MEETING OF THE NATIONAL BIOETHICS ADVISORY COMMISSION

Sunday, April 13, 1997
7:50 a.m.

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I N D E X

P R O C E E D I N G S

DR. SHAPIRO: Let's get ready and bring today's meeting to order. If we could restrain all the animated conversation that is going around the table, we could begin our session.

First of all, I want to express my gratitude to members of the commission, all of whom are putting in extraordinary amounts of efforts to help us meet our 90-day request from the President. You will hear me thank you many times. I only do that many times because it is on my mind almost all the time, so thank you very much for all the efforts everyone is making.

Every member of the commission has been very responsive to all the various unreasonable requests that we make to produce materials, think through things, and so on and so forth, and I am very grateful to all the members of the commission, particularly so, of course, to those who have to travel a long way to be with us today. I am very grateful for all the efforts.

I also want to extend the commission's thanks to all those who have provided us with commissioned papers. We gave quite a number of scholars very short deadlines to produce--the ones I have read; I have read I think all of them that have come in so far--a really very thoughtful analysis of the issues that are confronting us, the particular aspects of those issues, and I am really very grateful to those authors.

I will get a chance, I think later on today, to thank some of them specifically, but I want just our meetings to show that I think, on behalf of the whole commission, we are very grateful for their assistance. I don't think we could have made our way through this problem in as effective a way as I hope without their help, so I am very grateful to them as well.

Welcome. We are going to begin our sessions directly.

Just to review the agenda with everyone, we will hear from Dr. Lo in a moment, dealing with some of the ethical issues.

At 9:15 we have set aside a half an hour for public comments, if there are any. People who would like to address the commission at that time are certainly more than welcome to do so.

We will then take a break at approximately 10:15. We will reassemble to look at the scientific issues. Dr. Greider will lead that discussion for us. That will go for about an hour, an hour and a half.

Then we will move on to discuss the legal and policy issues which will take us up to lunch, and indeed part our period after lunch.

We will then go into a discussion of our work plan, the various propositions that we might want to think about.

I think just what we will do after that depends a good deal also on the nature of our discussions that proceed from now until then.

We hope at the end of the day to reserve an hour, namely between 2:30 p.m. and 3:30 p.m., if that is needed, to hear from the two principal subcommittees of NBAC--one on human subject protection, one, the Genetic Subcommittee--to hear about their plans.

So those are our plans today. It is an ambitious agenda. I don't want to take the time slots with too much rigidity. We might find we need more time in some areas, less time in others. We will just have to make our way through as carefully and as effectively as we can.

So once again, thank you all for being here today. And a welcome also to the members of the public who are here to observe the committee in its sessions. And let me now turn directly to Dr. Lo. Bernie?

ETHICS ISSUES

DR. BERNARD LO

DR. LO: Thanks, Dr. Shapiro.

Last night, most of the members of the Ethics Committee were able to meet with--

THE REPORTER: Excuse me, Dr. Lo, would you pull your mike forward?

DR. LO: Sorry. I have been using this sort of as a Teleprompter. This made sense at about 3:00 o'clock this morning. I don't know if it still does.

(Laughter.)

DR. LO: We met with Professor Brock over dinner and had a-- We had thanked him for not only his paper but for coming out last night and engaging in a really wide-ranging discussion about Beatrice Raison's(?) paper and beyond.

I wish I could report that the bucket has sort of definitively solved all the ethical issues raised by cloning. We haven't. I think it was very important for us to sit down and talk it through. It is the first time we have had a chance to talk, however informally and tentatively.

I think it is fair to say many of the members of the bucket have not yet made up their minds about what position to take on the issues, and how to sort of formulate these issues.

However, let me say that there were clearly two lines of thinking, and this again was reflected in the papers presented at our last meeting.

On the one hand is a line of thinking that says there is a right to reproductive liberty, and it was important to note that if you start with that presumption it really sort of sets the rest of the argument and it actually creates a

presumption that opponents need to come up with compelling reasons to override that reproductive right.

Moreover, those who would believe in that reproductive right to procreation would argue that you don't really have to benefit, unique or see the benefits for this new technology. A preference on a part of a person or a couple can use it, rather than other forms of reproduction are key, and may be sufficient to justify it.

So that was one line of thinking which some people I think were sympathetic to, but I don't think it was convincing to all.

Another line of thinking really looks at what are the harms of potential use of cloning of human beings. And there are several harms offered and, again, none of them turned out to be compelling to all the people there.

One harm that people are concerned about was that this represents an attempt to determine almost the complete genotype of the offspring, and this is a radical change from the usual genetic lottery which takes place either in sexual reproduction or any other type of ART, where you can choose the partner, but you can't choose the way the genes sort out as genetic material from the two partners involved.

And why is this ethically important? Some people are trying to say that this sets expectations for children to sort of try and replicate the prior template, to the extent that genetic material has a strong influence on outcome, realizing that of course environment, rearing and such are also important.

As I said, this was not a compelling argument to everyone in the room.

The second harm was that cloning of human beings would undermine the orderly sequence of generations and lineage. It is actually interesting.

We tried to say, if you had a person who cloned himself or herself, how would you draw the family tree? Who would the genetic parents be? Would it be the parents of the original of the template? Would it be, if you only have one genetic parent, the person who was cloned? Would you actually have two parents, but not equal any more, but cloned, and perhaps the woman who donated the mitochondrial DNA? How would you sort that out?

And what would the ethical concern be? People were trying to say that it is important to a child to have clear genetic relationships and, to the extent that this technology confuses them in a way that is felt to be different from some of the blurring of roles created by other forms of ART, this is an objection. Again, concern that not everybody shared, much less supported.

And a third harm was I guess a combination of hubris and narcissism; that ordinarily reproduction, procreation, requires some kind of cooperative relationship between two relatively equal and separate individuals, both of whom contribute equally to the genetic make-up in the child. And to allow cloning of human beings, the objection runs, would reinforce the pernicious idea that individuals are really independent of other people and don't need to depend on other people.

Now these countervailing harms were felt by a number of people not to be strong enough to override any punitive rights of reproductive freedom.

Criticisms were made that these harms were poorly defined, they are speculative, they are not significantly indifferent than concerns raised about other forms of ART that we accept and, moreover, that these harms were unlikely to occur in and of themselves if a whole lot of other things about families and child-rearing did not also change.

So we didn't settle any of the ethical dilemmas, but I think we are left with three questions that I think we need to think through a lot more, in addition to

trying to better articulate the reasons for and against the cloning of human beings.

Let me just sort of list those three questions I think we need to focus more attention to.

One was what ethical concerns or objections would be strong enough to reach various possible conclusion? And let me just sort of put out three conclusions you might want to reach.

One, what concerns would justify--

Well currently, let me say, there is a moratorium imposed really by Executive Order that did not require, I think, the kind of in-depth ethical justification of reasons that we are going to be called upon to supply.

So, first, sub-questions.

What ethical concerns would justify a continued moratorium on the cloning of human beings?

Secondly, what ethical concerns would justify setting the presumptions such that the burden of proof would lie on those who would start cloning, as opposed to the burden of proof lying on those who would oppose cloning?

In other words, is it up to those who would start cloning to come up with sufficiently weighty reasons that would be convincing, or does the presumption lie the other way; that cloning should proceed unless someone can come up with compelling objections?

And one of the concerns I have is do the reasons that might justify a continuing moratorium necessarily justify setting the default, one way or the other? Well, actually we have it just by saying the default, so that the burden of proof lay with the proponents of cloning.

And, finally, what sort of concerns would justify opposing cloning in a sense of having a permanent regulation or ban?

And one of the things that was interesting in the room--this is more sort of a not a whole, or a rogue, but just sort of one person's sort of intuition about what was transpiring--was that there is a lot of support for the idea that a continued moratorium would be something they might support, whereas they didn't think the arguments that would lead them to supporting a continuing moratorium would necessarily lead them to set the presumptions one way or another, or to support permanent regulation or ban. I think it would be important for us to tease out why certain reasons would lead us so far and not further to try and articulate.

Two issues I think we did not discuss, but I think would be important for us to discuss in the future as we continue this work.

The second is how do we incorporate the religious-based objections to cloning of human beings in our thinking as we make the report?

Both at our last meeting, I think in some of the written materials which were so nicely prepared by the staff of this meeting, we find that many people with religious beliefs coming out of certain traditions--most traditions, actually--find their religion provides very strong justification for opposing cloning and supplies sort of the ethical punch, so to speak, for the harms that I discussed earlier, the way that secular arguments do not or may not.

I mean, we have heard these concerns about turning procreation into manufacture, idolatry against God, and so forth.

How do we draw upon that religious belief as we make our report? I think it is the problem of, in a society that has a separation of church and state, how do we take them out--strongly held religious beliefs which are not universally shared, which are very divergent--in making public policy.

And a third issue are ethical issues I don't think we have really started to discuss. And some may be easy and some may be difficult, but I think we

need to give some attention to ethical issues regarding scientific research on DNA and cloning of DNA in cells and animals, which may or may not be a simpler set of ethical issues.

And there are ethical issues regarding cloning research on human cells ultimately. You need to correct us on the best way to phrase this, because I know the policy bucket brought up this book.

As opposed to cloning of human beings, cloning research using human cells that would stop short of implantation, what are the ethical issues involved there and how do we analyze those with regard to the ethical issues I discussed with Carol Greider, the cloning of human beings.

So I think clearly we have a need to try and clarify and articulate better the ethical issues that we have been hearing about and deal with it ourselves, and then there are some other ethical issues that we really haven't started to really focus on, but I think we really need to.

Let me stop there and invite any of the other people at that meeting, which was pretty wide-ranging and not always easy to follow, to add on any impressions, concerns, with regard to the rest of the meeting.

DR. SHAPIRO: I don't know, Bernie. It sounded pretty coherent from your description. Maybe you helped out your colleagues, those of you who met.

Well, I think those are an interesting set of issues. And I am anxious to hear from other members of that bucket, so to speak, and see if they have anything they would like to add or elucidate and then, of course, to turn to questions and responses from members of the commission.

Yes, Jim?

DR. CHILDRESS: I would just like to thank Bernie for a creative act of bringing order out of chaos. No, we did have a very lively discussion and I

think this was a very strong statement of the kinds of issues that were involved, but also that need further attention.

I just want to make one observation about ways to think about religious-based objections.

First of all, many of the religious-based objections also can be stated in, and the proponents will state them in, terms that are accessible to others; that is, not all of them depend on a revelation or some particular conception that might not be open to others. That will vary from tradition to tradition, but at least some of the arguments are re-stateable in secular terms accessible to public policy.

Second, one way to think about the religious-based objections is to think about them providing part of the social cultural context in which policy has to be formulated, so we have to take account of those as part of the context in which we think about whether policies are desirable or feasible so they serve as setting a kind of larger social cultural constraint.

DR. LO: Jim, if I could follow-up on that for just a second. I think that many of the rest of my fellow commissioners are also blessed by being inundated with a lot of electronic and beeper mail.

Some of my mail comes from people with very strong religious beliefs who noted, that asked-- At the last meeting a number of us were sort of trying to do what Jim just more or less articulated in asking various groups, religious groups, people who presented work from religious backgrounds, and said can you articulate that in terms that don't explicitly--in secular terms--that don't explicitly rely on scriptural belief or religious doctrine?

And some people wrote to me and said we think those kinds of questions really demean our religious beliefs; that to ask us to try and articulate our religious beliefs, which are based on scripture or doctrine, in secular terms is a false

understanding of what we are trying to say.

And I was actually struck with that issue. And I think it does pose a question of us because I think many of these religious objections do have weight in accordance with those who don't necessarily share the assumptions in scripture or doctrine, but I think, for those who are true believers, being asked to articulate and rephrase their views in secular terms is an insult and doesn't respect them or their beliefs. I think that is the argument they would have.

DR. CHILDRESS: May I respond?

DR. LO: Yes.

DR. CHILDRESS: I quite agree. No. You are quite right.

And that is why I suggested there be a range, at least in some context. For some traditions, it is possible for them to restate them in those terms. On the other hand, even where, in many cases, where the traditions don't themselves restate, what they are proposing in secular terms, we can see the overlap of convergence.

For example, some of interest in family relations may be stated in a strongly religious way for a particular tradition. On the other hand, that is something that people can argue for from very different grounds and can see as very important for other reasons.

DR. SHAPIRO: Thank you. Alta?

PROF. CHARO: I don't know if this will turn out to be a useful way of doing this, but after reflecting on the experience with the Embryo Panel, where a similar set of concerns were raised, I came to feel that people who make arguments based on scriptural doctrine can be heeded in two ways.

One, for people who share that same fate, the argument from the doctrine is going to be transferable, and there will be a lot of people in the United

States who share that fate, regardless of whether or not the people writing the actual report do.

The second though is that, even when the argument that is being made can't be used because, without sharing the faith, the argument doesn't have any kind of persuasive power, the fact of the belief and the fact of the opposition or support for a policy, in and of itself, can be important regardless of the source of the reasoning for reaching those conclusions.

And when objections are so deeply felt that they drive people to extreme action--you know, running to Washington to testify in front of a commission, or inundating people with letters, or whatever--indicates, you know, really passionate belief. That simple fact of the depth of feeling can be used, even if the underlying reasoning by which you arrived there can't be transferable.

And I think that it is possible to then incorporate depth of public sentiment into the thinking process where that is one of the factors that has to be taken into account as a harm to be avoided. For example, the offense to deeply felt sentiment. Not a trump but a factor.

DR. SHAPIRO: I think-- Just to make a comment, I think the latter comment you made Alta is, for myself, I think that is really quite correct.

And I interpreted Jim's statement regarding social context to be really dealing with exactly that issue. It was a very helpful way you described it.

I think it is an important part of the social context and, as we know, in struggling with the various ethical and moral theories and approaches to this, that these contexts are an important additional element which we have to--I believe--we have to give some consideration to because we are talking about public policy here and I think those are important issues to conflict. Thank you.

Eric?

DR. CASSELL: Well, I think, Alta, that is a really a very central point. And if we look around at what has happened in disparate beliefs, they must have often been confrontational. In the society at the present time we only have to think about abortion to see that. And it would be a pity if whatever we do comes in and is more fuel for the fight, or gets seen as another issue that one can fight about, rather than an issue in which we all trouble our way through a solution to. So I think we have some choice in how that comes out.

DR. SHAPIRO: Other comments? Yes, Tom?

DR. MURRAY: Yes. I was one of the people who kept, who repeatedly asked the religiously-oriented thinkers at our last meeting if they could also try to state their concerns in ways that would be accessible to those who did not necessarily share all their faith commitments.

I am going to continue to do that because it is one thing to say that we should respect your belief just because you hold this belief deeply, and I think we should respect those beliefs, but it is difficult to know exactly what to do with that when one comes to making public policy.

We can respect your sincere belief and wish public policy to embody that respect in some sense, but it becomes difficult to incorporate that, to determine a public policy according to that, because then you essentially have everyone who has a deep belief, you give everyone who has a deep belief a veto over anything with public policies.

We don't ban blood transfusions because there are some people who believe it is deeply offensive.

Whereas I think many of those commitments, as Jim said, can be stated in ways that are accessible, that we can understand. I mean, we can understand, even if we don't share the particular faith of others.

And I think that is extremely useful if that can be done, and particularly because I think religious traditions in the United States sometimes do a much better job of addressing concerns that are probably some of the concerns at the heart of the initial opposition to cloning than those of us who tend to think of this as more philosophically.

So I think it important for the public discourse to have those beliefs, to have those commitments explained as clearly as possible and as publicly accessible a way as possible. And I am going to continue to try to do that.

DR. SHAPIRO: Yes, Alex?

PROF. CAPRON: I think Tom has really segued into the reason that we had a tough time last night in the ethics bucket discussion. Because the framework that Bernie provided is a very elegant representation of the house we were in, but what was going on in the rooms, the actual arguments, are what gets messy. And I agree with the comments that a number of people have made.

What we really need to do, and I hope we are going to do it some this morning as a whole group, is to ask ourselves, if we read the views of particularly those who have objectives, can we find reasons that are persuasive for deciding where the burden lies, and/or is a moratorium and/or a ban justified, and how persuasive are those reasons?

And I think it is fair to say that some fairly fair-minded people around the table last night were very far apart on those issues. And we almost need sort of-- what Bernie tried to do yesterday but we didn't have any markers there--of starting to catalog all of the issues that have been raised and go through them.

What Tom's last comment makes me think is that there is a way in which the analytic philosophical approach to these things may not fully capture the sense that some people have that there is some cumulative effect to these kinds of

arguments that is not totally a matter of strict logic; that two arguments that are disparate should not necessarily combine in some way to be more persuasive than they would be individually.

And yet I have a sense that, from the public point of view, it is kind of, "Well, this is bothersome, and there is that, and there is that," and there is this sort of cumulative sense that this is troubling. And I read that in the e-mail that we have gotten from outside and that we have exchanged amongst ourselves; that sometimes people said, "Well, I can't exactly put my finger on it, but this is bothersome."

The problem will be for us, and for Kathi Hanna, to put that down in a way which people not immediately engaged in a discussion would be at all moved by, or convinced by, and it may be that in the end-- This, I think, is what was happening last night a lot. People who were saying, "But that doesn't seem enough of a reason for this. I want to hear another reason." And we would look for another reason. That is I think where we were last night. And that is why it felt messier to live through it than to hear Bernie speak about it.

(Laughter.)

DR. LO: I think these comments are really helpful in sort of giving the rest of the commission who wasn't at this dinner a sense of the dynamics.

And if I can again sort of put a suggestion, an interpretation, of what happened, I think Alex's point that--

Well, what happened is every time somebody said, "Let me try and articulate an objection which I think reads, mainly reads, to say I reject the cloning of human beings," someone would state an objection, hands would shoot up, voices would be raised saying, "Well, but that is not really true. How about this?" And, you know, "I am not as certain as you think. I am not sure of that." And so that objection would not get accepted and someone else would try and raise another.

I think Alex's point that, even though no one objection was telling, I would bet, even though there was no sort of formal poll taken, that for many of us there were enough objections out there that are a little bit troubling that adding them all together, although no one is compelling or definitive, as Alex was suggesting, the cumulative effect of them all may be enough to in some minds to justify a continued moratorium, even though they would not justify, because they all sort of fall under sort of the analyst's scalpel, would not cling to that same cumulative set of objections, would not justify regulation of banning, or stronger permanent measures, or even setting presumptions, in other words.

DR. SHAPIRO: Okay. There are a number of commissions who want to speak. Let me go directly to them.

First of all, Alta, you had your hand up. Alta?

PROF. CHARO: Oh.

DR. SHAPIRO: Or has the issue been taken care of?

PROF. CHARO: Actually very brief to Tom, but actually, yes.

I don't think that anybody is suggesting you don't want arguments articulated in as sensible way as possible. The question is what to do with the residue. And I do think it begins to play into policy concerns when people have deep-seeded feelings you can't break down into secular arguments, because there are intermediate issues, intermediate options that can deal with taking account of peoples' feelings without being vetoed.

How well and how widely things are advertised, in what settings they are discussible, whether or not there is public financing are all examples of the kinds of intermediate issues that can be used to demonstrate the sensitivity without becoming trumps when something has happened.

DR. SHAPIRO: David?

DR. COX: Yes. To me that is a very nice segue because I think that in complex issues like this, having general discussions of possibilities and getting a sense of peoples' feelings, is a great place to start. But when the rubber hits the road it is in the context of a specific proposal.

And I, for one, think that I would respond very differently personally on these different general issues based on the specific proposal in front of me. So that in one proposal, I may be more in favor of-- It may be that the reproductive rights take the upper hand; on another proposal it may be the harms take the upper hand. And so that I think because people are so divided, perhaps this is the reason; is that this is going to be a situational thing and it really depends very much on the specific proposal that is coming forward.

From the scientific point of view, there are a myriad of different specific proposals that are going to be coming forward. And I really, Bernie, loved your articulation of the discussion last night. Whether it was actually what happened or not and is relevant is--

(Laughter.)

DR. COX: Because it was extremely helpful. Okay?

Now, I think a way forward by which one could, if there were a moratorium continued, have a process by which you could look at the specific proposals and not have to decide ahead of time whether you wanted to go in favor of the presumption of no harm or in favor of, you know, the presumption of harm, you could look at each individual proposal and see how it came out.

DR. EMANUEL: David, what do you mean by "proposal?" Can you just flesh it out?

DR. COX: Yes. So-- And I say this as a scientist not a philosopher. But I think that these things can easily-- They have to work together.

So, in the scientific community, what happens is you have something called peer review. And so scientists, in conjunction with non-scientists, would get together and have a proposal that would involve something involving nuclear transplantation.

And the scientific community would look at that--a panel much like ours not dealing with the ethics-- but saying, "What is the scientific merit of this in terms of outcomes, in terms of experimental design, in terms of probably of something meaningful?"

Once that had been adjudicated, then a panel dealing with the kind of issues that we are talking about--the ethical issues--can say, "Well, the scientists say that this has scientific merit." All right. In fact, I would do it that way because there are all sorts of things that the scientists would say don't have scientific merit and if they are put forward--because if they do--we don't want to consider them.

But if you had that set of things, just because it has scientific merit certainly doesn't mean that that means it should be done.

But then one could have a group of people sitting around discussing the kinds of things that we are now, in terms of potential harms and potential benefits, and say, "In this context of something that the scientists say has scientific merit, how would we adjudicate these potential harms and benefits?" And there could be 10 or 20 different sets of venues and you could see, with each one, how it comes out.

But I think to have a pronouncement overall how it would come out, I just don't see how-- It is very situational to me.

And I don't know that at the end of the day maybe they all will come out on one side or the other, but without that process I would be very uncomfortable trying to hypothesize.

DR. SHAPIRO: Okay. Zeke?

DR. EMANUEL: I just wanted to make a few quick points, some of them really echoing what has been said.

The presentation we got in Dan's paper were framed in a sort of, first consider the rights, then consider the benefits and harms, pro and con.

And I, for one, have found that a little lacking, not because it is not clear and precise but because what I have begun to express to myself is a sort of moral value scale. It is not clear to me--and this echoes I think what Alex said--that everything can be characterized either as a right or a harm.

Now, in our society we have gotten very much so that in public discourse it is either a right or it is a harm or benefit, and it seems to me much of what the cloning issue does is suggest that not every consideration, either pro or con, can be well captured as a right, in the language of rights, or in the language of benefits and harms.

And I am not sure that framework, as elegant as it is, as traditional in the analytic philosophy world as it is, is the correct one.

And part of what I think we are struggling with is that our ability in the public to express values has been significantly reduced by only using those kinds of values. And part of what I think our challenge is, is to express values that matter that may not be easily captured in this way.

So this is my statement about the fact that I think we are confronting this moral value scale. The ability to express our values in a publicly coherent way.

PROF. CHARO: Can you give me an example just so I can really understand what you are saying?

DR. EMANUEL: Well, it is a bit circular because whether-- I mean, part of the ruckus last night is whether things that we might characterize this way can be put into the social values or social harms.

But the issue, for example, of family relations and disrupting or, in a more neutral language that Dan Brock preferred, changing the conception of family relations so that it is not clear. You can't clearly say who is a father anymore, or who is the father.

Now, is that best understood as a social harm, a potential social harm? Is it best understood as a different kind of value, the value of integrity related to parental and family roles?

I, for one, you know--to put my cards on the table--I don't think it is captured as a social harm. I don't think it is coherent, it gets to the nature of the value to characterize it that way.

The second point, and I think this is somewhat controversial--and all of these are going to be controversial--is that it is unclear to me that we can have a neutral framework here and a neutral starting point.

Whatever the presumption is, whether the burden of proof is on the pro, that they have to have a compelling reason to go forward, or the burden of proof is on the negative that--those who are against cloning--that they have to show why there is significant harms, in the language we have just been using, we are not going to have a neutral starting point.

We are going to-- That presumption already is going to push us one way or another. And I think it is very clear for us to recognize that because I think the guise of neutrality here is not one we are going to be able to hold to.

The third point. It seems to me a lot depends upon our understanding of reproductive rights and whether there is a right to reproduction that includes cloning. And here is why I say that.

One of the conclusions I came to at the end of the discussion last night is that, if you believe that cloning falls under the moral notion of a right to

reproduction, that seems to me to say that the burden of proof is on those who want to restrict it. They must show substantial harms. And that that is going to be very hard to overcome someone's right.

If, on the other hand, you think that reproduction by cloning is substantially, qualitatively, essentially--whatever word you want to use--different and that it doesn't normally fall under the rubric of a right to reproduction, that seems to me to suggest you go the other way; that the presumption is negative until-- That at least you don't have a strong rights-based claim and that the presumption is probably more conservative.

In any case, I think everyone at the meeting, and I would welcome people who disagree with this summary, suggested that the right to reproduction by cloning, if it exists, is not unlimited, and that it is going to have a lot of constraints to it, so that it is slightly different than other rights, or other ways of conceiving of that right.

PROF. CHARO: (Inaudible.)

DR. EMANUEL: What?

PROF. CHARO: Nothing.

DR. EMANUEL: Sorry.

And the last thing which, in some ways, circles back to the top, again I think it became quite clear to me that a lot of the--and it was a very lively and I thought certainly informative, to me, discussion of people who, you know, deeply disagree--a lot of it depends upon one's I guess world outlook, as it were; that really how much you weigh, or whether you consider things harms, how much you weigh these other values depends a lot about how one understands one's self and the world going.

And it seems to me we may come up against significant

disagreement because, even with 18 very reasonable people entering into a very open discussion, it is hard to-- We don't all have that same kind of perspective.

All of this was simply on the issue of implanting. We never got beyond the issue of implanting cloned embryos. We never got to the issue of research. And there may, in fact, be much more agreement on our committee, and I certainly had the sense there probably was a lot more agreement.

DR. SHAPIRO: Thank you. Diane?

DR. SCOTT-JONES: My question comes actually from Zeke's comments.

But back to what David said. David, you gave a very nice description of the peer review process, and it seems that you are asserting that the scientific community exerts control over itself through the peer review process and it seems that that, in an ideal sense, is what happens.

It seems though that that process is more systematic in the case of publicly funded research, but that in privately funded research the peer review process might fall far short of your very nice description of it. And I just wonder if you could comment on that? Do you see the peer review process as acting as it should throughout the wide variety of research funded by various sponsors?

DR. COX: So my point about bringing up peer review was sort of like, you know, using something to kill cockroaches, you know? You can get rid of most of them, which would be the non-scientific stuff, but there is always a roach around--

(Laughter.)

DR. COX: --so that you have got to keep always vigilant if you don't want to have any bugs in your kitchen.

And I think that for a commission that would really be looking at the

ethical stuff, what it would do is it wouldn't mean that some things wouldn't slip through that wouldn't be, you know, of high scientific merit, but at least most of the review would be of things that would be of higher scientific merit than if you looked at the whole kit and caboodle.

And so nothing is perfect and that is why peer review by itself isn't sufficient. When you look at how grants work at the National Institutes of Health, it is that there is the peer review system and then there is something called the advisory council of the different institutes, which basically gets the last roach, you know. So I think that you need checks and balances and different levels of doing it. Okay? I--

DR. SCOTT-JONES: May I comment?

DR. COX: I quite agree that, outside of federally funded work, that there is less of a structure of peer review and that we could pay some attention to that, but using it as a model-- As much as scientists complain about peer review, in many ways it is a real savior for the field.

DR. SCOTT-JONES: Okay. David, I am glad you got around to answering my question at the very end. Your example of roaches I guess was very cute and clever, but I would like you to state your answer to the question.

Is the peer review process different under different conditions of sponsorship, public or private, and you are saying, in the end, that it is?

DR. COX: Yes.

DR. SCOTT-JONES: Okay.

DR. COX: However, what I don't know is that the quality of the process is significantly different. Okay?

DR. SCOTT-JONES: Okay. You are saying, in your judgement, it is not?

DR. COX: No. I would not-- Let us be crystal clear. All right?

DR. SCOTT-JONES: Okay.

DR. COX: Is research that is carried on outside the aegis of the National Institutes of Health and federal funding have less adequate peer review--adequate review, scientific review--than work done in the NIH and under federal funding? And I am not sure that I would say that that is the case.

It is less of a clear structure. All right? But I am not sure that necessarily means that no one is minding the store outside of the NIH.

DR. SCOTT-JONES: Okay. Just in the interest of being crystal clear, and I don't want to belabor this point, you are saying that it is not substantially different from NIH to other sources. But are you saying that it is good and as it should be in both instances?

DR. COX: It can be better in both instances.

DR. SCOTT-JONES: Okay.

DR. SHAPIRO: And I understood David to say that you want it to be better in both instances and that he was unsure, not as certain--

DR. COX: That is correct.

DR. SHAPIRO: --in the privately funded research as he is in the publicly funded. That is what I understood you to say.

DR. COX: Thank you for clarifying my thoughts.

DR. SCOTT-JONES: Thanks.

DR. COX: That is exactly what I meant.

DR. SHAPIRO: I hope I didn't--

DR. COX: Roaches aside.

(Laughter.)

DR. SHAPIRO: I can just see a new stamp being developed at the NIH, "Roach."

(Laughter.)

DR. SHAPIRO: David, you had your hand up before. Is there another point that you wanted to make?

DR. COX: Yes. I just wanted to ask Zeke.

I heard you loud and clear, but in the context of specific proposals how, in your framework, would you see this context of specific proposals, people bringing things to you to adjudicate? Because what you are basically saying is we can't be neutral--right?--and so, if we can't be neutral, then would you suggest that we consider it in a situational case, or that we just simply come down one way or another?

DR. EMANUEL: Well, I guess I am still a little vague on the proposals, whether the proposals refer to, in my mind, and the people who have thought about this more--you and Carol and others. One issue is whether we let it go ahead with animals, whether we let it go ahead-- cloning--with humans for the purposes of research, and then the question of implanting.

The first two we didn't even get to in our meeting, and I have my own views and I don't think actually-- I think there may be funny problems with it. But, again, my speculation is that there is going to be less disagreement on that.

When we get to the-- The problem is when we get to implanting, and do you mean there is one proposal on implanting, or multiple proposals on implanting?

DR. COX: No. I think that-- I-- So here is, if I may, here is how I envision this just personally. Okay? And it is sort of a priority kind of thing.

I can't consider the issue of implanting before I have certain facts and other things that are before me. All right? And personally that requires animal work to get some of those answers, so some of those answers would be what are the physical harms to an embryo, the risks? Okay? Basically, if I implanted a cloned

embryo, that that embryo wouldn't come out with significant developmental defects. Okay? I can't adjudicate one way or another unless I have some facts about that. Now, I want to make real clear that is not an ethical statement; that is a fact-based statement. But I use those kinds of facts to come to ethical conclusions.

