it possible to make these embryonic germ cells. So that by the time the mouse embryo got beyond the time when they had gone into the gonad, you couldn=t get them to multiply any more, these primordial germ cells. So I think that the idea ofXand I=ve seen it written hereXof using what is called this partial-birth abortion method in order to be able to get gonads to make embryonic germ cells is scientifically unfounded in the sense that we know that in the mouse that the gonads at that late stage of development would not beXthe germ cells in themXwould not be able to proliferate in the same way.

So, the other point I wanted to make scientifically is that the cells derived by this route, from blastocysts, have been called embryonic stem cells. The cells derived by this route have been called embryonic germ cells, or EG cells. And in many, many properties they are identical. They both, as I said, will grow indefinitely. They both will differentiate into many different cell types in culture: you know, nerve cells, cartilage cells, muscle cells, and so on. And they will also bothXit=s possible for both of them to be incorporated back into a developing chimeric embryo, as I=ll describe in a moment.

However, we did find that in some of our EG cell lines that were derived from mouse embryos there was a significant difference from embryonic stem cells, and that relates to a process that=s taking place during this migration. And for reasons that would take a long time to go into, there is a process of what=s called Ademethylation≅ of the DNA that=s taking place during this time. Genes undergo a modification of their DNA called Amethylation,≅ and part of this process of becoming a germ cell is to strip off the methylation from certain imprinted genes. And we did find that this property of some genes being slightly altered in their methylation pattern was retained by some of the embryonic germ cells and Xone assumesXthat it was affecting their ability to differentiate.

So I think that we can=t say scientifically that these two cell types are exactly identical. We know from work with the mouse that there are differences in some EG cells in the methylation of their genes from embryonic stem cells. And I think for this reason one would want to be able to scientifically study, pluripotential stem cells from both of these sources. But I don=t think that it=s scientifically justified to say that these cells are exactly identical to embryonic stem cells.

Another point I wanted to make here is that these pluripotential embryonic stem cells are not easy to grow if they=re going to be maintained in the state in which their chromosomal complement is normal. So I know some people in the popular press have maybe given the impression that these cells are very easy to growXwe grow liters of them, you can just do it in a simple growth medium, and any scientist can do it. That=s actually not true; these are very, very difficult cells to grow. They need a lot of care and attention so that the cells that have acquired spontaneous mutations don=t overgrow the normal cells, and it is something that you have to have a lot of experience in growing cells to work with.

Then I addressed here many of the issues surrounding the potential of pluripotential stem cells for cell replacement therapies and the possibility of deriving cell lines that are genetically identical to a patient and wouldn=t be rejected by the immune system. I think that you probably covered some of these issues. I just wanted to reiterate, maybe, that I hope some scientists have said that although these pluripotential stem cells do have the ability to differentiate into many types, there=s still a huge way to go to learn how to do this reproducibly and that it=s not going to be just throwing a simple genetic switch to change a stem cell into a nerve cell, or a stem cell into a pancreas cell, although this is where the benefits of these cells come from. We still have a huge amount more to learn and there=s a lot of basic research that needs to be done.

The other point is that it=s not going to be easy to get these differentiated cells back into a patient so that they find the right place in which to grow and to repair damaged tissue. But this is a problem that=s inherent in all stem cell therapies. It=s not something that=s unique to the pluripotential stem cells and their derivatives; even if you had a multipotent stem cell, even bone marrow stem cells, which we know quite a lot about, are not easy to get back into just that little niche in which they have to proliferate and grow. There=s a lot of ongoing research here, but it applies to all stem cell therapies.

The other point was that I think one of the great benefits of the pluripotential stem cells is that they will be perhaps more accessible to the kind of studies that one will need to do in order to try and alter perhaps the histocompatibility or the antigens on their surface so they will be compatible with the recipient.

And I did just want to raise one other future application of stem cells, which maybe you=ve had already, but I just wanted to reiterate this. And this is really a slide I made when I was talking to some groups about how somatic cell nuclear transferXor what would be called cloningXhow that might be used therapeutically. This is the kind of scenario that one might do: to take an unfertilized egg from a donor, a woman who with informed consent has donated eggs for this research purpose. And this unfertilized egg wouldXthe genetic material from it would be removed, so now it will contain no genetic material from the donor at all. Meanwhile, we have an adult patient who needs, for example here, a blood cell transfer. Adult cells would be taken from this patient; they could be, for example maybe in the future, just simple skin cells. And a somatic nucleus could be taken, theoretically, from one of these cells and transplanted into this enucleated, unfertilized egg. Then it would be activated artificially and cultured in the test tube to the stage when it is at the blastocyst stage. This could then be taken and grown in a petri dish, as I described before, to give rise to embryonic stem cells and could then be differentiated into a blood stem cell and returned to the patient. Since all of the genetic material would have come from the patient, they would not be rejected at all. And so I think that in the future this might be one of the applications of the embryonic stem cells.

PROF. CAPRON: Could I ask Dr. Hogan just a question on that point?

DR. HOGAN: Yes.

PROF. CAPRON: Is there any reason to think that the mitochondrial DNA in the egg will have any influence on utility of the stem cells as sources for transplant material, for tissue for transplant?

DR. HOGAN: Well, in this case the mitochondrial DNA would be human. I mean it would be different.

PROF. CAPRON: Right. But it=s not the mitochondrial DNA that the patient had. It=s the egg donor=s mitochondria.

DR. HOGAN: Yes, it is. And there are a few inherited disorders in humans in which there are abnormal mitochondria, and this affects the development of some of their tissues. But I think you=d obviously screen your donors for carrying such mutations.

MR. HOLTZMAN: I guess the question is, Is there any reason to believe or is there knowledge whether the mitochondrial DNA encode surface antigens that would affect the rejection?

DR. HOGAN: Not that I know of, no.

PROF. CAPRON: That was indeed the question. And in other places in your paper you suggest that we would explore many of these issues through mouse research, that we don=t need to use human cells.

DR. HOGAN: Yes.

PROF. CAPRON: And that would be true of the transplant work as well?

DR. HOGAN: Yes.

PROF. CAPRON: Thank you.

DR. HOGAN: Yes, yes, yes. No, I think that=s an important point I wanted to make here somewhere if I got through it allXthat I personally believe that 95 percent of all the basic research is going to continue with mouse embryonic stem cells, for a whole range of good scientific reasons. And that only after having done those preliminary experiments in obtaining the feasibility studies would one want to start exploring it with the human embryonic stem cells.

PROF. CAPRON: Thank you. I=m sorry for the interruption.

DR. HOGAN: Oh, don=t be sorry. That=s all right. All right, well, that actually came to the next point, which was, really are human pluripotential stem cells the preferred cells? And I would say noXfor basic research it=s still mouse because we have a whole range of mouse mutantsXwe know about the mouse genes; we can manipulate them. I also wanted to raise the point that I don=t know how many of you know, but I know that Jamie Thomson has published deriving primate embryonic stem cells, both from I think the rhesus monkey and the marmoset. And again one could imagine doing feasibility studies with those cells, again, as preliminary to working with the human embryonic stem cells.

So now I wanted to pass on to perhaps something that I can make a contribution to in terms of the ability of mouse pluripotent stem cells to differentiating culture, because I know that this is something that, again, the lay press is particularly interested about. As I said, embryonic stem cells can be grown indefinitely and will differentiate in culture to many different cell types. One of their usefulnesses for the mouse developmental biology community is actually to put these embryonic stem cells back into a host blastocyst to make something called a Achimeric embryo.≅ And this is illustrated in this slide here.

What I want to show you is work that has been done by a number of groups with pluripotential stem cells that carry a genetic marker that means that you can stain them blue. It=s a gene that will enzymatically turn a chemical substrate into a blue precipitate, so it=s a way of genetically marking or flagging the cells that have been derived from the embryonic stem cells, or the ES cells. And I=ll just go through this particular scenario, which is the one I=m most familiar with. People will take embryonic stem cells that have been grown in culture and will inject them back into what=s called a host blastocyst, here shown in yellow. And these cells will mix in with the inside cells here and will form a kind of pepper-and-salt mixture of cells inside the growing embryo, and will contribute to the developing fetus here. And so that if you were to take out these mouse embryosXthis is about a nine-day mouse embryoXand stain them with this chemical reaction, the cells that were derived from the stem cells here will turn blue. And you can see that this is an embryo in which we=ve estimated more than 75 percent of the cells in this fetus were derived from these embryonic stem cells that were originally grown in a culture dish.

Now the really crucial point here is that for reasons we don=t understand yet, these embryonic stem cells only contribute to the growing fetus here. The placenta and what=s called the Ayolk sac≅ around the embryo come from the blastocyst. These embryonic stem cells can=t make the decision to become trophoblasts or endoderm. This placenta=s made up, for the sake of argument, of trophoblasts, and this yolk sac is made up from endoderm. And this has been very well studied and I think is illustrated in the next slide.

The next slide is the experiments that have been done by Andros Nagy at the University of Toronto. He worked out a way of genetically making the cells of the blastocyst hereXor actually these embryo cells, it=s the same thing hereXmaking them so they grow more slowly, genetically disabling them. So when it came to this mixing together here, these host cells were at a terrible disadvantage and grew more slowly so that the embryonic stem cells could colonize all of this fetus. So that all of the pups that were born were derived from the embryonic stem cells that had been cultured. But the placenta and the yolk sac still came from the blastocyst; even though they were growing more slowly, they still had to give rise to the placenta and yolk sac.

So this actually is a slide given to me by Andros Nagy showing one of these embryos that had been derived exclusively from embryonic stem cells that were, maybe 19 days before, growing in a culture dish. But notice here the yolk sac and the placenta were yellow; they came from the host blastocyst into which the embryonic stem cells were injected. And no studies to date in the mouse have shown that the embryonic stem cells can give rise to the whole embryo, by which I mean the yolk sac and the placentaXthe whole system that, working together, gives a viable newborn pup.

And I want maybe to just go back here for a moment. I think very recent research, maybe only in the last two or three years, has really focused on how the very earlyXwhat happens to these cells in this little group of cells here that will mean they can become organized into an embryo that has a head and a tail and a back and a front.

It=s emerging that it=s actual signals from this trophoblast and from this endoderm, very localized signalsXwhat are called organizing signalsXwhich are coming from those cells that are telling these inside cells what their spatial coordinates will be.

This is a slide taken from my own research and my lab on mouse embryos. We have found that there are actually factors which are madeXthis is the trophoblast here, which eventually will form part of the placenta; it gets pushed away

and forms part of the placentaXis making chemical signals that are telling these cells how to be organized in a coherent fashion.

There are also other signals. This signal is called BMP-4Xbone morphogenetic protein-4. The signal from the endoderm is something called Anodal,≅ and again is a secreted chemical factor, which is organizing these cells so that they start to move to form a primitive streak and become lined up in a way that means that they will now, each of them, acquire an address. It=s as though each cell now, as it moves into this primitive streak, gets a ZIP code and it tells it is it going to be the head, is it going to be the trunk, is it going to be the tail, is it going to beXwhich part of the embryo it=s going to be.

I think in my paper to you I gave the analogy that these are like iron filings, if you like: These are the poles of a magnet that are lining these cells up now so that they can get organized to form this primitive streak, which is the very first time at which an embryo now is coherently organized in such a way that it will give rise to an individual embryo with at this end a head and at this end a tail. And as I said, every cell now in this little discXthis is a depiction of a human embryoXwill have a spatial address and know where it is and what it=s supposed to do. And if the embryonic cells don=t get that organizing signal, they will be chaotically arranged, they won=t know where they=re supposed to be, and they will form totally disorganized embryoid bodies.

So now what is an embryoid body? Because this is something that again, the popular press seems to have picked up on. If one has the embryonic stem cells growing in a culture dish, as I said, in order to get an embryo out of themXa fetus, a newborn pup in the case of the mouse embryonic stem cellsXyou would have to deliberately and with great foresight put them back into a blastocyst. But what most scientists who are interested in the differentiation of these cells do is to keep them cultured in a petri dish and to induce them to differentiate. And one of the ways of inducing them to differentiate is to put them so they=ll grow as little clumps of cells. And when they do this they start to differentiate into a disorganized mass of tissues.

This is a slide that was given to me by Dr. Tom Deutschman at the University of Cincinnati, and he is one of the world=s experts at growing these embryoid bodies. It=s a photograph of a dish that maybe was only nine centimeters across, and it shows you many hundreds of these little embryoid bodies that he grew from mouse embryonic pluripotential cells. So each little embryoid body is only a few millimeters across. But if you look at one of these embryoid bodies you see that it=s a

little cystlike structure, and here he=s shown very clearly that you can get blood cells being made inside this embryoid body, other ones may will be beating with muscle. Some of them have a very primitive kind of nervous tissue in them, neuroectodermal tissue, in them.

But this is what an embryoid body is. And as you can see, you can have hundreds of them in a dish. If you put one of these back in a uterine transfer in a mouse, it would not form an embryo. The only way of getting an embryo from these embryonic stem cells is to put them back into a normal blastocyst where they receive these organizing signals.

And I just wanted to tell you that these disorganized structures, like embryoid bodies, are typically seen in some kinds of germcell tumors in humans. In the ovary in particular there are benign tumors called Ateratomas,≅ that arise from germ cells which are starting to grow abnormally. These are benign tumors; they can have many differentiated cell types in them, and pathologists have actually described structures not unlike this, which they call Aorganoids,≅ or in some cases I have actually seen Aembryoid body≅ used in a pathology textbook for describing the sort of structures that are seen in teratomas.

This is actually a section from a mouse teratoma that I made showing a bone, quite well organized bone tissue; there=s secretory epithelium, and you can see skin. Here is some pigmented neuroepithelium as would be in the pigmented structures in the, you know, in an eye. But you can see it=s all disorganized, and I don=t think anybody would call this a developing fetus or a developing embryo.

