35th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: All right, colleagues. Let's begin this morning's meeting. Let me remind you what our agenda is this morning.

We will hear momentarily from Professor Sagoff on the patenting issue which we are considering and then we are expecting the President's Science Advisor to come and speak to us regarding some issues that are on their minds and they would like us to possibly address, and I think we perhaps should be through, roughly speaking, with both of those issues at 9:30 roughly. We will just have to wait and see how long the questions go and so on.

And then we will spend the rest of the morning discussing our upcoming agenda.

We will adjourn no later than noon today.

As in all such cases, there is no reason to use up all that time unless we have something useful to say but I do think we will probably spend roughly till noon.

So, Professor Sagoff, welcome. It is very generous of you to be here this morning. We very much appreciate your presence here and we look forward to your remarks.

PRIORITY SETTING FOR FUTURE PROJECTS

GENE PATENTING

MARK SAGOFF, Ph.D.

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DR. SAGOFF: I am delighted to be here and flattered as well. Thank you for inviting me. I am not only glad to be here myself but because I think the patenting issue has reached a stage of urgency and brightness through your consideration and I hope to convince you to put it on your agenda for action.

In this brief talk I will say -- I will try to characterize where we are and the problems we confront and then suggest what might be your response.

DR. SHAPIRO: If you could just -- I just want to interrupt for a moment to tell you that if this phone connection works there is one member who

will be here by conference call.

DR. SAGOFF: Right.

DR. SHAPIRO: So if you hear a voice coming out of the air you will know it is not your imagination. We do have someone by conference call. Mr. Holtzman is in Boston, I believe.

DR. SAGOFF: Starting about 15 years ago for the first time the U.S. Patent Office has adopted a policy of routinely issuing patents on what are in effect products of nature, including genes, proteins, organisms and most recently expressed sequence tags and single nucleotide polymorphisms.

In consequence, the Patent Office, the PTO, has been flooded with applications for patents on genes, proteins and other such naturally occurring materials on which it has now issued patents on thousands. As one journalist reported in the Scientific American PTO needs a hundred years just to review pending patents and some applications, including from insight pharma -- some insight pharmaceuticals and human genome scientists submit

thousands of sequences at a time.

Now as you know the controversy over gene patenting first came to a boil in 1991 when then director of the NIH, Bernadine Healy, decided to seek patents on a large number of expressed sequence tags, EST's, government scientists had worked out in our laboratories.

The Human Genome Project Director, James Watson, calling the attempt to patent genes or gene fragments sheer lunacy, resigned from his position.

Healy's successor, and this is all well known, Dr. Harold Varmus, instructed NIH researchers to place their discoveries in the public realm. He said, "I do not believe that patenting at this stage promotes technology development and it may impede important research collaborations here and abroad.?

Gene sequences and the proteins they express occur naturally. Thank God they do, otherwise none of us would be here. Yet the Patent Office allows patents on these molecules providing they are cloned or more generally isolated and purified. As one PTO

official states this policy, "In order for DNA sequences to be distinguished from their naturally occurring counterparts, which cannot be patented, the patent application must state that the invention has been purified or isolated."

In other words, to obtain a patent on a gene one must isolate the sequence, identify the sequence, and to patent a protein that sequence expresses one must obtain a pure sample of it.

Now this is really a tremendous departure historically from the way the Patent Office and the courts have treated products of nature in the past. There have -- there are occasional examples in the past of the patenting of a naturally occurring material but it has always been and explicitly been in connection with a particular use or application of that material or a particular way of synthesizing or obtaining it.

For example: I may have mentioned a number of these cases. The Supreme Court held in 1853 that Morris could -- that Samuel Morris could patent the

telegraphic instruments by which he used the magnetic spectrum but not the magnetic spectrum itself. Only insofar as the magnetic spectrum were engaged by that particular instrument.

Similarly, in 1928, an Appeals Court held that General Electric Company could not patent pure tungsten even though pure tungsten did not ever exist in nature. It is always found -- it is active in combination with oxygen or something. It is very difficult to purify. GE had purified it and asked for a patent on pure tungsten and the court held, as you might expect, that it could have a patent only on pure tungsten in connection with that particular way of purifying it or a particular use of it, for example, in light bulbs.

The controlling case here is -- occurred in 1860. It was a fascinating case. It is also one that brings out interesting and relevant ethical considerations. The New York Eye Infirmary sought a patent for anesthetic ether. It had discovered ether's anesthetic properties. This discovery ranks

among the greatest boons to mankind. In spite of the immense importance of this discovery the District Court disallowed a patent for ether itself on the grounds that ether remains a product of nature even when it is used for anesthetic purposes.