DR. EMANUEL: Okay. I think I understand now. In the run-down, for example, that Dan did for us of harms and benefits, there is clearly a place for the issue of, you know, the potential harm that might arise as a result of implanting, if it goes awry, et cetera.

One of the questions you have to ask before is, say that harm is high and say that harm is low, is it going to weigh the argument in any case? And it may turn out that it, you know, whether it is high or low, it actually has no bearing because other values turn out to be more important.

I mean, it would seem to me that if you had a right for reproduction, this harm would have to be very high to override that right because we know that there are going to be some risks with it. It is not going to be zero. But as, you know, because a right is very important you have to sort of jack up the harm a little to override that right.

On the other hand, if you decide there is no right and there is some other compelling harm which doesn't depend upon the risks, as it were in a scientific manner but might depend upon your sort of understanding of social processes, you might say, "Well, even if that harm to a particular embryo, or to embryos, was low, you still might want to prohibit it because you think these other harms are more important."

DR. COX: Absolutely.

DR. EMANUEL: So in that way it depends. I mean, I think everyone has agreed it depends somewhat on the weighing of these different values

and the sort of weights you give to those values, or the likelihood, or their impact. It is going to be open to judgement and that may depend upon the situation.

On the other hand, it may not depend upon the situation.

DR. COX: But I guess--and this will be my final point on this--is that what I am seeing is that these pieces of factual information simply narrow the scope of the theoretical possibilities. Okay?

I view it sort of like it is a space. Okay. And it is quite a large space right now we are all dealing with here. But by using some very concrete facts, it narrows the space that we have to consider, and to me that makes it easier to deal with. That is all I am saying.

DR. EMANUEL: I guess I-- Sorry for going on this long.

DR. SHAPIRO: There is a lot of people who want to talk so let us--

DR. EMANUEL: Sorry.

DR. SHAPIRO: Go ahead.

DR. EMANUEL: No.

DR. SHAPIRO: I mean, go ahead.

DR. EMANUEL: I mean, it seems to me we should take the best-case scenario and the strongest-case scenario and see if we can come to agreement on that one. That would be my suggestion.

I am sorry for going on so long.

DR. SHAPIRO: That is okay. Eric?

DR. CASSELL: Well, I don't want to revisit the heat of last night, but in fact as we did argue, the argument was--the fact of the argument was--as important as the individual positions.

In other words, what Zeke said before is that I came to realize that my believing this thing is a harm or a benefit in part comes from my overall viewpoint

about my structure of values--I would put it in my terms--the whole structure of values in fact. And there is no value set for a whole bunch of values put together, and that is the way the population--to pick it up from what Alta said before--that is, in fact, the way it goes out of the world.

The view of whether there is a harm or a benefit, or a good or a bad, or nice or a not-nice, comes from the whole structure of values of the individuals out there. And we just have to concede that there are multiple such sets, and that we have to accept that is the given. And then we start from there. There isn't one answer to this.

DR. SHAPIRO: Alex?

PROF. CAPRON: I think the exchange that David began by his first intervention is very productive of our thinking of the link between this ethics discussion and our later policy legal discussion, and I want to try to draw out an aspect of it I don't think has been fully identified. Actually there are perhaps two aspects.

One, it seems to me that, in response to Diane's concerns, I would add another layer, which is not just private funding of research but privately funded clinical activities, many of them funded by patient dollars.

And I think there we have every indication. If we contrast what happened in the recombinant DNA area, where there has been a very orderly process which has had many of the characteristics that David describes, you have local processes within departments and also within the study sections at NIH that are deciding about the scientific merits of research, and then you have those that survive that process coming before the Recombinant DNA Advisory Committee. And there have been, you know, complaints and problems with that committee perhaps, but that is the process that is close to that.

And you contrast that with what has happened in the *in vitro* field

where the clinical application has moved privately out there and there is really no knowledge about a lot of what happens. There are professional societies and they have established standards. There is no indications that the standards have been very well adhered to by many of those private clinics, et cetera, et cetera. And that really is a way of our framing, or speaking, about this.

Obviously cases, as it were, individual protocols and their merits and whether or not they deserve to go ahead, both on scientific and on ethical grounds, makes a lot of sense when you are talking about research protocols.

But the question then is, if your general stands in your second response, which is I don't know enough yet to make a blanket judgement about a lot of this stuff, it makes sense if we were only talking about research, and there the kind of notion, well we have a moratorium on the clinical stuff because it is simply too premature, would be fine if we thought it was going to be a moratorium that was obeyed just because it was a voluntary moratorium.

And I have heard from people who have gone out and talked to clinics that now do *in vitro* work, that many of them feel themselves very interested in, have patients who would be interested in, and are more or less just waiting to learn the techniques, and if they think the techniques are not that difficult, to apply them in some of these places who are fairly sophisticated scientifically.

So then the question would arise, what then is the role of "cases" if you are dealing clinically? And this is where it loops back to the ethics discussion because we talked about thinking about the cases, the prototypical cases that would be made. You want to clone to recreate yourself. You want to clone to use an exemplary genetic models, or the sort of positive eugenics view. You want to clone to replace a child. I mean, all these different reasons.

And the question, in my mind at least, about thinking about those,

was are any of those so persuasive, if you were operating in the mode of you need a really good reason to say if this should ever go forward clinically, that you have enough of a reason to say yes, that burden has been met?

But I wasn't thinking that you would then assume that individual cases would come before some review panel and this parent would say, "We really have found a wonderful exemplary model that is better than our own genes and we want to use it," or "Our loss of our child has really grieved us and we should be able to reproduce this way," and someone else would be told no.

That is a separate judgement as to whether or not you would ever want a technique that, a policy technique, that required making judgements on the merits of individual people's reasons.

You are shaking your head no, and I would shake my head no, too.

DR. COX: Absolutely not. The Supreme Court, not local.

PROF. CAPRON: Right. But it is not just that it is the Supreme Court, or local, or whatever, it is that it seems to me that, if you get to the point of saying that there are good enough reasons that people should be able to use this technique, you then more or less are in a posture, it seems to me, of saying, as to the clinical uses as opposed to the research, it is then carte blanche. That is to say people, for one reason, you are talking about motivations that people would have, and if I discovered that the motivation that is persuasive is I say I want to give my child the best start in life and so I want to do it for that reason. It has nothing to do with vanity. It has nothing to do with this or that. Then I will say that is the reason. I mean, it becomes absurd.

So I think, on the clinical side, it becomes very hard for me to imagine a regime that didn't have worst effects by having anyone sit in judgement on people's reasons and it really is kind of-- There is a line, when you cross the line, then

you stop asking individuals.

Now I may be persuaded that that is not right, through the discussions, but I begin by thinking that your discussion of some sorting out the good cases and the bad cases may apply to research, but I don't think it is going to apply after that.

And Bette in particular, in our policy discussion, was pushing towards can we develop some regulatory mechanism? And I think you will hear about it; that we think that is one option to think about vis-a-vis the research side. But when you get to clinical it becomes much harder.

DR. SHAPIRO: Thank you. Bernie?

DR. LO: Well, actually, this works out well. I want to follow-up on Alex's view and sort of actually suggest a different position though.

One of the things that is very clear, if you accept the model of reproductive rights, is that people really don't have to provide reasons that are convincing to others. We say it is a private decision as long as, you know, the parents, the procreators, are doing what they think is best, however misguided or foolish other people may seem. We are not going to examine it; we are not going question it.

And I think it is exactly what Alex described; the sense that if you allow the cloning of human beings, then you should not inquire into the reasons why any particular person or couple wants to utilize the technique, first of all because it intrudes on their privacy and, secondly, it is a game; that people will learn what they have to say and they will just say it, and it is sort of demeaning to put everyone through that.

On the other hand, I think most of us would say, of all the conceivable reasons for cloning a human being, whether or not you think they are all acceptable or none are acceptable, some seem more acceptable to others. And to sort

of lose control over the notion that there may be some instances where more people may find it acceptable and some where almost no one finds it acceptable and to say that is out of our hands from a policy point of view is troubling. I think some people would use that very sort of slippery slope. If you start to allow from the most compelling cases, you are going to have a lot of gall to say then we can't do it at all.

So I think that we need to sort of sort it through, it seems to me, this time-honored tenet in sort of reproductive ethics that we don't look at peoples' motives in a public policy arena, although as individuals. And I would actually suggest more and more, as a clinician, I do start to encourage people to look more at their motives and to--and reasons, maybe motives is the wrong word--and to counsel the motives. So I think this whole idea of sort of non-directive genetic counseling I am not sure holds any more.

That I have someone come in my office and say, "I'm interested in having the test for BRCA-1 and -2 done," I don't just say, "Well, you know, I will lay them out, pro and con; you know, it is up to you to decide." I sort of say, "Do you really understand what the long-term risks are in terms of your insurability, employability, and have you have really thought what it would mean if you want to test your, you know, your eight-year-old daughter." And to try to push them beyond what--

And to give a recommendation, as well. I think one of the things people learn from HIV counseling is you make recommendations. You don't just do what I call the Chinese menu approach where you can either choose A or B.

So I think we may want to look again at this sort of neutrality of reason in reproductive decisions.

DR. SHAPIRO: Okay. We have quite a few members who want to speak. Let me go to Diane next.

DR. SCOTT-JONES: Okay. The question that I wanted to ask when I first raised my hand is actually a question of Bernie, and Bernie it is in response to your presentation.

I was struck by your assertion of the right to reproductive liberty. You asserted it quite strongly and competently without any sense of ambivalence about it. And I would just like to ask some questions about it because I have been struggling to try to understand the discussion in your group and to try to place it in the context of the other reading that I have been doing in preparation for this.

In thinking about the right to reproductive liberty, it seems to me, as a developmental psychologist, that that right is automatically limited in the context of a relationship; that is, between a man and woman the right to reproductive liberty is automatically limited and it is one that creates conflict in marital relations when one partner or the other wants to reproduce and the other doesn't. So it seems to me that this notion of the right to reproductive liberty as an unassailable right isn't one that holds. It also doesn't hold in our social policy.

For example, in Welfare Reform, there is the notion that certain persons who are without resources should not be reproducing; that they are doing something wrong in reproducing.

So I am just wanting to understand this idea that the right to reproductive liberty is an individual right because it doesn't seem to me that it is a right. Unless we go to asexual reproduction, it isn't a right that exists within an individual without consideration for a relationship, and it isn't a right throughout our society that is acknowledged in our social policies.

DR. LO: I am probably not the best person to answer because I personally am not a strong proponent of any right, of any very broad right, to reproductive liberty. I think there are others who may have.

But it seems to me one response to what you have said is that, in fact, when you look at the right as it is currently practiced, it is not restricted to couples in a relationship, or even marriage.

I mean, many would like to say it should be that way, but there is nothing that prevents me as an individual person from going out and paying a woman for her egg and paying her--another woman--for gestational service and making it extremely contractual, depersonal, and with no sort of ongoing interaction between us other than sort of literally a contract that I will try and enforce.

And certainly there are lesbian woman who say that, you know, they are forced to have sperm from someone and then they don't-- They would prefer not to be able to-- They would like to be able to reproduce without that, and they may want-- Some may want actually a very, you know, ongoing relationship with the sperm donor; others may not. So that I think that if, I believe, if we are going to allow reproductive liberty for people who are not in either a formal marriage or an ongoing committed relationship--we will call it--it does seem, at least in those cases, to be an individual right.

I think your suggestion that the right to liberty really occurs within sort of a context of an ongoing relationship with another person, who shares in the sort of not just the genetic participation but ideally in something further, starts to get I think to some issues Zeke was talking about.

DR. SCOTT-JONES: Okay. Maybe I didn't ask the question well. I simply want us to recognize that the assertion of the right to reproductive liberty isn't uncomplicated. It isn't simply, in all instances in our society in which it would be played out, it isn't simply a matter of the individual's choice to reproduce. It isn't simply in all cases going to be recognized as an individual right.

DR. LO: I actually personally share your concerns.

But I just want to say if you look at sort of what John Robertson was saying or Macklin, that they say-- If you give John Robertson the germ of a right to procreative liberty, it is going to end up saying, you know, you have, you know, there is no justification for banning, prohibiting, regulating cloning any more than other ARTs. So I just think if you start there, it tends to go in a certain direction.

DR. SHAPIRO: Bette?

MS. KRAMER: I would like to go back to the interchange between Diane and David on peer review in the private sector.

One of the issues, a private conversation yesterday in the law and policy bucket, was, as Alex has pointed out, about what has taken place in the clinical setting and in the private setting once federal funding for human embryo research--excuse me--for the *in vitro* program was concluded.

I gathered--nobody said it straight out so maybe I am under a false illusion--I gathered that there was no peer review for research in the private sector, so if I am wrong, please correct me, and would you explain to me how it does work? Perhaps my confusion is between research in the private sector and then clinical in the clinical setting, but could you please amplify that?

DR. COX: Yes. So-- And actually Steve is probably in a better position to do this than I, but I will make an attempt at this.

So it is a different structure of peer review, but in-- We are talking about the private sector. Okay? I simplify that by meaning "companies." All right? So we are talking about a company, in the sense that they are providing a product, a clinical product. How do companies deal with the scientific merits of what they are doing? Almost all companies that have this kind of clinical stuff have a scientific advisory board. The scientific advisory board is made up of independent experts who aren't like company hacks. I mean, they come in. They are paid by the company to

basically give independent scientific advice.

Now, whether the company pays any attention to that scientific advice I think is the point that we are discussing here, but it is not that they don't get independent scientific advice. All right?

But I would be very interested in what Steve has to say.

DR. SHAPIRO: Steve, do you want to speak to that issue?

MR. HOLTZMAN: Well, I think it is very important to get into the distinctions between, if we are talking about basic research and then clinical research, and do you mean clinical work such as performed by the kind of clinics that Alex is talking about, which are not subject to FDA regulations, versus if you are talking about clinical research on the development of a product which would be subject to FDA. And I was struck, Alex, when you wanted to make that distinction.

What I was thinking of was germ-line gene therapy which would be a clinical procedure and would be subject to review under current--

PROF. CAPRON: Whoa.

MR. HOLTZMAN: Well, actually by the FDA.

PROF. CAPRON: Yes. Of course, the stance of the review process is that it doesn't yet. It isn't willing to "entertain" such proposals but, yes, in theory.

MR. HOLTZMAN: Right. That won't work. For that matter somatic gene, somatic gene therapy is subject to review. You do have to go to the FDA so, in the sense of peer review--

PROF. CAPRON: Correct.

DR. HOLTZMAN: --under IRB regulations, so that I--

It depends on what your paradigm is. I was struck by your policy point that, if we think of reproductive freedom--right?--that no one wants to get into interrogating the motives of the individual, though we could all sit here as human

beings and say there is a big difference between choosing to abort because it is a female versus other reasons. All right?

Well, in the case of somatic gene therapy, I think there would be a big difference between going in and saying, "I am delivering a gene for this therapeutic good with an intent" versus, "I am delivering this gene to change eye color." And that would be a pertinent aspect of the review as probably construed either by RAC or FDA.

PROF. CAPRON: I suppose the contrast is the contrast between what is really clinical research in the sense that the technique is novel, but it is being tried out in human beings who come forward as "patients." They are infertile couples or whatever.

MR. HOLTZMAN: Right.

PROF. CAPRON: And that notion of private, where it is just a clinic and it doesn't have the scientific review process, and it doesn't have much visibility, versus the sorts of uses there.

But even with that one, Steve--the example you give--if we got to the point that gene therapy were a technique that did not involve risk to others, or maybe unusual risk to the patient within the range of medical procedures, I don't imagine that at that point someone would be in a position to say, "Well, your reason for wanting to have blue eyes versus somebody else's reason for wanting to have blue eyes is a good enough reason."

I mean, once things move into the practice arena, for all sorts of reasons that Steve alluded to, we don't--or I guess Bernie alluded to, rather--we don't start judging the individual cases very much. It is more where there is a harm to others' rights that we find ourselves doing that.

DR. SHAPIRO: Okay. Let me turn to some other commissioners

who want to speak.

And let me also warn Bernie, before we complete this round, I would like to turn back to the ethics bucket and see--hear--something about plans going forward so that will come. You have at least a few minutes to think about that.

DR. LO: Keep talking.

(Laughter.)

DR. SHAPIRO: Who wrote that magic pad you had there a few minutes ago that gives you all these hints?

Larry?

DR. MIIKE: Is this mike thing on? I don't know if this thing is on.

In these discussions I often get confused between intellectual ethics discussions and applied ethics discussions.

I want to return back to the religious side, since we spent so much on that and we seem to have just sort of cursorily gone over it.

Maybe what I would like to say just simply refers to what other people said about it. When I listen to religious scholars, and in thinking about this I was doing two things.

One was what do they have in common? And I think the generational aspects of it. I think maybe that is one we are talking about, trying to secularize a particular religious point of view. So it is clear to me what, at least the major things, are that they have in common.

The other side about the issue about the ones that say to us, "This is my belief and you insult me if you even begin to question about how we can translate that," well, you know, this of course is a two-way street. But in order to respect that point of view what I then translate that to mean, in the practical terms, is that, "Okay, if that is your belief, where do you draw the line in terms of what is a human being

and what is allowable, if at all, on your religious perspective in this spectrum; that we go from, you know, separated cells, and what is a human being, when does that--"

I heard some talk about when the soul possesses the body, or conscienceless possessing, and those are the kinds of practical points of view that I would be looking at from a religious perspective.

We are not going to satisfy everybody, but I think that I would feel comfortable if I can get clear, from a religious perspective, about do they have a line that-- Do they have a line at all that they can draw, and how does that fit our applications?

And then the second point I would like to make is totally different, which is that, in our discussions, and I think we would all agree that once the science is out of the bag, somebody is going to do it no matter what we try to do, or if our conclusion was to prohibit entirely-- Sorry. If the whole world's conclusion was to prohibit entirely, we would still see it going on.

So perhaps there is some time in the ethical discussions later on that says what is the ethics of the cat out of the bag, and how do we deal with that?

And so I think that in terms of our deliberations, I would like to spend a whole lot of time on a regulatory model because, if we have the cat out of the bag and if we, as public policy makers, are addressing the issue about how to minimize harm in that area, then I think we have got to really deal with the regulatory issue.

DR. SHAPIRO: Thank you. Jim?

DR. CHILDRESS: I very much appreciate Zeke's comments this morning. They helped me become a lot clearer about his position as we discussed it last night, though I am not sure I am more convinced today.

But I would like to make two or three observations that may help

sharpen our discussion for later.

First, I very much like what you did this morning in terms of saying, "rights, benefits, harms," and then let us call that other area something like "expressing social values," or "symbolic policies" that indicate that some things are very important, even though we can't reduce them to any of the other categories.

But then it seems to me the hard task of interpretation, and much of what we are doing in this is trying to interpret our society's convictions as expressed in law, policy and the like, for purposes of doing an analysis that can then be a basis for policy. And I guess we would still face a difficult question there of trying to determine what kinds of social values are expressed in our various policies.

I think Diane Scott-Jones is right that this is often very complicated to try to determine what, in a particular society, for instance, how are we to understand reproductive rights. So I see this as an important part of our process, and so I thank you for your contribution to that.

But, secondly, you commented that it was unclear whether we could have a neutral framework as a starting point. I guess I have felt all along that to set the discussion up in terms of how we set presumptions is already to assume that there is no neutral framework; that everything really hinges on setting the presumption, and so it requires an argument about why we start somewhere rather than somewhere else.

And so it seems to me that the critical question then, again, is a matter of our interpretive enterprise of trying to understand what our society is about, what values are important, and so forth. We have to try to figure out a way to think about setting presumptions. And do we start from reproductive rights or do we start somewhere else?

And it seems to me then part of the argument about presenting different kinds of cases is really to try to determine whether human cloning is

relevantly similar to, or substantially different from. What else goes on under a heading like reproductive action or reproductive liberty?

And that again is a very complex interpretative debate, but it seems to me important ground--to pick up something that David Cox said--not only to present cases in terms of scenarios about individual actions, but also to present various kinds of policy options, and to think about the implications of the kinds of options that Bernie mentioned in his remarks.

So there, in effect, are the kind of material we will be working with when we try to think about the implications of different approaches to rights, harms, benefits, and this last area of social values.

DR. EMANUEL: Can I just ask one question?

DR. SHAPIRO: Yes, sure.

DR. EMANUEL: Sorry for jumping in.

But, Jim, I have been, over the last 12 hours, I guess, perplexed by this idea of what people mean by is it going to be qualitatively different, essentially different, somehow different enough from what has gone before?

It seems to me no one has articulated what that criteria of qualitatively different would be, and I would urge, or say further, whatever those criteria are, they are already going to presume your answer to the question. I don't think there are some independent criteria there. You know?

Because the basic description of asexual reproduction versus reproduction requiring contributions from two people suggest to me some qualitative difference. On the other hand, you know, John Robertson said, "It don't look any different to me." So, I mean, it seems to me you are not-- There is not-- There is going to be no independent criteria there for qualitatively different, which is why I put forward the argument I don't believe we are going to have a neutral framework.

DR. CHILDRESS: Right.

DR. SHAPIRO: Jim?

DR. CHILDRESS: The question is showing the quantitative difference. The issue is, is this a morally relevant difference? And that then reflects the problem of interpreting values. I am admitting that is a complex interpretive process.

DR. SHAPIRO: Thank you. Alta, you had your hand up before. Do you--

PROF. CHARO: Yes. Actually it is exactly on this point, or related to it so--

I feel like--

DR. SHAPIRO: Use your mike.

(Laughter.)

DR. SHAPIRO: Even for you, Alta.

PROF. CHARO: I feel like we might here have limited ourselves unduly by confusing the discussions of reproductive rights that take place in the literature and thinking based around ethics and morality, and the discussions of reproductive rights that are grounded in U.S. Constitutional law.

And I feel like I am hearing the two being used interchangeably. They should be kept separate because our freedom of action in the area of morality is often much greater than it is in the area of law.

To use a concrete example, I think that often these kiss and tell books in which you excoriate your parents, particularly if you are a Hollywood celebrity, in my view are immoral, but they are certainly protected under the U.S. Constitution.

Law will often permit people to engage in actions that are clearly

immoral for reasons that have nothing to do with the proving of the behavior itself, but have to do with the, you know, corollary problems of trying to regulate that behavior and, you know, more problems come from trying to regulate speech than are worth overcoming this one, immoral form of speech in which you take your mother to task because you are a neurotic kid of a celebrity.

Now, take this into the reproductive rights area and I think you can see very clearly that the discussions here about whether reproduction is an unrestrained right, ought to be an unrestrained right, et cetera, sounds very different in the land of morality and ethics than it does in the land of Constitutional law.

And so we have the privilege of determining, as individuals, or as groups, that something is an immoral exercise of one's ability to reproduce even though we do not have the capability, under U.S. law, to actually forbid it with the whole apparatus of the state behind that.

I have no problem telling a cousin of mine that she has absolutely no business having a kid under these circumstances, even though I have no ability to enforce that.

Nonetheless, I think we often turn to the law for guidance, and in our discussions about reproductive rights in the ethics area, out of a kind of enduring confusion in the bioethics field that comes from this intertwining of philosophy and law and medicine, because it is in law that you often find the concert applications of these discussions.

And so I think people look to the law almost-- They should have been looking to the law really as simply the outer limits of what their policy implementation can be, but they have gotten into the habit of looking to it for guidance as to what the discussions ought to be.

And so, for example, when we have been talking about what is

reproduction and whether or not cloning is consistent with our existing notions of reproduction, I think people are likely to look to the legal cases for guidance, and there really is some.

And it turns out, in fact, it is a very complicated thing where the courts have really never clearly identified what they consider reproduction appropriation to be about.

Sometimes it sounds like it is about genetic transmission which, up until now, has always been vertical, but with cloning it can be horizontal, in a sense.

Sometimes it sounds like it is about gestation.

Sometimes it sounds like it is about the opportunity to rear a child. Depending on the cases you look at, you see different aspects of parenting being emphasized in the cases about what is reproduction.

I think those things are valuable for guidance but we should absolutely not let ourselves get limited by them. We have the ability to come to absolutely independent conclusions about what is the essence of reproduction for the purpose of moral and ethical discussions.

Similarly, depending on the role we think of ourselves as having as a bioethics commission, I think we are in the position to be able to both say we think something is a terrible thing to do, maybe get a vote of 18 people based on whatever is recognized; that you think it is a terrible thing to have a child by virtue of cloning at this stage for 18 different reasons.

And, at the same time, when you get to the level of thinking of policy, saying now, "What policies would actually further this ethical viewpoint?" And looking at the policies that are based on, you know, prohibitory models, you might nonetheless find that you can't implement them because there are legal obstacles to them.

Actually you will think, when we get to that point in the discussion, that the contract papers indicate they really are, but there could have been.

And you would be left with a statement that said, "We think it is bad. We would like to prohibit it, but we can't figure out how to get there, so what we are going to do is look for all of the intermediate ways that we can discourage the behavior we think is immoral, even though we can't prohibit it."

And that is where you get all of these efforts that you, Diane, have identified, like, well, we can't stop people from reproducing, but we can create financial incentives and disincentives, et cetera.

But by keeping these things separate, I think it actually makes it a bit more creative, and it binds the discussion, and it gets us out of this trap we are putting ourselves in.

DR. SHAPIRO: Thank you. Tom?

DR. MURRAY: Right. Alta very nicely expressed the distinction between ethical concerns and public policy concerns, and they are inter-related but they aren't-- It is important for us to recognize that they aren't identical things.

Now to the ethical concerns. I think one of the challenges, primary challenges, I think that the commission has is inclusiveness here.

And by inclusiveness, in this context, I mean making sure that whatever the ethical concerns are that we get as full a set of them before us as possible and get their strongest most forceful expression. I think I have said this before, but I am just going to say it again. That, I think, is one of the main challenges.

Some of the things are--some of the ethical concerns--are relatively sort of straightforward and we can identify them and we can critique them and evaluate them and decide how persuasive they are. Others are more difficult to elucidate.

And I take it that part of what--in particular I recall--Zeke and Bernie tried to do this morning was say, "Look, there are some of these things that are difficult to talk about." But that makes sense to make it all the more important to try to talk about them in the clearest manner and most forceful manner of which we are capable.

When you do frame things in terms of sort of rights and harms and leave it there, if I may try to restate what I think--I will put my version in of what exactly Zeke was trying to say--is that that may leave out what we see as damage to, or the undermining of values that deserve consideration in their own right that are not easily represented or reducible to the concern that is expressed by the language of harms.

They can be so translated, but that translation leaves a great deal out that can be really important.

And part of what is really important, and this is problematic in a pluralistic society, is, as Courtney Campbell pointed out in this paper for us, is that much of what is going on here has to do with assumptions about the human good; about what is, what makes the good lives for women, for men and for children. And I think that is part of our challenge.

Now, to renew my--the other--challenge I want to make externally, that is to people not sitting on the commission, particularly those people representing religious perspectives, it is important that you say to us, say to the public in the most accessible way possible, just what your concerns are because, at a minimum, if you fail to do that, you will be missing a great opportunity to enrich public ethical discourse.

At worst, it will either be an expression of dismissiveness on your part, which I take it is inconsistent with the humility all of us should feel, or it is an

expression of a lack of confidence in the position that we can't find a way to express it. And I don't think that is a position we want to have; that you do and ought to be able to express things forcefully.

As a method, I would propose that, in one of our forthcoming meetings, we actually take--this is certainly for the ethics group, or for the Bioethics Commission--we actually take some of the kinds of cases, both some of the most sort of sympathetic and some of the least sympathetic, and we talk in some detail about what it is we find about those cases that is repugnant and what it is we find about those cases that generate sympathy on our part. And I would propose that as something that we ought to do soon.

DR. SHAPIRO: Thank you. Arturo?

DR. BRITO: The emphasis thus far of Bernie and the rest of members, and really everybody who has spoken up, has been on the use of cloning technology as the form of reproduction, and rightfully so because those are the things we need to think about in the future.

One of the distinctions that we made in the law and policy bucket was looking at the legalities and the policies of the use of cloning technology, not necessarily for reproduction but for research purposes, possibly as a process for reproductive technology, but also for genetic diseases, cures, et cetera.

Was there any discussion yesterday in this regard, and what were the viewpoints there, and were they any different? And I realize, and it is important I think we all realize, that this is going to touch upon a lot of the problems with both conflicts that the Embryo Research Panel reached.

And I just want to say that I think we have to keep in mind that obviously we are looking at this in the future to see when human cloning becomes a reality--you know, we are trying to look at this far ahead of time--but it is a process

and it doesn't exist right now, so I think we also need to address this process of looking at the technology or the research into cloning first, so I would like some comments on that.

DR. LO: No. I think your comments are right on target. We didn't get to talk about that last night, but it is going to be one of the things on our agenda, what we need to do, which I agree totally that is crucial we look at those issues.

DR. SHAPIRO: Zeke?

DR. BRITO: Oh, I'm sorry.

DR. SHAPIRO: I'm sorry.

DR. BRITO: Also another sort of side, too, because I think-- But just a comment on-- Initially, when you talked about the--

You said, if I heard you correctly, Bernie, harms of potential uses of cloning. I think you meant potential harms of cloning. And I think it is important to make the distinctions.

I don't know if you are reflecting some personal feelings there in a subtle way or not, but then you went on to say the "undermining orderly sequence of generations," et cetera. I understand you mean that as a potential harm, but when we use language we want to say-- I think we have to be real careful, and I think Zeke touched on this a little bit. What we are talking about a potential harm would be is a change in orderly sequence, right? So, okay.

DR. LO: I stand amended.

DR. BRITO: That is what you meant?

DR. LO: Correct.

DR. SHAPIRO: Bernie, just to ask another question of my own with respect to the first part of Arturo's question. I guess it has come up before.

I guess it was a third of your points, or categories, that you started

off with. It had to do with cloning issues that occurred in cells, and so on, well in advance, or before in some sense, of cloning of humans. That you were going to look at that but didn't get to it last night, as I understood your comment. Is that correct?

DR. LO: Well, I guess it is best that we didn't look at it last night. I think we need to look at it. I hope that cloning of cell lines, you know, particularly non-human ones, will I guess-- It is now being done--

DR. SHAPIRO: Sure.

DR. LO: --so that I think hopefully the cloning of DNA probes in non-human cell lines, I hope, is something we can deal with.

DR. SHAPIRO: Yes. And that may come up again later on this morning when we deal with the science section, in any case.

Steve, I am not sure, did you have your hand up?

MR. HOLTZMAN: I was just going to weigh in on the side of Zeke and Tom, but I don't know if that is necessary so--

DR. SHAPIRO: Well, now is your chance.

(Laughter.)

MR. HOLTZMAN: I found myself sitting here and thinking about what if we were talking about cannibalism and would be-- And what would be the--

PROF. CAPRON: Talking about what?

MR. HOLTZMAN: Cannibalism.

PROF. CAPRON: Oh.