Okay, I think that covers that issueXmost of the issues I=ve covered so far. One of the points I wanted to make, just to get back to the issue of whether you as scientists, would makeXas I said, if you take pluripotential mouse stem cells, if you deliberately put them back into a blastocyst and put that into the uterus of a mouse, you can get a fetus being born. And as I said, with disabling the blastocyst cells you could get the whole mouse that was born to be derived from the embryonic stem cells. I can say that, though, we know now with new cloning technology and nuclear transfer technology that it=s theoretically possible to do this now with anyXto take any somatic cell by nuclear transfer into an unfertilized egg, and then by activating it you can get a clone of that somatic cell. And the technology for doing that nuclear transfer, the kind of microinjection equipment you need, the years of experience you need, is not that much different from injecting a pluripotential cell into a blastocyst.

So I think that if one is going to want to regulate cloning either using nuclear transfer or using embryonic pluripotential stem cells, one of the best safeguards against human cloning by either of these methods is really to license IVF clinics and require that physicians in them account for every human egg or embryo that=s obtained, what happens to it, how it is used. And this is not done in the United States; it is done in the United Kingdom [U.K.]. Right from the very beginning, IVF clinics were required to be licensed, to keep very strict records of everything that they do, and for this to be inspected openly and to be available for public scrutiny. I personally believe that this is something that should be instigated in this country. So maybe I=ll just finish there.

DR. SHAPIRO: Well, thank you very much; we very much appreciate the remarks. Let me start off the questions just by going to an issue that I think you raised very directly but I just want to make certain I understood it. It was your own judgment, I believe, that as you saw the scientific agenda unfolding in the next while, you thought most of the experiments in this area would continue to be done on the mouse, mouse ES cells. You used the number 95 percentXit doesn=t matter exactly what the percentage isXbut you think that that=s still where the sort of mainstream of the scientific work is going to be. And what I=d like toXat the same time, that extra 5 or 10 or 15 percent, whatever it is, I took you to mean is really critically important. I just want to make sure that that=s how you felt. I=m not putting words in your mouth.

DR. HOGAN: No, no. I feel it=s tremendously important, obviously, for the therapeutic application of the basic research. I just wanted to perhaps allay the fears that now everybody was going to switch over from using mouse to using human.

DR. SHAPIRO: Thank you. Let=s see if there are other questions from the Commission. Yes, Diane?

DR. SCOTT-JONES: You mentioned that in the U.K. IVF clinics are licensed and that you believe they should be here in the U.S. so that the persons who work in those clinics would account for every ovum and every embryo. Is that practical? Can that be practically done?

DR. HOGAN: I see no reason why not. I can=t think of any reason why it wouldn=t be practical.

DR. SCOTT-JONES: Okay. Our understanding is that in treating infertility, the doctor in that clinic would create so many attempts at conception that

there would just be so many of them that it seems that what you=re saying would not be practical. Is that not a correct way to understand how they do their work?

DR. HOGAN: I really don=tXI haven=t been involved in an IVF clinic; I don=t really know. But I assume that maybe, let=s say if you get 10 fertilized eggs, they have to make decisions already based on the consent form as to whether they are going toXhow many they are going to replace and what are they going to do with the extra ones. I think the woman will have already consented to certain ways of handling those extra ones, and they have to go along with her wishes, either to freeze them or to discard them. And they must keep records of that, what they do with them, so that if she wanted to know what happened Xor the couple wanted to know what happenedXthey would be able to tell her. And you would certainly avoid some of the things that have gone wrong, for example, in California in IVF clinics where ova were used without the woman=s consent. And I think she has a right, they have a right, to know what happened to their embryos. So records must be there already, soX

DR. SHAPIRO: Larry?

DR. MIIKE: All right. I assume that your research also includes efforts to develop embryonic stem cells into ultimate therapeutic products. That=s sort of a pre-question to my question.

DR. HOGAN: Well, my research, which is done in my laboratoryXno, we=re actually more interested in my laboratory where these primordial germ cells come from in the first place. But I have some experience with watching them differentiate and also advising a colleague who=s interested in differentiating them into the stem cells of the pancreas, the islet cells for making insulin. I have helped him do some preliminary studies of how you would go about doing that.

DR. MIIKE: The reason I ask is that we=ve read from you and from other scientists that the issue about somatic nuclear transfer is the customized tissue for an individual patient.

DR. HOGAN: Yes.

LARRY: Unfortunately, that route means you create an embryo expressly for research purposes or for a product line, whereas in the aborted fetuses or in the excess embryos in a fertilization clinic, they=re sort ofXthey had a purpose for

creation and they=re used because they=re not needed or they=re destroyed in that process.

DR. HOGAN: Well, I kind of justX

DR. MIIKE: Let me just finish my question, please. Everybody assumes that the best way to go, that=s what I seem to hear from scientists, is the customization process. But it seems to me that if you go down that route that every time someone needs something you must do a specific procedure for that person. If you go down the other routes about multiple cell lines or getting rid of histocompatibility complexes, then you have a very large source of common material for a whole bunch of patients. So my question would beXI understand as scientists you want to go down multiple routesXbut it seems to me that the ultimate way to go is to have more of the mass-produced method than the customization method. Because it does go back to the ethical issues that we have to face.

DR. HOGAN: I agree; yes, I agree. I would just like toXI mean, you=ve been through this. The somatic cell nuclear transfer does not involve at any point the fertilization or the bringing together of new genetic material. And although you have an embryo, maybe we have to define embryos in different ways. I don=t see why we have to have one blanket term for an embryo that covers everything. Maybe we have to move on from that and see something that is not creating a new combination of genetic material, which is not by the sexual bringing together of gametes. It=s different from somatic cell nuclear transfer.

DR. MIIKE: But for those who object to the procedure, once that is combined that is an embryo that could, if you implanted it, assuming certain thingsX

DR. HOGAN: Yes.

DR. MIIKE:Xif you implanted in utero would become a human baby, and I think that=s the basic objection to that route.

DR. HOGAN: But now you can sayXI=m just arguingXbut now one can say any diploid normal human tissue, my skin cell, has the potential now to be a human baby.

DR. MIIKE: Yes, but once you=ve done the somatic cell nuclear transfer, you actually have a cell that if you implant in a uterus can become a baby. There=s a difference between that and a skin cell or a nerve cell or a blood cell. That=s the kind of arguments we heard. I guess my question is really about the ultimate purpose.

DR. HOGAN: No, it=sXI mean, I=m not an ethicist. It=s your problem. [Laughter.]

DR. SHAPIRO: Steve, then Alex?

MR. HOLTZMAN: First off, thank you for your testimony. I think the clarification about how the similarity of words like Aembryo≅ and Aembryoid bodies≅ can get in the way of an understanding was very usefulXin the popular press there=s that misconception. This will follow on to Harold=s question about the need for moving on to experimentation in human cells. Clearly, if the goal is not the creation of a baby but rather the creation of differentiated cell lines, you don=t need the whole apparatus of the trophoblast and the yolk sac. So one could imagine lines of experimentation where we=re trying to derive culture conditions to take the cells back and let them become ES cells and differentiate without needing oocytes. There=s a lot of progress right now in proteomics defining the kinds of growth culture conditions, the factors that you described that allow for that to happen.

DR. HOGAN: Yes.

MR. HOLTZMAN: And it seems to me a promising line of research would be to be looking at human oocytes and even human embryos and asking what is going on over time in terms of the changing conditions of the protium to recapitulate that in culture so we wouldn=t need oocytes or embryos to do this? It seems to me that might require working with the human embryos to try to define that to get away from them. And I=m just wondering whether it=s accurate to say that, you know, we=ve got 5, 10 years of experimentation with the mouse in front of us as opposed to moving more quickly.

DR. HOGAN: Oh, no, I think that one hasXthe 5 to 10 years, I=m sorry, is to work out how to differentiate them reproducibly, how to get the differentiated cells back into the right place so that they will continue to be maintained. These sorts of more applied problems I wanted toXI know sometimes the impression is that this is something that=s going to happen really quickly and these pluripotential stem cells are

going to solve every problem of stem cell research. It was that, really, where I felt the time gap was going to be.

No, studies in mouse development in particular as to what makes a cell pluripotential, what genes have to be expressed in that cell. But now its genetic program has gone backXthe video=s been turned back to the beginning again, and you can start off and reprogram it. That=s something that=s a very active area of research and I think we already know to a certain extent something about that. But whether it would be possible to take any somatic cell andXin order to turn any somatic cell back into a pluripotential cell you=re going to have to alter its genetic program. And you can do that by putting it into the cytoplasm of an egg; how you can do it in culture is without altering its own genetic material irreversibly. I think we can think of ways of transfecting genes into it, misexpressing something like Opt-4, which is a gene that=s in the early pluripotential cells. But by the very doing of that act you have altered its genetic material and now will make it unsuitable for transplantation because it will have got new genetic material that is designed specifically to express a gene at high levels. And what you want to put back into a person is something that is completely unaltered and has the right, normal chromosome constitution and right genetic constitution.

DR. SHAPIRO: Alex?

PROF. CAPRON: I have two questions: one is just a naive scientific question and the other one has to do with the beginning of your testimony. At what point do the diploid cells, which I gather the germ stem cells are as they=re migrating, give rise to haploid cellsXthe gametes?

DR. HOGAN: Well, in the case of the female it=s not long after they get into the ovary that they undergo the first stage of meiosis. In the male, it=s not until they start to proliferate around the time of puberty.

PROF. CAPRON: But there=s no problem with the stem cells that are still in this migration process; those are still completely diploid.

DR. HOGAN: Yes. Except, as I said, they are undergoing the stripping off of the methylation from some of their imprinted genes. We found that, and another group has reproduced our findings as well, that some EG cells had a slightly different methylation pattern to some genes, which in itself is very interesting and is a very kind

of active area of research as to how this methylationXindeed here at Princeton is one of the leading groups in that.

PROF. CAPRON: You commented in the beginning of your testimony on patenting and the material transfer agreements, the difficulties that could be posed for basic researchers by the existence of commercially sponsored research leading to patents. And later in your paper you remarked that Dr. Gearhart=s method is a modification of a patented method that you have. And one of the questions that I guess I was unclear on before I read that comment was whether the talk about NIH funding for the processes of creating EG cells or ES cells, which the Government has not funded in human beings, was sort of water under the bridge by now.

DR. HOGAN: Yes.

PROF. CAPRON: Or if there would be expected in the normal development of science to be the creation. If there were now funds available to Gearhart and Thomson for their work that were not connected to a corporate sponsor but were NIH-sponsored, if it would be expected that there would be further modifications that would be separate enough. And I realize I=m asking you to speculate, but the difference between what you did and Gearhart did was apparently enough for him to claim a patent on his small modification.

DR. HOGAN: Yes.

PROF. CAPRON: Are there really in this field likely to be dozens of slightly different techniques, which means that there wouldn=t be the control if there were now to be Federal funding for these techniques. There would be publicly available, perhaps patented but not restricted in the same way as the corporate ones were.

DR. HOGAN: I think that=s very difficult to predict. I think that experience from issues of patenting over drugs, tissue plasma activator, and blood-clotting factors have shown us that this can lead to years of litigation by different groups claiming that their patent was first or better orXI mean it was the first, really.

PROF. CAPRON: Right.

DR. HOGAN: I don=t know whether that might ensue if then other groups had slightly different methods for making these pluripotential stem cells. Other

companies would start arguing about were they really different or were the cells that had been derived really different.

PROF. CAPRON: You=re not asserting yourX

DR. HOGAN: Whether EG cells are really different from embryonic stem cells. I don=t know what we=re going to...will happen.

PROF. CAPRON: But you=re not asserting, for example, that your patent precludes Gearhart=s application.

DR. HOGAN: That would be an issue between Vanderbilt and Johns Hopkins.

PROF. CAPRON: But it hasn=t been raised just yet.

DR. HOGAN: I=m sure that they=re raising it, yes.

PROF. CAPRON: Oh, so you think that they are? Well, that=s very interesting. Thank you.

DR. HOGAN: I=m just saying these are things that are going on.

DR. SHAPIRO: I think we=re now getting into another area. Eric?

DR. CASSELL: I was interested in your comment that we=re partly to blame for this careless language about embryosXthat all the things we=re calling embryos are not embryos in any meaningful reproductive fashion, so that the somatic cell nuclear transfer does not produce embryos in the fashion that most of us sitting around this table mean when we say Aembryo.≅ Could you enlarge on that? Because if that is in fact the case that=s a matter of education, that we get unstuck from careless language.

DR. HOGAN: Well, there=s absolutely no doubt that it=s an embryo, you know, a somatic nucleus into an unfertilized egg that has been activated to start the cleavage process. There=s no doubt that that has the potential to give rise to a complete organism, and in that definition is an embryo. But the British Warnock Committee took up the use of the word Apre-embryo≅ for that, which I think is dangerous and I don=t want to go into that at all. But it is scientifically, it=s a differentXthe embryo is a

continuum, and I think you can draw distinctions between an embryo that has implanted and has undergone the primitive streak process and now is further along this continuum than the fertilized egg and the cleavage-stage embryo. And a scientist would look at these quite differently. I don=t know how you couldXyou really do have to use the word Aembryo.≅

DR. CASSELL: See, it=s not just our problem, it=s your problem too.

DR. HOGAN: Well, no, to me it=s not a problem because I would say it=s a Acleavage-stage embryo≅ or it=s a Ablastocyst≅ or it=s a Agastrula≅ or a Aprimitive streak-stage embryo.≅ To a scientist, you have to be quite specific about what you=re talking about in terms of what stage along the embryonic process you=re at.

DR. SHAPIRO: I think the problem for us, that we and many others are troubled with, is what is the moral relevance of these different stages that you can give names to, if any. I mean, are they differentiated in some moral sense or not? That=s a difficult problem that we=ve been struggling with.

DR. HOGAN: Obviously, the further along the process they are, becauseXyou must know this information, that in normal reproductive processes 60 percent of cleavage-stage embryos or blastocysts never implant and are spontaneously lost.

DR. SHAPIRO: Yes.

DR. HOGAN: So I think the probability of a fertilized egg ending up as a baby is not particularly high.

DR. SHAPIRO: Thank you. Any further questions at this time? Well, thank you very, very much. Once again, we appreciate the trouble you took to come here and we=re very pleased to have you here. Thank you very much.