In Morton versus Eye Infirmary, 1862, the Appeals Court said -- and this was the controlling -- this has been, as far as I know, the controlling idea about objects of nature and their patentability -- the court said, "A discovery may be brilliant and useful and not patentable no matter through what long solitary vigil or by what importunate efforts the secret might have been wrung from the bosom of nature or to what useful purpose it might be applied, something more than mere discovery is necessary." Something more than the fact that it was unknown beforehand is necessary.

So a new force or principle brought to life must be embodied and set to work and can be patented only in connection or combination with the means by which or the medium through it operates. It can only

be -- until the 1980's that -- so whatever, prostaglandins, vitamin B-12 or whatever -- it is always in connection with the use or the kind of production process patent and not a product patent.

All this change in the 1980's and I talked a little bit in the handout you have about why we can look more in the questions.

In any case, on the basis of its new policy PTO in the 1980's -- I am just going to talk about one gene patent, just one, of the thousands and thousands, the tens of thousands. Nobody knows exactly how many are pending. And this will give you a feel as to what we are about.

On the basis of its new policy the patent office in 1987 granted a product patent to Genetics Institute for purified and isolated erythropoietin, a protein the body makes in minute amounts but which is a life saver in larger amounts to people suffering from anemia.

Genetic -- there was then -- after 1980 there was a race among many companies to purify

erythropoietin because (a) the first one who purified it would own the protein given the -- and this would, of course, be a tremendous cornucopia of riches. Yet Genetics Institute by sheer force of effort, they isolated the protein from human urine and patented that protein, erythropoietin on the basis that it had purified the first sample of it, which it had.

Four months later the Patent Office issued to Amgen another patent on the same protein. Amgen had invented an ingenious way of mass producing erythropoietin by isolating the relevant gene and inserting it into Chinese hamster ovary cells. With its process EPO could be produced in huge amounts at an affordable price but Genetics Institute owned that element of nature, that particular protein, so it sued, of course, for patent infringement. Amgen had hugely more resources to bring to the legal battle and managed to find a technical difficulty to invalidate the previous Genentech patent so Amgen got the ability to market this protein, which otherwise Genentech could have blocked.

The story is now playing out again because Transkaryotic Therapies in Cambridge, Mass., has got an even more ingenious way of activating people's own genes to produce this protein and Amgen, which is now making over $2 billion dollars a year on its EPO, has engaged in what its vice-president calls a no holds barred, no expense spared litigation against TKT to prevent it from its gene activation therapy, which would activate your own genes to produce this protein but as long as the protein is being produced in a commercial way and money is being made on it the patent is now Amgen or so it claims. And there has already been a first round where Amgen sued TKT even for developing the technology to begin with and now there is going to be tremendous litigation.

Well, that is one example and I could give you any number of others. You know the strange doings with human growth hormone. A story that has obviously been in the papers because of the -- where the University of California at San Francisco and a biotech company are at loggerheads as to who owns it

and so on. It goes on and on and on. Clotting factors. It is there.

At any rate, let me now just list the problems that this presents to our society. The first, I think, is the moral and religious problems that religious and moral leaders bring in their objections to patenting products of nature. They think that the distinction between discovery and invention is the crucial one, not between what is known and unknown, that is what is novel in some sense even though it exists because it is unknown.

The reason is that design confers intellectual ownership. It shows that you have taken that inventive step, that you understood it enough to contribute knowledge to the world, the knowledge of how something is designed that other people -- this is the quid pro quo of patent law -- that other people can use to build something better. With mousetraps that is fine but with proteins you cannot build a better gene because of the way they all fit together as it were. It is the product of nature itself that

is at issue, not a design that somebody can somehow improve. So the quid pro quo is lost and many religious leaders, of course, believe that even though God failed to patent his designs nevertheless they were the inventions of someone other than Amgen.

The second problem lies in the sheer amount of litigation that the society is confronting especially in the agricultural area. It looks like there is an enormous hit to the research budgets to the progress of the technology because litigation is endless in this area. At the moment every member of the biotech -- of the IBO, Industrial Biotech Organization, seems to be suing every other member and it just iterates all the way around and it is a horror.

The third problem is the one that Rebecca Eisenberg so brilliantly pointed out in her Science article in Science. An anticommons has arisen where everybody has to pay everybody else because everybody owns a little piece of the action, that is to say -- here I guess I am going to stop with this -- I will

just stop with this quotation from -- one from Carl Siccomb, GEO of Garst-C, just a typical small genetic seed maker.