DR. CASSELL: It is only 9:15.

(Laughter.)

DR. CASSELL: Eric says he wants to take a break. He is getting hungry.

(Laughter.)

MR. HOLTZMAN: I started feeling that talking about rights and harms wouldn't seem to get out what would be the most important issues we were probably try to get at with notions about fundamental practices that help define ourselves regardless of your specific value set.

Now, having said that, the real problem is that who is the "ourselves" that is at stake? These are not merely traditional kinds of practices; they run very, very deep, but you don't want them to get into discussions of human nature. They wouldn't, you know-- Wittgenstein would say it is only conventional, but it is a very deep convention.

And I think that, maybe from a policy perspective, one could think about if we are in a society in which a lot of people, many people, feel that we are talking about a practice that touches that fundamental sense of ourselves--all right?--that that policy has to try to acknowledge that fact. And that maybe gets at a way, in my mind, of the kind of points of trying to elicit the secularization of the religious perspectives.

DR. SHAPIRO: Thank you. Eric?

DR. CASSELL: Well, Steve, there is no question that what you say is correct; that there are certain things that, in being a human, that we just pull away from very quickly. But there are not a lot of them. And you have to be careful.

I mean, it is like the incest taboo. Well, that is universal. You can find it everywhere. You--

It is not true of cannibalism. Cannibalism is found in a number of places. It costs them a fair amount in terms of their viral disease, but that is how God deals with things.

(Laughter.)

MR. HOLTZMAN: Well, I--

DR. CASSELL: So you have-- But you have to be careful about it because, as it appeals to that, you know, it is not long before you are spreading out to one that we all know is true to one, well, my feeling is that human beings never do that. That is the difficulty with that.

MR. HOLTZMAN: And I agree.

PROF. CHARO: And as I said before, incest is not universally disapproved of.

MR. HOLTZMAN: But that is--

DR. CASSELL: I done your sister or brother, actually.

(Laughter.)

MR. : It is a situational argument.

DR. CASSELL: Yes. That is right.

MR. HOLTZMAN: But I don't think-- I mean, that is setting up a false dichotomy with this. It is either absolute or it is situational, as opposed to contextualizing peoples' understanding historically and culturally, and that these things run very deep. All right?

And our culture right now is one in which this issue runs very deep.

DR. CASSELL: It does seem to.

MR. HOLTZMAN: Okay? Yes, there are cultures in which there is cannibalism. Forget the viral arguments for a moment. Okay? And we can think--

I am sitting here and thinking of, you know, the cases people point to of when cloning would be obviously morally you couldn't feel repelled by it, and we think of the lifeboat cases of cannibalism. Even within our culture in which we can get our arms around it, and yet we have a certain policy framework of dealing with it.

So I don't think one-- I mean, it is a tradition in moral discourse to

say you are either absolute or you are situational and we can't-- Cultural relativism. But there is something between.

DR. CASSELL: Could I just respond? I don't want to--into joking--I don't want to take away from the comment that you made, which I think is absolutely true, but there is something about this that struck a nerve in which people said, "Oh, you must absolutely not do it;" scientists said, "You must not do it." And I, I--

Oh, isn't that interesting? Why did they said that? And that is-- Part of all this, that is one of my problems. Why did it make such a fuss? So-- And I haven't actually heard the answer. Why did it strike such a chord?

MR. HOLTZMAN: Maybe because practice is like having children, and our role as parents, our role in relation to children, all of these just are very fine and noble to how we think about ourselves. You can go through a logical process by which you say, "Well, it looks like this practice, it looks like this practice, it looks like this practice."

And then, as Alex said, you add up the arguments and they don't seem to be a problem. It is kind of like the Aretaeus(?) paradox, the problem with the heap--right?. You keep adding grains of sand and there is no one additional grain of sand that turns into a heap, but of course you can get a big pile of sand.

PROF. CHARO: I think there is also, Eric-- Very quickly, I think there has been a synergistic effect here. You not only have all the sensitivities of reproduction; I think you have all the sensitivities about death, because, although it is physically inaccurate, I think there is an emotionally compelling sense out there that by duplication of the body one somehow transcends death, whether it is by bringing back the dead child or by cloning one's self that one lives on after one's own death.

I mean, it is kind of the physicalist manifestation of these emotional views that you live on through your children, but now you really live on through your

children.

I think it is just the synergy of these two very sensitive areas coming together that has really heightened everything.

DR. CASSELL: Whatever, it is something.

(Laughter.)

DR. SCOTT-JONES: There is another--

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: There is another fear that I would like to mention. I don't think it is necessarily a reasonable fear, but I think that is the fear of powerful people being able to create and control people who are not at all powerful; people who are themselves powerless. I think that results from a misunderstanding of the role of genetics in human development, but I think it is a very real fear.

After our last commission meeting, I went home and I watched a videotape of an "X Files" episode where there were individuals created through cloning. They were called drones. And they were workers in an agricultural setting. They never passed childhood. They remained immature their whole lives. They were without language. They were without affect. And they went about working in a mindless kind of way.

I think that is a fear of some people; to create a population of people who would be controlled by the powerful people in our society.

PROF. CAPRON: Well, one--

DR. SHAPIRO: Alex?

PROF. CAPRON: Yes. One comment about this heaping up of things, and so forth, and then the reverse reasoning that goes on.

Leon Kass made a point which we discussed a little bit last night in the ethics group, and that is you may interpret that argument, the John Robertson sort

of argument--this is really very much like *in vitro*, surrogacy, all these other things we do--in two ways.

You may say, "Well, that means that it is very hard to draw a line here." It may also cause you to say, "Well, we really ought to be looking more critically at some of those things which are being cited as the justifications here." That they, by sowing the seeds of a result, if you thought the result was problematic, themselves ought to be reexamined.

That is an even harder thing for this commission to do and I wouldn't know--since we have all been participating in this, we are all in this together--that we have really been talking still about the architecture, about the ways of thinking about it, about what ethical arguments count is that the arguments, about the role of ethical arguments, in legal analysis, or in the commission's work, the difference between having a right to do something and it being the right thing to do and so forth.

But we haven't yet grappled. And maybe your challenge to Bernie a few months ago, to tell us how we are going to do this, is how are we going to get our hands around those ethical arguments themselves and have a discussion as a commission about them?

Because to me, at least going through the law policy bucket yesterday, I came away thinking that the law policy bucket can also give you policy alternatives but which ones of those end up being persuasive is entirely dependent upon the analysis, the ethical analysis. And we have a long way to go on that, because we haven't done it this morning in the last hour and a half.

DR. SHAPIRO: Bernie, let me turn to you not to necessarily to answer that whole question, but if you want to you can, but let us just discuss for a few moments, before we break from this session--this part of the session--what the plans are going forward and, if time allows, I myself have a whole series of questions, but

we may have to wait until later.

DR. LO: I think that is a crucial question, sort of what the ethics bucket can do in the remaining time we have under our charge to really forward this discussion.

We are going to meet April 23rd, and I think before that meeting, and at that meeting, we have a host of important tasks to try and do.

One I think is to try and more clearly articulate the reasons for and against cloning. And we have heard a lot of talk about that. And I particularly want to set the challenge to members of this commission to try and articulate a little more clearly, and a little more forcefully than has been done up until now in the discussion, these kinds of concerns that are not easily expressed in terms of rights, wrongs and harms.

And so I am going to call on some of you on the committee, who have been saying that there are such concerns, to try and articulate that for us, you know, on paper at the next meeting, because I think if we can better articulate those concerns that would be a very, very big service.

The second thing I wanted to do is to do something that I had hoped to do last night but clearly didn't have the time, which was, as several people suggested, discuss actual cases, both cases that seem to present compelling arguments to some for allowing cloning of human beings, and then others in which many people seem to have a strong revulsion, so to try and sort of sort out the reasons why.

I think there are two reasons for that:

One, in examining cases, we may be able to either come up with reasons we haven't thought of or better articulate reasons we are now groping with; and, Secondly--I think this goes back, Alex, to the President's Commission--the perception that sometimes it is possible to get agreement on what to

do in actual cases, even when you can't agree on what the reasons are. And I think that that may be helpful.

The third issue I want to talk about is whether we have sufficient concerns at this point to justify certain policy recommendations and not others.

And in particular I want to examine the question of whether there is enough concern that we would want to recommend a continued moratorium on cloning of human beings, independently of whether it is scientifically appropriate--an ethical moratorium--to be able to sort of have more of a discussion without sort of the heat of it is going to happen by some rogue IVF outfit.

Are there reasons that would justify a continued moratorium that may not be weighty enough to justify either setting presumptions on how policy should be guided or almost a policy itself in terms of regulation or prohibition?

And then finally, fourth, I want to get back to the issue of the ethical concerns regarding research on human cells that involves the cloning of those cells, but stopping short of implantation.

Because I think that that is an area that we haven't talked about yet because the cloning of entire human beings seems so challenging, exciting, disturbing, but there clearly are a lot of very deep and serious ethical objections to even doing research that doesn't need implantation that we need to sort of think about, particularly if that is going to be an important concern for our policy regulation.

In terms of specifics, what I am going to do after this meeting--watch it; I am going to do it at breaks as well--is to try and talk to people, assign some specific tasks, and ask everyone on the committee to sort of do some real work on paper for the meeting in 10 days, I guess it is.

DR. SHAPIRO: Let me just make a few comments that at least occur to me on these issues.

First of all, as I think ahead to our report, whatever its impact, I am hoping it will send a series of public signals that are worth sending that-- Signals the public will want a group of thoughtful people to have a say about these issues, even though there will be issues on which we can't agree, even though there will be issues on which we cannot reach any final agreement, or even any recommendations in some cases.

Nevertheless, the argument and the way we proceed can send out a series of public signals that would, at the very least, carry the day forward in a productive way.

We can't assume that the ethical issues, as troubling and as deep as they are, can in any way be finally resolved--many of them--here, since they have been argued about for centuries and will be argued about for centuries more, many of these, but that shouldn't discourage us. That should not be a discouraging fact; that should be just taken as something which can frame the way we go about it.

It may be helpful, Bernie, as you and your colleagues think about this, to go at it the opposite way around from what I understood.

Paula Georgia(?) was unable to be with you yesterday from what I understood was the nature of the conversation. Obviously the most gripping part of this is the cloning of human beings. That is what caused, you know, the emotional response many people have talked about, and so on.

On the other hand, there is something to be said, or perhaps there is something to be said, for coming about it the other way around; that is, starting with item number three, as I understood you, and working your understanding up, looking as you go about how these ethical issues change from step to step.

It may, for one thing, get a lot of the ground past you; that is, there might be some agreement in the group on many of those issues.

And then, of course, it will not make the other ones any easier, the ultimate ones, but at least we will have accumulated a sense of confidence and understanding and perhaps even a vocabulary that is helpful in dealing with the bigger issue.

It is just a suggestion. Perhaps you and your colleagues could think about. It might be helpful.

DR. LO: If I could clarify, do you mean step to step in terms of research versus research, preimplantation versus attempted cloning, or do you mean step by step in terms of recommendations about a moratorium versus recognition?

DR. SHAPIRO: I meant the former as the first way of going about it.

We have said, very quickly here, many times--that is, when I say "we," not we as a commission, but as I have heard individuals talk--that there is widespread agreement on, for example, what we might do with animal models. If that is true, it is useful to think that through and why, and why, as you go ahead, there are new ethical issues that come up on the horizon and how you might deal with those.

It is just as a tactical, as opposed to a strategic comment I am making. It is not meant-- I don't want you to take more from this than I intend.

DR. LO: Let me just put something on the table which I think we need to sort of keep in mind, and that is the debate on both animal research and preimplantation research, in many respects, has already been very polarized.

DR. SHAPIRO: Uh-huh.

DR. LO: And one of the things that may present an opportunity, although it may also present a pitfall, is that the debate on cloning of human beings is fresh, or fresher. People have strong feelings. It is I don't think as--

Physicians are not as flexible as they appear to be, for example, on

human embryo research.

So I think it is an intriguing agenda you set for us and we need to think about which way to deal with it.

DR. SHAPIRO: Okay. Thank you.

STATEMENTS BY THE PUBLIC

DR. SHAPIRO: I know we had scheduled at 9:15 public comments; people in the room who wanted to address the commission. We have no one who has signed up, but let me just ask if there is anyone in the audience here today who wants--who may wish--to address the commission?

Yes? If you would just tell us your name for the record, please?

DR. CAVANNAUGH: Thank you, Doctor. My name is John Cavannaugh O'Keefe(?), over at the American Bioethics Advisory Commission Project and--(Inaudible) I do want to respond to the two issues that came up today.

The first one that struck me really very forcefully was that, in the last full meeting of the NBAC, not every speaker, but many of the people who came to present testimony here, talked a great deal about dignity. And I may have missed it, but I don't think that anybody here used the word "dignity."

I think that if you can pick up the new word "bucket" and learn how to use it; you can pick up another word, dignity, and learn how to use it.

I think that the word dignity does represent a really forceful long-term effort by people within religious communities to put their concerns in language that is accessible to everybody.

And I think that it is worthwhile taking a look at two things. One, what do people mean by dignity and, two, why is it that at this meeting, talking about ethical concerns and teasing them out and-- How was the issue of dignity overlooked?

I do also want to respond directly to Dr. Cassell's question about

why was there such a furor over cloning.

And about three or four years ago I was working with a friend, a peace activist. Nebaric Alwad(?) is a Palestinian peace activist, the first Palestinian to speak up for a campaign of non-violence from the Palestinians, and he was exiled for that some years ago. He worked with the Syrian Government for some time to see if the Syrians would sponsor a conference on terrorism. And in that discussion, obviously a number of issues came up really pretty forcefully. Why were the Syrians talking about-- Where did the Syrians get the chutzpah to talk about terrorism?

And in that discussion, which led nowhere in the end, one of the things that came out was that the Syrians felt really very forcefully that there was no difference between the bombing or destroying military targets with some collateral damage, including civilians, women and children, which the Israelis were doing, the Syrians said-- They didn't see any difference between that and just simply going after people in the marketplace.

But I think that most people do see a definitive break between killing women and children as collateral damage in a military campaign, on the one hand, and killing women and children outright on the other. Most people would see that as a very sharp, definitive, frightening, disturbing break.

Similarly, in all ART, there is some confusion about what is happening between the generations, what is happening between the parents and their children? Cloning represents a definitive break. It is a definitive-- There is nothing left of the dignity of the parents.

Doctor, thank you very much.

DR. SHAPIRO: Thank you for your remarks. They are very much appreciated.

Is there anyone else who would like to address the commission

today before we go on? We want to make sure there is an opportunity if any of you are inclined to do so.

(No response.)

DR. SHAPIRO: Okay. Thank you. We do have a few extra minutes now before our scheduled break. We have some guests coming regarding the next session, which will start at 10:15 a.m. And we do have a few minutes before the break. We may not need the full half hour to drink coffee. I don't know if there are other things you want to do at the break.

But let me ask a question. Bernie, I will put the question to you, but there may be other members who were with you last night who may want to comment.

I was trying, as I was thinking of the various comments, to get a sense--I guess, as Alex put it--of what was going on in the rooms; that is, there seemed to be a lot of energy and I sort of think of molecules bouncing back and forth of these-- There seemed to be a lot of energy in that sense.

But you had described this meeting so effectively and so well, you seemed to have-- I don't-- I didn't hear it reflected today, the energy that many of you referred to. And I would just like to get a better sense, so I could understand better of where the disagreements were, on what points people tended to disagree?

Now, Zeke mentioned some before, but I don't want to really put the question only to you, but to any members who were there last night.

DR. LO: Well, let me start by saying, I think one dynamic that I think occurred numerous times is someone would say, "Well, let me try and present a concern, an objection, I have that sort of would be an inclusion that we should not do cloning of human beings," and they would try and articulate it.

And other people would say, "Oh, no, wait a minute; that is speculative, who is being harmed? Is that wrong really different from harms and

wrongs that we tolerate in other contexts of life as well as ART? Is that change, in and of itself, going to cause dramatic changes in values and dignity?"

So that some people would say, "Well, but if you, even if you have this sort of genetic confusion as to who is the parent and who is the brother and who is the sister, if it is within a context of an ongoing stable, loving, rearing environment, which is so important, can't you overcome what questions the cloned child might have about who is my true genetic parent?"

So that whatever concern was raised from an analytic point of view, others could say not only do I find that intellectually unconvincing, but I think on some level people said, were saying, "I understand your concern but that would not lead me to the conclusion that that argument, in and of itself, or in the context of other arguments you have heard tonight, would lead me to support a rejection of cloning of human beings."

PROF. CAPRON: Do you want to hear a few of the arguments that were put out?

DR. LO: Yes.

DR. SHAPIRO: Yes.

DR. LO: Go to it.

DR. SHAPIRO: Exactly.

PROF. CAPRON: There were two that spring immediately to mind.

One of them was I think a little related to a point that Diane mentioned a moment ago about the notion of control. And it was that there is--some of these are drawn, for example, from Leon Kass' materials that we had--a notion in ordinary reproduction, in sexual reproduction, say--

DR. LO: The old one.

PROF. CAPRON: The old fashioned.

DR. LO: Yes.

PROF. CAPRON: --that there is an openness inherent in that process to the results of the chance combination of the genes. And that that "instantuates" an important value that, if lost, would be a diminution of human beings.

There is another version of that same idea, which is that the attempt, which many people would regard as foolhardy and likely to be unsuccessful, should set the path for someone; that is to say someone says, "I want to have a child because, either in my own life or in the life of someone I am using as the source of the DNA, I see a path that was desirable and I will set this child on the path."

The Mozart idea. You know, I will have a great pianist and composer for a child because those are the genes I am getting. And I will construct the child's life with that expectation.

It reflects an attitude toward the dignity of the person--and Mr. Cavannaugh O'Keefe would be interested to know those kinds of terms were being used yesterday--the respect for the individual as an end in his- or herself and not something that we can control.

And then people would say, as to both of these arguments, not that we do it differently and so it is all right, but certainly an impulse people have in having children is to say, "I want to rear them a certain way." And we recognize that.

And the question is, if confronted with that, if we could sort of boldly say, "Parents control their children's lives, in toto," and we all think, well, we all try to do that a little bit, but when boldly confronted with it, we back away and we say, "No. We not only recognize it is impossible, but we recognize that it is really inappropriate;" that the unfolding of this child from within, as an individual, is something which-- That child's own life has its path and we can effect it and help and so forth, but there is a limit.

And so if you add this other technique on, it would be sort of an endorsement of the "we can control the child's life and it is appropriate for us to do so" view. So that is one argument that was-- Or that is sort of one or two arguments, depending on how you see it.

Another one was this question of the disruption of family lines. And to me, you know, one of the interesting changes was--I put forward the question-- would there be, would this be a child of the person, if it were done within a family? If I had a child this way, would it be my child or would it be my parents' child? And I was told immediately, "Well, obviously genetically it is your parents' child." I mean, you know, that is true. It has your genes and it got it genes from the mother and father, your mother and father, so then grandpa--

And then we were told, "But, you know, we do that already know with adoption and all these other things." You know, we conventionally say, "Alex, you are the dad of this child and your wife is the mother, even though genetically it is your parents'."

But then I ask if that is the case, then what is all this concern about getting my consent to use my DNA? You should have my parents' consent because otherwise we follow a principle in reproduction that if my sperm and my wife's egg are to be used, or someone else. If I go to a clinic and they say, "We would like to get some sperm to use to create," I have to give consent for that. You can't simply take these things and use them. You have to have consent for that use.

And if that is the case, then that suggests that not only do we have a disruption, but it is sort of a question, "Is that the right thing?" Should we regard this as something to which one person or another gives consent, or actually is consent out the window? Usually we think of consent as being very important.

These are the kinds of issues, some of which go back, it seems to

me, to a basic stance which is, is the natural normative in any sense here? And I think both from some of the religious things I read and from Kass' view, there is a very strong sense that the natural is normative; that the fact that that--

And I think you can read Kass' response to your letter, Mr. Chairman, to that. His first point is that basically there is a change from that which has been, and that sexual reproduction is not only evolutionary desirable--why should we go back to behaving like bacteria?--but rather it is normative; that the notion that each child represents coming together, formerly in coitus but now in other means, but of two people; that that is normative.

And then you have the view of someone like Joseph Fletcher on the other side; that the exact opposite is the truth. That the most normative is that which embodies the human, God-given--if it pleasures you, I suppose, but we cannot put that on it--ability to manipulate the world but that, like all of medicine, it represents the highest flowering of what is distinctly human, and that chance and taking no responsibility for the way the world is ordered is the least human thing to do.

I mean, the creatures of the world who cannot control the world perhaps are stuck with that, but we are not stuck with that. We were given these great powers and that using them to replace choice, in place of chance, is the greatest indication of-- And that is normative.

And so you have these-- These are the kinds of conflicts, it seems to me, that we are going to have to grapple with. Those were only a couple of them.

DR. SHAPIRO: That is very helpful. Let me hear Tom, Eric and then Larry, then we are going to break.

DR. MURRAY: Alex, you are absolutely terrific at conveying both what were a couple of very important points around which the discussion flowed and even the flavor of the arguments.

I have to stop though when you get to your interpretation of what lay behind the latter dispute.

Yes, one way of sort of filling in the blank there is to just to take Leon Kass' kind of perspective and say, well, this is a natural form because Leon thinks it is.

There are other ways to cultivating it though, ways that I think I would be more inclined, I suspect, and what Steve says he would be more inclined, and others may feel the same; that there are some fundamental social understandings, social meanings and social practices.

I mean fundamental in the sense that they are so constitutive of what matters to us, not simply because they are normal in some evolutionary biologic sense, but because they are so fundamental to our self-understanding that we would object on those grounds.

PROF. CHARO: Are you talking about Brandywine(?) said that?

DR. MURRAY: I--

PROF. CHARO: Because if you are the anthropology doesn't support you and it is-- I mean--

DR. MURRAY: I am not saying human; I am saying us. We are the--

PROF. CHARO: Who is the us?

DR. MURRAY: Us.

DR. CASSELL: That is one of the points of yesterday.

PROF. CHARO: These 18 people? I already feel like I am ready to go with--

(Simultaneous discussion.)

PROF. CHARO: This family stuff just makes me crazy because I

know it disparates almost everybody here about it.

DR. MURRAY: Well--

PROF. CHARO: So don't put me in the "us."

DR. CASSELL: Well, that is one of the points. That is one of the things that made the argument yesterday was exactly that; that the talk about the natural as being normative. Normative for whom? Normative for which group?

PROF. CHARO: Unnatural for whom?

DR. EMANUEL: Actually, that phrase, "natural as normative," never came up last night and--

DR. CASSELL: Leave out that thing.

What did come up was certain statements of, "I am sure that this is a thing that disrupts the family, or it changes the way the family is." Negatively. I mean, natural is normal or not.

But whether you call it natural is normative or views about the family, views to whom? And the business of our understanding that in fact there are many views about the family and that when Leon talks, Leon talks as though there is one view about the family. There isn't one view. Not in this society, anyway. That is on the one hand.

On the other hand, there was a spilt that is a very common one that I always find very interesting. For convenience sake, conservative liberal, the mutability of human beings; that in fact they are able to handle changes in how things come about and we assemble and make lives, and meaningful lives, as opposed to the view that there is a right way to do things and if you don't do that you have a lot of trouble.

And those two views are-- We can find that anywhere throughout the society; that particular fight, particularly at the present time.

PROF. CHARO: Add one more thing to your list, please. It is just-- It is the illusion we have in the legal setting, by virtue of judicial opinions, that we have only certain kinds of families, or that when we recognize a trend in the families as a necessity we will only recognize those to the extent that they actually will fit-- shoehorn--into the old models of what I would call la famille savage(?), the family in the wild. When in fact, you know, the courts are mixing and matching relationships all the time.

We have got a rhetoric, an illusion of one set of rules and one set of numbers, of kinds of families, and a reality underneath it completely different, and that failure to recognize all these legal fictions is just screwing us--

DR. EMANUEL: Is that normative, too?

PROF. CHARO: It certainly--

DR. EMANUEL: Or is that just a description? I mean, part of the issue is whether it is descriptively accurate or whether it is normatively persuasive.

PROF. CHARO: The courts have been using la famille savage as a kind of normative concept and they will only bring in the real people who are in the families to the extent that they can sit in slots that are identified with that wild version of the family.

And so they arbitrarily cut out or bring in people who don't belong in there, or shouldn't have been cut out, because they need a one-to-one correspondence between the people that they will bring in under the law and the people that nature would have brought in through sexual reproduction absent any kind of human assistance. It is crazy.

DR. SHAPIRO: Okay.

DR. EMANUEL: Sorry.

DR. SHAPIRO: Larry?

DR. CASSELL: Well, you get a sense of it now?

(Laughter.)

(Simultaneous discussion.)

DR. : Turn up the air conditioning.

DR. SHAPIRO: Larry?

DR. MIIKE: I am just kidding. I am kidding most of the time.

Is it useful-- You know, when I hear these discussions I never-- I have a hard time distinguishing between people worried about people's motives or about the product, which is the cloned human being. Is it useful to sort of try to artificially tease that apart?

I only raise that in the sense that it seems to me most of the objections are about the motives, and then the motives of people who could then control the infant who was born. Sometimes I think I am in a discussion about welfare mothers and the number of babies they should have.

But, anyway, just an observation is that it would be useful for me if, in your discussions, you sort of try to separate the motives side from what is repugnant about, or if at all, about the product of the cloning which is the child.

DR. SHAPIRO: Bette, do you have your--I'm sorry--do you have your hand up?

MS. KRAMER: It was just to go back to what is normative and what is not normative. I remember when I was growing up and interreligious marriage was a no/no, interracial marriage was a bigger no/no, and all of the things that were normative back then are a joke now. And it seems to me that the only constant is change.

DR. MURRAY: That is what Mr. Herod(?) has said.

DR. SHAPIRO: Thank you. Jim?

DR. CHILDRESS: This is not an observation about last night, but rather picking up some things from this morning that I think we may need to attend to more. One is really what are we to do in the ethics area as a public body? And someone talked about public ethics as a particular kind of enterprise. I think that-- And I may have been getting at some of this and this distinction between intellectual and practical.

Here we are as a public body trying to think about ethical matters. Sometimes we think about judgements we would make, or particular groups would make, about particular acts like cloning.

But it seems to me that one of our fundamental tasks is to try to figure out what values in this society, as a public body, we think are important for thinking about the problem we have been assigned to deal with.

And at that point I don't think the distinction between law and morality is actually terribly helpful. I think, as a matter of fact, getting at societal values we do have to think about law, we do have to think about policy, we do have to think about practice, we do have to think about religious groups, and in effect, when I was talking about an earlier complicated interpretive task, part of what we have to do is try to put all that together in some kind of meaningful way to think about policies.

Second, it seems to me that if we are thinking about public ethics, we do have to take very seriously--again, another one of Larry Miike's points--that matters like, if this is going to be done anyhow, then what should we do? Well, at that point we will be thinking about various kinds of harms that might occur, and so forth, and that, it seems to me, is a fundamental ethical task, too. So ethics in a public context, trying to pull together a whole range of values in the society, and then trying to deal with things that are likely to happen, even though we may think they are not ideal, really makes our task a lot more complicated than say simply trying to reflect

through, you know, ethical theories the way most of us, or many of us, do in our private academic activities.

DR. SHAPIRO: Thank you. I would like to break now unless there is someone who wants to make one last statement here?

(No response.)

DR. SHAPIRO: Okay. Let us take our break now and try to reassemble at 10:15 a.m., which is 20 minutes from now. Thank you all.

(Whereupon, at 9:55 a.m., there was a brief recess.)

DR. SHAPIRO: It seems to me the only thing that slows down the commission is the need to get more and more caffeine as we go along.

(Laughter.)

DR. SHAPIRO: I can remember one meeting where we didn't have any and everybody got very nervous.

(Laughter.)

DR. SHAPIRO: We will deal with that at some other time.

Well, the next item on our agenda is, of course, is the scientific issues. I am going to turn to Dr. Greider in just a moment.

But I want to extend my gratitude to Drs. Rossant and Orkin not only for being with us here this morning, but for the material they produced for us which has been extremely helpful and which I enjoyed very much. So thank you both very much for being here. We very much appreciate it.

Carol?

SCIENTIFIC ISSUES

DR. CAROL W. GREIDER

DR. GREIDER: Okay. We had a lot of discussion this morning that touched briefly on the issue that there has been quite a lot of discussion about the

ethics and issues surrounding human cloning relative to producing a human being. But there has been little discussion, and we really haven't had a chance to really get our hands on, on some of the other issues surrounding cloning that go up to stopping short of producing a human being.

And one of the questions that I had was what are the scientific issues and benefits, as well as concerns, stopping short of actually producing a human being? And so I hope that in our presentation this morning we can get that discussion sort of launched so that we can have some sort of meat to sink our teeth into when discussing these issues about cloning.

So, unfortunately, our science bucket wasn't able to meet separately as the other buckets were able to meet separately yesterday, and so instead what we are doing is we are bringing our bucket discussion to the entire NBAC.

And we have two presentations this morning from the two people from whom we commissioned papers. You should all have copies of the paper by Janet Rossant and Stuart Orkin.

And what we plan on doing this morning is allowing both Dr. Rossant and Dr. Orkin about 15 minutes to present briefly some of the issues that they raise in their two commissioned papers. And then we could open up to discussion among the commission members to ask questions of the two presenters.

The other thing that is going on in the science bucket is that we have written a letter that was addressed to 54 different scientific societies asking them specifically to state their views on cloning and outlining specific issues that we would like them to address on cloning.

And we have gotten responses back from a handful so far, and we are hoping to have more responses shortly. And I think you were all given copies of the responses that we got from those scientific societies.

What we are planning to do in the future with those is to write up a summary to help everybody digest those. We would like to give you all the raw material to look at, but we will be preparing a summary for the commission at a later date, hopefully not a very much later date.

So those are the two things that are ongoing. We commissioned these two papers, we are going to have the presentations this morning, and then this letter for scientific societies.

So, without further ado, to, you know, allow us to start discussing some of these issues, I will hand the podium over to Janet Rossant, who will discuss some of her issues that she raises in the paper that she presented to us.

DR. SHAPIRO: I would like to just intervene for a moment. Those of you who may not be able to see conveniently here, there are a lot of empty chairs there, if it is more convenient for you. I will leave it to your own judgement. I will wait to see what I can see from here.

DR. : Are we going to have slides as well?

DR. GREIDER: No. Just overheads. You should have received a copy of Dr. Orkin's paper in your packet this morning.

MR. HOLTZMAN: Could we follow that point? I think a number of us--or at least I know I--didn't get the Orkin package this morning.

DR. SHAPIRO: We do have extra copies of the paper. Just let Henrietta know if you want a copy of Dr. Orkin's paper. Most of us received it either last night or this morning.