OVERSIGHT AND REGULATION: LESSONS FROM THE ETHICS ADVISORY BOARD

DR. SHAPIRO: We have now two additional visitors who have been kind enough to come up from Washington to be with us today from Hogan & Hartson.

They are Barbara Mishkin and Robert Brady. Welcome; it=s a great pleasure to have you here. We once again appreciate the time and effort you=ve expended to come here and we look forward to your testimony.

Ms. Mishkin, of course, has long experience in the area that we=re struggling with, dealing often with Federal regulations in biomedical research, has lots of experience with the Ethics Advisory Board and also with the national commission before that. So it=s a special pleasure to welcome you. And we have you listed first amongst the two, not first in status, just first on our agenda. But if that=s all right with you, we=d like you to go ahead.

MS. BARBARA MISHKIN: Thank you. Good morning, everybody. It=s a curious experience being on this side of the table, actually. Novel.

I have provided you with two packets of materials, which I assume that you have. The first oneX actually I remembered after I agreed to come and talk about the Ethics Advisory BoardXis, I think, a fairly comprehensive review of the activities of the board, its charter, and to some extent what happened to it rather abruptly at the end. And it was a plea to the Congress to reestablish an ethics advisory board. Since I gathered you wanted to learn what lessons we might gather from the experience of the short life of the Ethics Advisory Board [(EAB)], I have prepared a single set of bullets here for you that I would certainly want to think about if I were considering recommending either to the Secretary of HHS or to Congress that such a board be impaneled. And the first thing that I would doXI=m just going to go through these bullets briefly and assume that you=ve read the background material and then leave time for you to ask questions and I can further elaborate on the areas that are of most interest to you.

My first bullet is that a board should be established, and it should be established as a permanent body, preferably through legislation. And that then incorporates the second bullet. My notion is that a permanent body can better establish a kind of corporate memory of how they dealt with protocols in the past. The EAB I think should be confined at least initially to looking at individual protocols that IRBs in the local area cannot approve because of restrictions imposed by the applicable regulations, whether it=s research involving more than minimal risk and no benefit to children or whatever the reason that an IRB cannot, under the existing regulations, approve the research. That then could go, if there were important scientific information they thought they could gain, that could go to an ethics advisory board, which

essentially would waive some of the restrictions so that the research could go forward with Federal funding.

Members learn to work together well if they are a continuing body. I think we learned in part from the President=s Commission that inserting too many new members abruptly into an ongoing body has a certain disruptive influence and makes it difficult sometimes to complete reports that you may be in the process of finishing. That it should be established by statute is to ensure that it can be a continuing body; there=s some allusion in the earlier materials that I sent you about the disintegration of the original Ethics Advisory Board.

That came about because the President=s Commission was being established, Congress had agreed that it should have a budget of X million dollars, but had neglected to appropriate the funds. And therefore when the President=s Commission was established, they were looking around for money with which the Commission could operate, and they noticed that the Department at that point had an ethics advisory board and raised the question whether or not we really needed two bodies doing the same thing. Well, it was not contemplated that we would do the same thing, and in fact Alex and I had several conversations about how we would work in tandem without stepping on each others= toes, I at that time directing the Ethics Advisory Board and Alex at that time having agreed, or was in the process of deciding whether to accept the post of the director of the President=s Commission.

Well, what happened was actually one of these happenstances of history that you cannot predict but that frequently happen, and that is that when Congress called to HEW [Department of Health, Education, and Welfare] for them to send someone up to the Hill to explain why they needed two such bodies, the person who really knew about the Ethics Advisory BoardXwho was the assistant secretary for health at that time, Julius RichmondXwas during that week in a helicopter flying over Cambodia with President Carter. And so they had to send somebody else up to the Hill to explain why they needed two bodies having to do with ethics, and some deputy secretary was called upon to go up there. His name, I think gratefully for everybody, I cannot remember. But he went up there, he had no knowledge of what the Ethics Advisory Board was supposed to do, and simply said frankly to the Congress he couldn=t think of any reason why we needed two such bodies, and so that was the end of it.

And the Congress decided thereupon to simply reprogram the funds from the existing Ethics Advisory Board so that the President=s Commission could get established. Well, it was done in such a peremptory way that no one back at HEW knew what had happened. And I was getting memos from the powers that be to please present my budget for the forthcoming year, and I was sending memos back saying we=re not going to be here next year, we don=t have a budget anymore. And they said we have no record of that, please send us your paperwork, and of course there was no paperwork. So I finally had to call Julius Richmond and say, APlease send me a piece of paper saying we=re not going to be here next year,≅ and he did it.

Well that, of course, was very disruptive. In my mind the board should have continued, because there are protocols that develop not only in the area of reproductive physiology but also in many areas in which you=re now enmeshed: how to go forward with research involving people with dementias of one sort or another, how to go forward with certain kinds of research involving children, involving people who are incapacitated in one way or another. And there are going to be problem protocols no matter how carefully you write your recommendations to either the Secretary or to Congress: No matter how carefully those are transformed into regulations, there are going to be protocols either where the applicability of the regulations is somewhat ambiguous or where they simply prohibit the kind of research that someone has proposed but everybody agrees it=s important research and we=d like to see it go forward.

And this, I think, is the role of the Ethics Advisory Board. And the best example of that is the attachment to the memorandum I sent you on February 3, which is a publication in the *Federal Register* of one of the Ethics Advisory Board=s little-known reports on fetoscopy, which was a response to a grant application submitted from the Charles R. Drew Medical Center in California to use fetoscopy for prenatal diagnosis for sickle cell disease. This was clinical research, but had not been done before. And we went about getting expert consultants and trying to think about what the National Commission had meant when it recommended to HEW that there be certain limits on fetal research. And we applied kind of historical understandings of what the National Commission had meant to this proposal and concluded that it would be appropriate for the Secretary to weigh the limitations and permit the research to go on.

Now that=s the best example that I know of, of how I think an ethics advisory board should work and why I think these kinds of things will continue to arise, and a board really would be a useful thing to have. If it were established by a statute,

then it would be a lot easier for someone who didn=t understand what the board was about to go up and tell Congress we didn=t need it anymore. It still could be wiped out, but it would take a little more effort on the part of those who wanted to do it in.

Members should be appointed by the HHS Secretary for staggered terms. I think that=s fairly obvious. People who are participants in the process of proposing members for such a panel have a better trust in the panel and in its work, and it=s simply a good way of getting the panel off to a good start to let the stakeholders be involved in the appointment of the people who will be sitting on the panel, much as the National Commission and the Ethics Advisory Board and the President=s Commission, and I assume this group of individuals as well.

The EAB should operate as an independent entity, and this is something that I learned very early on in the National Commission=s life. We had a practicing lawyer on the Commission who had been in HEW fairly far up in the administration, and one of the first issues he raised was the question of the independence of the Commission. We had an executive director who was an administrator in HEW at that time, and questions arose as to whether we could do our work by ourselves or whether plans for certain witnesses or plans to go into certain issues or reports that we might be drafting could be amended or revoked by someone in the Department who wanted us to go off in a different direction. And so very early on we actually sent the question to GAO [General Accounting Office], I believe, as to whether or not that body was independent and got a confirmation of our independence from GAO. And that finallyXyou know how the government worksXit wasn=t until we got that recommendation, or that opinion, from GAO that we were permitted to have our own letterhead, this, of course, being a very important aspect of one=s operations in the Federal Government.

So this is very important: that although the EAB would presumably be appointed by the Secretary, its operation should be independent and they should recommend, they should forward their advice to the Secretary, but there should be no opportunity for anyone in the administration to guide their deliberations or to edit their reports in any manner.

Obviously, it needs to have adequate resources, and I=ve indicated here some of the resources that it should have. We can go into those with more particularity if you want, but I think they=re fairly self-evident and don=t need to be explored in great depth.

Obviously, it should be subject to the Federal Advisory Committee Act and everything should be in public. Again, this assists in public acceptance of the board=s results because it enhances the credibility of the board=s operations: If the public can see them at work, if they can see their draft, if they can see how everything is going along, it really enhances the credibility of what they=re doing.

Now the next bullet is that their primary responsibility should be the review protocols; I=ve already discussed that. And I think also it was a good idea in the original Ethics Advisory Board=s charter that they had the right to recommend to the Secretary whether or not a waiver that they had concluded would be acceptable for a particular protocol, the fetoscopy one being an example, whether that waiver should be generalizable to other similar protocols. And in that instance, in the fetoscopy instance, as you have seen we did make that recommendation and Secretary [Joseph] Califano did in fact generalize the waiver to similar protocols using fetoscopy in that manner. And his determination is at the end of the report from the Ethics Advisory Board.

I think the reports need to be published in the *Federal Register*. Two of the Ethics Advisory Board=s reports were published in the *Federal Register*; the one that you have there and the much longer report on human in vitro fertilization, federal funding of human in vitro fertilization. Two other reports that we issued were never published other than by the Ethics Advisory Board themselves. And they now are rare documents. In fact, when I wanted to review one of them recently I had to call up the library at Georgetown UniversityXtheir Bioethics Library, because I knew they had copies of everything that we had doneXand I asked them if they still had a copy of that report, and they looked and said, AOh yes, we do. In fact you gave it to us.≅ And so they let me borrow it back and make copies of it and send it back to them. But these are now rare books and they ought not to be. They ought to be accessible because now the issue has already arisen again as to access to data from ongoing biomedical research under the Freedom of Information Act. We did a whole report on that and I thought it was a pretty good report and nobody knows about itXexcept for the library at Georgetown and a couple other rare book libraries, probably it doesn=t exist anymore.

So that=s kind of my overview. And I would be very happy to answer questions that are either general or specific on the Ethics Advisory Board or the National Commission or anything else I=ve had my hands in.

DR. SHAPIRO: Thank you very much; we very much appreciate that. Let me turn to members of the Commission to see if they have any questions. Alex?

PROF. CAPRON: Well, I just thought that for the completeness of the record we should make sure that everyone knows that we not only reprogram the EAB monies, but I reprogrammed Barbara Mishkin as the deputy director of the President=s Commission, which was our great good fortune. And there is also, I suppose, some particular historic coincidence that we heard from Dr. Hogan first this morning and then from you, Barbara, because it was, of course, Pierre Supar from the Vanderbilt University Medical School whose application for approval of human in vitro fertilization research was your major report, your most famous report, which has gone on sitting on the corner of the desk of the successive secretaries now for almost 20 years, soon to be 20 years.

MS. MISHKIN: Exactly. And Dr. Supar, as you may have readX

PROF. CAPRON: Has since expired.

MS. MISHKIN:XDied without ever getting an answer to his application for Federal funding. So that=s one reason why we need some sort of action forcing legislation, I think.

PROF. CAPRON: And I just want to be clear: obviously, the interment of the EAB, although it was from the happenstance that you described, has become a permanent situationXI mean, there hasn=t been an EAB as such since thenXyou may have noticed that this Commission recommended the establishment of a special panel regarding the psychiatric research issues in our last report and had many of the characteristics that you described. But from what you=re saying, the EAB that you envision would have the same jurisdiction as the regulatory EAB that was contemplated and that you briefly participated in. I=m not clear whether you=re saying that although it has the name AEAB≅ it really has some different or broader mandate. One of the issues that always arises is whether the body is, although ongoing, limited to a particular set of issues, for example around cloning or around stem cells or wouldXif you=re envisioning an all-purpose EAB.

MS. MISHKIN: I=m envisioning an all-purpose EAB because it=s impossible for us to contemplate now exactly what=s likely to be needed. You probably remember that the original National Commission=s report on fetal research essentially finessed the question of human in vitro fertilization because it was their conclusion that that was too fanciful at that point even to deal with and that it was so far down the line that there was plenty of time to think about that later. Well, that was, what, four years

before Dr. Supar=s application for human in vitro fertilization reached HEW? So we cannot predict.

I think it should have fairly broad jurisdiction and authority. One of the two reports that were never published from the Ethics Advisory Board were reports that were initiated by the Secretary of HEW. And I think it should always be open to the Secretary, possibly on request from one of the constituent institutions or agencies within HHS, to request EAB review of a particular question. One of those came at the request of the CDC, and the other from the NIH. And so I think it ought to be fairly broad. It certainly would have to deal with any protocol within the Public Health Service jurisdiction that came up, and that would be very broad. It would include the psychiatric, it would include fetal research, stem cells, what have you. But it also ought to be able to look at other things at the discretion of the Secretary, who would pass them on. How much broader it should be, whether it should establish major policy, I think, would depend on whether or not your Commission is an ongoing body at that point, or whether you have a predecessor to take that role.

PROF. CAPRON: Succesor.

MS. MISHKIN: Pardon me?

PROF. CAPRON: A successor.

MS. MISHKIN: A successor, right. Sorry. A successor to take that role, because as you know, as each one passes off into the sunset another one seems to emerge to take its place. And if that were going to happen to this body, then the EAB would not need to be a policymaking entity.

PROF. CAPRON: Right. As I suggested to Patricia Harris and the Secretary, I was glad to have the funds but the notion that had been presented to Congress that we didn=t need the EAB because we had the President=s Commission made me think that we didn=t need an Army because we had an Air Force.

MS. MISHKIN: Exactly.

PROF. CAPRON: Different roles.

MS. MISHKIN: Exactly.

DR. SHAPIRO: Larry?

DR. MIIKE: One question and then a second question just because of your answer to Alex just now. Would this be DHHS-specific or would it be applied to the rest of the Federal Government enterprise? The Department of Energy, the VA, the armed forces?

MS. MISHKIN: I knew that question would come up. And it=s a very difficult question. I, at this point, think it ought to be HHS-specific, because most of the difficult questions that arise in biomedical research are going to be protocols that are sent for funding to the Public Health Service. I should think that you might want to permit the EAB to take referrals from other agencies, maybe through the Secretary.

DR. MIIKE: For example, national labs do a lot of similar research now.

MS. MISHKIN: Yes. And whether or not you think they ought to have their own EAB or whether or notXI mean it=s going to depend on volume, I think, more than anything else. And so initially you could have this EAB, much as OPRR now does review of IRBs for the other Federal agencies that have bought into the common rule.