He says, "Here is an example of what could happen with EST patents and the current backlog. Here at Garst we have been specializing in stacking genes with different traits. Some genes come from outside sources and some we develop. So we developed a project that contains herbicide resistance, it has got insect resistance, and then suddenly you wake up one morning and some company has slapped you with a lawsuit because it got a patent -- it applied for it ten years ago and our gene stack contains one of its EST's or one of its gene fragments. Now we are trapped into a legal situation where we are forced to pay royalties.

"In effect, we have to give our profit away but we cannot sell the product anymore. We spent ten years and millions of dollars to develop that product and if we had known that the patent had been applied because you do not know what patents have been applied

for and had a chance of issuing, we would have never done the research. How as a manager of business can I plan for the circumstance like that?"

It is a totally unacceptable situation.

DR. SHAPIRO: Thank you very much. Are you through?

DR. SAGOFF: No. I just -- I wanted to say that I think NBAC is the -- is the only hope the public has for intellectual and moral leadership in this area. There is no other political authority to step forward to issue any kind of advice or criticism of current policy.

DR. SHAPIRO: Thank you. I just want to say that this is not the first time someone has sat in that seat and said, "You can put your finger in the dike but only you." Maybe that is right.

(Laughter.)

DR. SHAPIRO: And maybe it is overly flattering to us as well but let me just see if our colleagues --

DR. _____: There is water up to our

knees.

(Laughter.)

DR. SHAPIRO: Steve, can you hear us?

MR. HOLTZMAN: Yes, I can. Thank you, Harold.

DR. SHAPIRO: Okay. Thank you. I just wanted to make sure. This is -- that voice is Steve Holtzman.

Okay. Questions? Alta?

PROF. CHARO: Continuing the great NBAC tradition, two questions.

(Laughter.)

PROF. CHARO: Mark, first, thank you very much for what was a passionate and helpful presentation. The first is kind of a bottom line question. All right. If there were no patents that could be issued in this area do you think that Amgen or Genentech or TKT or any other company would ever invest -- would ever have invested anything in the search for as usable form of EPO?

DR. SAGOFF: Yes. In fact, much more because

they would not be wasting their time trying to isolate it from urine. They would have gone straight to the -- to the genetic manipulation and insertion.

MR. HOLTZMAN: Isolating it from urine was the precondition of getting the protein to get the amino acid sequence to, thereby, infer the DNA sequence so the idea that anybody was isolating it from urine as a production method is, in fact, false.

PROF. CHARO: Could you make that out, Mark?

DR. SAGOFF: No.

DR. SHAPIRO: Steve, do you want to try that again and talk a little slower?

MR. HOLTZMAN: If you go back to the early 1980's what was known is that there was a principal in the body that was responsible for red cell production. All right. That principal has come to be known as EPO.

DR. SHAPIRO: Right.

MR. HOLTZMAN: Which was before there was structural gene cloning as we have in the 1980's. Therefore, the way you found the gene was to isolate

the active principal, that is the protein, in this case from urine.

DR. SAGOFF: Yes.

MR. HOLTZMAN: Once you have the protein you got the amino acid sequence of the protein. Once you have the amino acid sequence of the protein you then through degenerate primers got the DNA that encodes the protein. Both Amgen as well as Genetics Institutes by the way, not Genentech, isolated the protein from urine not as a production methodology but as a necessary step in order to be able to get the amino acid sequence and hence thereafter to be able to get the DNA sequence.

The representation that Genentech -- that Genetics Institute was going to produce EPO through a production methodology which is ridiculous is a mischaracterization of the situation.

DR. SAGOFF: Of course, it could not possibly produce EPO through isolating it from urine any more than clotting factor could be isolated from, you know, getting it out of the blood of pigs, which is the way

these things were first found. At the time you are right, of course, there was --

MR. HOLTZMAN: As a matter of fact, clotting factor up until three years ago that hemophiliacs were getting was, in fact, being gotten from isolation from plasma and also from recombinant DNA insulin was being gotten from pigs and cows and, in fact, still is in some instances.

DR. SAGOFF: There are a lot of problems with contamination of bacteria and so forth when you try to isolate it from plasma. These are -- all of this -- what he says is true but it is obvious that the -- that you are not going to get EPO from urine. The reason that Genetics Institute -- of course, if I had said Genentech --

PROF. CHARO: No, that was me.

DR. SAGOFF: Okay. That was you. -- went forward, however, was to get that patent. The issue was getting the patent by purifying. That was what needed to be done first commercially.