DR. GREIDER: Anybody else need one?

PRESENTATION BY DR. JANET ROSSANT

DR. ROSSANT: Okay. So my task, as presented to me by Carol, was to really deal with some of the background issues in terms of the science of

cloning, both in what has happened in the past leading up to the famous sheep that we have spent so much time thinking about and also to think about futures.

And so what I am going to focus on mostly in my presentation is actually where we are at today and where we may go in the future, in terms of applications of cloning and nuclear transfer technology in the animal side. And I will end up with a brief discussion on how this might move into more direct applications to human. And then Dr. Orkin will obviously take that much further.

So I just want to remind you a little bit about what we are talking about when we talk about the stages of development involved in cloning and other kinds of genetic manipulation. I am going to touch on other kinds of alterations that you can do to mammalian embryos. And so I just want to remind you of the stages of development.

This is the stage of the egg. This is the stage at which you have two nuclei, one derived from the male, one from the female. In normal reproduction then, these two nuclei come together at fertilization and development proceeds.

I will show you in a minute that in nuclear transfer, of course, what you do is replace these nuclei with a nucleus from another cell and that is what is going to then program development.

But in normal development these two pronuclei carry the genetic information to encode everything that is going to give rise to an adult organism.

And as development proceeds, cells divide until they get to a stage called a blastocyst and, at this point, you have the first differentiation event occurring into an outer layer of cells called trophectoderm and an inner group of cells, the inner cell mass.

Now, we know that these outer cells give rise to the placenta. And this little group of cells are still what we call pluripotent. These are cells that, in a

mouse embryo, a pig embryo, a sheep embryo, cow, and presumably also in the human embryo, these cells still actually have the capacity to form essentially the entire organism, with the exception of these outer cells that are going to make the placenta.

So it takes, in a mouse, about three days--in humans, five or six days--to reach this point, and at this point we have two-cell parts formed.

I mention that because, if we think about what is going on in terms of nuclear transfer and the developmental potential of cells, we know that in terms of cellular development these early cells still can do everything.

They have not changed in any way their genetic potential and, in fact, you can separate blastomeres, which is what these cells are called, at the two-cell stage in the mouse and, in fact, up to the eight-cell stage in the sheep and cow, and still regenerate blastocyst and regenerate whole organisms.

That is a form of cloning. Okay? So it is possible to clone by separating out these identical cells and making one individual embryo develop into several. So that is one form of cloning.

The second form of cloning, of course, is the one that more attention has been drawn to, and that is nuclear transfer cloning.

Nuclear transfer cloning was first developed in frog embryos. And in those experiments, by John Gerdon(?) in the '60s and '70s, it was shown that adult cell nuclei, when put back into the frog egg, could reprogram development right through at least until the tadpole stage.

Since that time, experiments have carried on in mammals, and the general protocol in all experiments now in mammals is shown here. There are some slight variations, which needn't concern us, but the general protocol, which was used in the sheep cloning experiments and other experiments as well, is shown here.

You take, in this case, not that fertilized egg, so the egg before

fertilization has occurred, and at the stage when the oocyte chromosomes are just beginning to get ready to make their last division, those chromosomes are removed from the egg by a pipette, ending up then with cytoplasm that has no DNA in it, no genetic material at all.

You then take your donor cell, whatever it is--and we will come back to what it is in a minute--and introduce that next to the cytoplasm, and the normal protocol is to use an electric current to essentially zap these two cells together.

The electric current fuses the membranes, the nucleus enters the oocyte and, in fact, this electric current also activates the egg--gets the thing started--and this egg now is going to behave, hopefully, like a fertilized egg, undergo those divisions I showed you, and generate a blastocyst.

In this case, instead of being driven by the DNA, the genetic material of the pronuclei, all of that is gone, and for this blastocyst to develop the DNA of the nucleus that you have put in there has to carry the information through, so--

PROF. CAPRON: Where is the mitochondria?

DR. ROSSANT: The mitochondria are in the oocyte cytoplasm and the mitochondria, which also do contain DNA--

PROF. CAPRON: You said a moment ago there was no DNA.

DR. ROSSANT: I beg your pardon. There is no nuclear DNA.

The mitochondrial DNA--oh, I have to be very careful and make sure I get it out to you right--the mitochondrial DNA is still there and is derived from the oocyte.

The nuclear DNA, which contains the majority of the DNA that is going to specify all the cell types of the body, is derived from the injected nucleus.

Now, I told you that in frogs it was possible to get an adult cell

nucleus to generate a tadpole but it, in fact, has never been possible to get an adult nucleus to go through and reprogram an adult frog.

So one was left with the possibility that, although we consider the DNA of the adult cell to be essentially the same as that of the egg, that perhaps there is some kind of changes that prevent the complete reprogramming of that material.

And so I don't think most people would believe that that is really the case, but it has been true that, when you do nuclear transfer in mammals, experiments that have gone wrong since the '70s and up until now, have tended to be very inefficient and that, until the recent experiments in the sheep, when you do nuclear transfer in mammals, you can only take nuclei from very early stages of embryogenesis and get them to actually reprogram the oocyte cytoplasm.

So in the mouse, the latest stage of nucleus that has successfully reprogrammed the eggs being reprogrammed in the egg cytoplasm is the eight-cell blastomere; in rabbit, 32-64 cells, a slightly later stage; then in the cow you can actually take those inner cell mass cell nuclei that I showed you and cell lines from the inner cell mass, and cows have been generated from the DNA of those cells.

But you will remember that I told you that, in fact, all of those cells are themselves still totipotential. The cells have not really made any major decisions about their future existence, so it is perhaps not so surprising that you can reprogram their nuclei.

The experiments that have really changed the concept here have come about in the sheep, largely from the group in Edinburgh. And they have shown that they can take inner cell mass cell lines, as in the cow--similar experiments--but also fetal fibroblasts, that is, cells taken from a much later stage of development, and of course also from the adult mammary gland.

And those experiments then have markedly extended our

understanding of what kind of nuclei can be reprogrammed in mammals.

So what did Dolly show us? Scientifically, Dolly was in fact the first demonstration that the nucleus of an adult cell can recreate genetically the whole organism, so that had actually not been demonstrated in any species before.

That is an important point because it suggests that indeed there is no absolutely irreversible changes in the DNA content of adult cells. And it is an important scientific point because it means that it should be possible not necessarily to recreate a whole organism, but it should be possible to reprogram adult cells in a variety of ways to change their fate.

And I will come back to that later, and I am sure Stuart will talk about that as well.

So that was the important scientific finding there.

If one is thinking about carrying on this nuclear transfer, and we could discuss why we want to do it in a minute, but let us just think for a minute about this process and its efficiency.

So Dolly exists. There is one sheep reported so far from an adult cell put back into an oocyte. That was one out of about over 200 transfers. That is clearly not very efficient. Efficiency will undoubtedly improve. There are various parameters that can be changed to try and improve the efficiency.

But there are also some potential limitations to just the ability of nuclei to reprogram the egg. And I will mention these briefly. And I will say, I think in each case, we actually don't know at all the extent to which these could be limitations.

First of all, species differences. I told you already that people have been trying to do nuclear transfer in mice and couldn't get beyond the eight-cell stage. Is that a real difference or is it in fact that the slight differences in protocols used

between mouse and sheep experiments are enough that, if those were repeated in other species, things would work?

We don't know. There are some real differences in the processes of embryonic development between mammalian species that might make it difficult to achieve nuclear transfer success in other species.

Imprinting effects. This is a complicated area that I won't go into much detail, except to say that in mammals the maternal and paternal genome are differentially active. And if those effects are in some way obscured or altered as the adult cell develops, putting that adult nucleus back into the oocyte may disturb the normal imprinting process, and that would have outcomes that would cause abnormalities of development.

Clearly, that can't be an absolute effect because Dolly exists, okay? So you can get 'round it.

Cellular aging is also being put forward as a possible problem, and Carol would be the one to comment on this one I think.

But as cells age they undergo a number of specific changes of cellular senescence and some of those include changes to the DNA. What happens when you put them back in an oocyte? Are they fixed, or are you going to have some problems with the long-term survival of nuclear transfer animals?

And, finally, if you are going to use adult nuclei that have been around a long time, is there going to be an increased mutational load on those nuclei that, again, could cause problems in the next generation of nuclear transfer?

And, as I say, I think in all cases we really just don't know the extent to which these are going to be limitations. But my feeling is that all of them will have some effect, making the likelihood of this being a highly efficient process, to take adult nuclei and reprogram the egg in any species, unlikely. Okay.

So why do nuclear transfer? What is the-- Why continue with this research?

In animals it is clear that one of the main impetuses to nuclear transfer is coming from the agricultural industry, and that I think is where the impact is going to be felt most.

The agricultural impact is that nuclear transfer provides a way, if it can be done efficiently, provides a way of improving the efficiency of generating and propagating genetically altered stocks. This includes both elite livestock. If you have a good genetic breed that has been generated by normal genetic selection procedures, the idea would be that, if you can use nuclear transfer, you can rapidly propagate that stock and increase its salability.

It is perhaps more important for genetically altered farm animals where DNA genes have been introduced into the animals, or where genes have been mutated in those animals because, for a variety of reasons, it is not very efficient to generate genetically altered farm animals by normal procedures that were used in mice, that is, transgenic productions, and other approaches have not yet been successful.

Nuclear transfer means that you could put DNA into cells *in culture* very easily and then take that altered cell nucleus and put it back into the animal.

What are the things that people want to do there? Some type of livestock improvement. Actually altering the genetic components of the animals, perhaps to improve efficiency, to introduce disease-resistance, to alter fiber production. But I think the big push is actually not in altering livestock, per se, for agricultural purposes, but altering livestock for actually pharmaceutical and medical purposes.

And pharmaceutical protein production in milk is a potentially big

industry. It is possible to express human proteins and have them secreted in the milk of large animals very efficiently, such that up to 50 percent of the protein in the milk can be derived from the human gene.

Again, this doesn't require nuclear transfer, but nuclear transfer may make it easier and faster to generate these animals, so that is one big push.

The other area is this area of xenotransplantation, mostly in this case in pigs. The idea being that one could take pig organs and use them, at least in the short term--I should say organs and tissues--in perhaps short-term and maybe even long-term graft situations as replacement tissues in humans.

The problems with that are multitudinous. The important ones is the problem of having the graft rejected.

There are some attempts already to genetically alter pigs to reduce graft rejection, and the ability to actually mutate genes, perhaps in cells *in culture*, and then make nuclear transfer pigs would make this a much more potentially viable proposition.

So these two, I think, are really where the agricultural push is coming in the industrial sense.

So that is a biotechnological push, and I think we are going to see that proceeding forward.

There will be regulatory concerns regarding both of these, the pharmaceutical proteins produced in the milk and a lot of concerns about the safety aspects of xenotransplantation, but I think that industry is at least pursuing them.

So what about the basic science side of things?

The basic science of nuclear cloning, nuclear transfer cloning, as I have said, tells us that the DNA of the adult nucleus is not really irreversibly changed although, as we grow old and our cells differentiate, we turn genes on and off in very

specific manners and we don't usually turn them back again, and if we did it would be a problem. If we suddenly started expressing globin genes in the skin, you know, it wouldn't be a good idea. So things are generally fairly irreversible.

But what the nuclear transfer cloning situation tells you is that it is not an absolute thing. You can reverse that process. If we understood more about how to reverse that process, then I think that would be very important in understanding how to reprogram human cells.

And so the basic knowledge that we are going to obtain from nuclear transfer, and a lot of other kinds of experiments in developmental biology and molecular biology, is basic knowledge that leads to potentially improved cell-based therapies for replacement and repair of diseased tissues.

And I am sure that Stuart is going to go into this in more detail, but I think that my personal feeling is that it is very unlikely that we will ever do this by actually taking our adult cells from ourselves, putting them back in an oocyte cytoplasm, and trying to use that to reprogram them.

But by understanding how the oocyte reprograms nuclei, we can use the clues we get there to try to reprogram directly adult differentiated cells *in culture* or to stimulate quiescent stem cells, which seem to exist in a number of different tissues in the adult.

And potentially also take early stem cells from--again from--human embryonic tissue and those cells that would be pluripotential, like the cells of the early embryo I showed you, drive them forward, drive those cells forward into the differentiation of specific cells that could potentially be used for cell-based therapies. So either going back from the adult, or forward from the embryo.

And all of this I think is very important. And it depends on basic knowledge that is obtained from the kinds of experiments and kinds of understandings

that we may get from nuclear transfer.

So, in conclusion then, I would just say that I think that work on nuclear transfer and other genetic and cellular manipulations of the early mouse, or rather the early mammalian embryo--that was my personal bias there--is already providing unparalleled insights into fundamental biological processes of development in differentiation.

And I think a great care must obviously be taken crafting ethical or legal guidelines on human cloning to avoid inhibiting legitimate research into animals or humans that really has, I think, potential for immense benefits in the future.

Thanks.

DR. SHAPIRO: Thank you very much.

At this time, Carol, do you want us to hold questions until later?

DR. GREIDER: I mean, I am willing to do it any way.

DR. BRITO: I have a quick question.

DR. SHAPIRO: All right. You have one which is described as a quick question. We will see.

DR. BRITO: Okay.

DR. SHAPIRO: Use your mike.

DR. BRITO: Yes.

DR. ROSSANT: And I will use mine.

DR. BRITO: In our deliberations yesterday, in terms of the legal and policy bucket meeting, we have to go back to basic biology to define what an embryo is. And an embryo is, once an egg is fertilized, is defined as an embryo.

DR. ROSSANT: Yes.

DR. BRITO: Then there is also the differentiation between an embryo and a preimplantation embryo.

DR. ROSSANT: Uh-huh.

DR. BRITO: I have two questions, very quick questions.

The first one is what did the cellular division--I want to make sure this is clear--that can occur in the laboratory; up to what level can that occur without implanting that embryo? That is the first question.

DR. ROSSANT: Uh-huh.

DR. BRITO: And the second, should we be using a different terminology to define an artificially produced embryo?

DR. ROSSANT: Okay. So the first question is to what stage can you essentially grow an embryo *in culture*? Is that--

DR. BRITO: Yes.

DR. ROSSANT: And so you can grow a mouse or a human or a cow, or anything else, up to that blastocyst stage that I showed you, continuously from the beginning of development through to the blastocyst stage.

You can grow the cells, the embryos, beyond that point and they will generate cell lines, some of them permanent, some of them not.

You cannot, at this point, grow a blastocyst *in culture* and have it develop morphologically normally as an embryo. Okay?

So you can potentially grow cells for a long time from embryo cells, but in terms of getting normal development *in culture*, blastocyst is really the end.

The second question-- Remind me what the second question was?

DR. BRITO: Should the terminology-- In other words, if you are not intending to implant that embryo, therefore it is not really an embryo, or that cell because it is not-- The definition of embryo is something that has a potential for human development or mammalian development, in this case, so--

DR. ROSSANT: Oh, okay. All right. So there has been an attempt

in the past to distinguish between what people call the preembryo and the embryo. My personal-- Personally, I find that an artificial distinction that is not justifiable.

If you can make a nuclear transfer embryo, any kind of embryo that you can grow *in culture* that can develop to the blastocyst stage is an embryo and has potentially the potential to go on and develop.

Once you grow those embryos beyond that point, if they are no longer carrying on the processes of development of the embryo and organogenesis, then they I think become cell lines and they do not any longer have the potential, if transferred back into the uterus, to develop normally. So I would make a distinction at that point.

DR. BRITO: Thank you.

DR. SHAPIRO: Any other clarifying questions? Because I am going to hold up questions until later. I think that might be helpful. Some may be answered by Dr. Orkin.

Dr. Orkin?

PRESENTATION BY DR. STUART ORKIN

DR. ORKIN: Thank you.

I think you will see quite a bit of correspondence between our presentations. The draft you have-- The paper you have is a draft which is still undergoing some changes so I wouldn't consider it--at least my version--a final.

What I will do is just cover a number of the issues which are in the draft and which highlight I think the key points.

The first, which really I think Janet has already mentioned, is really the extent of manipulation that would be required in human cloning. And one of the questions I pose in the draft is really, how does this technology, if it were ever applied, differ from what is done in assisted reproduction? For example, in IVF clinics.

And the points are that, first, I think it is different both in the extent and the type of manipulation. And principally, as Janet noted, at the bottom I think we have considerable uncertainty as to the success in human, if this were ever really contemplated, and for a number of reasons.

We don't even know whether it would work. The time to gene activation is within the oocyte. We don't-- There are clearly deleterious affects of manipulation of embryos, taking nuclei out, putting nuclei in. We don't know the effects of aging or mutations that accumulate in cells, particularly the adult cells. And also this issue of imprinting that Janet also mentioned.

So I think in aggregate, we have a number of technical issues, scientific ones, which really mean that any human cloning would have inherent risks which I think are unacceptable, and many of which are completely unknown. The science hasn't been done and hasn't been developed to the point that we even know the extent of the risks, nor how to circumvent them if we should want.

Thank you.

So-- And this, I think, makes it-- These points I think are the central ones in conceptualizing really what would be the applications of research to humans because the practical issues are really fairly overwhelming.

So I have divided the applications really into two kinds of various-- One, in principle what could you do, and then, in practice, what might you actually do?

So in principle, I think there really is only two general areas in which I could imagine cloning in this context being at all imaginable and perhaps useful.

One would be in assisted reproduction. This would be for couples with infertility. And it would be really just a subset of infertilities as it is known--and

sorry for the spelling here--but I think that, because of the complexities I have already mentioned and also the amount of really investment of really the public in the research, to get to a practical solution, if it were possible, I don't think there is sufficient justification for this kind of application, per se.

This is my own personal choice, even apart from any of the scientific issues.

The second area which is the one Janet has touched upon, I think is a legitimate area in which one could imagine substantial application, and that is in organ-based or cell-based therapies for either organ or tissue transplantation.

I think we are all aware that there are a host of human disorders that are either acquired or inherited for which transplantation of organs, including bone marrow as an organ, really is curative.

And I think we are all familiar with bone marrow transplantation, and kidney transplantation is really the prototype, both of which were recognized several years ago with the awarding of a Nobel Prize for that development. And that really is a triumph in medicine. And we are all aware that there is a shortage of organs of any kind for transplantation.

In addition, other kinds of sort of imaginative, new medical therapies that people are considering, such as gene therapy, which is another topic that is on the sort of public horizon, but isn't really here yet as a technology, would also benefit from the ability to have cells available representing different kinds of tissues.

So I have broken down the transplantation in three different ways.

The first is transplantation requiring an individual. This would actually be having, going forward with implantation and having an individual born. This is I think, as I will come to, very unreasonable and unimaginable, given the kind of technology we are talking about.

But I just want to mention, which is also in the draft, that this is not a new concept in a sense. There are actually families that have had leukemia within the family, either a parent or a child, who then choose to go on and have another child in the family with the prospect of that child being a compatible match for transplantation.

This has obviously stirred considerable debate as to the ethics of this, but it is going on now. This would be obviously an extension of that, in a different way.

A second kind of transplantation would use cells or tissues, but would not require an individual as the donor. And this might be based on the use of early embryonic cells, or ES cells, and Janet has touched on that and I will come back to it in a couple of minutes. So this would not require any implantation.

And then a third possibility, which I think is somewhat like Star Wars kind of science at this point, and that is transplantation requiring cells but not requiring a donor individual or even an embryo.

And this would require, would involve, for example, reprogramming adult cells into another kind of cell. For example, taking a skin cell and transforming it into a liver cell for liver transplantation. I think this is kind of Star Wars science, but at least the implications are there from the sheep cloning.

So how, in practice, can we envision any of this cloning or cloning research being considered?

In the draft document, I actually compare, at least from an investigation standpoint in medicine, how this kind of technology would relate or compare to the history of organ transplantation or the current gene therapy.

And I think it is pretty clear that the kind of technology we are talking about here has risks that are far beyond any of these other interventions. And

so I think the bottom line, as given here, is that any human cloning with the intent of embryonal implantation is ill advised and in conflict actually with any notion of clinical investigation as it currently exists.

Because, in fact, any of the experiments that would be necessary to determine the risks involved to the developing embryo, or any manipulations to overcome those risks, obviously place an embryo, a perspective embryo and perspective individual, at risk. So I think it is in violation of any notion of clinical investigation as we currently understand it.

So that cloning, as we are talking about it, represents a far greater and I think qualitatively different process than any of the other kinds of medical interventions.

And so then the question is how can we, you know, having said this, can we do anything? And I think the prospects, from a research standpoint, are still there and have to be taken seriously. And I think this follows very much from what Janet has already said.

So, first, I think the potential medical benefits do in fact warrant encouragement and support of animal cloning research, as well as human embryo and cell research, in order hopefully to get eventually to the kind of cell-based therapies or the kind of science that one needs to get to those cell-based therapies.

And the important point I think is--and I am sure everyone here appreciates it--is how can this be done with appropriate regulatory oversight on the process? And I have proposed in the draft at least a number of criteria that one might apply in this kind of regulatory oversight. The first is that I think any sort of body looking over this kind of research will need to foster the development of science of animal cloning in general. In other words, I wouldn't dissociate the research in animal science from any research in cloning that might eventually be applied to human.

I think right now there are almost two different activities, the veterinary or agricultural community, and perhaps those dealing with mouse and human on the other side. And it would be nice actually to have one body that would integrate that kind of research, or at least have a way of bringing it closer proximity.

This group would obviously have to monitor and regulate reasonable research on early embryos, but only with material not intended for implantation, so this would be certainly within days *in culture*.

The research-- You have to insure the research involving early embryos addresses testable hypotheses in some rigorous manner. And the important point it has to be under some peer review by scientific experts.

In addition, I think the oversight, in terms of ethical, societal and legal issues, will have to be integrated within this kind of regulatory body.

And I think, finally, having this kind of regulatory body in place to monitor the research and potential obligations will also provide a forum therefore for discussing and monitoring any potential clinical applications as they might come along in the future, I think, so one wouldn't be caught off guard, for example; one would have some mechanism in place for eventually considering any clinical applications.

So I imagine this kind of research, presuming it goes forward, going in stages.

Phase 1 is one that is clearly ongoing, and that is the basic research and animal cloning, agricultural largely, and the cellular mechanisms that are involved in this kind of reprogramming of cells that Janet Rossant mentioned.

And the cellular mechanisms I think will be elucidated by other kinds of research, not just animal cloning research, but by basic research into developmental biology and molecular biology that is already ongoing.

And I think one needs to integrate the activities in the different

settings, and I don't think that is going on at the current time. And I think that is one very important function perhaps of any sort of oversight group.

Phase 2 of research, which is not going on at present, would be judicious research using early embryos not intended for implantation, including nuclear transfer or reprogramming of fates of pluripotent cells *in vitro*. If this phase does proceed and is useful, in terms of the information obtained, one might then imagine going on to Phase 3, which would begin only if were deemed possible to generate differentiated cells *in vitro* for clinical experiments and for transplantation.

And one would need then preclinical experiments, presumably in primates, or at least other animals, to justify any kind of transfer of this kind of approaches to humans, and obviously oversight and monitoring.

And Stage 4, which is not ongoing, we hope, is implantation of any manipulated embryos. And I don't see this as possible to sanction for the foreseeable future.

So if I could summarize then the kinds of approaches that I think Janet and I have touched on, it is really the major positive benefit from a human health point of view besides the general knowledge that would come out of the research. It might be new kinds of cell-based therapies for transplantation or the other uses of cells in treatment of disease.

And one could imagine these cells coming from a number of different kinds of sources. I think the source that would be most acceptable to everyone--but, as I said, it was sort of Star Wars technology--would be to take an adult cell, let us say a skin cell, and dedifferentiate it, that is revert it back to a pluripotent state, and then somehow redifferentiate it into a specialized cell, perhaps a liver cell again, and use that for therapy. That would not involve embryos at all and I think that would be certainly a laudable goal. That is the most difficult I think.

A second possibility would be to introduce nuclei into an oocyte by fusion, have an early embryo which would not be implanted but would then, this early embryo, the cells from it, would be used for *in vitro* differentiation, again to obtain cells for some sort of cell-based therapy.

And at the top, a sort of variation on that, where one could use cells, either embryonic stem cells or cells derived from some primitive germ cells in humans, and these cells, which are totipotent, could then be used, perhaps with nuclear transfer as well, to obtain something similar but not perhaps identical to what one would call the early human embryo, from which one could use cells again in some sort of cell-based therapy.

I would like to emphasize I think this is all very high-tech. We don't know how to do it. I don't think anyone knows how to do it. And the research that we are talking about is the only way to learn how to do it, if it is at all possible.

And I will put in the caveat that much of research is unknown. We don't know whether we are going to succeed when we begin, and I think this is a clear area in that respect.

I think I will stop and take any questions.

DR. SHAPIRO: Thank you very much. Maybe someone could turn up the lights.

Alex?

PROF. CAPRON: I have four questions of clarification, the first to Dr. Rossant.

You used the term "adult cell," and I just wanted to understand whether that is a description of a cell from an adult organism or a differentiated cell that would also exist in say a six-month-old child, or even a newborn child? What does that term mean to a scientist?

DR. ROSSANT: Well, I don't know what it means to a scientist. What I was using-- I really meant just any cell from an adult in that situation.

But we clearly consider the process of development and differentiation a continuum, so throughout development cells become more specialized. And certainly there are highly differentiated cells in a six-month fetus, and highly differentiated cells in adults.

PROF. CAPRON: I didn't mean fetus though. I mean, when you say "adults," do you mean--

DR. ROSSANT: Oh, I mean anything post--

PROF. CAPRON: Post delivery?

DR. ROSSANT: Delivery, yes.

PROF. CAPRON: Okay. Is there another term that scientists use there? Because I have a sense to the lay-person, particularly with the emphasis that Dolly was a six-year-old--or whatever she is--sheep, the notion of adult usually would mean from an adult person. Is the term "differentiated cell" just an equivalent?

DR. ROSSANT: Yes. Except to say those could be embryonic cells.

PROF. CAPRON: Okay.

DR. ROSSANT: I told you that, you know, at the blastocyst this stage they are already differentiated.

PROF. CAPRON: Okay. We might call them "specialized?"

DR. ROSSANT: Specialized. That is what I would use.

PROF. CAPRON: Okay. Fine.

The next is a question, perhaps it is more to Dr. Orkin.

We haven't fully decided this, but we have sort of decided that, although cloning has been described as arising both from embryo splitting and from

nuclear transplant from an adult cell, which is using a specialized cell, a somatic cell, that we were only really going to end up probably talking about the latter, I think.

And I wonder if there is a category in between which would be the transplantation to an egg of a nucleus from another fertilized ovum?

So you have the transplantation--you don't just have splitting of the embryo--you have transplantation, and it is a therapeutic use of the technique that Dr. Orkin didn't address, but I understand from your obstetrical colleagues that there might be a situation in which a woman's egg, for some reason, is not good for carrying the fetus to term--there is something about the egg and the woman has spontaneous miscarriages, but it doesn't have to do with the chromosomes--and so if you can get another egg and transplant it in.

Can you comment on that? Does that seem a potential therapeutic use and would-- That wouldn't seem to me to be in the same sense cloning as we usually use the term, but it is a use of the nuclear transplant technique.

And the reason for thinking about it is, if we are looking at state statutes or potential federal statutes that use the phrase "the transplantation of nuclear material from one being to another," that might encompass that, but it doesn't raise all of the same kinds of issues.

DR. ORKIN: I will take a stab at it. I would put that under the assisted reproduction class.

In other words, I could imagine that an infertile couple would ask for this kind of procedure and, in that case, it might involve the transfer of, just as you described, embryonic cells, but I think the problem is still that the technical aspects are such, the hurdles are so large, that it is not clear how one would ever get to that stage in a practical sense.

PROF. CAPRON: Okay. That--

DR. ROSSANT: Just-- Not to disagree with my eminent colleague on the right, but I think this would be a very rare occurrence in which one would do that, number one.

But in fact it might be worth considering because I think the technical hurdles actually, for that kind of manipulation, would be less because you could envisage a situation in which you took one fertilized egg that had the bad cytoplasm, took the two pronuclei right out of that egg, and put them in good cytoplasm.

That procedure is actually very efficient. It can be done in mice and everything. It is a very efficient procedure. Not 100 percent, but it might be efficient enough to be considered in a human *in vitro* situation. So perhaps it is something that, if you are considering these options, has to be thought about.

I would consider that something like nuclear, pronuclear exchange, and call it something different, because it certainly is not cloning in the sense that we are talking about here, nor is it taking from a specialized cell.

PROF. CAPRON: Right. Right.

DR. ROSSANT: The reason it works is because they are from non-specialized cells.

PROF. CAPRON: But you are referring to doing it at the pronuclear stage?

DR. ROSSANT: Yes.

PROF. CAPRON: And has it been done in mice?

DR. ROSSANT: Yes.

PROF. CAPRON: Post-fertilization but before splitting?

DR. ROSSANT: Yes.

PROF. CAPRON: And does it seem to work there as well, or is

there an advantage to doing it at the pronuclear stage?

DR. ROSSANT: Well, in the mouse--and I don't even remember if it is true in the human--in the mouse, the two pronuclei never form one nucleus before the next cell division, so in fact you have to move both the pronuclei.

PROF. CAPRON: The next question is related to the reaction you had to this last question, and that is that Phase 3-- I wanted to understand. Phase 3, which you describe as preclinical, that is studies leading up to the use of this implantation in a sense? Is that correct?

DR. ORKIN: No. Not necessarily. Not necessarily. I could imagine any sort of cell-based therapy, that one would apply in a human experiment, one would like to hope-- Well, the hope is there is considerable preclinical evidence that it might actually work, and perhaps evidence in a species other than sheep, or one might want to know primate, which would be the closest related to it.

PROF. CAPRON: Okay. Then that--

DR. ORKIN: Because there are species differences and it is not immediately obvious that experiments in sheep or cows would be applicable to human clinical experiments.

PROF. CAPRON: Where would you put, in this categorization, research that involved implantation but did not involve delivery of a child?

Obviously, morally a very controversial step, but in the case of other therapies not involving reproduction, it is the sort of thing that happens all the time. That is to say you use it in very low doses to check toxicity and so forth, and you use it in a small number of people on a therapeutic dose, in Phase II and then Phase III, a larger number, and so forth.

In other words, you are stepping out into somewhat unknown territory. You have done all your preclinical work in animals, you have done it in, and

so forth and so on. Where would you put that other? Or is that inherently something that, in your view, could never happen?

I mean, in other words, if you ever take the plunge, it is from the moment of fertilization right through the implantation and birth, or is that a barrier, the fact that you can't legitimately do that means that we should never take that up, that further step?

It is a compound question.

DR. ORKIN: As I said, this is a difficult issue. This is what I put in Phase 4.

PROF. CAPRON: So you are putting that in Phase 4?