DR. MIIKE: My second question isXnow you=ve got me confused, though. I thought that your conclusion and analysis was that a policy-setting body should be separate from a review-type body. And if, for example, the possibility was that if this Commission or something like this disappears then you would consider an EAB doing both. And I find it difficult to agree with a body both setting policy and dealing with specific projects.

MS. MISHKIN: Well, to a certain extent, once you review a specific project and you recommend that similar protocols be permitted to go forward without further EAB review, you have in fact created a small policy, not a very large one, but a focused one. And my sense is simply that we need an ongoing policy commission or entity, and that if we don=t have a successor to this Commission or if this Commission is not continued, then I would rather have the EAB absorb that responsibility than have nobody in place to do that, to carry forward.

PROF. CAPRON: It=s not a policy, it=s a policyoid. [Laughter.]

DR. SHAPIRO: You may have a slide it affects. [Laughter.] Any other questions before we go on to Mr. Brady? Well, thank you, thank you very much.

FDA JURISDICTION

DR. SHAPIRO: We=d also like to welcome Robert Brady here this morning, who is also a partner in Hogan & Hartson and specializes in pharmaceutical biotechnology, and wants to talk about an issue that has been very much with us both before and now and that has to do with FDA jurisdiction. Thank you very much for being here.

MR. BRADY: Thank you, Dr. Shapiro, and thank you for inviting me. I=m delighted to be here. I=m more delighted to be here with my partner, Barbara Mishkin. I bask in the glow of her reputation, I think, here in this group.

Let me make a few disclaimers, which is only appropriate before an ethics commission. I do actively represent biotechnology companies and help professional groups who have, I think it=s fair to say, an intense interest in how FDA does or plans to regulate these materials. And indeed, the summary I=ve given you today and the paper that Kathi Hanna has asked that I prepare flow from a document that I prepared a year ago on behalf of a number of biotechnology interests to be distributed on the Hill when they were making a mad rush to regulate or to legislate cloning. So I just wanted to disclose that I have those commercial interests working in my thoughts on this subject.

PROF. CAPRON: We also have a copy of that document.

MR. BRADY: Yes. What I propose to do very briefly today is just give you the overview of how FDA does and may in the future regulate stem cells and related cellular and tissue materials. And I guess the points that I will make are four or five. The first is that FDA has a broad authority that=s decades old. In the case of the Public Health Service Act that regulates biologics, it was first drafted in 1902, and the basic approval standard remains the same.

The second is that those statutes are broadly written in a way to give FDA enormous flexibility. With that enormous flexibility comes enormous discretion. And there=s probably no greater example of the discretion that FDA has exercised than in the area of tissue and cellular materials, in vitro fertilization clinics being the classic example of an area that FDA has historically, wisely decided until now not to regulate.

The fourth point is that that enormous discretion is not unreviewable by the courts, but the Supreme Court and other courts have repeatedly granted great deference to FDA=s exercise of discretion as to how it interprets and enforces its act.

And the last general point I want to make is that none of us who practices in what we call FDA lawXmy teenage daughters refer to me as an AFDA geek≅ because I=m so narrowXthe whole issue of what=s practice of medicine and what=s a product is largely never discussed in my world. Once it gets to me, it=s a product. It may to the doctors on the panel be puzzling because it=s practicing medicine, but the Food and Drug Act and the Public Health Service Act largely ignore that issue, and it=s an issue that professional groups, I think, will want to debate more fully in the future.

Now, let me review FDA=s statutory authority. They use two laws to regulate therapeutic products. The first and most obvious is the Federal Food, Drug, and Cosmetic Act. Under that act they regulate new drugs and medical devices. In my political science world, a new drug is basically a chemical entity, a synthetic chemical, as opposed to a biological product, which is derived from human or other cellular material. The standards that FDA uses under the Food and Drug Act to regulate new drugs and medical devices are basically safety and efficacy; that=s what you have to prove. They regulate the clinical investigation stage of those products through the IND process. The statutes are largely ethics-blind other than informed consent and IRB requirements being met. I view FDA=s work as largely the blue-collar work of this process; it comes at the tail end and they=re highly skilled technicians to look at the data and make sure it=s safe and effective, but not to make ethical judgments on how these things ought to be used.

The other and principal act that will regulate stem cells is the Public Health Service Act, 42 U.S.C. 262, which again was written in 1902 with the approval standard of Asafety, purity, and potency.≅ I=ve always found it curious that the word Aefficacy≅ has never been a statutory requirement for a biological product, and in the last decade I=d say 70 percent of the most important therapeutic products under development are biological products whose only statutory standard that it works is framed with the word Apotency.≅ FDA in the mid-70s, through the back door, addressed that by defining Apotency≅ to include Aefficacy≅ in the traditional drug sense. The Public Health Service Act requires licensure for products that move in interstate commerce. Now that in and of itself is an interesting issue in this area. What constitutes interstate commerce? And FDA has defined three different ways that a biological product can move in interstate commerce. The first and most obvious is that

the product itself, the cellular material, is moved from D.C. to New JerseyXthat=s standard interstate commerce, Federal jurisdiction.

The second theory that FDA put forward in 1993 as a basis to regulate these products is that a component of the product, not necessarily the finished product, move in interstate commerce. That is an all-time classic FDA theory that courts have accepted, regrettably not in the area of biotechnology, but in important areas like vegetable oil, where a manufacturer in Michigan got five of the six oils he processed from MichiganXGod knows how he got vegetable oils from MichiganXbut the sixth came from Ohio. And the courts said that the movement of one of those components in interstate commerce gave the Food and Drug Administration the right to seize that product even though it hadn=t moved further from the state of Michigan. That=s called Acomponent theory jurisdiction;≅ it=s been widely upheld, but it=s been upheld in much more simplistic situations than what we=re facing in the world of cellular materials.

The third and most interesting, and the least tested, is FDA=s assertion that if the patient moves in interstate commerce they have jurisdiction. That I find intriguing and one that FDA put forth in 1993. No one commented on it one way or the other; people had more important things to do, I guess. But it may well be an issue as we move towards, someone used the word Acustomized≅ therapies, and as we move to a worldXand I get all my scientific information largely out of *Time* magazine, I must concedeXbut when you read the recent *Time* magazine piece on the new gene revolution, you get the impression that in 10 or 15 years we=re going to be in a very different place in terms of therapeutic products. And I see it in my work, a lot of entities moving toward customized clinics and the issue of where the Federal jurisdiction lies if I go in and have one of my cells removed, have it manipulated, and then put back into me here in Princeton, New Jersey. If the only way the Federal Government has control is the fact that I took the Metroliner up from D.C. last night, that could raise an interesting policy issue. But we=ll leave that alone.

So biological products have been regulated since 1902 by the Federal Government. The definition of biological product is in my handout. It=s a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, etc., etc., or analogous product. Nowhere do you see the word Atissue,≅ Astem cell,≅ anything else. All of these materials are considered analogous products for purposes of regulation under the Public Health Service Act.

One other important point in this area with regard to the regulation of these materials is that all of these various cellular materials have to be Aapplicable to the prevention, treatment, or cure of a disease or condition.≅ And that term was only added to the Public Health Service Act in 1997, with little debate or discussion, but may have tremendous impact on which of these new cellular materials are regulated by FDA, depending, of course, on their intended use.

There is another provision of the Public Health Service Act, 42 U.S.C. 264, which FDA has increasingly used in the area of cellular and tissue material to regulate, and it addresses the spread of communicable diseases. And much like 262, which was written in 1902, 264 is, again, decades old and was written to deal with the spread of communicable diseases by immigrants coming into this country. And it gave the Public Health Service Act the authority to quarantine my grandparents in order to make sure that they weren=t carrying infectious diseases into this country.

HHS and FDA over the years have taken what was basically a quarantine statute and have used it in very inventive ways. Among the more notable uses prior to its now active use in regulating cellular material, my favorite use was when FDA banned the movement in interstate commerce of what I call Acircus turtles.≅ When I was a kid, you used to be able to go to the circus and get little turtles that had painted shells. Well, those little beasts apparently were heavily contaminated with salmonella, and FDA banned them under this provision in the, 70s. This provision, for purposes of the FDA world, was largely dormant. I didn=t view banning turtles as a major public health effort by the FDA, but it is now an active and important part of the way FDA regulates cellular and tissue material, and I=ll go into that.

Tissue and cellular material has no particular statute. It is, as I said earlier, it falls under FDA=s broad authority to regulate biological products. It has largely been ignored by FDA, by design, by decision, until the 1990s. Throughout the >70s and >80s, issues would come up to the FDA about should we regulate, pardon me, should they regulate tissue. And largely FDA said, AWe=re just going to stay away from that, we have enough to do, we don=t know how to.≅

Bone marrow is a classic example. Bone marrow developed totally outside of the FDA regulatory system but it=s probably one of the most important therapeutic biological products of the last 25 years. It could have been regulated. There is no doubt that FDA could have regulated bone marrow. Some argue that it can be regulated only by the Health Services and Resources Administration. I disagree with

that; I just think it was a wise exercise of FDA=s discretion to say no, at least at that time, although the sons and daughters of bone marrow, peripheral stem cells and umbilical cord stem cells, are now being actively regulated by FDA.

But there was really almost a conscious decision by FDA to stay out of this area. And then certain episodic problems forced FDA to deal with itXheart valves, human heart valves. The transplant community was thrown into a state of panic when about a decade ago FDA decided that human heart valves would require premarket approval under the medical device law. That took about six years and several court cases to get FDA to say, AWell, maybe not, but we=ll deal with them differently.≅ Things like skin, tendons, bones, corneas were largely ignored by FDA. And then HIV came along and dramatically changed FDA=s focus on all these materials. And IXreally two things have changed their focus.

The first was the intense growth of interest and concern about infectious diseases. I used to do biological products back in the >70s when hepatitis B was the only real concern in terms of infectious disease. HIV, hepatitis C, all the new infectious agents have dramatically increased FDA=s focus on tissue generally. That led FDA to take its first step into the regulation of tissue and cellular material in 1993, when it issued an emergency final rule to regulate what I call older traditional tissueXstructural stuff, again, skin, tendons, corneas, things like thatXthe focus was totally transmission of disease.

There was an intense media interest in a bunch of body parts that were being imported from Russia that allegedly carried infectious contamination. There were reports of dura matter that was HIV-infected, and a patient, I think in West Virginia, that allegedly became infected. So FDA was forced to address for the first time in a somewhat systematic way how it intended to regulate tissue. It decided to do that not by imposing premarket controls under the Food and Drug Act or the Public Health Service Act licensure provision, but to set standards under that old-fashioned quarantine provision, 42 U.S.C. 264. Those standards would still apply to what I call the old issues, but really are infectious disease testing, good manufacturing practices, and recordkeeping so that you can trace where these various tissues go. That was 1993, and that was really FDA=s first modern articulation of a regulatory policy in this area.

Also in 1993, with regard to the products you=re talking about here, FDA issued its first systematic policy statement on human somatic cell therapy products and gene therapy products, and said for the first time in that document that these are

biological products subject to licensure; that means premarket approval. That means you can=t go to market. That caught a lot of commercial interests by surprise. Some unintended surprise, some faint surprise. A lot of people and a lot of commercial interests to that point thought that all these cellular materials were the practice of medicine. And a number of commercial interests were off and running with clinics, customized clinics, around the country thinking they had no Federal regulatory oversight whatsoever. David Kessler was the principal author of this document and the document was intended to put these folks on notice that, no, no, this requires premarket approval and INDs for biological products.

Then, in 1997 FDA, with the helpXif you look at the papersXof Bill Clinton and Al Gore came out with a broad, comprehensive proposed policy on the regulation of cellular and tissue-based products. That analysis was an attempt to step back and have the FDA look at this incredibly diverse area and say, AAre we doing it right, are we asking the right questions, and are we calibrating the level of regulation against an inhibition on medical progress that may result from over-regulation? Or, if we don=t regulate enough, especially in light of the issue of infectious diseases, if we=re not regulating sufficiently enough, are we going to cause serious public health problems?≅

That process took about a year and resulted in the publication of a document called AA Proposed Approach to the Regulation of Cellular and Tissue-Based Products.≅ It didn=t change the basic statutes or principles that apply, but it basically said we=re going to try to breakXbased on risk and therapeutic intended use, we=re going to try to break the world up into two kinds of products. One we call Astandards≅ products, which will not require premarket approval but merely have to meet certain standards focused on, again, infectious disease testing and proper processing and holding and distribution practices, etc. And then anything that isn=t a standards product will go through the traditional FDA premarket approval either as a biological product or in some cases, some of these biotech products that include cellular materials but also include biomatrixes that may have more of a medical device effect than a therapeutic effect, those will be considered medical devices and preapproved under their standard. This document was published in >97 to great fanfare.

I=m basically going to end by talking about what analysis they used to decide what=s going to be a standards product versus what=s going to be a premarket approval product because that, for purposes of regulation of stem cells, is the issue. And there are four questions. My next page was really the broad policy questions, the five broad policy questions that drove their analysis. But then the next page are the four

steps that when a biotech company comes to me and says, AWell, what am I? Am I a product subject to standards or am I a product subject to premarket approval?≅ it has enormous implications. Enormous implications for the amount of data and the time to market. And to a commercial entity, those of course are two critically important questions.

FDA has decided to pose to companies, and to seek answers from companies to, four questions to determine which side of the line you fall on. The first, and probably as it=s turning out the most important condition of whether you need to have premarket approval, is whether or not the product is minimally or more than minimally manipulated. And indeed with stem cells, we=ve seen the world already break down, not break down in a bad sense, but minimally manipulated umbilical cord cells for autologous use, for instance. FDA has already at least tentatively decided those will be products subject to standards; those will not require premarket approval. They think that ultimately those same umbilical cord cells, minimally manipulatedXwhich minimal manipulation means largely you can do more than freeze, separate the cells, the same kinds of things you do to blood and blood components. My guess is that they will move allogenlic umbilical cord cells over to that side of the regulatory fence, which is still standards; you=re going to have to meet standards that are promulgated but you don=t need premarket approval.