Now to get to your question, there is no

doubt that people -- that these companies would put plenty of money into this. They were doing it even before the Patent Office made up its policy. That is people were pouring money into genetic engineering during the '80s before it became at all clear that there would be -- what the patent policy would be and we were in competition at the time and one of the reasons the patenting came to the fore was because of international competition with Japan and unless we have patents the Japanese will get ahead of us and so on.

In England, especially Japan and Europe where there was no patenting at the time, there was enormous investment. So I think that that would not be a problem.

Second, if there was a patent by process or by product by process, if Amgen got a patent on putting the gene in, you know, cells, and expressing it that way it would certainly suffice. That would be a wonderful way of making it. It would make all of its profits but it would have no case against -- it

could not block a different way of making it, TKT's way, and I think that suits our intuitions.

PROF. CHARO: Well, then that actually leads perfectly into the second question if I may because I am trying to completely understand the nature of the objections here. I have got to confess I have only followed this field from a distance, right. In reading the shorter piece that was distributed yesterday by you, the one from Issues in Science and Technology --

DR. SAGOFF: Yes.

PROF. CHARO: -- you begin the article by outlining the two distinct purposes of patent law. First that inventors get what is called a natural property right to their inventions. All right. A kind of natural law argument.

DR. SAGOFF: Yes. Right.

PROF. CHARO: Which seems to be the source of concern for the religious leaders because it seems --

DR. SAGOFF: Absolutely.

PROF. CHARO: -- to convey the notion of not

only intellectual collaboration but intellectual primary authorship of something. Right? And the second has to do with the kind of instrumental purpose of creating incentives for investment.

DR. SAGOFF: That is right.

PROF. CHARO: And at the very end of the article in the last paragraph you say that a new statutory framework could provide monopoly commercial rights that industry seeks without creating the implication that industry invents, designs or owns the genes.

DR. SAGOFF: Right.

PROF. CHARO: Okay. But now I guess I am now confused because if the major concern here is really in the -- either symbolism or common understanding of notions of intellectual ownership and what the word "own" and what the word "property" mean because, of course, they have very different notions in law than they do in common usage, which is one of the sources of tension here, that -- and that, therefore, that is the major concern and you, indeed, advocate monopoly

commercial rights --

DR. SAGOFF: Right.

PROF. CHARO: -- for the instrumental purposes then why are you asserting that the monopoly commercial rights are not needed and are counterproductive in the examples that you have given, including the example of EPO? It seems like in the article you are only arguing against one basis for patenting and now I am hearing two bases independently being raised.

DR. SAGOFF: Yes. There are two questions here. First, the patents are too broad is what I am saying and also they imply intellectual ownership which perhaps religious leaders, you know --

PROF. CHARO: And they would not -- and the religious leaders would not be -- would not be calmed by kind of a class on what property means in law versus what it means in common parlance?

DR. SAGOFF: No, actually they would be calmed by a narrower construction of these patents, that is if they were patented in the same way -- on

some analogy with our planned patent acts or, you know, our hybrid patent acts, they could see that it was not the gene itself or the protein itself that is being patented but that in connection with a certain process of making it. If you hybridize a plant -- somebody else can make the same plant differently, asexually or something like that, and get a patent on that way of doing it.

Now it is a distant analogy, however it is the narrowness of the patents and their connection with the process and the use that spares us from thinking that the product itself is the intellectual outcome of this inventive step that Amgen or whatever has taken.

PROF. CHARO: Thank you very much.

DR. SHAPIRO: Alex?

PROF. CAPRON: I want a little further elaboration on what you think we should be doing, not topic-wise, clearly the question of patenting of genes, human genes, is the topic, but my sense is that it is unlikely that we will be in a position other

than by endorsing the view of lawyers or others who are able to interpret the patent law and the decisions of the Supreme Court in this regard. We will be unlikely to say anything about whether the patent statute has been read correctly.

The question that I took it that people were saying needed to be addressed is not whether there is a problem under the existing interpretation but whether it is right or not for companies or for individuals to own human genes. Is there something wrong about that? I mean, that -- if there is a -- if there was an emotional and, therefore, newsworthy punch to the group of religious leaders who Jeremy Rifkin gathered together those couple of years ago, 1995, to issue this call for the moratorium on patenting genes, it was not that the patent office was being flooded by these things and was not able to issue them fast enough and that we were, therefore, going to have commercial problems of the type that you quoted from the person from the plant company or it was not that back in 1980 the Supreme Court had gotten

it wrong and Chakrabarty -- you know, in statutory terms and Justice Brennan had it right. It was the notion that somehow it was -- there was something wrong with people owning this.