DR. ORKIN: Yes. So I would just say that, with present knowledge and predictive powers that I would have, I would say it is not permissible.

Obviously, if one ever got to that point of using embryos in an implantation sense, one would be obliged to monitor the development of those embryos with all the kinds of technology which one can use to monitor an embryo *in situ.*

PROF. CAPRON: Well, *in situ,* but-- I mean, the concern that I have here is that I think we need to express the ethical problems with any particular approach, and I understood you to be saying you see very substantial ethical problems. You didn't spell them out, and we have been grappling--not too successfully yet--with them this morning.

But with the research process of getting to the point of doing an implantation and carrying it through, and I would expect, although I don't know this, that if a person is working agriculturally with sheep, or cows, you might have a process in which you interrupted the pregnancy at various stages because you were concerned about is the development normal, and what you learned new scientifically

from the process.

Clearly, however, that is not the kind of presumption we would go into in a human pregnancy, and so when you say that further research could answer that, if I understand you to be saying, if you ever got to that stage you would see it, because of enough preclinical knowledge, that you would say that if we ever got to it, it would be on the basis that we were going to carry through.

In other words, you monitor the sense of is there a gross abnormality, but only the kind of monitoring that is not disruptive of the potential of that life to lead to a born child.

DR. ORKIN: That is right. If you ever got, I think, if you ever got to that stage, the intent would be to go forward, but it isn't clear to me how one could get to that stage. I am no ethicist, but I have a problem with that.

(Laughter.)

PROF. CAPRON: And--

DR. ORKIN: But let me just bring up one other idea. I mentioned the notion of choosing to have children as potential transplant donors, which is a known kind of event.

One could imagine, extending your arguments--and I am not proposing this at all--but one could have an embryo implanted for development to a point at which you could get material for transplantation and then interrupt the development of that embryo, which I think would obviously bring major--

DR. SHAPIRO: Ethical issues. Yes. Obviously.

DR. ORKIN: But I recognize that even without being an ethicist.

PROF. CAPRON: The final question, information, is you made reference to stem cells at some point and their own totipotentiality.

Are the kinds of research techniques that are being talked about, in

terms of basic science and having these cells to manipulate and to study in the laboratory, ones which anticipate that the cells will be--these cloned cells from nuclear transplant--will be different and more advantageous for research purposes than stem cells?

And I want to understand. One of the reasons that is given for not precluding the research is about the value of these cells as objects of study. And I am trying to understand what is there about the cells that makes them better objects of study than stem cells in terms of the totipotentiality?

DR. ORKIN: Embryonic stem cells, you are talking about? Which use of stem cells? Stem cells can be used to describe stem cells of a tissue. For example, bone marrow has stem cells.

PROF. CAPRON: Yes. Yes.

DR. ORKIN: Or stem cells in the sense of embryonic stem cells?

PROF. CAPRON: I meant the non-embryonic stem cells.

DR. ORKIN: Non-embryonic. Well, I think the main advantage would be any of the embryonic white cells would have greater potential than any of the kinds of stem cells in--

PROF. CAPRON: Greater potential for what?

DR. ORKIN: For different pathways. In other words, one can now purify or have evidence that there is a blood stem cell but, for example, a stem cell that would give rise to a liver is more hypothetical in a sense. And one does not have the capability right now of having that at hand. It might give a--

PROF. CAPRON: And so are you suggesting that it is hypothetically then possible to grow a liver from one of these embryonic stem cells?

DR. ORKIN: Or stem--

PROF. CAPRON: An embryonic stem cell?

DR. ORKIN: Yes. The liver stem cells you might grow either from an embryonic stem cell or from an early embryo.

Now, as I point out in the draft, one can, even with embryonic stem cells with a mouse, which is the best embryonic stem cells we know of, you still cannot do that, so we are talking about experimental notions, but theoretically I think it is possible.

PROF. CAPRON: Thank you.

DR. SHAPIRO: Thank you. Tom?

DR. MURRAY: I only have half as many questions as Alex. One each.

DR. SHAPIRO: We are going to put a limit in a minute on the kinds of--

DR. MURRAY: And I will try to make them brief.

DR. SHAPIRO: --combinations of questions people can ask.

DR. MURRAY: Dr. Rossant, if I-- I am wondering if I read your paper correctly about Dolly, because I think it is just interesting even to have our facts straight. Is it--

Am I correct in thinking that it is not clear that Dolly actually came from a fully differentiated adult cell, but possibly from just a sort of tissue stem cell that we have just been talking about? Is that true?

DR. ROSSANT: Yes. I think-- I mean, that is acknowledged in the paper and that certainly is not clear. There were no attempts in those experiments to make sure that they were really, that the nuclei were from cells that were highly differentiated.

I contrast that with the experiments I described in the frog where, in fact, there were great pains taken to try and prove that the nuclei were from really fully

differentiated cells.

So it is possible that those less differentiated cells might still be in mammary gland, or sort of the growth of the mammary gland later might be the ones that worked.

That is a-- I am not sure that is a necessary limitation because a lot of tissues do have cells that are less differentiated, not right at the end of the line and so-- But that is true.

DR. MURRAY: And what people find, at least many people find, a concern about trying to clone a whole person; it isn't that the degree of the differentiation of the cell from which the cloning is done; it is the fact that it is a preexisting break.

But I think what your paper brought home to me in a way that reading Wilmut's(?) didn't quite so graphically, is that really differentiation of cells, even in adults, is a matter of degree, and we ought to think about-- So a whole different-- It is not a question of adults with everything fully differentiated. I mean, I knew this in theory, but I think it may be relevant as we go along.

In fact it leads into my question to Dr. Orkin.

Thank you both, by the way, for excellent, clear, helpful presentations.

Dr. Orkin, I know that you are aware that there is a Congressional ban on federal funding of any research with human embryos. Some of the things you described include what struck me as a potentially very desirable goal of learning how to dedifferentiate cells, at least to the point where they are pluripotent; that is, incapable of, not an embryo, incapable in fact of becoming an embryo, but perhaps capable of being differentiated into a variety of tissue types.

How much of the important science can we do by being able to do

research on mammalian embryos but not human embryos? Will we begin to understand the processes of dedifferentiation and redifferentiation?

Is it possible that we could do most of the basic science that needs to be done on that sort of animal embryos and, as we come to understand the mechanism, be able to then take your cells, dedifferentiate them to the point where they are now pluripotent, create cells, stem cells, of a tissue type that would actually help treat diabetes, help treat Parkinson's disease, help treat other sorts of things, without ever actually creating a human embryo, without ever creating the entity that at least some Americans find, would find, offensive to do research on?

I just really don't know the answer; I am curious.

DR. ORKIN: I don't think any of us know the answer, but in theory I think you are correct; that you might be able to. However, as Janet brought out, there are significant species differences in the way early embryos and cells are programmed--deprogrammed, if you will, and reprogrammed.

And I think it is unlikely that we have sufficient information from other kinds of experiments, short of eventually doing it with human material. But, you know, I think that we shouldn't say--

We shouldn't take the position that if none of the human experimentation goes on we will not learn some of the other basic principles. They are coming from experiments in mice and rats, primates or sheep. So basic principles are coming from that kind of work.

However, if one wants to apply it in a practical sense and ever get to the cell-based therapies that we might think would be useful, it will be necessary at some point to do it on human material, I suspect.

And the experiment-- The option of doing it directly with adult cells in deprogramming or reprogramming; that is, as I said, sort of the Star Wars

technology. That is probably much more difficult than the notion of taking some cell, that is an embryonic kind of cell, that has been reprogrammed by an egg. I think the egg may know much better than we would for quite a while.

DR. SHAPIRO: Thank you. Zeke?

DR. EMANUEL: Yes. I want to thank both of you for really clear presentations.

And actually I think this distinction between sort of embryo research, cell-based therapy, and then cloning for implanting is certainly helpful to me because the ethical arguments, as I think Dr. Orkin clearly expressed, are different at each level, and probably the most contentious ones are on the implanting and we might be able to agree earlier on.

And I wanted to-- Well, I wanted to ask you a question. We have heard different assessments of the value added to being able to clone human cells, embryonic cells, and see them develop through the blastomere stage, for our scientific understanding and the ability to make manipulations.

We have heard everything from it is going to be essential that we do that to the marginal benefit of cloning in this scientific enterprise is probably not going to be that great; that we have a lot of other techniques available to us, looking at pluripotent, bone marrow stem cells, or liver cells; that we can probably make a lot more progress there without introducing this other bogeyman that will get everyone up in arms under the rubric of cloning.

And I wanted your assessment of that. And I understand that if you are going to bring it to therapy in human beings, at some point you are probably going to have to do something that looks like a work in human embryos, but short of that, for the scientific advances.

DR. ORKIN: Janet?

DR. ROSSANT: No, you go.

DR. ORKIN: I think most investigators would contend that the basic principles and largest bang for the buck is going to come from basic research outside of human embryos. I think most of us would agree on that.

However, I think there are species differences, and if one wants to get to an application down the line it is going to be important, at some point, to have some human material work or research.

That is one of the reasons why, in considering the oversight, what I suggest is that some mechanism be established to have oversight over the animal cloning research independent of human research, and perhaps incorporate within that some more developmental biology perspectives as to the mechanisms that are pertinent. And then that body would be able to monitor and regulate, if you will, more invasive kinds of research that we are talking about.

DR. EMANUEL: You agree?

DR. ROSSANT: Yes. I guess the only thing I would add-- I think you were trying to make a distinction between whether we need-- Well, correct me if I am wrong. But were you trying to make a distinction between whether we need the nuclear transfer aspect of cloning in order to move ourselves forward in these cell-based therapies, and do we need that in humans?

DR. EMANUEL: Right.

DR. ROSSANT: And I think I would say there I would think probably minimally that the nuclear transfer technology, understanding how the oocyte reprograms the nucleus, can be understood at the basic level in other species. We may need to check a little bit because of species differences in humans. But that even without that understanding from nuclear transfer, we are going to be able to move forward in terms of cell-based therapies.

But I do agree that, in order to move cell-based therapies in humans forward, we are going to have to work eventually with some human embryonic type cells. I don't think we are going to be able to avoid that.

So that I know in essence is a different issue, but it is related.

DR. SHAPIRO: I would like to ask about, just for clarification, one point here because I am not sure-- Perhaps I wasn't listening carefully enough.

I thought one of these questions was do we need human embryonic material to really push forward the scientific frontier, or is that really essential? And I thought that the initial answer was no, not at this stage. Perhaps some other stage down the road it would be.

Now, did I understand you to be saying the same thing?

DR. ROSSANT: Well, I think--

DR. SHAPIRO: Whether it is nuclear transferred or not.

DR. ROSSANT: Yes. I think we are saying the same thing. We have got to get a long way and understand the basic stuff on animals, but we will need to work with human embryonic material.

DR. SHAPIRO: Good. Thank you.

DR. EMANUEL: Even if all we want to do is the cell therapy kind of route?

DR. ORKIN: Likely.

DR. ROSSANT: Likely. Because the alternatives are the Star Wars approaches.

DR. EMANUEL: Right.

DR. ROSSANT: The more likely approach is to work from the bottom-up, rather than the top-down.

DR. EMANUEL: Understood.

DR. SHAPIRO: Bernie?

DR. LO: I also want to thank both our presenters for very lucid and very helpful presentations and papers.

First, just two questions. A quick question and a longer one.

The quick question is to rephrase the previous two questions. Would it be appropriate to say, based on your answers, that you do not think a continued moratorium on research involving nuclear transplantation/cloning on human cells, a moratorium in the foreseeable future on that research would set back scientific progress? Is that a fair inference to make from what you said?

And would most or all of your-- Would most-- Would the consensus of your scientific colleagues in the field agree with you on that?

DR. ROSSANT: I will try it first. I think that, my personal opinion and I know one that is reflected by certainly a number of scientists, is that a continued moratorium on human nuclear transfer research involving any implantation or process would be fully supported.

I think it would be harder, when you move that back and say, would we continue, should we continue, to have a total moratorium on all aspects including *in vitro*, then that is a harder one.

DR. SHAPIRO: Okay.

DR. LO: I thought I heard the two of you say a couple of minutes ago that the biggest bang for the buck in basic science was actually studying these processes in animal, in other species, although eventually you would want to do some human cell research if you were going to do either cell therapy or-- So part of what I am asking you is--

DR. ROSSANT: Yes, that is quite right, but you are now dealing with the scientist saying, "Oh, let us be careful about regulation."

DR. LO: Right.

DR. ORKIN: I think as sort of a general statement, most scientists are uncomfortable with the notion of moratoria or banning of any kind of science as long as it can be subject to some oversight.

DR. ROSSANT: Yes.

DR. ORKIN: So I am not comfortable with the notion of banning any kind of research, however--

DR. LO: We are talking about a moratorium, not--

DR. ORKIN: --I am comfortable with the notion of a moratorium on implantation, specifying that. Or, with implantation, whether to proceed further or not.

But I would also say--I think we are both saying--that the biggest bang for the buck is going to come from the more basic work. However I think if one takes the position that, "Well, we will sit tight and we won't do any human work for X number of years," we may miss the boat in a sense, because research very often is synergistic in sort of parallel areas and it will be, I think, an advantage to having some research go on.

DR. LO: Let me ask--

DR. SHAPIRO: If it can be appropriately long.

DR. LO: Thank you. Let me ask the question I was going to ask, which has to do with your next-to-the-last slide, your different phases in Phase 4.

You said very strongly that you thought, at the current time and for the foreseeable future, to attempt to implant any manipulated human embryo through nuclear transfer would be unethical because of the unknown risks and the lack of adequate animal preclinical experimentation?

DR. ORKIN: Yes. I think besides the ethical issue, it is just a bad

experiment.

DR. LO: A bad experiment? Oh, okay. How widely--

On the other hand, we have heard anecdotes saying that, to the effect that people who have sort of talked to clinicians working in commercial for-profit IVF enterprises say they are ready to go; that they think there is a tremendous advantage to being the first out to do this, there is a huge market in it, and they think that, "Why not be the first one to take the first step?"

Can you give us a sense of whether you think your ethical concerns are shared among people outside sort of the academic sort of research tradition and really fold in, you know, the commercial idea for enterprises?

Do they share your ethical concerns, or are they set to start cloning as soon as they think the ethical concerns are looked at?

DR. ROSSANT: You have this M.D.

DR. LO: I am an M.D. I just--

(Laughter.)

DR. ORKIN: Well, I don't-- I don't-- I haven't spoken to anybody in the IVF clinic settings.

My brief survey of non-scientists and non-medical people I have come in contact with, since David called me three weeks ago to commission this paper, I don't think anybody is in favor of implanting.

I mean, there will always be people who want to do things first and sometimes for the wrong reasons, and I don't know whether anything can be done to prevent those people from doing something idiotic, if you will, if they want.

DR. SHAPIRO: Carol?

DR. GREIDER: I just wanted to add a response that we have sent out questions to a number of societies, and a lot of the societies that are involved in

that sort of research. You know, IVF sort of research was included there, and so we should be getting responses from them. We have some of them I think in the packet, and we will be summarizing that shortly for you.

DR. LO: Okay. One of my concerns is in the novel, the commercial IVF organizations, that are members of SARC(?) for example. And what my concern is, is that the ethical, thoughtful scientists share your concerns and--

DR. ORKIN: I would hope so.

The other thing is I think the major drive, or the major motivation for IVF clinics is obviously economic and, if the procedure doesn't work and can't work efficiency, which is I think what Janet said and what I have implied, it is not going to be very useful to them anyhow.

DR. LO: Well, you could run that argument that if clients are willing to pay, and it is a very profitable procedure--and if it doesn't work too well--because you get more shots at it.

DR. ORKIN: But if it fails every time they won't be willing to pay.

DR. SHAPIRO: Thank you. Alta?

PROF. CHARO: I only have one question.

(Laughter.)

DR. SHAPIRO: Good. I will give you some credit for another question later.

(Laughter.)

DR. SHAPIRO: If there is more than one clause in this, you get no credit.

(Laughter.)

PROF. CHARO: For both of you, I would like to draw your attention to--

DR. : There goes your credit.

(Laughter.)

PROF. CHARO: Dr. Orkin, I would like to draw your attention back to pages 14 and 15 in your own paper where you talked about how research might proceed and build a little bit on Bernie Lo's comments.

You suggested that if it were to proceed it ought to be accompanied by scientific peer review and a set of guidelines for what is ethical or unethical practice regarding embryo research, an oxymoron in some people's minds because there is no version of embryo research that is ethical, but for other people there are shades of gray.

DR. ORKIN: That is why I think it says "reasonable" in quotes.

PROF. CHARO: Fair enough.

DR. ORKIN: I deferred on some of those issues to those more expert.

PROF. CHARO: Now, in the absence of federal funding, there is the absence of a federal office that would serve that function as part of the funding process. I am interested in your impressions, and I know that they are going to be anecdotal, of the degree to which there is sufficient private sector interest in this field; that there will be a fair amount of funding from large and influential funders for a variety of research avenues that would use embryos, such that you could try out the idea of essentially, in the private sector, creating its own voluntary kind of ethics and technical review board in which its own set of self-derived and self-declared rules would apply, protocols are reviewed, and in which scientists voluntarily submit their protocols to this kind of voluntary society-based protocol review, not just kind of guidelines, but actual protocol review in order to control the development of this research and stage it perhaps the way you suggest.

What is your impression of the likelihood that all of those things might happen, given that there will always be rogues, that even this could happen?

DR. ORKIN: This is a tough one because I really have no first-hand knowledge on the degree of private capital available.

My own view would be however, though, that if one brings this work to the public scrutiny, open in terms of federal support of research, it is likely to make it more reasonably peer reviewed and I think higher quality. I think the kind of positive science that might be supported in a private sector may not be of the same quality.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I have two questions to ask, one of Dr. Orkin and one of Dr. Rossant.

Dr. Orkin, I have a question about the progress of science and the way in which a scientist makes a decision about what to pursue in his or her research program.

In your excellent talk to us, you mentioned that you think some areas are not likely to be pursued in humans in the foreseeable future simply because it wouldn't be a good choice for a scientist to make to pursue that line of research.

But in reflecting on your comments, I recalled an article that I read in *Science*. It was written by Watson, who is credited with discovering the structure of DNA, and he was giving advice to young scientists, and he was encouraging young scientists to be risk-takers, to do things that would go against their mentors perhaps. He was encouraging a different mentality among scientists than that which seems to underlie your comments. Your comments seem to have underlying them almost a kind of conservatism that a scientist is going not really to do what is risk-taking.

And I just wondered if you could comment on that? What do you

see as the culture or the atmosphere that exists in the training of people who might pursue this kind of research?

DR. ORKIN: That is a difficult question, but I would discriminate here research being done in strictly a laboratory setting and that done on people.

In other words, I think what Watson's comments refer to is risk-taking in an intellectual sense. When your mentor says, "I don't think you can determine the structure of DNA," he says, "No, I am going to do it," and he determines the structure of DNA.

I think that is different from risk-taking when it comes a clinical situation. I think one has to be conservative in terms of patient protection.

DR. SCOTT-JONES: Okay.

And the second part is related to Dr. Rossant. In your paper, you talked about the research that was done in the 1960s by John Gerdon, and there were attempts to clone frogs. And it would seem that the motivation for that was simply to understand more about gene regulation.

Could you say just a little bit more about what motivated that research? What was driving the scientists? And, again, my goal is to understand more about what scientists, how scientists make a decision to pursue a given line of research.

DR. ROSSANT: Okay. Well, what-- I think clearly you have to move back to sort of the 1960s where we understood much less about how gene regulation occurs. We knew that all cells contained DNA, we knew that DNA encoded genes, and we knew that cells, as they develop, expressed into genes.

But it wasn't clear that, since development is a sort of progressive specialization, it really wasn't clear whether that specialization occurred by an irreversible process of losing pieces of DNA or changing them into some way that

could not be brought back, or whether it occurred just by turning genes on and off.

And that was really the basis for his experiments. It was really to address that fundamental issue. And the fundamental answer was, well, if the DNA must be still there in a form that can be reprogrammed. And, as I say, I think, although his experiments never got an adult frog, it was if you can take a skin nucleus and get a tadpole, that is good enough for me. You know, there is a lot of DNA and a lot of genetic material there.

And so that scientific question, using that technology, has really not been addressed since. I mean, everybody accepts that. There have been many moves forward to understand how that process occurred, how genes are turned on and off without changing the DNA.

The experiments that took place in the nuclear transfer in mammals, I think were driven a lot by different things. One was, first of all, was this really true in all species?

And, in fact, when it was found that in nuclear transfer in mammals it was less efficient than in frogs, that was a bit of a surprise because the mass embryo develops quite slowly, lots of time for everything to be reprogrammed, and it didn't happen.

So there were some questions then. It can't be the DNA; what are the other things that happen in cell specialization? So there was some-- It led into other questions of how cell specialization occurs.

So those were the driving forces.

And then, beyond that, the reason why all the nuclear transfer experiments you have seen in the last few years have been done in cows and sheep is because of the agricultural importance of being able to make clones. So that was really driven by the biotechnology, with some science coming out from it because they

need to understand the science, but the technique drive was by technology.

DR. SHAPIRO: I want to just ask a follow-up question on that. I had the impression, when all this news first broke, that many scientists claimed in public they were very surprised. They were surprised that the cells contain this potential still if we program it properly; that somehow they thought still that there was some reason why this could not be done.

But your paper says quite the opposite; that no scientist, from watching the experiments, ought to have felt that way.

DR. ROSSANT: No. I don't see why they were surprised. I think what people were surprised-- It really was thought that it could not be done, and the reason has nothing to do with the DNA, but for technical reasons.

DR. SHAPIRO: For purely technical reasons?

DR. ROSSANT: Yes.

DR. SHAPIRO: And that shouldn't have been so surprising.

DR. ROSSANT: But the scientists did, in print, say they were absolutely amazed that adult cells still had the potential and, you know, I think we need--

DR. SHAPIRO: Well, that came across very clearly in your paper. That was actually very helpful.

DR. ROSSANT: Yes.

DR. SHAPIRO: David?

DR. COX: So I would like to ask a question of Dr. Orkin, and it is a complicated one and I am sorry.

DR. ORKIN: We have had a lot of easy ones.

(Laughter.)

DR. COX: It basically has to do with how new technologies are

applied in clinical practice with human beings in this country, and the rules and the process by which that happens.

Certainly we know one format by which it happens, which is that there is peer review research and it is done on animals, and then it is done in experimental carefully controlled human subjects trials with human beings, and then it becomes standard of practice, getting applied in clinical work.

But in the case of reproductive technologies, that hasn't been the path. And so new things that come along, and it doesn't have to just be reproductive technology, but certainly in the case of nuclear transplantation, what would be the process, if someone said they weren't interested in the academic research, and they weren't interested in that because they decided that they, A, want to use human material now and, B, they want to drive this forward?

So, as a physician, speaking solely that way, not as a person in the private sector, what would be the response to anyone trying to carry out that kind of process? What controls exist in our society, if any, for dealing with that kind of behavior? And how is the public protected in that regard?

DR. ORKIN: I am not certain I am the right person to answer this question. I think, you know, the public is protected by some government agency, like the FDA, I imagine. They are protected by local IRBs and hospitals. And I am not certain what kind of protections exist outside in the private sector. And I think that is another reason to try to bring it more in the open.

DR. SHAPIRO: We will get to some of this in a few minutes.

DR. COX: Yes.

DR. SHAPIRO: Did you have another question, David, or is that it?

DR. COX: No. I just wanted to-- The-- I don't know the answer to that either, Stu, but I think it is a very important question that we try and get some

information about.

DR. SHAPIRO: Larry?

DR. MIIKE: Clearly I wanted to focus some of our deliberations on the issue around cloning to develop a human being and cloning to do what is--I think everybody would consider--legitimate ends for the good of society in terms of the research. These are the kinds of areas we are talking about.

But scientists often get thrown a totally different paradigm and they have to change their assumptions about everything, and that leads to a next rise. Even with a gradual knowledge, you have leaps in knowledge.

Might not this be one opportunity? Because what I hear is that, yes, you can-- Well, let me back up a second.

To me, the package is the issue and not the contents. The oocyte is the issue and not the DNA. Because it is the oocyte that allows you to do all of these kinds of things.

The problem is that when you take the contents and put it in the package. To people with certain religious points of view, or moral points of view, that is a human being. Animal rights aside, a lot of that will go on in the animal arena.

Does that necessarily-- Doesn't that change the paradigm? And that tells you that you don't have to think about the animal research as being applicable in an identical situation in the human side, and you will be learning what the human oocyte is capable of doing from your animal models that are doing the classical combinations?

And perhaps you may come out and still be able to use human tissue that-- I am assuming that there is some human tissue research that would not be objectionable by most or maybe everybody, but would that-- What are the possibilities? And I know I am just asking you to speculate, but if we learn so much

from animal models, you don't really have to replicate that in a human model in order to reach the aims that you are getting. Perhaps you just need to put one particular gene in the oocyte and it can do stuff like that.

DR. ROSSANT: No. I agree. I think that-- I think I stated in the paper that I think what we all understand from knowing in animal models how the oocyte reprograms the nucleus. It may give us clues as to not how to sort of make a soup necessarily, but the key components of the oocyte cytoplasm may then be applicable to changing adult cells, or stem cells, from other tissues. I didn't say that very clearly, but I agree.

If you understood what the oocyte did, those components may work on adult cells without having to use the oocyte, per se. Yes.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Two points.

DR. SHAPIRO: Only two?

MR. HOLTZMAN: Well, the first is just a statement. I think, and it will come up I think in the next section, we have to be very clear about different kinds of research. People are using the term "peer review," and it is very different whether you are dealing with clinical research, an IRB review.

Peer review typically is about papers or grants and, for the moment, to imply that stuff in industry--I am thinking here of the biotech industry--conducted by scientists who, you know, a few months ago were your colleagues at Harvard. They just happened to come across the river. I don't think the nature of the kind of research they do, often in collaboration with other people like yourselves, changes.

So I think we shouldn't put a quality standard here and think that industry is bad research.

DR. ORKIN: No. I didn't mean that kind of industry. I was

referring to sort of like for a closet.

MR. HOLTZMAN: And so I think-- And that comes to the differences between what is clinical research, in the sense of FDA-regulated versus clinical practices, which it is unclear of the nature of the regulation.

The second was a question. It is a question for clarification, and I guess it is to Dr. Orkin.

The most likely research program you are laying out, or for potential utility in the mid- to longer-term, is for the cellular transplants, where the goal is these pluripotent different stem cell populations for transplantation.

Am I correct in thinking that there is really two different lines of research? One is going to have to be going down somewhat simultaneously, but the first is having to do with the conditions for culture in say the ES cells, so that you can get these differentiated populations?

And you could have had that discussion before Dolly; that that is a research program totally independent of the issue of this nuclear transplantation.

And that the new line of research having to do with the nuclear transplantation is because it now makes conceivable, or you can now think about autologous cell transfers, and therefore overcoming the potential rejection issues.

And so the reason I am asking for that clarification is I heard one line of questioning that seemed to be going down the path, "Well, you don't have to bother with the nuclear transplantation; you can just go down this other path," but you wouldn't be addressing the potential for allogeneic or for autologous transfer, which does require seeing whether you can establish the conditions under which the somatic nuclei could be reestablished, reprogrammed.

Is that accurate?

DR. ORKIN: Yes. I think that is accurate.

I think the main power--and I think it is in the draft--is that you can select cells out of a predetermined genotype for these purposes. That is the key.

DR. SHAPIRO: Carol?

DR. GREIDER: Can I follow-up with a question? This is more of an immunology question and I don't know if you will be able to answer it, but following exactly on what Steve just said, the idea of autologous transplantation as sort of the hope of what you would use these cell lines for.

Is it known whether, when you take a nucleus and put it into a oocyte and then differentiate it, whether the immune cells would differentiate so that you would even get an autologous situation, or is the reprogramming/deprograming going to change the groups of genes that are expressed such that it won't be autologous?

DR. ROSSANT: I think it should be fine. I don't see any reason that would be a concern. Unless, of course, you would view the lymphocyte.

PROF. CAPRON: Because that is changed?

DR. ROSSANT: Because that actually has changed DNA.

DR. SHAPIRO: Arturo?

DR. BRITO: In the process of our deliberations and our discussions--and I think as a commission we are progressing--sometimes I think, at least I have to go back and answer some questions that the media will ask, or the general public, or people had, that we forget.

And one of them is this fear that we are producing identical human beings. And the way I usually answer that is, number one, is to say that you cannot, you know, that you can't control for other factors other than genetic material, et cetera, but even taking that and putting that aside for a second, we also have what Alex alluded to with his question earlier about the mitochondrial DNA.

And I think it is important to discuss, in our paper, the scientific, the differences between what that small percentage of DNA is and how that effects this clone, and how dissimilar the clone would be to the original cell.

And should we get to the point where there is actually animal--or further animal--or human implantation, et cetera, how dissimilar would that be just from a genetic basis, and what do we know about the mitochondrial DNA? And is this just a step in the process?

If we get to the point where we can actually produce a human clone, that is dissimilar only to the mitochondrial, then are we also going to be trying to transfer--or an animal clone--are we going to try to transfer mitochondrial DNA?

So what I am really asking is for an elaboration and an explanation of what the dissimilarities would be on a genetic basis?

DR. ROSSANT: My-- Can I just-- My personal feeling on this whole mitochondrial thing is that this is a little bit of red herring. It is a small proportion of the DNA that encodes largely the proteins that the mitochondria, which is a sort of energy source of your cell, needs to function. They are not encoding genes that code the color of your eyes, your hair, that encode how your brain works, or anything that we think of as the qualities of a human being, and I don't think they encode personalities.

DR. BRITO: You don't-- But how much of that has been mapped out? How much of the mitochondrial--

DR. ROSSANT: All of it, pretty well.

DR. BRITO: Then it is-- Okay.

DR. ROSSANT: So it really is I think a little bit of a red herring. It is absolutely true that the mitochondrial DNA would not be a copy of the adult, but I think that is a minor thing.

It has been suggested, of course, that there are a few rare mitochondrial-inherited genetic diseases and this gets back to the pronuclear transfer situation that could be fixed that way. That is a different issue.

But I think when-- I think that we should accept that, if this were to happen, we really would be cloning essentially the total genetic material of an adult human being.

DR. SHAPIRO: Carol?

DR. GREIDER: If I understand the way diffusion works correctly, the mitochondria are also going to be transferred as well, so you will end up with mixed mitochondrial oocytes.

DR. ROSSANT: Well, you might. My-- I am not sure. That may have been looked at in the animal systems. The amount-- I mean, the amount that comes in from the oocyte would be much larger than from the blastomeres. They predominantly are going to be of the oocyte type.

DR. COX: If I could just make a really quick point in this case. I am sorry to do this.