Just about everything else is from my trying to read the tea leaves, because all of these decisions that are going on about what=s minimally or more than minimally manipulated are being made in confidential meetings between FDA and particular companies. But if you=re more than minimally manipulated, you=re going to require premarket approval.

In the area of stem cells, therapeutic stem cells, probably one of theXI assume one of theXmost important steps for a commercial entity is cell expansion, and that, FDA has concluded, is more than minimally manipulated. So my sense is that based on these criteria alone, at the moment most of these stem cell products will require INDs and then the traditional gamut of adequate and well-controlled clinical trials to establish safety and efficacy.

The three other questions, just very briefly, that FDA asks are whether the product is for homologous or nonhomologous function. If it=s for homologous function, then they may move it to the standards side. If it=s for a nonhomologous function, then they clearly say, AWell, in my mind that=s unnatural, therefore you have

to prove it works, and that requires premarket approval.≅ The third is whether or not the tissues are combined with non-cell, non-tissue components. There they=re really focusing on, Does the addition of some non-natural component to the natural tissue change the safety or efficacy of the product? And in FDA=s mind, the only way you find that out is to put people into a premarket approval mode and require clinical data to be developed. And the fourth is whether or not the product is used for a metabolic, read systemic, function as opposed to a reproductive or structural function. Those are the four criteria, I think, that summarize where FDA is going. My view is that FDA is going to treat the vast majority of these stem cell products as premarket approval products, putting them through the traditional gamut of clinical data to prove safety and efficacy. That=s it.

DR. SHAPIRO: Well, thank you very much. We appreciate your remarks. Larry?

DR. MIIKE: In the investigation of your drug approval process, if I were a researcher and starting to do phase 1 trials, am I required to come to you or is it only because I intend to go through a product line succession?

MR. BRADY: In the IND regulations there are certain exceptions that allow you not to come to the FDA if you=re doing research not intended to expand the labeled indications or to expand the promotional claims made and one or two others. So there are specified bases upon which you as a medical researcher would not necessarily have to have an IND. I will say that of the maybe 1,000 active INDsXand that=s a real rough numberXprobably three-quarters of those are what we call Aphysician-sponsored≅ INDs. And I=ve always viewed most of those as a physicianBsponsor kind of hedging his or her bets as to whether or notXbecause if you don=t conduct the study under an IND, it will be viewed by FDA from a legal status as interesting science but nothing they can base an approval on. And so I=ve always viewed most of those, say, 700 physician-sponsored INDs as folks who aren=t quite sure which way the data=s going to go but want to make sure that if it=s good it may be useful for approval purposes.

DR. MIIKE: Just one other question. What is a product under FDA jurisdiction? The reason I ask that is, for example in Dr. Hogan=s presentation, you get cell lines or stem cells under a licensing agreement and it sounds like it=s a commercial transaction.

MR. BRADY: Yes.

DR. MIIKE: But that=s not a product that=s under the FDA jurisdiction.

MR. BRADY: Right. To be under the FDA jurisdiction there are two elements. First, there has to be an entity, a cellular material, but they also have to have an intended use. And that intended use ultimately has to be for therapeutic purposes. And remember, the IND doesn=t kick in until you=re going to put that product into human beings. All the preclinical data and research is not covered by the IND and doesn=t need FDA approval.

DR. SHAPIRO: Alex?

PROF. CAPRON: Two questions. One, just to have a clarification on the exchange you just had. The 1,000 INDs are in the biologic area?

MR. BRADY: No. I think that=s a rough figure for the total, but I=m not sure. Actually, it may be on the NDA side. But I was trying to just give you a relative look at how many are commercial.

PROF. CAPRON: One point that you mentioned just in passing and that bears most on our discussions, it seems to me, is when you said that many of the things that are going on in the development or application of policy, as Barbara Mishkin said before, in effect the development of policy as you apply it in the FDA, are occurring in the setting of private discussions between the FDA and product developers.

MR. BRADY: Yes. Right.

PROF. CAPRON: Biologic products, here. And of course something very similar to that happened in the recombinant DNA story with the human applications where during the period that the Recombinant DNA Advisory Committee was reviewing actual protocols and making recommendations to the director whether they should be approved if they were federally sponsored and sort of making advisory ones, I guess if they weren=t going to have Federal sponsorship they had commercial sponsorship, they were also going through the FDA process. And the difference there is that the RAC met publiclyX

MR. BRADY: Right.

PROF. CAPRON:XAnd the FDA process was not public. And now that we=ve moved away from having the RAC spend very much time on actual protocols and look more to policy issues, all that=s moved inside at the FDA. And the same kinds of issues, it seems to me, would arise in contrasting the kind of recommendation that Barbara Mishkin had for an ethics advisory board subject to the Federal Advisory Committees Act and reliance on the FDA, which came up as an issue when we made our recommendations about cloning. And the FDA asserted shortly thereafter its jurisdiction in this area and the issue obviously arose, well, Do you need any of the kinds of things that the presidential Commission was talking about here if the FDA could Aregulate≅ the area?

Would you comment on any ways in which that=s an inaccurate picture? I mean, are there ways in which the FDA=s processes can be made more public, or are they basically, because of the proprietary interests, always going to have pretty much a behind-closed-doors aspect?

MR. BRADY: That=s a difficult issue because, of course, how you manipulate those cellsXif I=m a commercial entity, how I manufacture my product in its crudest terms is probably often amongst my most confidential commercial information, trade secret information. And FDA is bound by statute not to divulge thatXquite properly so. What FDA has tried to do is they=ve had a couple of proposed rulemakings to implement this >97 policy and they=ve tried to string, to cite examples of the kinds of technological steps that would fall on either side of the line. But I don=t have a good solution for that, nor am I the right person to ask, because indeed I represent commercial interests who would have a strong view that that not beXat least prematurely released. At some point, all that information gets into the public domain. And I think FDA is trying to communicate generally without stepping on trade secrets.

PROF. CAPRON: Have they ever utilized advisory bodies made up not of scientistsXI mean, obviously they had their advisory bodies on the readiness of any particular drug to be approved. Have they ever used ethics-type, mixed bodies with public members and so forth to give them advice in any of the biologics areas?

MR. BRADY: No. There are on manyXin 1997 the Reform Act required consumer interests on all advisory committees, but I can=t recall one that was specially constituted to look at these broader issues. And on a personal note, I=m a big fan of the FDA. I think they perform a very important function, but I guess I=m cautious about trying to give them too many functions. They have a hard enough job, with the

resources they have, figuring out whether the things that show up are safe and effective. And they=re also now struggling with something the pharmaceutical industry wants, which is to be able to promote the economic value of products. They=re not economists, by and large, and I=d be a little worried that if you then threw on them a component that they evaluate the ethical issues, they=d break down.

PROF. CAPRON: Thank you.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: On this issue, Alex, you know, when the FDA came out and said that it had the authority to regulate cloning, I think the point that was trying to be made was some of the concerns the Commission had about IVF clinics running out and doing this, because it would be considered practice of medicine, the suggestion was that could be allayed. I don=t think there was ever the suggestion that the FDA was saying, that people were saying there are no issues left. There are still the moral issues. And then, with respect toX

PROF. CAPRON: And my question wasn=t intendedXI=m sure, Steve, you understandXto suggest that that=s what the FDA was saying.

MR. HOLTZMAN: I think certain people said there are no issues because FDA=s got it, and I think that was wrong. But I think they were specifically going through the issue of whether people could run out and do it. I think the FDAXlet=s distinguish, also, what=s in private and what=s in public with the FDA. When you go to the FDA and say, AThis is my method,≅ that=s proprietary, all right? And they are just looking at the safety and efficacy. Having said that, they then come out with Apoints to consider≅ documents, which are public documents where they do seek comment, in order to be giving guidance and how they are thinking about broad classes. And those can embody inputs, not of a purely ethical nature, but do reflect broader kinds of concerns. A classic example in the last couple of years would be the Apoints to considers≅ on xenogeneic transplantation. So it does become a body that solicits and provides guidance in an open kind of way for categorization, but does stay away from saying, AWe=re going to get into the ethical realm.≅

PROF. CAPRON: Can I ask a followup on that? Since the FDA=s announcement about its jurisdiction over cloning, has the FDA done anything along the

sort of line that Dr. Hogan was mentioning by analogy to the fertilization and embryology authority of moving into the IVF clinics and doing anything there?

MR. BRADY: They have suggested in a proposal that they published about nine months ago, and I have it here, that those types of products may well fall into the standards category, and they=re looking at that. And you know, as I said when I started, that=s an area that FDA has wisely, from a public policy standpoint, stayed away from. I fear that because of the dramatic escalation of technology in IVF clinics that FDA=s going to be forced to figure out credible ways to stay out of there, that the logic they=re applying to Brady Biotech when I walk in would be equal, could be equally applicable at the IVF clinic in Fairfax, Virginia. They suggested that those areas are things that they=re looking at, but they=ve given no indication as to where they=re going.

DR. SHAPIRO: Ms. Mishkin wants to make a comment I=ll get to right away. I just want to pick up some of the thought you may have heard and that I may have heard in this last comment. That is that as FDA looks at the IVF clinics and the so-called products there, that that seems to fall on the standards side of the line to them?

MR. BRADY: Yeah, that wouldX

DR. SHAPIRO: If I get by the Aminimally manipulated.≅

MR. BRADY: I=m sorry?

DR. SHAPIRO: How does that get by the Aminimally manipulated?≅

MR. BRADY: Well, therein lies the issue, and having set these standards in 1997, they tried very hard not to go into that area. But again, I think having set these standards they=re now forced to look at earlier exercises of nonenforcement and reevaluate. And where that=s going to come out I have no idea.

DR. SHAPIRO: Okay. I want to turn to Ms. Mishkin, then Trish, then we=re going to have to call this part of the session to an end.

MS. MISHKIN: I just wanted to comment very briefly that this kind of an issue in my thoughts about an EAB is the kind of thing that the Secretary in fact could refer to an ethics advisory board because it is in some sense how to interpret

existing regulations to, let=s say, new circumstances. And there=s no reason why such issues should not be referred to an EAB with FDA providing its input and its point of view, but other people in the public and with other stakeholders being able to provide theirs.

DR. SHAPIRO: Thank you. Trish, last question.

PROF. BACKLAR: I=m just thinking, sir, that you said you thought that the FDA would be wise to stay away from regulating the IVF clinics, and I would like you to prove the cause why you would say that.

MR. BRADY: Yeah, that may have been a tad flip, but my experience at and after my time at FDA is that FDA is a wonderful body that=s politically naive and they get clobbered in these matters. I wasn=t saying that from kind of a public health perspective, I was saying that more from a public policy perspectiveXthat FDA has wisely moved slowly. And indeed, when you look at the 1997 proposed approach, FDA focuses its kind of levels of risk on things like autologous transfer versus allogeneic transfer, on how much risk our consumer/patient is willing to accept. And when you look at it from that light then I think IVF clinics would fall in an area where one accepts more risks because it=s your own personal decision and your own tissue, often. So if you look at the logic of FDA=s 1997 proposal, they=re still trying to preserve the ability to regulate carefully in that area. Whether they can sustain that given the push of the rest of the technology is a question for the future.

DR. SHAPIRO: It doesn=t sound convincing, but we=ll leave it. We=ll wait and see. Well, thank you both very much. We very much appreciate you being here. Thank you for coming. We=ll take a 15-minute break and then reassemble at 10:30.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: I=d like to begin. Now we have a short period of time left this morning for further deliberations both with respect to the HBM Report and with respect to our ongoing discussions of stem cell issues, on both of which I=d like to make just a little bit more progress so we can produce appropriate materials and generate an appropriate level of discussion and consideration at our meeting in March, which is the first week in March, I=ll remind you all, in Washington. Now I think, I hope Kathi will

be back in a minute, but I mean, I think we ought to start just by revisiting certain aspects of the Human Biological Materials Report, which we discussed yesterday.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: For the record, should we note that commissioner Charo, who abstained from the past discussion, is now with us?

DR. SHAPIRO: Yes, right. Thank you very much. So noted. I think it will probably not be possible, as I looked over this situation last evening, to generate an entirely new report, although we may get a very substantial part of that done by the March meeting. The principal reason for this is to give adequate consideration to the voluminous public comments we have gotten. A large part of those, well, a significant part of those, have to to with actual factual matters, like updating our information on the Armed Forces Pathology Lab and so on, and what=s going on there and so on and so forth. There are significant issues of fact, I don=t think that change any of our considerations, but really do need to beXwe do need to go through it and make sure we=ve got things as carefully as possible, and that=s going to take some time.

So I just don=t think that we can both completely rewrite chapter 5, which is clearly on our agenda and will be done for the next meeting, and go through all the rest of the material and update that and respond as appropriate to public comments, and get that out in advance of the March meeting. So my tentative objective there is to get a new chapter 5 done, that of course will contain all the recommendations which result out of our own discussions, and as much of the revision of the rest of the material as possible. We will send out a revised copy before the meeting, which will be, as I=ve just indicated, redone to the greatest extent possible; there=s going to be material moved to appendices and so on that are currently in the body of the report. The reason I want to send out the entire report as it exists at that time is because I think, in judging from yesterday=s discussion, it is quite important that as we go through the recommendations we don=t forget what we said in the body of the report, because there are a lot of examples in there that were asked for yesterday that in fact are already in the report. Whether they ought to be amplified or there ought to be further ones is an open issue, but a lot of thatXI heard yesterday quite a number of requests that in fact already exist in the document. So we will send out a complete document in that sense, although there will be, undoubtedly, further revisions required for chapters 1 through 4 in response to

public comment and in response to our own considerations in the structure of the recommendations as we are coming up to them. So that=s my objective to take us to the March meeting with respect to that report.

Now you all have in front of you, I think, very helpful suggestions that came up yesterday at our meeting and which Alex has formulated in actually written form which he passed out to everyone. Has everyone got this particular sheet? All Commissioners? I think they were at your places, at least that=s where I found mine. So ideally I want to as our first item of business on this issue to turn to those and ask Alex if he has any comments, and then to see if any Commissioners have any questions regarding these particular suggestions. Alex?

PROF. CAPRON: Well, let me just make clear what the attempt was: in a sort of scribe-like fashion, as you say, to reflect the discussion. And the numbering, if it=s not clear to you, point number 2 is what was on the sheet passed out yesterday called Recommendation number 4. In the process of writing that up and talking to Kathi about it, it seemed to me, for those of you who are looking the previous point number 4, that the first two sentences were largely repetitive of Recommendation 1. They were simply a statement that the Common Rule provides adequate protection for unidentifiable samples and that no special restrictions apply.

And so following along Larry=s suggestion of taking out that initial phrase about Aresearch should be mindful,≅ what appears here is, in effect, a rewriting of the rest of that. I must say that one thing that came up in that discussion with Kathi is I asked her whether there was any difference between Aunidentifiable≅ as used in Recommendation number 1 and Recommendation number 4 where it says Aunidentified,≅ it used to say Aunidentified and unlinked samples.≅ She said, ANo, those are the same things, but Carol Greider wanted us to use the latter terminology that=s in 4.≅ And I said that I find confusing throughout our reports when we=ve, and even in these few pages of recommendations, when we do use different terms to mean the same thing, and I guess it=s maybe my lawyerlike mind that says, If you=re using different words, do you mean them to connote something differently?≅ And if the answer is no, then I think we should simply agree on definitions.

If we need to set those out someplace, if that=s what people agree uponXI mean, if other people are agreed to that, I think we should resist the impulse to use synonymous terms that are different. There are small typos that occurred here. The

ACommon Rule≅ is usually, I think, capitalized. The word ARule≅ is capitalized. Two other comments as I saw these in typed form, if I may, Mr. Chair?

DR. SHAPIRO: Yes.

SPEAKER: The first sentence under Recommendation 1, which is basically the way it was after we added the word Aindependent,≅ reading it through as typed up here I realized that it=s missing something. When the word Aunidentifiable≅ is first used and then goes on, Aor rendered unidentifiable,≅ I wanted to know, Well, what does the first one refer to? And I think what we=re saying is either Aunidentifiable as already stored≅ or Aas stored≅XI guess you don=t need the word Aalready≅X≅as stored or rendered unidentifiable.≅ Is that clear to everyone, what that would mean? That is to say, there are certain repositories that have anonymous tissue samples. Those are unidentified as stored. Others have ones that are identified in some fashion, and they would be rendered unidentifiable by a process independent of the investigator. And I just thought that for the reader coming to this that if we don=t have that additional couple of words Aas stored≅ in there that what we=re distinguishing by the Aeither/or≅ is not immediately apparent.

MR. HOLTZMAN: So is this where we could use Aspecimen≅ versus Asample≅ to make that clear?

DR. SHAPIRO: I=m sorry, Steve, I didn=t hear that.

PROF. CAPRON: As either Aunidentified specimens≅ orX

MR. HOLTZMAN: We had this idea of Aas stored≅ wasX

PROF. CAPRON: Well, whereXjust remind me which is the specimen, Aspecimen≅ is this thing that=s sent to the researcher? No, other way around. That=s the *sample* of the specimen.

DR. SHAPIRO: The specimen is Aas stored.≅

PROF. CAPRON: All right. And when the samples are either stored as unidentified specimens orX

MR. HOLTZMAN: No: AWhen the specimens are unidentifiable or the samples have been rendered unidentifiable.≅ That=s the way you get at it.

DR. SHAPIRO: I think we understand the point, and I think it doesn=t need elaboration. I agree with that. And we will clarify that. And I think, just to take your mind back to it, it=s an issue that Alex just raised, and we=ve talked about it before, and it is an unfortunate characteristic of the current draft, not only since we use recommendations, that we draw up a set of definitions that we ourselves use, then when we describe other people=s attempts to do these we move to another set of definitions and so on. All that has to brought under some coherent form. And just to say a word about Carol=s concern: It wasn=t that she was trying to use two different words for the same thing. She was identifying two different kinds of situations to which the same rules would apply. But they really refer to two different kinds of samples. But this needs, obviously, some careful work, so I think your point is well taken.

PROF. CAPRON: Okay. The other point beyond what is in writing in front of you is on point number 2; obviously the intent was to contrast individuals who were unidentifiable with the groups to which they belong. And I think again, the emphasis just linguistically to bring this through to the reader would be improved if, at the end of the second line, where it says Aresearch using such samples may potentially harm,≅ I would say, Aan identified group.≅ And then that really underlines the contrast between unidentifiable individuals and an identified group to which the individuals belong. I don=t have anything beyond that to add to what=s here.

DR. SHAPIRO: Okay. I really want to thank you for articulating this. It really was very helpful and I think a very faithful representation of the discussions we=ve had around these issues. So thank you very much and that will certainly help.

I want to go back to some of the other recommendations. Just to highlight one. There are some we didn=t get to and we=ll just have to deal with that. There are some that are going to be changed that are interrelated, and the changes are interrelated, and so on. And then we had one issue, which I can=t say we resolved but we certainly had a kind of straw vote on the issue, and I just want to remind you about that latter in case any of you want to consider it further. It was an important issue that Alex raised, and that was what we meant by Aexisting.≅ I think it first came up in Recommendation 5 or what was Recommendation 5 in yesterday=s materials. And the question was whether Aexisting,≅ if I just can remind you in a shorthand way, referred to just before the researcher requested the sample or whether it was something that

referred to a specific date after new regulations were implemented or something of that nature. And while I don=t want to use the strong word Adecided,≅ because we agreed yesterday that we were not holding things up and down, for purposes of writing the recommendation we took the former definition of that, although there was disagreement among us on that. And that=s how we=ll proceed, but if any of you wants to say something further about thatXnot now; we don=t have a lot of time this morning for that. But clearly that=s still an issue that if you feel strongly about we ought to be talking to each other about it, or any other methods, between now and next time we meet.

Now, considering some of the other recommendations over which we have some considerable work to do, I want to, not in any special order, but what was Recommendation 10 yesterday is key to that issue. That=s the so-called consent, which we jointly agreed needs to be reformulatedXI don=t want to go through the whole discussion we had yesterdayXbut needs to be seriously reformulated. And I thought it would be helpful since that is central to this in many ways, and how that works out may very well flow down the other recommendations as well.

I wanted to select a Commissioner to work with Kathi on this as it really requires some careful thought and Alta, unfortunately, was the only one taking a nicotine break outside, so I asked Alta to work with Kathi on that and to consult the transcriptXAlta wasn=t able to be here yesterday, but to look at the transcript and to begin to formulate some new versions of Recommendation 10, which seems to me to be really critically important. The other issue that came up, with which we all agreed but contaminates as currently written a number of the other recommendations, was this notion that someone could give a blank check for any and all future uses of their materials. That occurs in a number of recommendationsXtwo I can think of right away, but may three or four, I can=t remember precisely. And I think there was general agreement around the table that that was not really a morally viable situation to be in. And so we ought not to be writing recommendations that allow for that.

PROF. CAPRON: At least as to Aidentifiable.≅

DR. SHAPIRO: As Aidentifiable,≅ rightXthe particular subset we were looking at then. That=s to identified, not to unidentified, right. I don=t want to get tied up in the vocabulary here. I have to remind myself each time just exactly what words apply to which one. So that has to be considered. Also, in Recommendation 12 that came up yesterday, which is perhaps the last of the recommendations we looked at yesterday, if I remember correctly, we do want to, we have to reconsider just what we

are asking. And I think, I don=t remember who it was, but there was an interesting model given to us yesterday in the discussion that when we=re dealing with the kinds of issues that are outlined in Recommendation 12, we really have a kind of hierarchy of things that we might want to consider. That is, we would want to make sure the IRB thought that this was scientifically valid in terms of approach, in terms that Diane raised yesterday. We wanted to deal with issues of prospective consent and how they function in that environment.

And then the question came, which has always been difficult for us to deal with, what do we do about the so-to-speak Aidentified≅ groups who have interests here at stake. How doXyou know, the old issuesXhow do we identify it, how do we know who to go see, and so on and so forth. But I interpreted our discussion yesterday to favor, in that respect, encouraging at the very least investigators to attempt to consult with some reasonably identified group out there, both to perhaps improve their research design and design it in such a way that answers the questions they=re interested in but yet would minimize harm. It may not be able to eliminate them but might minimize them. And that that was a useful thing to encourage and/or require people to do without, I don=t think anyone was thinking about any kind of either veto of being able to do this or giving or recommending a veto. Nor was anyone thinking of saying, for us being in a position to say there are certain kinds of research that are out of bounds. You can=t ask those kind of questions. That is not a matter that we are taking up. That is, there may be some questions too upsetting to ask and so on. That=s not what=s, I don=t think anyone on the Commission raised that issue. And it=s difficult in writing recommendations in this area to make sure you get those things pretty straight, but that=s a task in front of us on Recommendation 12.

On Recommendation 11, there was considerable concern that we really had not distinguished in ways that would beXwe=d failed to distinguish how this issue comes up in research versus clinical situations. And a suggestion was we really needed to distinguish these two and therefore write a recommendation that dealt with those in appropriate waysXdistinguishing between research situation feedback of research results and all the issues that come up there versus the issues that come up in the clinical situation. Now...

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes?

PROF. CAPRON: Didn=t we also distinguish between recontact in order to involve the enrollment process from recontact with results?

DR. SHAPIRO: That=s right.

PROF. CAPRON: And then within the results there=s theX

DR. SHAPIRO: Correct.

PROF. CAPRON:XCall it clinical results versus research.

DR. SHAPIRO: That=s right. That=s actually a better way to put it. Thank you very much. And that=s correct. And so that needs to be accommodated. Now, of course, I haven=t looked at the transcript yet, which is unavailable, but I just went over these things quickly. Those seemed to be the areas that needed some direct focus, and we will make sure that they get it. But there may be others, and now it=s time for Larry.

DR. MIIKE: Yeah, it=s just that, what I=d said yesterday was that in the rewrite we should consider reorganizing how we put these together.

DR. SHAPIRO: Oh, yes.

DR. MIIKE: For example, all of those group issues might be under one heading, because right now they=re sort of parsed out in consent andX

DR. SHAPIRO: There=s a series of organizational issues of that type, and I=m glad you reminded me, which really need to be addressed regarding how we group these recommendations, how we phrase themXrecommendations or conclusions. A number of those issues came up yesterday including the one Larry raised as well as the issue of, you know, what if someone needs some support and is interested in the simple question, AWhat if I deal with existing samples versus those to be collected? Where do I go quickly to find out what I have to do?≅ That has to be attended to as well, and so we will follow up on all of those suggestions. We will read the transcript carefully. I=m glad you reminded me about that. Alex?

PROF. CAPRON: I have had two people independently approach me, to whom these were sent as part of that circulationXwe sent them out to a lot of

peopleXwho said, AWhy was it that the Commission seemed to decide that the existing Federal regulations were the framework for its discussions?≅ And I should say that both of these were people who had been involved at one point or another in some of the predecessor bodies, which perhaps were operating at a time when the slate seemed to be blanker and they were freer simply to write. And I guess the way to formulate this would be to say their view of what an ethics commission might be doing is to say, AWhat is an ideal arrangement in terms of the balancing of competing interests in an area that affects human subjects?≅

Set that forth and then look to two factors. One is, Are there certain constraints in the real world beyond the balancing of those interests that say you can=t get there? And then second you might say, well, how well does that fit with Federal regulations, and suggest places the regulations might need to be changed. And I think it is characteristic of our report; I don=t think these people mischaracterized our report. It seems to proceed from a sense that here=s a regulatory frameworkXdoes it fit this situation? If it doesn=t, where might a little tweaking go on instead of saying what=s the ideal arrangement?

We are very far down the course on this, and I think we are more or less committed to that framework. It may be something that as a matter of methodology we need to defend a little more clearly as to why among the ways one could go about approaching this area we happen to have chosen this. It=s not necessarily only in this recommendation chapter that we can say that. It may be earlier in some of the introductory materials. But I underline it simply because spontaneously people, knowing I was on the Commission, said, AGee, I got a copy, I read it, and I didn=t see that, because what we have here are comments on the regulations, I didn=t see that.≅ It may be that the people never wrote inXthese are people who didn=t respond, and maybe you=ll never hear it from anyone else. But since two people whom I respect put this to me spontaneously, I guess IX

DR. SHAPIRO: I think that is a helpful comment, and we should have some material in there about it. I think that is a helpful comment. I remember well the discussion when we decided that. But yes, I think that=s helpful. Any otherXSteve?

MR. HOLTZMAN: There may be a more general point there, and that is for people to go back and ask the question on the conclusions we reached: Are they truly supported by the preceding four chapters?

PROF.. CAPRON: That=s a rhetorical question, Steve, isn=t it?

MR. HOLTZMAN: No. I think it, no, I disagree with certain of the conclusions, and the recommendations. We all know that. But I care very much that the Commission when it issues its report has solid argument leading to those conclusions and those recommendations. And I don=t think it=s there. I think it shows the history of a subcommittee that was going in a certain way. The full committee has chosen to go in a different way, and I just don=t think we=ve got the solidXand I know what that solid argument would look like with certain of the approaches we=ve adoptedXand I care very much that they have strength and intellectual integrity, even if I disagree.

DR. SHAPIRO: Alta?

PROF. ALTA CHARO: It would be helpful, probably, if you were to make a list of those things that you think are indefensible as currently structured in the report so that one could then decide whether you=re correct or whether people disagree with you but now want to write the explanation that you find lackingXto put some specificity to the objection. I think in the context of what Alex was raising, it=s probably worth noting that the decision wasn=t made so much that the report had to be structured around the regulations, but that we had spent a great deal of time early on in this particular report discussing this topic as if it were a situation that was occurring against a backdrop of no current regulation, and people were discussing what goes on with tissue and how it=s used as if there were no current regulations. And there was a sea change when everybody finally got educated about the existence of the current regulations and how they do in fact affect this area.