But lest it be lost at this point, mitochondrial DNA is normally only transmitted by the mother, and in the context of cloning it is probably an interesting point to make.

DR. ROSSANT: That is right.

PROF. CAPRON: But could we just have one more word of explanation from the-- Among-- These are genes. Are there enough different alleles here that different mitochondrial combinations express the cell's ability to power-up, and do whatever functions the mitochondria are responsible for differently, so that there could be some difference in the functioning of the cells with different mitochondria or--

DR. ROSSANT: Presumably, yes. I mean, there are allele differences.

PROF. CAPRON: In terms of the efficiency with which they enter?

DR. ROSSANT: Yes.

PROF. CAPRON: So that--

DR. ROSSANT: Yes. But, you know, we all-- Most of us are doing pretty well with different mitochondrial DNA.

PROF. CAPRON: So that the range is not significant, you are saying? I am trying to understand. I mean, usually if you were saying, you know, there is a great little power plant going here, and a not very efficient power plant going here, that you would expect the organism itself to manifest some of that difference in the way it produces proteins and so forth, but--

DR. ROSSANT: Well, I mean, there are alleles that really are damaging. There are some that--

PROF. CAPRON: Yes. But short of the diseased ones, that the rest of the range is, as far as we can tell, unobservable in respect to--

DR. SHAPIRO: It is a new story.

PROF. CAPRON: Or it hasn't been studied enough? I mean, any answer is--

DR. ROSSANT: Well, I am not an expert on mitochondrial DNA.

DR. SHAPIRO: I guess from your speculation--let us put it--you would expect very little impact, but some things are unknown.

Excuse me. Eric, do you have a question?

DR. CASSELL: No.

DR. SHAPIRO: Well, we are running past schedule, which is fine, but I don't-- We do have--are very fortunate to have--Drs. Lo, Orkin, and Rossant

here, so if there are any further questions we certainly should feel free to take the time now to ask them.

Yes, Bernie?

DR. LO: Just to follow-up again on this discussion about mitochondrial DNA. Again, is the view you are expressing a consensus, or near-consensus, view among the reputable scientists in the field that, for all intents and purposes--

(Laughter.)

DR. LO: This is a point that, as Arturo said, that does come in the--

DR. ORKIN: I think phenotypically--

DR. LO: Phenotypically--

DR. ORKIN: --you wouldn't expect any differences.

If you are asking is someone genetically identical who has different mitochondrial, by definition they are not, but the idea of generating humans to be identical I would say is preposterous so I--

DR. ROSSANT: I--

DR. LO: But you are saying if you wanted to as much as possible control the genetic genotype of the offspring, for all intents and purposes, doing it this way is the same as doing it with a 100 percent DNA transfer, if you could get the mitochondrial--

DR. ROSSANT: In terms of what we, as people, think of as human traits, I think that is--

DR. LO: Is it--

PROF. CHARO: I would love to ask just one more thing, but on a different-- No. Also on the mitochondrial issue, but from a different concern. Carol convinced me last month that it was a red herring.

The fact that you are combining in an unusual fashion some paternal and maternally derived, you know, adult cell-derived, as well as oocyte-derived, mitochondrial DNA means that you get this add-mixture that is not typical in the usual kind of fertilization process. Is there any reason to believe that that is, in itself, going to be associated with higher rates of abnormal development at the two-cell, four-cell, eight-cell--in other words, the early--stages of embryo development?

Is there any reason why anybody should be concerned in terms of effects on embryo development, fetal development, or child outcome of that phenomenon?

DR. ROSSANT: Well, again, I think that there is enough nuclear transfer data in animals, especially with embryonic nuclei--never mind--which will would carry over mitochondria, to suggest that that is not a major concern.

PROF. CHARO: Great. Thank you.

DR. SHAPIRO: Arturo?

DR. BRITO: Can I ask a true/false question? This is a--

(Laughter.)

DR. BRITO: Is it-- Is it-- Okay. It is true or false. A clone, the way that the scientific technology is now, a clone is genetically identical to-- Is the equivalent of identical twins? That is false, right?

DR. ROSSANT: Except for the mitochondrial being--

DR. BRITO: Right. Right. That is what I am saying. So it is-- Okay. That is--

DR. ORKIN: Or except if you take a nucleus of a female and introduce it into her own oocyte, then it would be identical.

DR. ROSSANT: Yes.

(Simultaneous discussion.)

DR. SHAPIRO: Carol?

DR. GREIDER: I am just going to restate something that David Cox said a few minutes ago, and that is that normally mitochondrial aren't inherited at all from the father, so if all those fathers sitting around the table think that they have contributed to the genomes of their children, that is only the nuclear DNA, and so that is the discussion we are having here. In terms of what we think of as normal inheritance and human genetic inheritance, the mitochondrial are not considered part of that sort of operationally.

PROF. CAPRON: We get it all from Eve.

DR. SHAPIRO: Okay. David?

DR. COX: In terms of talking about potential things that happen as a result of nuclear transplantation and not sort of embryonic defects, or prior-to-birth defects, but is there--and this is for either Dr. Rossant or Dr. Orkin--in live-born animals that are a result of nuclear transplantation, are there known problems with those individuals that aren't normally seen in live-born animals, or that occur at higher frequency in animals conceived as a result of nuclear transplantation, as opposed to normal sex?

DR. ROSSANT: There is some data to suggest that--I think mostly in cows--that you get a what I think is called the "large calf syndrome," so that the animals are unusually large. It is not fully understood.

And I have been unable, in the time available, to really track down the background on this, but my-- I think that it is related--and not necessarily just to nuclear transfer--but to any kind of manipulation in those embryos. And it may be something to do with culture conditions.

So there are-- It goes back really to the sort of risk side of things. There are still some unknowns in terms of just how all the manipulations that you do

to undertake this process actually affect later development. And those presumably are not genetic changes; it is something that went wrong during the culture.

DR. ORKIN: You know, if those changes-- We don't know, but if those changes are due to imprinting, for example, which would seem possible, we know of several human disorders in which imprinting is disturbed and those are very often associated with neoplasms, so that might be a long-term risk that one would never assess.

DR. SHAPIRO: I have two final questions--Steve and Zeke--and then we are going to have to move on.

MR. HOLTZMAN: One of the what I find most compelling concerns that have been raised has to do with the somatic mutation rate of these adult cells, depending on the number of rounds of replication they have been through.

When you talk in terms of thinking about the research program and the responsible research program, how do you think about that in terms of the source of the nucleus? That is, would you be more comfortable if you could find earlier cells that hadn't been through as many replications?

For example, in the Dolly case, there is some postulation maybe it was a mammary stem cell as opposed to a fully differentiated cell. Do you have any thoughts on this?

Is that a fair question?

DR. ORKIN: I think all things being equal, you would want to take the youngest cells available, but I think everyone should recognize, for example, with bovine transplantation, there are also some adults and sometimes considerable ager years, and we don't have a good sense of how many replications those cells have had, but they have been in the body for a long time, and they do quite well.

DR. ROSSANT: I would also point out in natural reproduction, of

course, that the sperm have been through quite a lot of cell divisions, too.

DR. EMANUEL: I guess the last question was to look at these issues of mutagenic load and imprinting and an estimate of the level of problems that we are likely to encounter there.

Now, I know it is a guesstimate, but we do have-- You suggested, just in the response to David's question, that there is some knowledge about the effect of imprinting; that we might have some information about the risks associated with that. And presumably, when we go from an embryo into, an embryonic cell back into an oocyte, you don't have, in the exact same way, a mother and father cell. I mean, mother and father gene contributions.

Now, they are not exactly a somatic nucleus going back, but can you speculate about those kinds of harms and how likely they are to occur?

DR. ROSSANT: I will have a go. We really don't know. In order to know, I think we need nuclear transfer experiments to work in mouse, where we can identify and monitor imprinted genes and how they change in their expression, number one.

But what we do know is that what happens to make the genomes different is that some kind of imprint is put on the maternal or the paternal genome during the mutagenesis. That imprint may not be manifest in terms of different genes being expressed until even the adults, so it has been assumed that in fact the imprint may well be carried on, is carried on, through cell division. It may still exist on adult cells.

Do we have any information that says that adult cells really are so imprinted? If they are, they are probably fine because you have a maternal and paternal genome, put it back in the oocyte. So long as the imprint is stable, you are okay.

There is very little information. There is some unpublished data from a Czechoslovak researcher, Dr. Ferrite(?), who has shown that if you take adult lymphocytes and fuse them *in culture* with early embryonic cells, you reactivate some of the early embryonic genes, including imprinted genes from the lymphocyte. And when you do that, you reactivate them in an imprinted manner.

In other words, the lymphocyte nucleus retains the imprint, although it doesn't express those genes. So it may not be a large concern. But that is one piece of data that I can provide.

DR. SHAPIRO: Once again, I want to thank you both for being here today and for your enormous help to this commission and the papers you produced.

I think that, as you all know, we are running a bit behind time, but I think we do have some ways of catching up here this afternoon. However, the summary reports will, I think, perhaps take a little less time that we had anticipated.

It is now 12:10 p.m.. Let us try to be back here as close to 1:00 p.m. as we can. We don't have any arrangements, official arrangements, for lunch. I am told there is a fast-food heaven downstairs, plus there is the restaurant, of course, here in the hotel for those of you interested in that.

Thank you very much.

(Whereupon, at 12:12 p.m., there was a scheduled recess for lunch, with the meeting scheduled to reconvene at 1:00 p.m.)

DR. SHAPIRO: Let me call our meeting to order. Drs. Lo, Emanuel, Backlar, let's sit down. Mr. Murray, too. I think Tom was also the last one at the copy machine this morning.

DR. MURRAY: I didn't know you were taking notes, Harold.

DR. SHAPIRO: I watch everything.

(Laughter.)

PROF. CAPRON: How do you think he got where he is?

DR. SHAPIRO: That is right.

We are now more seriously behind time than we were before but, as the next item is extremely important, other things we scheduled will have to give way, if necessary.

But I really want to now get on to the legal and policy issues, and that will be jointly presented by Alta and Alex. I think Alta you are going to begin?

LEGAL AND POLICY ISSUES

PROF. CHARO: Yes. I hope that you found, passed out in front of you in your seat, something called "Law and Policy Issues for Consideration by NBAC," which is a summary of discussions that took place yesterday.

It was me, Alex Capron, Larry Miike, Arturo Brito and Bette Kramer, meeting with Lori Andrews, who was the contractor who did the kind of legal status of all the things that are implicated by the cloning report for us, a kind of miracle work, for those of you who haven't bothered to read it yet. Six hundred footnotes in three weeks.

MS. KRAMER: Amazing.

PROF. CHARO: It is amazing, isn't it?

And Lori provided us with an extremely detailed accounting of the

kinds of laws at the federal and state level, as well as pending legislation, that would affect things ranging from research on embryos that are derived from cloning of human cells all the way up to some of the familial patterns that might emerge--or at least the confusion for law about the familial patterns that might emerge--in the follow-up day, if it ever comes, when a baby results.

And our task was to try to take that, hoist it through another very extensive and helpful contract, which we got very late in the week from Bob Plategan(?), on a kind of political history of voluntary moratoria in the area of genetics. And just today now we got the last of the contract, so I think it really kind of fit into this rubric, which is Martha Knopper's piece on international reaction.

And what we did is we tried to identify the full range of policy options that could be considered with absolutely no attempt to identify which ones ought to be pursued.

This was purely for organizational purposes, a soup to nuts, what could be done, and what are the legal obstacles that we now know would be posed by adopting any of those approaches? What would be the laws that already further those approaches? Where are the places where it obviously connects to the ethics and science discussion?

So please think of this as an extraordinarily sophisticated--well, sort of sophisticated--much better outline than we could have had before those contracts came in.

And that was the purpose of getting together with Lori, to work this thing through, was to get to this outline.

Let me quickly just run through the first part of it with you to make sure that everything is clear.

"A" is the one that talks about our policy options in the area of

research without any attempt to bring a baby into the world. Alex will then take over in the second half. And this is priority only, so I am going to be very brief.

We have arranged them from what we think of as being kind of the extreme, most extremely supportive position to the most extremely restrictive position, and so the first policy option would be total permissibility of research on human cells derived through cloning and accompanied by federal funding for that research. We considered this to be kind of the most supportive possible position.

And if this were one that the commission really wanted to adopt as their kind of bottom line, it would require a variety of things, including lifting of Congressional prohibitions on certain appropriations for embryo research, reversal of the 1994 position by the Clinton Administration regarding federal funding for any research that makes embryos specifically to do research on them without an attempt to transfer.

It would nonetheless have certain protections in place, certain human subject protections people have said over the years.

And "D" kind of surprises me. I didn't remember seeing this in there. There used to be a requirement that an ethics advisory board review these protocols before they could be funded. That requirement was deleted by the President a couple of years ago, so put a question mark on that one.

Alex may speak to that perhaps. I misunderstood the history in that area.

The second one is total permissibility of this kind of research, but absent federal funding. It is a kind of step back in terms of supportiveness.

Please note that one of the justifications that is often raised in taking a position like this is that it means people who will host things don't have to be "complicit" in them by virtue of their tax dollars being used; an argument that has

come up by people who want to isolate tax dollars that might be used for Defense Department-related and nuclear-related research.

Next are two versions of what we call conditional permissibility. And we phrase conditional permissibility that way because we didn't want to jump the gun guessing on regulation, guidelines, you name it. It is simply the idea that this kind of research could go forward subject, conditional upon certain kinds of rules, whatever rules one might want to adopt here.

And we tried to think ahead of time about the kind of categories of the rules that people might think about. One might be governing the origin of the cells.

For example, lots of people have suggested, publicly, that anybody whose cells are used ought to have knowledge that their cells are being used. Alex has now said perhaps it should be their parents who acknowledge that their cells are being used, but regardless. Especially rules about the source of cells of both the oocytes as well as the cells used, nuclear DNA would be used.

Perhaps rules--and scientists have consistently alluded to this kind of thing--that restrict the use of these cells in the human species until a time when sufficient animal research has been done that would count while we exhausted that avenue for getting some basic science results, and we really need to move on to human species.

Another might be one that would ask for other more elaborated rules about the management of the cells, how long they develop, et cetera. It even might speculate about a special body set up to do it.

And all of these kinds of things, by the way, are discussed in the Embryo Panel report that-- That is two years old, three years old now, with a list of possible rules. It is not an exhaustive list; that is, we know we would never adopt it,

so it is not-- It does not control us, but it provides some guides for people who are trying to think about these things.

And because, in this particular one, under Number III, there would be federal funding, all the human subjects protections that we have would govern. Okay?

You take away the federal funding, the concerns about the kinds of positions remain the same, but rather than having a federal body, like the one proposed in the Embryo Research Panel that oversees the protocols, and rather than necessarily having human subjects protections, you might look for analogies to something like a specially-appointed body with control, although not funding, in the private sector.

And you might look to the U.K.'s Human Fertilization Embryology Authority for that kind of guidance.

Finally, the most extreme restrictive approach that we identified for people to consider was, one, total prohibition. And we identified three ways in which that can be accomplished.

Through a voluntary moratorium among members in the research community and the clinical community. The enforcement for this usually stems from reputational damage. People are embarrassed by the fact that they violated this. Sometimes it is more stringent; publications won't agree to publish their articles. Things like that.

And Bob Plategan's contracts give us a nice background for realizing this moratoria do intend, do actually work, with very few violators.

Second, through state legislative action. But this necessarily will mean a patch-work of rules, some of which may be more clearly drafted than others. Right now, there is only one statute that clearly seems to govern in this area, from Louisiana.

Or through the kind of federal legislation that we have seen introduced by Senator Bond and Representative Ehlers.

Finally, in conclusion, we tried to identify, as applicable to all of these things, two big kind of other things to think about.

One is that, on the matter of policy generally, clearly all these options would have to be considered in light of the benefit necessity of the research and the clinical needs. We thought that it is important to emphasize that education is an essential aspect of this.

And finally, perhaps counterintuitively, that the presence of federal funding in this area, and the clear identification of it in research, might have one of the untoward or unexpected side effects of slowing down clinical applications toward making babies because of the complexity in the clinical arena of moving rapidly forward with things that you can identify very visibly as research, experimental-- You know, red lights and yellow lights, flashing; it tends to slow down both patients and doctors.

So that that is a kind of unexpected effect of federal funding as we noted.

And with regard to Constitutional limitations, we found that two arguments that are raised frequently--scientific freedom and limitations of federal jurisdiction--probably would not succeed in a court, even though the scientific freedom argument is quite compelling in its kind of ethical dimensions.

The arguments are that reproductive liberty pose significant challenges to anything that smacks of a real serious prohibition in this area, not necessarily to regulation of one sort or another--there it poses simply a kind of medium challenge to be specific about your regs-- but real prohibitions would take some serious discussion among the ethics people and the law people and the science

people in order to come up with a good set of justifications for prohibition.

DR. SHAPIRO: Thank you very much. Alex, you want to just go on?

PRESENTATION BY ALEXANDER M. CAPRON, L.L.B.

PROF. CAPRON: Yes. Like the presentation that Bernie gave, this presentation presents a structure that doesn't necessarily convey all the nuances and richness of the discussion that we had, and I am sure that the other members of the bucket will fill in.

And you will notice it has a more elaborate aspect to it--seen here on paper--than it necessarily will have because there is a lot of repetition. The points made under Number I are sort of repeated under Number II, or points under A are repeated under B, and so forth.

We did make this basic differentiation though between cellular research and research that would lead to transfer to a uterus with the intention, although we didn't put the intention in the title, of creating a human being.

Here we have the same range from most supportive to most restrictive on the policy options, and it begins with federal funding. Under this heading, we divided it, in thinking about something that would be still at a research level where it would be going through an NIH-type peer review process and any other regulatory process that was added to it, looking at the protocol and saying, "Is it necessary, is it appropriate in its development, are the human subjects concerns, the traditional human subjects concerns, of safety and so forth all taken into consideration?"

And to the extent that a human being could result from this, we also though medical malpractice restrictions would apply; that is to say someone who did something which the profession regarded as unprofessional could be subject to

discipline and penalty for that.

If the procedure were developing in the clinical setting as opposed to with a research protocol and the funding was more of a Medicare/Medicaid-type funding--and we somewhat humorously noted that given changes in the reproductive technology, one might even be over 65 and be somehow involved in this process; certainly on the male side that has always been true, but it could be also on the female side--the same kinds of considerations would apply for malpractice.

And this complex area of wrongful life claims might play in if there were something either inherent to the act of creating the child, or something about the circumstances that was a wrong to the child.

Similar considerations apply without federal funding, except there would be less expectation that the federal regulations would apply to the research side. They could apply if the institution voluntarily adhered to the regulations, but they wouldn't necessarily apply unless our parallel effort to expand the scope of regulatory protection for all subjects has already taken effect.

And I won't repeat the clinical side.

We then moved down to this notion of conditional permissibility, which is more or less a way of saying some form of regulation, oversight, differentiating among the cases in some fashion.

And here, in addition to the special requirements about the origins of the cell, that is to say somebody's permission there, we also recognized that there would be special considerations about the welfare of the gestating woman.

Alta mentioned, for example, if a woman had to go through many, many repeated attempts at pregnancy to achieve this--ala achieving Dolly with 227 attempts--there could be a lot of concerns, as there has been in the *in vitro* area generally.

And obviously likewise, special requirements might apply to the child; everything from protection against excessive publicity, which was a provision that was written into the RAC guidelines for gene therapy--that the institution would do everything possible to protect, and so forth--to more substantive ones.

The movement to conditional permissibility without federal funding does assume that somehow state or federal regulations could be drafted to apply to research that is privately conducted. And there obviously are a great many things that are done in private medical practice in which there is some form of oversight for the process.

That is the model that we had in mind, again, with reference to the British system of the use of the Human Fertilization Embryology Authority.

Finally, prohibition. And the considerations there are the same. Many of the considerations on the policy side are the same, with a greater emphasis on the infertility relief as opposed to the other clinical uses that might arise out of the cellular work in cancer, or regeneration of organs, or whatever.

We also recognize that one of the policy considerations are the non-medical reasons; that is to say an eugenic reason not because the couple couldn't have a child, but because they want to design the child in a certain fashion.

And we placed additional emphasis on the ethical and religious dimensions of the use of the techniques and the societal impact of limited or widespread use. And here we may be dealing with something as to which there is really very little, other than speculation as to whether or not there would be limited or widespread use.

The Constitutional considerations are the same, expect that the third consideration comes much more clearly into focus. I think it was the sense, in the discussions in the committee, that the issue of a reproductive liberty is not resolved. I

don't know--members of the bucket should speak up--that we were, any of us, really fully convinced by the Robertson-type argument that there is an obvious liberty.

If one has questions about that, the questions can go in two ways.

One could either say that the argument about all reproductive liberty is not persuasive, or one could say there is a reproductive liberty in the use of sexual techniques because that is the most that could have been contemplated by anybody's thinking about privacy previously. But it wouldn't extend to this new asexual method.

And either of those could be arguments that would be raised. These would obviously be claims that could be advanced both by any couple wanting to do it, and by the researcher/clinicians doing it on their behalf--a challenge to any restriction or prohibition.

DR. SHAPIRO: Thank you very much. Are there other comments, suggestions and so on from members?

PROF. CAPRON: Could I just say one more thing about the framework?

It may be possible, given the timing of our report, that what we would end up reporting upon is, in effect, these policy alternatives, even if we are not, even if we haven't reached a full conclusion as to which ones we, as a group, endorse.

So, I mean, part of the outline you should consider here is if there is anything here that the group as a whole thinks just doesn't even bear mentioning or, conversely, something--a hole--that we have left that you want to fill. We ought to know.

And then there is the further question, whether by May 26th or whatever, we will be resolved to say, you know, IA and II, or V, or something, or whatever, are where we are.

DR. SHAPIRO: Okay. Thank you. Zeke, then Bernie.

DR. EMANUEL: In light of the previous discussion by Stu Orkin and Janet, where does cellular work with cellular therapy fall in here? Because it seems that--

PROF. CAPRON: Under Number--

DR. EMANUEL: --you have got a gap.

PROF. CAPRON: No. It is under Number I. We thought of that as being--

DR. EMANUEL: Well, it says "research on human cells derived through cloning without intent to transfer to a uterus," but it doesn't talk about clinical therapy options. Right?

PROF. CAPRON: Well, which do you mean by-- I thought you were referring to the cellular work they talked about, the development of--

DR. EMANUEL: Right. But at the end of the development is presumably the-- I mean--

PROF. CAPRON: Oh, you mean--

DR. EMANUEL: The cellular work was not-- Maybe I heard it--

DR. MIIKE: May I give you an easy answer?

PROF. CAPRON: Yes.

DR. MIIKE: I think we define all of that as research. I wouldn't leap ahead of the research and say it is clinical applications. That is why, in the discussion, we talked about-- You can't leap to that without going through the accepted scientific protocols of animal research models and setting up base before you jump into that, so when you talk about clinical applications of cellular techniques, I consider that research that falls within this realm.

PROF. CAPRON: Is that responsive to your question?

PROF. CHARO: I think, Zeke, that we can include this.

DR. EMANUEL: Well--

PROF. CHARO: And I am just taking notes about things that need to be done to improve this and to clarify it.

And I think it is fair to say that any clinical applications are going to come after research, but we will be able to find a way to incorporate in here issues about how it is that the clinical applications would then come about and whether or not there would be any control on the sequence of research to clinical application.

Just as we have had that concern about baby-making, we can incorporate that into concerns about doing it in non-baby-making application areas.

PROF. CAPRON: But, Alta, isn't it true that when we were talking about it, Number II, to use the colloquialism you just used, refers to baby-making.

PROF. CHARO: Right.

PROF. CAPRON: Yes. And so that--

PROF. CHARO: Number I is about all other things.

PROF. CAPRON: Yes.

PROF. CHARO: Right. And all-- I think all Zeke was asking for was real vivid, you know, verification that this is not just about embryos here; it is about applications--

DR. EMANUEL: Cells.

PROF. CHARO: Well, yes, but--

DR. MIIKE: Well, no, I disagree. And this gets to the issue about what can we be expected to reach conclusions on in 90 days?

The question to me is that we address the kinds of issues that are immediately before us and we also sort of forecast what we-- Those kinds of questions we need to raise, instead of these eight issues that have to be addressed if that time comes. But I don't think we can substantively address them right now.

DR. EMANUEL: Let me just clarify what I heard from Stuart Orkin and what that sort of sparked in my mind, and why it might be relevant--I think might be relevant--here.

There is a certain kind of research you might do to understand the process of cellular differentiation, redifferentiation, where your goal is you want to understand the process.

There is a separate kind of research where what you are trying to do is really reprogram the cell for a specific kind of therapy that you are going after. And they may for awhile be similar, and they may diverge.

And it seems to me, when I read your thing, one of them sort of applied more to the basic science research rather than when they might diverge, and your sort of clinical research, or your research with clinical intent gets going, even before, even if you are not talking about implantation.

PROF. CAPRON: See, I don't think clinical could include fertility clinical; that is to say the creation of a baby, or it could include treatment of cancer--

DR. EMANUEL: Right.

PROF. CAPRON: --or treatment of diabetes--

DR. EMANUEL: Liver failure.

PROF. CAPRON: --or liver failure. And--

DR. EMANUEL: Yes.

PROF. CAPRON: I mean, clearly the treatment of cancer, liver failure, that kind of research, understanding cellular differentiation and redifferentiation--whatever--that is Number I.

And Number II is really when you have got the intention, if you are successful, of creating a child through that particular nuclear transplantation and then implantation in the uterus.

DR. SHAPIRO: Oh, well--

PROF. CHARO: I think--if I may Harold?--I would like to try again to explain the logic here, and that obviously if it is not working, it is not working, and this may be evidence it is not.

The idea had been not to divide these two areas into research versus clinical; it was, first, all--all--manipulation in these cells without an intent to transfer an embryo to the uterus versus all the ones that have the intent to transfer into a uterus. Because we saw a very clean distinction in the concerns between the ones that have children emerging and the ones that don't.

Now, among the ones that don't, you do then have lots of sub-categories and you are quite right that people's intent of the cellular research can vary.

But there is one very fundamental similarity that they all share, and that is--although with the exception now of the stuff about dedifferentiation--up until now we have been thinking that all of this work that involves nuclear transplant, you know, nuclear transfer from a somatic cell to an oocyte all therefore require work on a zygote, and as soon as it divides into a two-cell, early embryo, and that was the unifying factor because that had been an issue politically and regulatory before. And so we put all of those things into one rubric.

Now, within that, we will obviously be breaking things out, but maybe this isn't working because it is clearly not emerging. It is obvious. And we may need to go after a different slice?

DR. EMANUEL: Now, I understand your rationale.

PROF. CHARO: Okay.

DR. EMANUEL: Here is why I think it might be different and, you know, I could be a minority and you should ignore me.

It seems to me that the justification for clinical--

(Laughter.)

PROF. CHARO: We won't ignore you if you are a minority.

(Laughter.)

DR. LO: But it makes us scared about being minorities.

(Laughter.)

DR. EMANUEL: Your weighing of its intent, the more-- The closer you get to clinical application that has real benefit to people who are sick, the way you might weigh that might be a lot higher than if you are just doing, say, pure research. The justification looks different and might be more persuasive for going on to do embryo research.

It seems to me--again, just personally, sitting here thinking about it--the balance begins to tip when you can have a direct therapeutic-- You are talking about direct therapeutic benefit and it really looks within reach as opposed to just understanding.

PROF. CHARO: Would you then say that it is consistent that to talk about conditions on making something permissible might include the purpose for which the stuff is being done? That would be-- So maybe that is the way it would be--

PROF. CAPRON: But look at our policy. Under Roman IB, the first thing that is there is "overall scientific benefit and necessity of the research." The notion is that certain lines of research might be more justified by their necessity and their benefit than others. It is not an unusual-- I mean David cited that before as a general method of science. This has an--obviously has--an ethical overlay.

I thought what had emerged from this morning was the sense that the fifth category here, or rather--excuse me, the third or fourth categories here, excuse me--the third or fourth categories here, some sense that for the moment, if we are not

talking about a statutory ban but rather putting in abeyance certain kinds of research that involve the transfer of the nucleus to the oocyte, if that work can go forward in the animal models and we can learn about what causes the nucleus to become totipotential, again, then the thought would be applying that knowledge to other cells which are never going to be embryos and are only going to be livers--or whatever--gets around the central uncomfortable stumbling block here which is creating an embryo.

And if we have a process that would judge how that research is going, how far it has gotten, is it at the point where it makes sense to do this or that, or if it gets to a roadblock in a sense, it turns out the only way to get these cells to differentiate, even if you want to end up with a liver, is to use the oocyte. We can't-- You know, we have done everything. We have gotten to that point.

Then that group would be faced-- As Larry says, we haven't gotten to that kind of balance though, but we had that process and those considerations of certain research being more compelling for the benefit that it provides than other research very much in mind when we were looking at the third and fourth methods, which I think particularly Larry and Bette in our group were very strong on urging that we consider. The RAC model, the Human Fertility Fertilization Board in England, and so forth.

DR. SHAPIRO: Let me ask a bigger question of clarification. And, Bernie, I know, is next on my list here.

Item I--and that is a Roman I or big I, whatever it is here--deals only with the research, as I understand it?

PROF. CAPRON: Yes.

DR. SHAPIRO: Although the motivations may come in as you have just talked about--

PROF. CAPRON: Yes.

DR. SHAPIRO: --and so on? But this is really partly in response to Larry, because my understanding of I is that is a research issue, set of research issues.

The part that I have a little hard time fully grasping now, as I get to Roman II, because you seem to have a distinction there between clinical and research. However, is the whole area is defined as the transfer to uterus for purposes of creating a clone?

PROF. CAPRON: Yes.

DR. SHAPIRO: It sounds to me almost like a definition.

PROF. CAPRON: No, no. But the difference here is that this would be two ways of imagining this arising. One way would be people say we can't literally do research on the embryo that is going to be implanted. I mean, we sort of-- That is the legal phase. And we are going-- It is going to be funded clinically by patients, or through their insurance, or whatever, at *in vitro* centers, or whatever, like that.

And the other is someone saying, no, this has to proceed as a research protocol.

I mean, Louise Brown was a human subject--right?--before she became a girl, and that--

PROF. CHARO: But not as a research protocol. She was the subject of an experiment. That is the distinction, Alex. I mean, Alex--

PROF. CAPRON: She wasn't-- What do you mean? There was a research protocol. They had a well-designed protocol to describe what they were doing, Steptoe and Edwards. She was in a research protocol. It went before the Medical Research Council, I believe, that they got funding from, I believe. But in any case, there was, within Cambridge, there was a research protocol.