The next part of the discussion, and this may be how you might want to write it up, was the question of whether or not the current situation under the regulations was sufficiently protective, overprotective, or insufficiently protective for what people wanted to accomplish. And that=s what led to a kind of comparison at all times between what one might want and what was currently in the regs, and there was a moment at which there was a conclusion that the current regulatory system was not far off from what people were aiming at and could be adequate with tweaking. And I think, written up in that kind of narrative fashion, I think the reasoning process becomes its own justification process.

DR. SHAPIRO: Other comments before we return to the stem cells? Okay. Excuse me, Alta, did you raise your hand?

PROF. CHARO: No.

PROF. CAPRON: I guess I=m not procedurally clear. what you=re saying is you don=t think, at this point, until we have a redraft of some of these controversial things, that it will pay off to try to give any more instruction to the people who are going to attempt that?

DR. SHAPIRO: Correct. I think we=ve got a lot to do and a lot of layout, and I think we=ve got to take another step before we go. Yes, Alta?

PROF. CHARO: With apologies because I wasn=t able to get here because of weather delays in the airports, etc., I was wondering if in the conversation yesterday that led to Alex=s number 1, his first clause here, whether there had been specific consideration of Margie Spears=s objection?

PROF. CAPRON: Of which?

PROF. CHARO: Marjorie Spears=s comments as recited in the staff recitation of comments.

DR. SHAPIRO: That=s the CDC, if I remember correctly?

PROF. CHARO: Yes. The CDC comment about public databases filled with coded information, which is protected by statutory guarantee of confidentiality but meets the definition of identifiability under our recommendations and therefore is not eligible for exemption from IRB review. It might nonetheless be eligible for consent waivers, it might be eligible for expedited review when it does get reviewed, but it is not exempt from the IRB process. I was wondering if that was discussed yesterday, because Alex=s draft does not make her any happier.

DR. SHAPIRO: Kathi? It was discussed?

KATHI: Yes, it was discussed, and there were additional statements in her full letter that expanded on that extracted comment that you saw in the staff analysis, where she said that it might be wise for the Commission to state that human biological materials are considered different than the kinds of data sets that she=s talking about. And I think she would be happy with that, if we just made clear that there are

other situations such as the CDC data sets that don=t use human biological materials, and that we=re not referring specifically to those.

PROF. CHARO: Then one last thing, and then I=ll go back to being quiet again?

DR. SHAPIRO: Okay.

PROF. CHARO: I=m good at that today. Just for the matter of record, I wanted to just repeat something that I shared with Kathi. I had mentioned in one of the e-mails, and I don=t recall if it was to the listserv or to Kathi, that the European data privacy directive, which is now a matter of tremendous discussion between the European Community and the U.S. Government State Department and Commerce Department, is, I think, pertinent to this report, and I think we=re going to need to do something about it. The directive states that Europeans would not be allowed to export data to countries that don=t have adequate and comparable privacy protections, and there=s an enormous amount of debate around the scope of that directive, and a lot of negotiation between the governments about its application to the U.S.

But clearly, since much of the directive is aimed at medical information and the pharmaceutical community is extremely concerned about it, it strikes me that it=s quite relevant here, because whatever we recommend would be the kind of privacy regime that would be the subject of comparison with whatever standard they are suggesting needs to be in place in the U.S. before they could export information from their own medical databases to our researchers.

PROF. CAPRON: How are they defining what is covered? What we refer to as medical databasesXdoes it include biological materials?

PROF. CHARO: I=m not able to answer all of your questions on this, but there is debate over almost every term of the directive, whether a transfer consists of a single e-mail from one person to another, or it has to be from an institution to an institution, what constitutes information? And as I understand it, none of it has been completely settled, but I just am not an expert on this. I just wanted to convey that I think we=re going to need to incorporate that analysis.

PROF. CAPRON: So are you suggesting that we have a witness ASAP from the relevant agencies? Or a memorandum, or something to brief us on this?

PROF. CHARO: I=m going to leave it up to the staff=s good judgment how it is that they think this information should be gathered. But I=m suggesting as just a member of the Commission that I think this is information that we can=t afford to not note, and to see the connection between what we=re doing here in this report and our negotiated stance vis-à-vis the European community or our international collaborative research efforts.

DR. SHAPIRO: Well, we will first of all try to get material directly to Commissioners on this; I=ve not read this; I don=t know, I haven=t got much of a comment on it, obviously. And we=ll see what is the best way, the most effective way to get us to have some discussion about this, whether it=s a witness or a paper or something.

PROF. CAPRON: Is OSTP involved in these discussions?

DR. SHAPIRO: I have no idea.

MS. LEVINSON: Yes.

PROF. CAPRON: I=m asking Rachel.

DR. SHAPIRO: Oh.

MS. LEVINSON: Yes. And I think I can get you background information. I don=t know that it=s worth taking the time; it is an enormous mess. I don=t think they know whether biological material would be included as information yet, but it=s already getting in the way of things like information on plane tickets, etc.

DR. SHAPIRO: Well, maybe then that would be very helpful, Rachel, if you can get us a briefing on it; let=s see where things stand. I do want to say one other thing that your comment reminds me of and I neglected to say before. There was, I think, substantial agreement that we needed to beef up what we said about confidentiality where relevant in this report. That came though in one of the recommendationsXI don=t remember the number right nowXbut we all agreed that that needed to be done, and that was another aspect of the things we need to work on. Larry, then Trish?

DR. MIIKE: Well, that last comment by Alta worries me because I=m not about to agree to our report being jerked around by some other unspecified and as yet unresolved issue. It=s nice to know what it=s about, and we should be aware of it, but if it=s all an enormous messX

DR. SHAPIRO: That=s all we=re going to need.

DR. MIIKE: I would be totally against it. Either to try to transform our report to comport to something we don=t know anything aboutX

DR. SHAPIRO: No, no, we don=t want to do that. I don=t think that=s what Alta intended. She just thought that it might be helpful to reference it in some way, if we understood what the nature of the situation was.

PROF. CAPRON: When we issued our Cloning Report we really didn=t talk about the FDA, and immediately the FDA was on the scene. I think it would be a shame to issue this report and for us not even to give any indication that there are a set of issues being dealt with by somebody that may affect the final shape of Government action on these recommendations because of forces that they have to deal with, that=s all.

DR. SHAPIRO: Trish?

PROF. BACKLAR: I was just nodding my head, agreeing with you about the confidentiality of the medical records that we spoke about yesterday.

DR. SHAPIRO: I see. Okay. All right, we have a lot of work to do here, but we=ll get, I think, a substantial part of it accomplished before our next meeting, but probably not all of it. So thank you very much for that. Let=s return in the few minutes we have left to our discussion regarding stem cells, on which we heard some testimony this morning. If you recall, we hadX

PROF. CHARO: Excuse meXsorry, Mr. Chair, just let me say for the record that I=m recusing myself again.

DR. SHAPIRO: Thank you. I appreciate that. We had gone through a sort of hierarchy of considerations as we went through our discussions yesterday, which included, as we went through and took a kind of rough stab at figuring out where we

were regarding the use of stem cells derived from fetal tissue and so on, and also the same thing for embryonic stem cells derived from discarded orX≅discarded≅ is the wrong word: excessXwe=ll have to find the right adjectives to use hereXembryos.

And I think it was true that for the most part, and I don=t want to claim complete agreement, that we really were all comfortable as far as that was concerned. And then we also began but did not resolve our discussions regarding the creation of embryos for research purposes. And then we began to circle back on what about the use of embryonic stem cells that may occur not from embryos that were excess in some sense of that word but may have had some other source, like produced privately and without Government funds somewhereXhow do we feel about that and so on. But then we did go on to talk about the creation of embryos for research purposes or for the creation of embryonic stem cell lines, and I think there was also disagreement I think on that issue, on that broad issue, among some who felt that they could start off by reflecting on what Larry said when he introduced this topic: that his own personal view was that ethically he had no problem with it. He did not think, however, it was good public policy at this time for a series of reasons, which he articulated and I won=t repeat. And I think, although it may not be going too far to say that the next step, I sense that many Commissioners at least, I don=t know how many, felt sympathetic to the idea that this was not the time to take up the issue of spending Government funds for creating embryos for research purposes. That there was a big scientific agenda, enough important issues to be resolved before that which were more important, and that that issue could waitXI think people had different reasons as to why it could wait, but they thought that could wait. I think that if I mischaracterized the discussion as others remember itX we will have a transcript in the end, so we don=t have to go on our memories only, and I haven=t consulted my notes on that this morning. Is that a fair characterization of where the discussion went, or not?

DR. MIIKE: Yes.

DR. SHAPIRO: So the issues that we will have to, we will try, of courseX

PROF. CAPRON: You have left out, I thinkXI couldn=t tell whether you said we came back to this, but most of our discussion focused on the creation issue and the funding of creation by the three methods. And I correctly say the first twoXthe first, which is now provable; the second, where we would in effect be saying Federal policy should be changed to eliminate the second clause of 511-A at least as to stem cells, and

the third, for feasibility and alternative issues, we weren=t ready to push. But then we came back to the question, What about the funding of cells created by these methodologies?

DR. SHAPIRO: That=s right.

PROF. CAPRON: And we had some discussion of whether it was feasible to identify cell lines by their ideology as, it were, and the answer seemed to be yes, actually, you probably could do that. And then the question was, Was there any reason to do that? Does the argument about use being separate from creation persuade? Or are their either prudential or ethical reasons to say, hold off on supporting certain use, because that=s really supporting creation.

DR. SHAPIRO: That=s right. That=s whereX

PROF. CAPRON: And that=s a very touchy issue.

DR. SHAPIRO: It=s a very touchy issue.

PROF. CAPRON: But I don=t think we can fully dodge it, because it was one of the things that Dr. Varmus I think explicitly was asking our advice on.

DR. SHAPIRO: That was the issue which came up at the end of the discussion, that=s quite right, and you=ve characterized it at least as I recall it, and maybe we could spend usefully a few moments this morning focusing exactly on that issue. That is, if we consider whether or not the process of creation, or just how these stem cells are created, should have an impact on whether research using such stem cells would be eligible for Federal funding. Larry?

DR. MIIKE: A couple of things. First, on that issue, my conclusion is that we felt comfortable about using stem cells derived from those two other methods, about aborted fetuses or excess embryos or IVF embryos, only because we could find some guidelines and restrictions that would also be related to the complicity issue on the creation. I can=t find a similar rationale when we talked about if it was created for research purposes, and then using stem cells derived from it. So my position at the current time, and I don=t think it=s going to change, is that that=s exactly why we were raising the issue about maybe a pedigree in terms of where these cells come from, in part, in terms of any possible Federal funding.

And then one other thing, Harold, is that I think that there=s agreement among the panelXof course the ones that were not here, we don=t know what they=re going to say yetXbut that we can address in more than a general way Dr. Varmus=s request for the six-week request about some ethical guidance for the stem cell research that they are moving forward on. Because I think we do agree that in terms of the stem cells from aborted fetuses or from the excess embryos, I don=t think there=s going to be much controversy, among ourselves at least, about those. So I think we can begin to address some of it.

DR. SHAPIRO: Well my view of the latter issue, not the former one but the latter one, that is Dr. Varmus=s particular request, I would hope that by our March meeting we will have material both that reflects our discussion here but also further work that the staff is going to do, which focuses on the ethical issues that surround us. I mean, we decide to talk about our recommendations and then come back and see how we might support them. And if we do come up with something that is helpful and useful and convincing, really, I think we could certainly advise whoever on just what our current thinking, or the stage of our current thinking is. I=m a little hesitant for us to be responding particularly to a particular person. I think that=s probably not a good model for us. But if we are at the March or April meeting, whenever it is, in a position to say, Look, these are the issues that we are focusing on, these are the issues that, in this area, the area that you=ve defined, not the broader area, if we=re in a position to do that, fine. We can communicate with anyone who=s concerned with this on those issues, and I think in that way we may, I don=t want to prejudge now, we may be in a position to respond to Dr. Varmus as well. We=ll have to see. Just see where we are. Kathi?

DR. HANNA: I wanted to just make a point here that we need to factor in and that is staff have had discussions about this, and we=re trying to get clarification on it, but it=s not clear, to me at least, in reading Harriet Rabb=s decision, whether she said anything about somatic cell nuclear transfer and using that technique to derive the stem cells. The letter is not clear. And so when you say, in responding to Dr. Varmus=s request for some assistance or guidance, I=m not sure yet whether we should be throwing somatic cell nuclear transfer into the mix as well, because it=s not clear to me yet.

DR. MIIKE: No, I wasn=t even considering that part. I was just considering the Thomson-like cells, and the derivation of those. That was all I was referring to.

DR. SHAPIRO: Alex?

PROF. CAPRON: I agree with you that Harriet Rabb=s opinion letter is not crystal clear on this. But I think it is quite reasonable to read it as saying that the stem cells derived from cloning are just like any other stem cells as far as they=re concerned. The issue that arises for those stem cells is the prohibition on the use of those stem cells as a source for nuclei to transfer, and so where the cloning is a repeated cloning into an embryo, at that point you couldn=t federally fund that, so that you couldn=t federally fund the creation of a stem cell line through somatic cell nuclear transfer, and you couldn=t use the cells that you have to go back and do a cloning technique. But it would seem to me that since the issue was before her, her silence on the other is actually in effect an opinion on it. It wasn=t something that she felt she had to say was prohibited by any existing policies. And so that any problem with it is the same as any other embryo that=s created for research purposes, since it can=t be created for implantation purposes with Federal funding. And certainly the policy that the President is urging is that that become statutory to prohibit that. But I think that there is an opinion buried there in that pregnant silence.

DR. SHAPIRO: In that case, we could get a clarification.

PROF. CAPRON: We may be able to get it. I don=t know that she feels any obligation to write opinion letters to us.

DR. SHAPIRO: No, that=s right. We may.

PROF. CAPRON: Just as we feel no obligation to write one to Dr. Varmus. But we may be able to, you=re right.

DR. SHAPIRO: Correct. We can=t order it. Absolutely.

PROF. CAPRON: We can=t order it.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: But it=s clearly at a point with respect to the question in front of us. Because the question in front of us really is we=re going back to our first recommendation. Effectively we believe that Government can sponsor ES cell research provided, howeverXand that=s the question, are we going to put in Aprovided,

however≅Xthat only with the ES cells where one can document that they did not come from research-purpose embryos. Any ES cell which came from, is the product of somatic cells, came from a research-purpose embryo.

DR. SHAPIRO: Correct. Right.

PROF. CAPRON: Yes, that would be our recommendation. But sheX

MR. HOLTZMAN: But you=re saying her silenceXshe=s agreeing that it is an idea, right?

PROF. CAPRON: Yes.

MR. HOLTZMAN: So again, I=m just trying to frame the fact that whether we throw in this Aprovided≅ determines whether or not there could be some Federal support for ES cell research from nuclear transplant.

DR. SHAPIRO: This particular issue I think is a very important one for us to be thinking about and further communicating about. Precisely this issue, whether it=s the somatic cell technology or some other technology. Larry=s position, for example, is that he=s not comfortable with the arguments that lie outside the EG and ES cells created either from excess embryos or fetal tissue sources. He just says that the arguments don=t work for him. And the question is, Do they work for any of the rest of us, or do any of the rest of us want to propose that to take the more extreme position, perhaps the Rabb position that at least I believe expressed that, you know, its source is not a concern. That Federal funds, just to take another position, should be, or research on ES cells should be eligible for Federal funds regardless of the source of the ES cells, or all ES cells. That=s another position. And I think we should all be thinking carefully about that and the arguments that we would mount one way or another, whichever position we took.

That=s going to be a very, very critical decision for us. And I think that our hope is that at the March meeting we will discuss and hopefully resolve at least in our own minds in some kind of way where we stand on this issue and whether we find the arguments convincing that we ought to restrict Federal funds, for example, to the first two categories yesterday, and not the third category and combinations of categories that are ethically similar to the third category, which involves creating embryos for

research purposes. One way or another, that=s what it involves, whatever technology is used.

So that is, I think, going to be a very critical element, and I really encourage us all to think as carefully as we can, communicate in whatever way with each other that we think would be helpful to our own train of thought. Because that=s going to be, it seems to me of the issues that come up, really quite critical to just how, what the nature of our final report=s going to look like.

All right. Are there other issues that came up yesterday in this area that you think would be useful to address at this point?

DR. MIIKE: You have to create a special mailbox for our committee meetings. A new mailbox. Otherwise, it could never get around to our accounts.

DR. SHAPIRO: All right. Okay. We=ll do so. Any other issues anyone wants to raise?

PROF. CAPRON: Well, are you saying substantive issues, or issues of our process, or which?

DR. SHAPIRO: Either way.

PROF. CAPRON: Well, we got a modified outline from Kathi on this report and I think it=s very hard, looking at this, to know how it compares with the discussion that we=ve had. But I thought one thing about the process that we got launched on at the last meeting, which we spent the last day and a half on, that offers a greater likelihood of coming up with a good report at the end was this notion of let=s really deal with the recommendations and then build outward from that. And I just hope that what looks like it=s still a very comprehensiveXand in the ideal world with a very much larger staff and more time probably totally appropriateXreport, that the question as to anything that=s written for this report would be, Is it necessary to support one ofXto defend, explain, and otherwise support one of the conclusions that the Commission has come toXand that we write backwards in that fashion to explain ourselves? Now it may always be that in the process of fully detailing scientific facts and moral arguments that one comes to the conclusion that the original conclusion is less defensible than one thought. Or as we saw in the process yesterday, that the clinical realities and the research realities complicate the simple decision and the simple-decision

conclusion has to be modified in some way. Either of those is possible, at which point we=ll deal with it.

But I hope that thatXat least my hope for that expectation of how we would go about itXis clear. I don=t know if I speak for others, but I have a sense that it will be easier for us to get through that final report if it grows organically in that fashion instead of being written alongside, as has happened with a few of our other reports, our deliberative process, sort of taking on a separate life of its own.

DR. SHAPIRO: Larry?

DR. MIIKE: I think the simplest way to address that is that there are certain descriptive pieces that need to be written anyway: just the science part, the history part, the regulatory part. And that as we move through here those things can beXin other words, we still need to have the staff write the raw material out of which we=re going to write the report. I fully expect this outline to keep changing. And I am an advocate of shorter reports. Maybe our Cloning Report sort of put us in a bind, because that was supposed to be a short-term report and it ended up with fairly voluminous background materials. I=m always for short and to-the-point reports, but obviously we have to have enough meat in it that it backs up what we=re saying.

PROF. CAPRON: Right. Well, during the cloning process, as the buckets were working away on their separate topics, we not only didn=t have full Commission participation because of the time and the need to have that bucket process going on, full Commission participation in each of those, but I recall from a couple of buckets that I participated in that we went over an awful lot of ground, including drafting of things that eventually bit the dust, that didn=t end up being central to the set of conclusions that we came to. And I agree that some of the raw materials can be written, but even on the science side there are levels of description and amounts of information that can be very interesting and illuminating, but the question to me is always, are they necessary in support of a personXnot just literally in defense of our conclusionXbut a person picking up the report and understanding what underlies the conclusion. This is not a critique of the outline or of any past efforts, it=s justXI have a sense we have still a relatively limited professional staff. Kathi is both in charge of a lot of this report and of the Human Biological Materials Report. We=ve just given her huge marching orders on that, and I think realistically we ought to encourage a process that grows out of this and is limited in that fashion, so as not to have adverse health effects on any of the people involved.

DR. SHAPIRO: I think that the next written material we see, which will be in March, really ought to reflect what we have been talking about. And we ought to see ourselves, so to speak, in that and how it=s formulated. And if that=s what one means by, sort of, the Capron way of writing backwards and so on, I think that that is a very important part of what=s happened, of what we should be doing.

PROF. CAPRON: Okay.

DR. SHAPIRO: Of what we should be doing next. So that we can feel we=ve reached a moment we can stop and go ahead with the next, the next moment. Steve?

MR. HOLTZMAN: But is the question just that? And what I mean is there=s a feature to our Cloning Report and the last report we did on decisionally impaired. There=s a certain kind of limit to that old style, not old style, OTA [Office of Technology Assessment] flavor of these reports. They=re very comprehensive, right? If you go and look at, for example, the report from the genetics and embryo commission out of England on the subject of cloning is much smaller, done in a very, very different kind of style. I=d recommend people look at it. Is this question really about what is the most effective communication style of the kinds of reports that are appropriate to a Commission like this?

DR. SHAPIRO: Well, I think that=s always an open issue, and people have vastly different opinions on this regarding what role we think the report plays. Is it supposed to be read by four people, is it supposed to have any educational component, are you trying to advance a whole series of understandings here on a much broader public? And at least it was my own view, that the latter can be an important aspect, not a central aspect, perhaps it can be an important aspect. And for that you need more material than, frankly, the British report has.

PROF. CAPRON: Right.

DR. SHAPIRO: And so my view is that that report=s just fine for certain purposes, and I certainly don=t have any criticism of it, but it completely fails on other grounds. And so we were going to try to find the right combination hereXI think both/and, but it=s not obvious to me which one of these is kind of superior.

PROF. CAPRON: I wasn=t arguing, by the way, for the British report.

MR. HOLTZMAN: And I wasn=t either

DR. SHAPIRO: I understand.

MR. HOLTZMAN: I was just raising it as a question, because in adopting a style youX

DR. SHAPIRO: It is a question, and we=re going to struggle with it. Obviously key to us for this report is to be able to answer the President=s letter. We=re going to answer that; whether we do anything else is, you know, secondary. Arturo, then Eric?

DR. BRITO: It may be partly my background, but it seems to me that the key here is going to be to emphasize the scientific advances that have come about and how they may have changed our perceptions, our ethical viewpoint. Even though David=s not here to discuss this today, yesterday he said that science is irrelevant in terms of some of the ethical issues. I disagree with that. The more I=ve thought about that, I think the science has made it more relevant in terms of how we look at embryonic development because of the new findings. And I think the key here is going to be to highlight historically, in recent history, really, the last 30 to 40 years, of how science has advanced to the point where we now understand embryonic development better, and how that may change some of the ethical viewpoints and public policy viewpoints on embryos. So I think we start from the scientific part of it. I understand that we have our conclusions in mind, but starting from the scientific development and from that drawing some of your ethical and public policy viewpoints I think might make it a little bit easier.

DR. SHAPIRO: And that=s, of course, also consistent with the President=s letter to usX

PROF. CAPRON: Exactly.

DR. SHAPIRO:Xin which he raises precisely the issue, I believe he raises precisely the issue that Arturo raises. Eric?

DR. CASSELL: Arturo just said exactly what I wanted to say, and I was brought to it by rereading Richard Dorflinger=s testimony, which is important to read from time to time. The fact is that the science underlying all of this is what changes how we see this. And we just have to make that very, very clear.

PROF. CAPRON: Could I offerX

DR. CASSELL: Otherwise we get into the business of moral relativism, and that=s not what we=re talking about. We=re talking about a better understanding of what this whole thing called embryonic development is.

PROF. CAPRON: An illustration, I think, of a sort of common agreement with that. I believe that during the period when Steptoe and Edwards were developing the successful IVF, they obviously had to do research. And to the best of my knowledge, the eggs that they got for that research were from infertile women. And there was a good deal of debate at the time whether the women in that situation were being exploited. Their view was that these were the only people you could go to at that point, to ask for them to expose themselves to the process, which was then a more surgically burdensome process, as well as whatever the endocrine effects and so forth are.

Today, it=s something that people feel justified asking people to do, either on a voluntary basis or on a voluntary basis for some pay, who have no other connection with it, to become egg donors, because the clinical benefits of being able to provide fertility to people who are now infertile are proven. But at the point when they weren=t, it was seen as too burdensome and improper, even, to go to those people and ask them to go through it. Now you can argue that they got it wrong in terms of which people were in a better position to provide voluntary consentXnormal egg donors or infertile. But from their point of view, and I think from the viewpoint of the women who agreed, there was a notion that the justification required was different.

And I think that=s what=s happened with stem cell. In the President=s letter there=s the suggestion of what you=re saying, there=s the suggestion that if the clinical possibilities of benefit are closer and the scientific possibilities are greater for knowledge than they were at a time when all embryo research was prohibited, that that provides a change inXand it=s not moral relativism, it=s the same moral standard, but just saying there=s a different weight on the scale as against the harm that=s done to the embryo. It=s less disrespectful to an embryo if it becomes something that=s used in a process that has great benefit than if it=s something that is just done for very little benefit that could just as well be done with a mouse. And that=s the kind of issue that we=re facing here. And I think it was supported by Dr. Hogan=s testimony this morning in the number of things that really can continue to be done with a mouse and probably, ethically, ought to be done with a mouse or a primate or whatever.

DR. SHAPIRO: Thank you. Arturo?

DR. BRITO: Just very briefly, I also want to say, I think also key here is that the words that we use in our deliberations as well as our e-mail and of course our final writings is even more critical. For instance, the use of the word, when we talk about stem cells, when we talk about embryonic stem versus germ cells, we need to be very clear about that. There are some subtleties, too. Using the word Acreation≅ of stem cells versus Ascientific development≅ of stem cells I think is important. And then when we go to differentiate totipotency versus pluripotency and defining that, I=m not completely convinced that we always talk about pluripotent cells as just pluripotent, because they may be able to reverse and become totipotent. So that=s an important thing. And in the, I think it=s the English deliberations, they=re very careful when they use the word Acloning≅ to differentiate reproductive cloning from other types of cloning. I think we need to start using that, those terms, because I think it=s going to be very helpful when we come to finalize our terms, and it=s a lot less confusing, at least for me, when hearing it.

DR. SHAPIRO: Thank you, Arturo. Other comments, questions at this time? Okay. You owe us 20 minutes at the next meeting. We are adjourned, thank you all very much.

PROF. CAPRON: While we=re here, is it possible to inquire about the status of any of our other works in progress?

DR. SHAPIRO: Absolutely.

PROF. CAPRON: Where do we stand onXit=s prompted in part because we were sent with these materials, materials relating to the Environmental Protection Agency and studies of pesticide toxicity in humans from *Science*, that came in our packet. We haven=t discussed the implications of that, which I assume related in some way to our report on the agencies and our general examination ofX

DR. SHAPIRO: Why doesn=t Eric bring you up to date on where we are on some of those other issues, including that specific question?

DR. MESLIN: That particular one was noted just for information purposes. That was what the content of the e-mail was that preceded materials being sent out. A panel was convened on that subject, and I thought it was of interest to

Commissioners; it was not directly related to any of our reports at this point, although clearly it could be if the need was felt. At this point that special panel has not issued a report. Once that report is complete I=d be delighted to send it to Commissioners and then they can decide whether they wish to incorporate it into ongoing work as needed. But at this point it was provided only for your information because I happened to participate in it.

PROF. CAPRON: Well, can you fill us in? Certainly some of the materials that you sent us from the environmental working group underline something of which we were aware, that the EPA had not, perhaps, advanced as far in the implementation of the Common Rule as one might hope, which was simply a reminder of the fact that we were doing a report two years ago on that, and where do we stand with that?

DR. MESLIN: The status of the comprehensive report is we have slowed its progress because we have prioritized two other reports. It is not completed, but it isX

PROF. CAPRON: Are we looking for a schedule as to when that will be back on our agenda?

DR. MESLIN: Yes, we will have a schedule for you for when it=s going to go back on our agenda. We=ll have it for you at the next meeting.

DR. SHAPIRO: Now, Eric and I talked about that particular issue, not only with respect to that report, but international efforts and so on. We will have a timeline available to Commissioners for those ongoing projects, as well as as we look toward the future and presuming the Commission gets extended and so on, a process we=re thinking about what we might do subsequent to those reports. A big issue. That will all be available in March.

DR. CASSELL: Certainly in the international one, if we just stay off it long enough, everybody=s arguing it back and forth, they ought to come to some nice conclusion that we can appropriate.

DR. SHAPIRO: Right. Sounds like a good strategy. Thank you very much. We=re adjourned.