And so it is more or less a difference at that critical juncture where you are ready, "ready," to make the transfer to the uterus. Whether you are then regarding this as--

In contrast to the way a lot of *in vitro* techniques have been developed in this country, where Alta's response is correct; that that--

I think they are, as a result of any formal research protocol, they are experiments, as it were, in the sense of jumping off the diving board or something, but they haven't come out of a formal scientific process that gets reviewed and would be regarded as being conducted according to a research protocol.

DR. SHAPIRO: Bernie?

DR. LO: I meant to ask the legal and policy bucket to help me think through--

THE REPORTER: Could you use the mike?

DR. LO: --a temporal dimension of your various policy options.

As I read it, these are sort of solutions that are put in place and, although we may revisit them, they could also be permanent.

Should we be thinking also of a time-limited voluntary moratorium, or even to impose a moratorium, as distinct from the prohibitions on page two? Do they involve different sets of policy considerations if you are having it?

If the moratorium can conceive of something it is going to be temporary, and then we are going to come back and readdress it after some passage of time or after research things have happened versus a moratorium that is envisaged as a permanent prohibition.

DR. MIIKE: I don't think any of us envision-- It has to be revisited. And the issue about if it gets legislated there should be a sunset clause and there should be some continuing evaluation of what is happening both scientifically and in

societal attitudes kinds of things so, yes. I mean, an outline like this doesn't capture every one of the nuances that we spent most of--

By the way, what is interesting to me in the process is that we spent a lot of time discussing the specific legal issues, but what always bubbled out was the policy issues that came across.

Just one reaction to Harold. I think I understand what you puzzlement is between the two because I think to me the second phase, if you talk about implantation, it is more about what might still go-- As long as we don't know what really is going to happen, you really need research protocols to find out what might go wrong, but you are also talking about human subject protection in an area, so it is a mixture. It is really not-- It is not really an extension of the preimplantation issues or simple implantation.

PROF. CAPRON: It might well be, Harold, that the-- If we are talking about federal funding, you know, we would have to call it research, and the clinical side just wouldn't-- I mean, it may be that that is sort of an outlining mistake here. I don't know how you feel about that, Alta, that--

PROF. CHARO: We will work on it later.

PROF. CAPRON: Yes. I mean, in other words, Harold's point points to a difficulty here.

But one of the reasons for differentiating was to say, even in a clinical setting where it is privately funded, there are some forms of legal regulation that go on--licensing standards perhaps, malpractice, and so forth--and it is not as though it is out in the forest primeval.

I mean, it is a little more--

PROF. CHARO: They are just not very good.

PROF. CAPRON: Yes. Not very effective perhaps, but--

DR. SHAPIRO: David, then Bette.

DR. COX: Yes. Even given some of these difficulties though I, for one, really like distinguishing between, you know, with the baby and without the baby. I think that is extremely useful to slice it that way.

PROF. CAPRON: If I could also answer Bernie's comment, to follow-up what Larry said.

If you had something that talked about conditional permissibility, in effect, it might say that certain avenues of the research are still not yet permitted.

I mean, you could say we have a moratorium now on germ line gene therapy. We don't have a statute against it. We don't even have a regulation that says it can't happen. But we have a committee that said we need to learn a lot more about it and we won't now entertain a protocol in this area, meaning "entertain for approval" a protocol in this area, because we don't think that the justification is there for it yet.

So in effect it is sort of like a moratorium, but it is with an oversight body so it is not even-- We might revisit it. There might be another group that would revisit it, as Larry says, after a sunset time, or there might be an ongoing process that is able to revisit it as issues arise. Any of those three.

DR. LO: If I could just follow-up on this moratorium issue.

As, you know, we look toward a deadline, there is a lot--an awful lot--here, a lot of tough issues to be worked out, and I think one possibility for us is to say we are not going to come up with a definition solutions within 90 days, but at this point we think we need to have a moratorium so we can sort of--we and the public and the public officials--can sort of sort through some of these issues.

Then it seems to me the issue of how you do the moratorium, if I could use Larry's terms, isn't just nuance; it is crucial. Is done through voluntary, a totally voluntary moratorium, is it done by Executive Order, is it done by legislation?

Do we set up a regulatory body like the RAC to whom we delegate authorities as to when do we lift that moratorium?

And it seems to me the attractiveness of a moratorium as a recommendation may depend on how the moratorium is carried out. I guess that is what I was trying to say.

DR. SHAPIRO: Bette?

MS. KRAMER: I just wanted to say that, you know, again I gather, as with the ethics bucket last night, this outline, although it is very complete, doesn't necessarily capture the discussion as it actually took place because it really was a very, very rich discussion.

We did spend a lot of time on the legal issues and though they may not show up in this outline, I think one reason they don't show up on the outline is that when push came to shove Lori pretty much told us that any of the possible policy options that we might consider or might recommend were all doable. So that kind of, you know-- And she certainly has got that all-- She has certainly got that all there in her paper.

I think that, again, there was a lot of discussion around the different research that might go forward, that the scientists were telling us might go forward, and we attempted to capture all those possibilities in the possible policy options. And it may be that what we need to do is just add some language under the different options that would indicate, that would indicate, that would capture that discussion.

And one other thing that doesn't necessarily show up here, or doesn't show up perhaps to the degree that we spent time on it, is again a discussion of a gradualist approach. And somehow or other, in being recast into this discussion, it just isn't showing up, but we did spend a lot of time on that.

DR. LO: Could you say a little bit more about what you mean by a

"gradualist approach?"

MS. KRAMER: Well, I think it was-- We talked a lot about the possibility of recommending a RAC-type body, although we were sort of opting for a different body, where we would try to-- We would try to benefit from the RAC experience. Where they have problems, we would, you know, we would restructure it, and that this would be an ongoing body.

Basically what it came from is that there is so much--our perception was--that there is so much unknown yet about the science and where the science might lead that there is lots and lots and lots of scientific work to be done before it ever really becomes necessary to address the possibility of doing research on a human embryo.

And that there really isn't any need to deal with that right now; that possibly down the line that there will be, but-- And so let us build in, let us build in the opportunity to address it, but when it becomes necessary. And let us not rush to that because it isn't necessary now.

And I think that that was confirmed by the presentations this morning.

So let us construct, let us construct an opportunity for all of the research to go forward on the animals, to explore that, to explore that fully, and then come back and examine the other possibilities when it becomes necessary. So that is what we were talking about. And then we just spent some time talking about how we might structure something that would permit that.

DR. MIIKE: If I may add to that answer, it also-- It came up in the context that the usual way one goes from research to clinical application, especially if you look at the FDA model, is to do everything that one must know for the basic, in the animal and cellular, non-human cellular level--or let me not say non-human

cellular level--but you do your basic research first, and then you move on to the application in the human area.

And I guess there was some confusion about what we meant. That all and everything that you can possibly know through animal models must happen before you go on to this area. That was not the answer. The answer is that if there a particularly application, say, in liver regeneration, or something like that, you would have much more focused animal and other types of studies before you move on. And that was my interpretation of our gradualism approach.

DR. SHAPIRO: An FDA model at the cellular level, a liver regeneration and regeneration came up earlier today. For those of you who haven't seen it, there are a lot of articles on that subject in *Science* this week. So I just found it interesting, and others might find it interesting as well.

Steve, did you have--

MR. HOLTZMAN: I have a couple of questions.

What you were just saying with respect to the gradualism, are you talking about that within both Roman Numeral I, as well as Roman Numeral II? I certainly understand it in Roman Numeral II; I am not sure I do in Number I.

And with respect to when you talk about RAC-like mechanisms, and we think of the gene therapy example, again we come to this problem of effectively gene therapy was viewed as a product.

And as for the private sector, non-federal funding, you can have a mechanism, the FDA, and then which was going to review the protocols as well. Are we recommending here that we view any such effort, under II, as a product, hence that there should be some regulatory mechanism? And are you recommending that a RAC-like mechanism applies to basic cellular research under Number I?

I am trying to--

PROF. CAPRON: Yes.

MR. HOLTZMAN: I find the one-- I think the baby-making versus non-baby-making is the critical distinction, and I think the kinds of issues that Zeke was raising can be taken care of with a refining analysis under I. So I agree.

PROF. CAPRON: Well, whether it is possible to have the same mechanism-- Thinking about both the cellular work and the implantation to baby work, we didn't cross that bridge frankly.

Bette, I think in particular, was urging the notion of a RAC-like body, and I must say I initially was very skeptical about that, and she convinced me that there was more to the analogy than I had originally thought.

You are certainly right, that there are some dissimilarities, but remember before there was gene therapy there was the RAC looking at the basic research. The reason for a RAC was physical risk to the researchers and to the larger world, if that research proceeded in a way which didn't take full account of all the risks and weigh them appropriately.

The concern here is a little bit different. It is why I originally thought it didn't make sense. If the objection isn't an objection in principle--that you should not use human embryos for research--then it doesn't do any good to have a committee to review the protocols because either you are rejecting that and therefore offending that view, or you are having them review protocols and saying no to them all. And it wouldn't make sense to do that. I mean, there wasn't a way of saying this is safe enough, or whatever.

But between what Larry said and what Bette said and what we heard this morning, it seems to me there is more of a sense that a committee would have some gradation, and it could lead for a further public process to the question of do we ever take that step and does it make a difference, if you are talking about it being taken

only under the extreme necessity and only with the fewest and whatever, or not?

But all the steps leading up to that--how far do you advance to the animal work, what non-oocyte cells would be available to do the same kind of thing--those issues we are not going to resolve in the next six weeks, but an ongoing body could review that kind of work. And that is, I think, sort of maybe where we are.

Whether we would have gradualism on the second, or sort of now a moratorium without a case-by-case review because there is no justification at the moment for doing this, really depends upon the ethics analysis that we started on today.

I mean, the real defensibility, both as a matter of persuasion to the public and a matter of sustaining this before the courts, will depend on how good the arguments are; that there is a reason why it is not appropriate, or it is wrong, or whatever, to allow people of their own free choice, with their doctors, to create a cloned child.

DR. SHAPIRO: Alta?

PROF. CHARO: I would like to take this opportunity perhaps to ask about where to proceed from here with things like this? And here is why.

This outline encompasses where, you know, the possibilities of where we want to be that apply to the things having to do with embryo research that just happens to be embryo research that is taking place with embryos live by cloning.

But we don't necessarily have to take on that topic because it was done in '94. There has been a Congressional statement of opposition by virtue of the appropriations. The administration stated its position with regards to exactly the kinds of embryos that would be implicated by these embryos live by cloning.

And a very baseline determination that would be important in streamlining this kind of outline would be do we really want to be trying to flesh out

all of these possible outcomes for a position with regard to embryo research, if we want to restrain ourselves for the moment at least, and the 90 day exercise, to those things that come up under Number II.

And I am very interested in hearing about this because, with regard to Number I on embryo research, putting aside even just the political history and the legislative obstacles that would have to be overcome if we are to address it at all, that is where, if people decided to go for a kind of shades of gray attitude about it--neither total permissibility or total prohibition--that we would indeed then have to go to the next level of thinking.

All right. Well, are the conditions going to be one that we can impose or come up with on our own, come up with a body that comes up with them, or come up with a body that comes up with some of them and with some of them on our own?

I mean, there are levels of iteration of your thinking about how it is that you implement the various conditions. It gets very complex. It is an exercise that would be silly to engage in if we weren't going to go whole hog, so it would be good to know now if people were inclined to go whole hog on it.

DR. SHAPIRO: I think that is an interesting question. It is certainly a question I intended to come to today, because it does effect so many things that we might do. I think you have--

Are you answering this question, or do you have another question?

DR. EMANUEL: My-- My-- I was going to ask you was there a sense or a consensus on which of these policy options ought to be recommended, or was there a sort of hold in abeyance and let us hear what the Ethics Committee, the Science Committee and everyone else thinks? And I guess--

PROF. CHARO: There was a sense that-- We are essentially in

stereo today because we have two chairs for the same bucket, but I can tell you that my goal has been to have absolutely no judgement made about where to go and to make this a service to the commission of outlining the options for people to discuss.

DR. MIIKE: Ditto.

PROF. CHARO: But I can't speak for other people.

DR. MIIKE: And Zeke, clearly it is the science and the ethics. We could only discuss, in a very narrow sense, what the legal applications were and what the policy ranges were, but picking among them could not be done without the ethics and the science side.

DR. SHAPIRO: David?

DR. COX: So, okay. At the risk of going first on this, I have a clear personal view with respect to your question, Alta.

And it comes first in terms of what I would really like to see us, as a commission, accomplish. Okay? It comes to some of Harold's points and points other people have made. And that is having a process by which we can have a dialogue in this country about these kinds of issues. So the statement I am going to make is based on that being the ultimate goal I would like to see happen.

That process-- It isn't clear. RAC has been successful in some ways but not in other ways. So I think that we need to be thoughtful about how to have an ongoing dialogue about this because I don't see that there is any sort of immediate action that needs to be taken. Okay? That is the good news.

Now, on the other hand, it has been really clear, at least to me, from the different testimony that we have had here, that certain people see this as an opportunity of opening the door, perhaps a back door, to rediscussion of the embryo research stuff.

We have people who are opening the door for two reasons. One,

because they want to open it; other people because they want to make sure it is closed. Okay? And this, to me, is like my two kids coming to me and saying, "Which one do you love most?" All right. I am not going to play that game. And I think that it is a mistake for the commission to play that game because if we do then, in my personal view, we run the real risk of not being able to have a process to put in place by which this could be discussed in a reasonable way.

But for myself--I think for a lot of people this may not be the case, but for me it certainly is--it is that decisions that I make in terms of whether I would like to see embryo research reinvestigated or not, or reconsidered, has to do with what the science in the animal work is going to be. So I am genuinely am not ready to make any decisions about that until, for awhile.

So my view is I would rather focus on the process by which we can have ongoing discussions of this, and not get into a rehashing of what the 1994 Embryo Panel was all about.

DR. SHAPIRO: So you want to go to II is the short answer?

DR. COX: Correct.

DR. SHAPIRO: Any other views on this? Yes, Carol?

DR. GREIDER: Going to I or going to II, I think, is limiting the way that we are necessarily thinking about that. I heard two different things going on. One, this issue of a RAC-like body, or some sort of oversight committee, a way to have an ongoing dialogue and a process. And I don't see why that has to be limited to I or II. That is--

DR. COX: Actually, that is--

(Simultaneous discussion.)

DR. GREIDER: I was hoping that these policy issues-- I mean, I absolutely understand breaking them down scientifically along not creating a baby and

creating baby. But I think that if we are going to come up with some policy recommendation, it is going to have to deal with both of those issues.

And it would be nice to try and put some sort of structure in place that dealt with both of them and have one structure that deals with both of these issues, although the answer doesn't have to be the same for both of them if we have some sort of RAC-like body in place to have a continuing ongoing evaluation and dialogue.

DR. COX: Let me clarify, Carol. I mean, by making that statement that I don't want to reopen the present status of embryo research doesn't mean we have to deal with either I or II, but I think that that is--

Alta asked a specific question; that is, do we have to reopen it or do we want to deal with I and II without reopening it? And I would like to deal with I and II without reopening it.

DR. EMANUEL: How can you deal with I without reopening it? Let me-- I am not a veteran of the embryo research battles, so I am not sure.

DR. COX: Well, can I try to be clearer, Zeke?

DR. EMANUEL: Yes. Yes.

DR. COX: Right now I don't know of any way of doing human cell-based work without reopening it. All right?

PROF. CHARO: In the private sector.

DR. COX: Okay. And the private-sector people can do it without federal funding.

PROF. CHARO: Yes. Right.

DR. COX: On the other hand, to have a process where if we talk about this kind of research ongoing with animals, as well as protocols where people are bringing it up, talking about ongoing with humans, so I am going in the private sector right now, so that it doesn't preclude a discussion of it.

PROF. CHARO: May I? Just for a moment. Just for sake of clarification here, let me-- Probably I should have done it this way when I introduced it. Let me just emphasize the existing regulatory legal landscape against which these options are being given to you.

With regard now to any research activity that uses embryos in the United States, there are zero--zero--limitations on what scientists can do with those embryos, if it is privately funded in a private setting, with the exception of some scattered states where there are laws that either clearly or potentially apply.

But in the vast majority of U.S. territories there are zero restrictions on what private scientists and private facilities--private money--can do.

And when it comes to federally funded facilities, or federally funded research, or intramural federal research, there is zero that you can do with embryos; that is research that is disruptive of those embryos. Okay?

So what we have got is a very binary system right now in the U.S.

And what is presented in Number I would be changes from that binary system. So please be aware that whatever you are talking about is going either to be about tightening up what goes on in the private sector, for which we think there is federal jurisdiction to do it-- that they can legislate to try to tighten up the private sector--liberalize the federal sector, one or the other, or both. All right? That is all for up grabs.

But we don't necessarily have to deal with this in the context of saying anything you want to say about the baby-making applications. All right?

Or we can do whatever we want to do on baby-making applications and make reference to the fact that the existing situation on embryos has the following effects on the kind of way in which baby-making applications are likely to develop in the U.S., against this existing backdrop, and speculate about how that would be

different if things were different without going into detail about how we think they ought to be different.

In other words, without making any judgements.

PROF. CAPRON: I mean, the speculation that Alta describes is what we regard as the paradoxical effect; that if you don't have visible research activity at NIH and the leading academic centers, then individual patients and their referring physicians may feel the field is more advanced.

And these private clinics that say we provide a clinical service in a way don't have this big question mark over their shoulder. "Wait a second. Why are you claiming to provide a clinical service if the leading researchers are still trying to understand the basic stuff?"

You remove that, which is the situation we have had with *in vitro*, and you actually get perhaps greater encouragement of less regulations.

DR. SHAPIRO: Carol wanted to speak, and then Arturo.

DR. GREIDER: So to respond to what you just said, Alta, I think that one could put a mechanism in place, RAC-like or whatever, that deals with both I and II without necessarily changing what is going on in the private sector or the federal sector. So you have a body that reviews research from both private and publicly funded, et cetera, but don't necessarily have any exact regulations.

So you put in place a mechanism whereby there is discussion of all these sort of protocols and what is going on that becomes inclusive, so we no longer have this binary system which probably isn't working.

PROF. CHARO: How--

DR. GREIDER: And I don't see that you can separate out the I from the II if you are going to have some sort of a policy that you really want to work going forward into the future to be able to accommodate changes that may come about in the

next 10 years.

PROF. CHARO: I am not sure I understand what you are suggesting. Just for clarity, have a body that doesn't have any--

DR. : Power.

PROF. CHARO: You say it doesn't affect the private or the public sector, so people in the private sector don't have to send any protocols in, people in the public sector can't have any protocols to send in, so what is this body doing?

DR. GREIDER: Well, I am saying--

PROF. CHARO: I don't understand.

DR. GREIDER: --it is not necessarily saying that, in the private sector, you have to stop doing what you are doing right now and come under these sorts of regulations, but there would be some changes in terms of, in both cases necessarily, that there would be some sort of funnel that information at least has to flow through. Again, I am not a policy-maker, but it doesn't seem obvious to me that you can't have some sort of a mechanism for review and oversight of all of this research that you can put in place--a mechanism--without necessarily legislating can't do or can do.

PROF. CHARO: And that could be anything? I mean, it could be like the NBAC has a meeting every six months with two days full of discussion of the latest in cloning, and where are we, and should we change things now?

DR. GREIDER: Well, I don't think it would be the NBAC but, yes.

PROF. CHARO: Right. But it could be anything? You are not being specific at all about what it--

DR. GREIDER: That is right.

PROF. CHARO: Okay. I am just trying to-- I just want to understand what it is.

DR. GREIDER: I am just trying to think of some sort of an option where you can deal with I and II together because I don't see, personally, how you can separate out these two issues if you want ongoing evaluation in order to say maybe. if we get so far along and we know something that will change the entire ethical way that we think about this, then we want some sort of mechanism to change it.

You know, sitting here today, in 1997, we don't know what is going to happen. And so if you want to put that sort of a dialogue--and give it real meaning--in place, you have to deal with I and II.

And I think that this binary system you described, in the federally funded and the private sector, also isn't necessarily the best way to go right now, so why not try and fix both of those things without necessarily changing overall how-- You know, we don't have to open up federal funding for embryo research in order to put that kind of thing in place as a mechanism.

PROF. CAPRON: The hard thing, Carol, is to know what your handle is on the private work.

DR. GREIDER: And I don't know. That is for you guys.

(Laughter.)

PROF. CAPRON: Well, it is not-- Let me emphasize, I think that is an example of something that comes back to the fundamental ethical view. And it would be a view either that the federal government is, in not funding it, is right; that there should be no research on created embryos, and all of these oocytes with the transferred nucleus are created embryos.

And then Alta's question to you was, well, what would this body do? Or it would be, in effect, saying that moratoria, that present ban, reflects a very basic sense that this is very highly sensitive work that can't be treated just like any other cellular work, but that case-by-case it should be reviewed.

And then you would say, well, shouldn't that apply to the federal as well? I mean, you can't-- I think you can't totally avoid it.

If you take David's view, you can avoid it because then you say the reality is that there is not going to be any federal support and, therefore, we are not going to give any recommendations to the President about how we ought to regulate this; the President and Congress have already said they are not going to tolerate it.

As to baby-making, that is a separate issue because there might be very wide agreement that we are not prepared to see babies made. And then the only question is how do you prevent private clinics from doing that? Because some of them may be prepared to do so fairly soon.

DR. SHAPIRO: Okay. I have a growing list here. Eric?

DR. CASSELL: Well, David, when you say you want the discussion to continue, and that was picked up a number of times, who is doing the discussing? Because if the people who are discussing it are the RAC, or us, or so on, and we don't get at the genesis of the original prohibitions--

There is a prohibition against embryo research not solely because the scientific community decided they didn't want to do it, but because there was enormous public pressure. So if by continued discussion you mean that somehow or other we move this out into the public so that public policy, science policy and public policy come together, that is one kind of discussion.

If you mean just the RAC is discussing it, that is a totally different thing.

What do you mean?

DR. COX: What I mean is the former, not the latter.

But let me make one point. Okay? See, I should listen to Harold more. Yes, Harold, it was Number II that I was interested in. And let me say why.

Okay? Because I would like to see this public policy, this public discussion go on, and a form for that. Okay?

But in terms of what the issue is, if I have my choice and I only get one thing that I want to do, I can see a process by which we can have regulation and oversight of baby-making, but without reopening the issue of embryo research. Okay? I don't see a process of really regulating, except just discussing Number I.

And so that I can see a clear path becomes a policy by which the commission can deal with Number II, but in some way I am like Carol; I would like to separate that in terms of policy and then go for this overall-- If we could have a way and we can have an open discussion in this country about Number I, I would like to see it happen. But that is a secondary interest to me.

DR. SHAPIRO: Jim?

DR. CHILDRESS: In the proposal that we have this national discussion, I expect all of you received a copy of "Building Public Trust," and NBAC is featured in that, as you know, and it basically views NBAC as providing a forum for dialogue on ethics issues including cloning. So I just note that NBAC is already--

(Laughter.)

PROF. CHARO: --that is the only thing in there about us.

DR. CHILDRESS: That is right. That is right.

PROF. CHARO: Somebody put in a word search.

DR. CHILDRESS: This puts us in that position and obviously without the power to do some of the things that we have heard, you know, about a RAC-like model.

DR. SHAPIRO: Thank you. Other comments or questions? Larry. I am sorry. You had your hand up before.

DR. MIIKE: A question for Alta and a question for David. How do

we avoid the embryo research issue in this charge about cloning?

And, number two, for David, I am now totally puzzled. You think you can avoid the embryo issue by just focusing on II? II seems to be an even worse issue than the embryo research issue.

DR. COX: But I think that, in II, in terms of having babies, it may be a worse issue but you could I think, that in the context of the public and private, just in general, we are in a much easier place of coming to a consensus there in terms of ways to regulate it.

Right now it is a federal law that basically says successes have to be reported in terms of things. Protocols and things have to be reported. So I just think it is easier--it is not an easier answer--but it is a more circumscribed thing that the commission can deal with rather than the research part of it.

PROF. CHARO: I think, Larry, that the ease with which we could work on the baby-making stuff alone depends, in part, on how we are going to come out on the baby-making stuff itself.

If we were to come out with something that was advocating a complete prohibition, whether through a voluntary moratorium, an imposed moratorium of X years, or a legislative ban of indefinite duration, then a lot of the connections to the basic science research that are essential for a more nuance review of the ethics for particular baby-making application are irrelevant because there will be no baby-making applications. So a prohibitory approach really does cut it off very cleanly from the research issues in many ways.

If the commission were to be leaning towards something that was much more tolerant of some children being brought into the world through this technology, but under very controlled conditions with lots of review for both ethics and technical aspects, then Carol and David's concern about the ability to do that

without having some organized way to get a handle on what has been going on at the research end all these years becomes more pertinent, although it is not insurmountable.

The answer regrettably is you shouldn't do it by having bad technical and ethical review or, to be more forgiving of the whole thing, by having the kind of review that is typical of medical applications that proceed based upon physicians' own review of the literature without any special body developing information for them. It is done through individual research and special societies, et cetera.

So the ease of that I think really depends on the kind of approach that we take.

Let me just say one other thing, which is that in some ways this is not necessarily the way you would slice the specific actions that we would then be proposing. This was-- If you look at what is going on here, what we are trying to do is identify where you want to come out with various options. But the individual actions you would take are actually easier to comprehend.

So, for example, if you were to focus on Number II, you might want to have an action that has to do with calling for a moratorium of X number of years, whether it is, you know, governmentally imposed or voluntary.

But you might want to also do things like call for professional societies to right now make statements about the standard medical practice, hopefully concluding that that standard does not permit anybody trying this on a kid right now because it is simply too dangerous. That will help plug up one of the holes in the medical malpractice area and states' standards areas by clarifying what is good and bad medical practice.

You might want to call for extension of human subjects protections to all people in the U.S. because then, to the extent that anybody in the private sector is doing a protocol that tries human cloning, the protocol can only proceed according

to the kind of IRB review we now have. Probably, again, that would mean all the risks that are so uncertain now would make it difficult to go through.

There are many actions you could take in association with things that discourage. And we had a version of this that sliced that way, and we moved back and forth, and we can try to identify all these things in many different ways. That is the point of having a group of people that will serve as the commission to try to slice it however you want.

But I do think it is possible to actually separate baby-making and research from one another.

DR. CASSELL: Well, it is possible if you recognize that you can separate them, but you can't take the influence of one away from the other.

PROF. CHARO: No.

DR. CASSELL: If you cancel baby-making, you push the emphasis onto the research that leads right up to that corner in anticipation of when that--

PROF. CHARO: We can separate the action items.

DR. CASSELL: Yes.

PROF. CHARO: Even if we can't separate the science.

DR. SHAPIRO: Okay. Bette, then Bernie.

MS. KRAMER: I am feeling very frustrated because I came away from yesterday's meeting, as sort of wild and crazy as the discussion was and it was just kind of free-ranging and all over the place, and I came away with a much greater sense of clarity than I am getting here today from this very well-organized--

DR. : Is that progress?

MS. KRAMER: --outline. And, you know, I am sitting here and I am so frustrated.

So I am going to, for a second, just say forget we ever stuck that

outline in front of you, and let me make a stab at something else. See if I can kind of organize what happened yesterday.

First of all, we started off with a discussion about what had happened when the federal government stopped funding embryo research, and what happened when it became a part of the private sector.

And Alex did a wonderful--he is gone--Alex did a wonderful job of describing that for us. And I think there was a sense that, oh, gosh, you know, let us not invite anything like that kind of scenario into this issue.

So, I am sure I am going to be corrected if I am misspeaking. You know, there were no votes. There was no attempt to come up with a consensus, or anything else. This was just my perception--okay?--of how the group felt as the discussion went on.

So I thought that, number one, that there was a sense that it would be better if there were federal funding for this research, both because of the other experience and--again, now maybe I am going to read something personal of myself into it--but it is for the people; it should be funded by the people. Anyway, that is just my thinking.

And number two, I think there was a very strong sense that we did not want to even attempt to try and stop scientific investigation from going forward.

So then it became, okay, how do you let the scientific investigation go forward without bumping up against, number one, some of the, well, the prohibitions that are out there on research on human embryos and, number two, some of the very strong values that have been presented to us that are clearly expressed against the possibilities of the baby-making?

So it would be for the present that we would take whatever measures that we could that we felt we needed to put in place to allow the scientific

investigation to go forward, and that of course would be within the scientific model of full research on the animals, et cetera.

And only in the future--in the future--would there be a consideration of research on the human embryos without the intent to implant. And that would not come about until that would await scientific necessity. That would await the time when we have been assured that everything that could be explored and could be understood, using non-human embryos, using animal mammalian models, had been explored.

And also, coincidentally, that maybe by that time there might be a change in the political climate where the prohibitions--the current prohibitions--may no longer be in place or might once again be addressed.

And further into the future, there would be the consideration of research on humans with the possibility of implanting.

But our feeling, our perception, was that this is so far off into the future, that there is so much that has got to be understood and accomplished before that, that it just was sort of silly to even sit and talk about it.

And it was only at that point that we began to talk about, well, okey-doke, if we are talking about something that is going to be evolutionary, how are we going to create this evolutionary mechanism? And that is, you know, how we--

So, I don't know if that makes any kind of--

DR. SHAPIRO: I would just like to clarify something in my own mind. I know Bernie, you want to speak also. I just want to seek some clarification here.

It seems to me that Roman II, for a wide variety of reasons--scientific reasons, religious reasons, ethical reasons, others, and combinations of all those reasons, human subject protection reasons--I mean, for a wide number of

reasons, I haven't heard anybody on this commission, or anybody testifying for us, suggesting that we are ready to go ahead into that area.

And therefore, however you describe the barrier, whether it is only with special permission about some very high-ranking group, or whether it is an outright prohibition, whether it is legislation, whether it is-- Whatever the barrier is, I haven't heard anyone say that they-- Well, I will put it this way.

Everyone has said they want a barrier now. Some people say now-- whatever now means. It seems to me that on that issue we are, at some level of generality, all agreed. Obviously, when we get down to details, there are important things to discuss in which we may disagree. And I know they are very important things.

But it seems to me at least we ought to come away here today saying, "Well, that is an area where we agree," for all the reasons that were presented to us.

And I just looked, Carol, at the letters we have gotten back from a few of the scientific society. Right. It is only a handful. I don't know if it is eight or nine. I didn't count exactly. They reflect this view. I mean, everybody reflects this view.

And it seems here in that area we have a coincidence that it is very easy for us, it seems to me, to reach a conclusion. We can start worrying about what the details are, and those are not unimportant at all. But it seems to me we are beyond that, from everything that I have heard from members of this commission, plus what we have heard about it.

So it seems to me what is-- And I think it is a very helpful outline, myself, here. That on that we are agreed.

I think Alta has asked a very interesting question, which we could

just try to engage in, in a few minutes--if we have breath to engage this today--and that is, essentially, do we want to say more than that, and in what way do we want to say more?

Do we want to enter into Roman I and deal with it? Are there other issues on which we wish to opine or reflect or educate people who will be reading this report, and so on?

And that, I think, is really a very critical important issue, but there is-- And there are lots of options there still. But it seems on Roman II, we are at the level I talked about, in general. We seem to be agreed.

Now, am I misreading somebody, or is there somebody who thinks that this is an unjustified kind of reading of where people are?

DR. EMANUEL: The only question I would ask you is whether you take that to be temporary or more long-term? And I say that seriously because I agree. I mean, we heard from the scientists today, and I think, in the ethics bucket certainly, the idea of a moratorium was agreed. The disagreement came out, how long, as it were, and how extensive? And that is not trivial.

DR. SHAPIRO: No, that is not trivial, and I will give you my answer to that in a second.

But Bernie and Alex did want to say something else. And Arturo also. Excuse me. I apologize.

DR. BRITO: I have-- I am getting a little frustrated because I think it is time-- We need to start coming to some sort of consensus, or not coming to consensus. And I, too--I shared with Bette yesterday--I thought this was an excellent outline, Alta, and Alex, and I thought--

PROF. CHARO: And Kathi.

DR. BRITO: Yes. Kathi, of course. The point is that I think-- But

the point-- The reason we made the outline was not to decide to come together as a consensus, and I think we can actually--

I have made a summary--five statements--that I think combine this, and Alta and Alex you can help me with the legal aspects of this. If you don't mind, I would like to read them and see what kind of consensus we have come to on this. Okay?

The first proposition I would have is a continued moratorium on federal funding of human cloning research of any kind.

The second was continue the moratorium on private sector research of human cloning research for the purpose of implantation.

The third is to call for a voluntary moratorium. And I say that because legally--correct me if I am wrong--we can not prevent the private sector from doing research on the embryos. Is that correct?

PROF. CHARO: No.

DR. BRITO: We could?

PROF. CHARO: We could probably legislate it at the federal level.

DR. BRITO: Okay. So two and three we may be able to do in the private sector, moratorium completely, or for all kinds.

But it was voluntary moratorium in the private sector for whatever kind of cloning research, human cloning research, at the cellular level.

And number four is encourage the animal cloning research to better understand blah, blah, blah, blah.

And the fifth proposition is to devise a committee, whether it is NBAC or we assign a commission, to oversee and regulate any private sector research on cloning, whether it is animal or human research going on.

And I don't know if-- I am trying to summarize and trying to

combine some of these things. Does that take care of the I and II in there somewhere?

PROF. CHARO: Are you suggesting that is a consensus of everybody's views?

DR. BRITO: I am asking. I am asking where people would differ at this point? We are talking about trying to devise something within six weeks, right? And at this point would anybody disagree with--

PROF. CHARO: (Inaudible.)--on one point.

DR. BRITO: I am sorry?

PROF. CHARO: I just want you to know you have got one person that differs on one point.

DR. BRITO: Okay.

DR. SHAPIRO: We will come back to that in a second. It may be helpful.

DR. BRITO: That is fine, but--

DR. SHAPIRO: Which point?

DR. BRITO: Yes.

PROF. CHARO: I wouldn't vote in favor of continuing the ban on federal financing. I might not advocate tackling that problem now, but that doesn't mean I want to vote in favor of kind of status quo.

DR. : I would differ on some points, too.

DR. BRITO: Okay. All right.

(Simultaneous discussion.)

PROF. CHARO: Exactly. It was simpler before.

DR. SHAPIRO: Bernie, and then Alex.

DR. LO: --at least in a preliminary way, where there is agreement. Second, sort of aligned with-- It has been suggested that, at the very

least, if we had to do, what would we recommend right now, I am not sure any of us would recommend proceeding with cloning of humans in the sense of implanting and trying to carry clones to term.

The reasons we don't want to do that may be very varied. Some would say, "No, not now, not ever;" some would say, "Not now because the science isn't perfect," and some would say, "Not now because I need more time to think through what these very difficult ethical concerns are."

But it seems to me that if we can say, "There doesn't seem to be an overwhelming need, there are various types of concerns; let us, at least at a minimum, start with extending the moratorium." Then I think after we have addressed questions of how long, who lifts it, under what conditions--

I think we also have to address concerns if some people say that doesn't go far enough; that by only having a moratorium rather than flat-out prohibition, which is conceived as permanent, some people will say you misconstrued the ethical concerns that we are expressing. We have to address whether that makes sense not just to us, but the public as a whole.

I would like to try and start with where we can reach agreement and then go forward. So if that is-- I mean, I second Arturo sort of pointing out some sort of test to see if we can agree.

I would actually like to suggest there also I think is agreement on the other issue regarding Alta's I, the research enough for not beyond the 14 days, not for implantation using human cells.

On the one hand, the practical reality is there is a legislative ban on federal funding and so, from a policy point of view, there has been a position made and I think this administration would probably support that it continue. But I don't want to talk for the administration.

On the other hand, we also heard today from a scientist something, which if we can--I don't know if verify is the word--but sort of discuss further; that right now there are not pressing scientific issues that cry out for study in human cells as opposed to other types of cells; that there is a lot of valuable--

We would not right now be setting back the scientific agenda, which may have promise for cell therapy that never goes through this--I mean, to go back to Orkin's Star Wars technology--that never goes through the totipotent stage that makes an embryo, but has the potential for whatever, cell transplantation, tissue transplantation.

There is not a pressing need to sort of do that research on human cells right now, so that maybe we could also carve-- No matter where we want to end up, some people may say, "Yes, let us have a ban on prohibition on federal funding and federal research now;" some would say, "But it is only temporary, when the science is ready, let us change," and those who would say, "You are right and I want to make it permanent if possible."

Then we have a question of what to do for the private sector. And, you know, one of the concerns I have is that--

There are two problems with the private sector. One, some people think it shouldn't be allowed to continue at all. And other think that is continuing in a way that is so unsupervised that it may be sub-optimal or even risky. And my concern is probably more the, are they doing it in the best possible scientific way?

At the Human Embryo Panel, we heard a lot of testimony from what I thought were reputable scientists saying they thought the level of "basic research" done in the private sector--now I am talking about IVF programs, not biotechnology programs--was second-rate at best, was mediocre. It was never published. It was never subject to peer review. It was sloppy. You couldn't tell what they were doing.

And what I am concerned about is that if we think we want research to continue, are we really getting valuable results from the current system of allowing the private sector no oversight? And some people say turn it off completely. Another option is to try and put some sort of voluntary regulation on it.

But, again, I would like us to try and see is there agreement?

But right now do we want to sort of advocate changing the current policy on preimplantation of human embryo research with cells that are derived by nuclear transplantation? I am not sure there is but, again, in the spirit of Arturo, I would like to see--

DR. SHAPIRO: Bernie and others on this issue on related--I don't know what the issue is here; we have another issue in our head, so I don't want to use that phrase--but on the question of what things may be easily come to some general agreement about, allowing for the fact that there are important details to be worked out, I think one is, as I have already said, Roman II--just to not have to repeat the heading each time.

And then you immediately get-- In my mind, it immediately raises the issue of the private sector/public sector. And my reading of what I am hearing, from members of the commission and others, is that not only would Roman II be inappropriate for federal funds, it would be inappropriate period. Okay?

And therefore, if we did agree to that issue--and others that I will call on still may have some different views on that--it would seem to me that that is an area where it is more--

If I think of the priorities, I think we should decide, try to decide, and put details behind it, what is classified here as Roman II? And I think we ought to all clarify the public and private issue as it relates to that.

DR. : Agreed.

DR. SHAPIRO: First.

There may be other things and we will do them. And Arturo gave us another, and we certainly can stop there.

But it seems to me that if we can't figure that out, that we are not going to--and we can't perhaps reach all conclusions today--but we won't be able to figure the other out. So I have a kind of a--

Whether or not we want to go to Roman I and, under what situation, I still think is a very interesting question which marries not only ethical issues but practical issues.

And I don't consider these--the practical issues--either irrelevant or unprincipled because in this area that we are trying to deal with those are real issues and we have to-- We are entitled to include them in our own deliberation.

So, Alex, I know that you had your hand up before and I didn't call on you.

PROF. CAPRON: Yes. It is to respond to your attempt to state a consensus.

I believe there is a difference, in a liberal democracy, between the world that we would like to live in and the world that we can construct through our governmental processes. And this issue may be one of those that test that.

I would like to live in a world--and I think it would be a better world in human terms--in which people did not engage in human cloning of human beings. The question for me is whether I can impose that view on others who may differ with me?

And if you are talking about a moratorium that would be imposed because at the moment it would seem, to people most knowledgeable in embryology and obstetrics and pediatrics and so forth, that it is irresponsible, given the present

level of animal knowledge, to do this, and that that risk to the potential-born child is so great that anyone on the medical side undertaking it would be doing something which would be regarded as a criminal act, you might even get an agreement on that, and that might be something which could hold up. But that is a very temporary sort of situation.

I mean, it seems to me that the animal research is going to go forward and you are going to get to the point where you can't make a solid prediction, but you can make the kind of prediction to where it doesn't, on the face of it, appear to be a horrible thing. That is the Louisiana situation. Now, Lori Andrews and her paper describes it as anomalous; that in Louisiana you can do *in vitro* work to lead to the birth of a child, but you can't do *in vitro* work to lead to perfection of *in vitro* techniques. But that is-- I don't know that it is anomalous; it simply creates a-- It is a particular division guided by an ethical view on where the risks ought to be allocated; that they ought not to fall on embryos, except on the embryos that have some chance of having life.

And, you know, you can disagree with that posture, but we have to be able to, if we were to recommend this with any teeth other than just, as I say, we personally would like to live in this world that didn't have embryos being carried, cloned embryos being carried through to babies, we have to be able to say that in the face of parents who would say that is the method of reproduction that makes the most sense to us, in the face of scientists who say they are prepared to go ahead and so forth, we have something which can withstand that kind of criticism.

Now, one of the advantages of the kind of regulatory cross-system people have suggested is that it not only builds in the red light, but it builds in a mechanism for saying that you can get to a green light. Now, as I say, it is not a green light that I particularly want to see turned on, but it establishes a certain greater degree

of reason.

As Alta said, it is easier to defend a prohibition that grows out of a regulation that has the possibility of allowing something than it is a flat prohibition, even though the individual who finds him- or herself on the negative side of the temporary prohibition still can complain, but their case isn't quite as strong.

So I am not sure that your nice statement of the consensus that we have carries through to the very area that our bucket was concerned with, which is then how do you turn that into policy?

I have no problem in our reaching consensus on a muddled basis. That is to say we don't all agree about the reasons why we are persuaded that it would be inappropriate to go forward. Some people would be doing that purely on scientific grounds; some people on science and ethics, and, among the ethical reasons, they would have a variety of ethical reasons. No problem in reaching a consensus out of disparate reasons. But it does seem to me that we have to think harder about what that means.

Also, you heard from the two scientists who were here that they did accede to our reconstruction of the world, to a certain extent. You don't really need to use human cells now, do you? And they agreed that was true. That probably it would be appropriate to learn much more about the animals.

But they also balked even at the word "moratorium" because it is against the scientific nature to say that there are outside limits on what you are going to do in your lab tomorrow when your own science develops. And, again, it seems to me that that is somewhat more comfortable in it being imposed on the scientific community and being accepted if it is with the mechanism that allows the point to come where you would say go forward.

But, again, I am not sure what I say to Steve, much less to the

private clinic that doesn't even have a kind of public structure that you have, with advisory committees and so forth for your company--just the lab that Bernie was describing, just the *in vitro* clinic that Bernie was describing.

When they say they want to do this research, you know, I, in effect, have to say that it is a wrong to use an embryo this way, otherwise what is the harm that I can describe as to the justification for the government telling you, you can't do this?

I mean, if they want to use a mouse cell I don't know what the government would say.

In the recombinant DNA area, it was the physical risk to other people. You do it, you flush it down your drain, and Palo Alto comes down with an epidemic. You know, that was the concern.

But there is no such concern here. There is no physical risk to other people in this. There are societal risks about the way society ends up, and so forth, but with the cellular research I think you have to say that using the embryo is, per se, wrong, and therefore the federal government, or the state governments, can step into what Louisiana said and say, "You cannot create an embryo and experiment upon it."

DR. SHAPIRO: Yes, but--

PROF. CAPRON: And if we can't say that, I am not quite sure what our hook is.

DR. SHAPIRO: You know--

PROF. CAPRON: I hate to throw cold water on--

DR. SHAPIRO: No. I find-- No. I tend to let others speak, but I find almost everything you say perfectly compatible to what I thought I was saying.

I have absolutely no objection to red light, green light, orange light mechanisms that become part of it. And I think we need to discuss issues of why it is

we feel this way.

I don't think we should just brush it all under the rug and, in particular, and that is why I highlighted the private versus public. Whether the case is strong enough to say something different to the private and public sector, that remains-- We have to articulate that.

PROF. CAPRON: Okay. I agree.

DR. SHAPIRO: I agree with that conclusion. Eric?

DR. CASSELL: Harold, I want to pick up on the last three. I think what you stated, we do all agree. We do all agree at this time about the baby-making problem. We are all agreed that we shouldn't do that.

And then the second thing is we are all agreed that not only the federal prohibition, but some way of influencing the private sector, that then becomes a task. How in fact do we get at the private sector, when government alone is not sufficient? Do we do it through professional societies, and so forth?

But we also have two other agreements, and Bernie said them. And as he said, we all agree, but then he said some might say there ought to be an absolute prohibition, and some say it ought to be this, and some say that. Well, then that leads us to another agreement. We are not sure how long it should go on, and we are not sure how firm and forever.

So we have three parts of the agreement; that is that we believe red light, green light, whatever you wish. You know that we are not talking about an absolute now and forevermore.

But we have a fourth one, which is that we are all agreed that we are not sure about how the thing should be. What the relationship of the science is to this later step, in which case we are all sure that a public discussion has to go on.

Well, that gives us five points of consensus and that is not half-bad,

considering the fact that it is only five minutes after three.

PROF. CHARO: I want you for my banker. You could get me so much more money than I now have.

(Laughter.)

DR. SHAPIRO: Okay. Are there others that want to speak? Diane, do you want to speak?

DR. SCOTT-JONES: I just wanted to ask are we trying to come to an agreement of some kind, even if it is Eric's points that we agree on? Is that what we are trying to do right now before we go home?

DR. SHAPIRO: Well, no. I don't think we have to come to agreement before we go home. I think that is not likely because each one of these require some careful statement, no matter-- I am just-- I just launched this part of the conversation to just get some sense to where people are because--

And let me go on to talk about what I think our next steps are.

Kathi and I are going to start writing tomorrow, or the day after tomorrow. As we go through the outline of the report you have seen, together with the outlines that have been added to it, like this one which was presented to us today, and we are going to get started.

And that is going to involve, at some points, guessing and sometimes making up our own minds, of course, and then just sharing it with the three just to see whether those points stand up.

This process will be informed by the work going on in the buckets, and what they think, and how they can help us think this through. But unless--my own view is that--unless we start committing these things to writing, it is very hard for us to sit carefully and think about the arguments.

So my intention is now to get to the writing quickly, recognizing

that early on there is going to be little recognition, or little association that you won't write down the first time, but we eventually come up with the report.

I don't deny that Kathi and I--that you, you know--really have that much knowledge that we are really going to get all this right, and it is going to take us a while to work through it. We can't all do it-- We can't do it in one day.

And so I think the purpose of the conversation now, as I see it, is to help give us some sense as to the kind of direction, the kinds of things that are on people's minds, and what they would really hope for out of this, and so on. So we are not taking any votes now. We are just trying to get a sense of where people are.

We have had an awful lot of input with all the commissioned papers, some of which arrived just days ago, so that we haven't all fully read them. We have had the testimony before us, of course, and of course the literature we have reviewed in the last while has been very extensive.

And so we are in a position to begin moving towards, you know, some kind of ideas which we may or may not deal or mold consensus around. We will have to wait and see about that. But, I mean, that is-- That is what I was trying to get going.

Zeke, then Bernie.

DR. EMANUEL: I wanted to endorse your approach, and I do think that there is consensus.

And I wanted to say something about the private sector here. I don't know if I am exactly in opposition, Alex, but--

I mean, it would be dangerous I think, on Number II, Roman Numeral II here, to permit the private sectors to go forward while prohibiting the federal sector, for two reasons.

One is we do have some experience in this area; that they are not

completely responsible. They don't report when they are supposed to. They don't collect data. And that would make me feel extremely queasy.

Second, if we let the private sector go ahead, it seems to me--and they succeed in some way, or try it--they preempt anything else in our debate. Right?

If we are uncertain about the moral values, they could preempt a decision of ours by forcing it, as it were.

And it seems to me, to the extent that we agree we are not certain about the answer, at a most cautious level--that it might be wrong, it might not be wrong; we just haven't heard all the arguments articulated to the fullest--to let the private sector run ahead and preempt us I think would be a mistake.

Having said that-- And I think this goes back to Alta's question, and I have a question and a statement. One is, Dr. Shapiro, how do you understand the charge to us from the President regarding Roman Numeral I?

And then I will just say here sort of I would feel slightly uncomfortable myself saying something on Number II without saying something substantial on Number I.

My own feeling is that I think a lot of the reasons I am worried about Number II, to be blunt, do not apply to Number I. And I personally find--I know it is mired in all sort of politics there--but many of the objections to Number I don't have a perch on me where they would.

And so I would personally feel much more comfortable stating something on Number I while we are stating something on Number II, analogous to this moratorium, ban, prohibition--however we are going to phrase it--because I think they are intellectually, if not inherently scientifically, related.

And I guess in part it depends on your reading of all sorts of tea leaves, practical tea leaves as well as what actually did the President want us to do.

DR. SHAPIRO: Well, I can't answer the first question because I simply don't know. I have not had that conversation and so I simply would be guessing and that is not appropriate, so I just don't know the answer.

On the second part of your question, the practical tea leaves, I am not sure on that either.

(Laughter.)

PROF. CAPRON: That is helpful.

DR. SHAPIRO: Bernie?

DR. : Prudent silence.

PROF. CAPRON: Can we call that Roman I and Roman II?

(Laughter.)

DR. LO: I want to support what has been going on I think in the last 10 or 15 minutes, which is trying to move towards seeing where points of agreement are. We spent a lot of the day, like last night, trying to articulate the differences.

And I just wanted to sort of follow up on this public/private issue that Alex and Zeke noted. I just want to point out that if we think, as a matter of sort of principle, that the temporary at least moratorium should apply equally to the private and public sectors, then it becomes an interesting policy question as to how we construct whatever it is--mechanisms--to assure that that moratorium is observed in the private sector. I would agree that the voluntary ban may not work.

I just want to point out that Bob Kochidegan's(?) paper, as well as very good, really didn't address clinical moratorium.

I mean, Martin Kline's(?) episode was a clinical episode. I think the thrust of that was really a scientific research moratorium.

I just want to say that in the clinical arena there are lots of examples of moratoria observed in the private sector. There are moratoriums on cardiac

transplantation, moratoriums on valve surgery, and the driving force was a recognition that it was hard to justify scientific and ethically because the risks seemed way out of proportion to the projected benefits at that time.

PROF. CAPRON: But in order-- But, Bernie, with something like the mitral valve surgery, here you had the individual, as I recall it-- Is it Harkin?

DR. LO: Harkidin(?).

PROF. CAPRON: --who was doing the surgery himself and was trying to develop his tool to do it, and he was having operative gap after operative gap, and his own conscience said to him, "I can't go on like this." And then it was that advantageous finding that breaking the mitral stenosis with his finger was better than trying to cut it, and it sort of led to a breakthrough.

But that was, more or less, faced with a problem, the conscience of the individual, not sort of an industry out there raring to go, already doing this--we have already seen what happened in the *in vitro* area--so I don't have quite the same confidence that this moratorium example from mitral stenosis, or even from the cardiac transplantation where it was the same kind of thing. You were having a disaster.

You could say on the artificial heart you had an effectual moratorium on the artificial heart, otherwise known as the artificial stroke machine, that we had going after Barney Clark because it just wasn't an effective therapy.

But here we are talking about something where part of the concern for the moratorium is a much bigger ethical sense, not just that it would be physically risky and, again, that is our view, but you may have Dr. Jones--not Dr. Jones--Dr. Smith saying, "I think I have enough knowledge now to do it, and I have a willing patient who will pay the tab and who are you to tell us that--"

DR. LO: Well, I think that is the discussion where--

PROF. CAPRON: That is the hard part of it.

DR. LO: Right. That is the discussion we need to have but, if it is a discussion framed in terms of we would like some way of trying to have an enforceable moratorium in the private sector, then is a question of technique and meaning so--

PROF. CAPRON: And maybe we should look and see if there are more examples of a clinical moratorium. It just seems to me that the two that you have cited are--

DR. EMANUEL: They also fly in the face of the history of the IVF community itself.

PROF. CAPRON: Exactly.

DR. EMANUEL: Which is not--

PROF. CAPRON: The very community that we are dealing with.

DR. EMANUEL: --not a laudatory community necessarily.

PROF. CAPRON: Well, I don't have to laud them or not. But just on the sense that there is a lot of delay built into the system, or strong professional practice that have the most conscientious slowing down, the most adventuresome, it does not seem to happen.

DR. SHAPIRO: Alta?

PROF. CHARO: I would like to build on what Bernie said because I think, rather than talking about public versus private, a possible and more fruitful way of describing the distinction there is going to be research versus clinical. And when I say "clinical," I mean including experimental; that experimental is part of what is being touted as a therapeutic intervention, and is not part of a systematic investigation for the creation of knowledge for the future.

The reason I say this is as follows. When you put it in that context,

the options for intervention begin to fall out, and some of the debates swirling here about the nature of the moratorium quickly get picked up. Research, public. All right? Well, you can say we will have a red light on financing for research, public. We are talking baby-making only now. All right?

Clinical, public. Well, it is so experimental that the few public insurance funds that exist are never going to finance it, so it is irrelevant.

Private. Now here is where the options for control in the private sector really differ, depending on whether it is a research setting or a clinical setting.

If it is a clinical setting, that is if it is the paradigmatic IVF clinic that is offering an experimental procedure to patients who are paying for it, even though it is very poorly developed and ideally should have been subjected to lots of research, well, that is where you could try a shut-down by federal legislation, call for a clinical moratorium that comes out of the relevant professional societies or the NSF Consensus Conferences, call for at least statements from professional societies that will guide malpractice litigation in the future which could be an indirect deterrent to particularly outrageous experimental practices. A whole variety of controls come to mind.

Private research. Right? Well, here actually there is already a mechanism by which private research is regulated. If we were to somehow say this has to be governed by the existing regulation--i.e., once again universal application of human subjects protection--you would have put in place no moratorium, you would have said you have got local decentralized IRB review, or you could say have a moratorium for two years and then it goes back to IRB review, or you could say, you know, the current regs are just not even good enough, we are going to isolate this one the way gene therapy was isolated, and then they will say if it is research and it is private nonetheless it has to go up through the RAC and we will give the RAC that

responsibility, or another body.

But the avenues are distinctly different. And I think that it may be a useful set of distinctions for guiding us when it gets down to kind of action items; what it is that you actually recommend be done to further the goal of a moratorium that is short-lived, permanent, has yellow lights--some of these already do--versus yellow lights we have to build from scratch.

DR. SHAPIRO: Helpful. Let me suggest two things. We are rapidly coming to our endpoint today and so we really have to find some way to wrap up. And let me just turn -- I know it has already been spoken. Tom and I spoke very briefly before. I don't think he would be heartbroken if we didn't get to the agenda of the subcommittee today, so we won't do that.

Jim, I don't know if you have something you really want us to look at today. If so, we should go over it pretty quickly.

DR. CHILDRESS: If we can maybe get three or four minutes to help out the Tuskegee. Simply let me see the committee report. The reason is, if there is action taking place with the current administration, so only two or three minutes on that.

DR. SHAPIRO: Okay. We will go through that.

DR. : (Inaudible.)

DR. SHAPIRO: Just a moment. We will get back to that in just one second.

Well, look, I think we have a lot to do here. It has been very helpful.

We will try to pull this together and generate some responses to these issues, and also assignments to committee members, commission members in the short run. Because we are going to go directly to trying to articulate in writing now

what we have just been thinking about, even though we have to accept the fact that we are going to have maybe large transformations from the first attempt--to put some of these things down--to the second.

I do want to make one general comment about private/public, which has slipped out here a number of times; that is, we have used those terms a little loosely, especially when we had pejorative comments one way or another.

And I think we all agree that, in both public and private sectors, there is both good and bad practices everywhere. And we don't want to-- We want to be a little more careful than we have been about using those phrases I think because, although I think I always understood what people meant in the context--a particular aspect of the private sector, or a particular aspect of the public sector--we really ought to be careful about that because we may be saying things that we are not intending to say. And that would just simply be unfortunate.

So I really do want to ask you to be careful when you use those words. It covers a lot of territory and we just want to be accurate when we use them.

So, you will hear from us, you will all hear from us very shortly.

Bernie has got a plan already for his group to move ahead, and they will go ahead.

We will certainly probably speak to both Alex and Alta regarding proceeding from here.

And to Carol, seeing what is next from her perspective on that area.

In the meantime, we will start, start us off, and we will start to get these propositions in front of you as soon as we can.

So while it is a little messy to conclude in that way, I do want to turn it in.

DR. CHILDRESS: I was actually trying to get one point in because

I had hoped we could get to the discussion of the outline as well.

It seems to me one thing has emerged, at least I would like to propose for your consideration as you are working on this, and it grows out of discussion.

And that is whether the ethics discussion is put in the right place in the outline. Because I feel that we want to make a case for shifting the order and having the legal and the regulatory background prior to the ethical discussion. And the reason is that the ethics discussion--

What do we expect the ethics discussion to address?

You expect it to address what kinds of issues should arise, or will arise in the context of thinking about policy, or what kinds of issues arise in thinking about the rightness and wrongness of particular items.

And it seems to me that our major focus has to be really on the policy questions. It seems to me that we can at least think about the shifting of that order and then ask, if we are really asking ethics questions, relative to what kind of policy options that we face?

And that comes out in the way the ethics discussion is formulated here because it is, under B, moral arguments in support of cloning. Actually, there are very few moral arguments offered in support of cloning.

The question that comes up is are there moral arguments in support of allowing cloning.

PROF. CHARO: Right.

DR. CHILDRESS: And that sort of captures what I am trying to get at in terms of the difference between raising the rightness and wrongness of the act versus the rightness or wrongness of allowing something to continue.

And it seems to me that if that sort of focus could be developed it

might be helpful.

DR. EMANUEL: Why would that change the--(Inaudible.)

DR. CHILDRESS: I am sorry?

DR. EMANUEL: Why would that change the order of where you would put it?

DR. CHILDRESS: It wouldn't necessarily. Those are two points; that I think there is a connection between them. But it wouldn't necessarily. But I think the way--

Well, the point of it is sort of the ethics part is dealt with, and then you get to religious, and then you get the legal and regulatory background and then you come to policy. And it seems to me that if we are going to connect the ethical issues more with the policy options, they ought to be put a little closer together, and then, with the background stuff leave them-- The regulatory ought to precede that discussion.

DR. SHAPIRO: Well, there is-- I want to turn to Kathi who wants to say something.

We will certainly give that some careful thought, Jim. Thank you very much for your suggestion.

Again there are, in the legal and ethical, there are-- In the legal and regulatory, there are background issues, and there are substantive action type issues. And they may not need to be all together, and so we may want to parcel this out in a different way all together.

Kathi?

DR. HANNA: Thanks, Jim, for that comment because I was going to suggest if anyone had--

This outline was just laid out based on the way that you decided to go and proceed

with your tasks. It certainly, in the final report, doesn't have to be sliced this way. And you might decide that you want to have some general discussion up front, background and science, and then you might want to have the ethical and religious and legal arguments underneath each policy option. So, any way. I mean, it can really be sliced any way, and I think that, you know, obviously Dr. Shapiro and I will have to talk about that, but if anyone has any suggestions for how they think that might look.

DR. SHAPIRO: I would say that-- I mean, when we passed out the initial outline, I guess it was last time, we got a lot of very useful comments back. Some people found it a very easy way to organize their thinking. So on their planes, trains, et cetera, on the way going home, if you can look at that, that would also be extremely helpful. We have had some very good suggestions.

So, Jim, let me turn to you now on the Human Subjects Subcommittee.

REPORT FROM THE HUMAN SUBJECTS COMMITTEE

DR. CHILDRESS: This simply builds on the discussion we had last time when we endorsed an apology from the President to the survivors of the Tuskegee Syphilis Experiment and to the African-American community for that particular experiment.

And, as you know from the media reports, action has already occurred in the sense that the decision has been made in the administration to make that kind of apology, with details yet to be worked out about when, where, how and so forth.

There was a second part of our recommendation that we, in effect, delayed until the subcommittee could look at it again, and also could get some additional information about what is occurring in the administration discussions, particularly what has been forwarded from the report that you had in your package from the Tuskegee Syphilis Experiment Legacy Committee.

And the Human Subjects Subcommittee would like to recommend again that we commend to the administration for consideration the other recommendations that appear in that report, which are:

To have a professionally-staffed center at Tuskegee, at the Tuskegee University, to preserve the national memory and transform the legacy of this experiment that would include public education, all the research, and analysis, and dissemination of findings;

Second, the NARDI(?) Health Initiative;

Third, a training program for health care providers to understand the social and cultural issues of both health care and research in communities of color; and,

Third, a clearinghouse to help investigators conduct ethically responsible research.

Those are the recommendations that appear. And apparently there are still matters of discussion within the administration.

And the subcommittee recommends that NBAC recommend that these be carefully considered by the administration as possible ways to respond.

DR. SHAPIRO: Thank you. Questions regarding this? As Jim said, this was before us last time, and further, and I don't know if we can make some resolution from NBAC about further adoption of these issues.

As I understand it, the proposal is that we encourage the administration to give careful consideration to these issues, which, just to make sure we understand, is not saying that we endorse each one of these, but just that they look carefully at it.

DR. CHILDRESS: As I understand that--

(Simultaneous inaudible discussion.)

PROF. CHARO: Call for the question?

DR. SHAPIRO: We do need a motion.

DR. : I so move.

DR. : Second.

DR. SHAPIRO: All right. Are there any comments or questions?

(No response.)

DR. SHAPIRO: All those in favor say "aye."

(Whereupon, there was a chorus of ayes.)

DR. SHAPIRO: Opposed?

(No response.)

DR. CHILDRESS: Thank you.

DR. SHAPIRO: Unless there is something very pressing, we are going to adjourn.

DR. : Boy, congratulations.

DR. SHAPIRO: We are adjourned.

(Whereupon, at 3:28 p.m., the meeting was adjourned.)