Is that the topic that you think we should address or are you suggesting that we get into these interstices of the patent statute and whether or not the law has been misunderstood?

DR. SAGOFF: I think that there are different ways of interpreting a statute and I do not think -- I think it is too important to be left to the lawyers actually, that one can, as the religious leaders do, refer to Chakrabarty's insistence that products of nature cannot be patented, which goes all the way back. But when you look at what the religious objection is, it is to the patenting of products of nature.

Now there may be a reason why -- a religious reason, a moral reason, a reason that has that kind of punch -- why we do not patent products of nature. Why not? The current PTO view is it does not matter as

long as it is novel, as long as it has been wrung out of the bosom of nature as it were, it was a secret before. It now does not matter as long as -- why do -- why do we not just accept novelty rather than as a condition? What is the importance of the product of nature?

Now there is a lot of -- there are a lot of reasons for that. One is the religious objection or the moral objection about intellectual properties that Alta pointed to as the primary one. But there are these other reasons, too, that affect the more utilitarian ones, the blocking patterns. The problem of the anti-commons that will affect partially the development of needed medical advances. I think that both of those reasons speak to the problem of patenting products of nature and that we ought to review the notion that the law might mean products of nature rather than simply novelty.

PROF. CAPRON: When one thinks about the solutions that would be put forward for those different types of problems --

DR. SAGOFF: Yes.

PROF. CAPRON: -- one seems to be a practical solution. In other words that if you had a group of patent experts or if you had BIO sitting down with the patent office that says, "Look, we have a problem. People apply for these patents. We do not know if they are going to be good patents and so forth. People go ahead and do their work. They build on an assumption that something is not patented and then it turns out to be patented and this house of cards or the log jam, whatever you want to say, is a problem."

That would not -- I mean, I understand that there is a -- one could say some moral urgency there if you think that the problem is that people are not going to be fed or diseases are not going to be cured because companies will drag their feet because of that unknown risk factor. I am not quite sure from a businessman's point of view why that risk factor is any different than a whole range of other risk factors and the market can discount for risk but even assuming that you could put some moral punch behind it but I do

not see that as a topic to which we would make any particular contribution.

The problem has already been nicely identified by others. The solution would be a technical solution. So I come back to trying to understand what is the core of the topic that you think NBAC should address.

DR. SAGOFF: Well, it is exactly the one that Alta pointed to and it was the original protest, namely that there is an essential distinction between discovery and invention. If we blur that distinction then we put ourselves in the -- we give ourselves credit, intellectual credit, by theft for what we never toiled to achieve.

Now that is a moral point and it is a moral point that many leaders have made. Is there a reason for that? I guess that is -- what it gets to is, is there an important distinction there between discovery and invention? Is it important to maintain a separation between the humanity and nature that Christian religion has always posited? People worry

everywhere that that separation is being completely destroyed.

PROF. CAPRON: But the quote you have here from the religious leaders does not make that distinction. It says, "We believe that humans and animals are creations of God."

DR. SAGOFF: Yes.

PROF. CAPRON: Not humans -- creation of God, not of humans I guess is what they mean.

DR. SAGOFF: Yes.

PROF. CAPRON: "And, as such, should not be patented as human inventions." To me it sounds less like simply an argument about what is out there as such as something inherently wrong with claiming the -- that our dominion over nature, which I think the Biblical leaders would recognize, extends to ownership, that there is a difference between stewardship and ownership and they seem to be objecting to that but they are not drawing a distinction between man and nature. It is many parts of nature, at least the animal kingdom of nature seems

to be something that they object to that type of ownership.

DR. SAGOFF: It is creation, not ownership. Actually they have no problem with your owning animals, personal property. It is that we created --

PROF. CAPRON: Only as a creative --

DR. SAGOFF: Their literature uses the word "creation." That human beings have not created these things, therefore they ought not to own them as intellectual property even though they have created them on farms as personal property and should own them as chattel. So the distinction is really one between of creation. Do we create these things or do we find them?

If we find them then we might want a regime whereby there is some sort of monopoly placed on them for the commercial purposes that you say you would not particularly be prone to deal with. But if that is the case -- if we find them -- but creation should be considered separately. The question of design, invention and creation is a moral matter and that is

-- and that matter has been lost in the very core, the very core of its applicability to our relationship to the world.

DR. SHAPIRO: Let me -- I am going to just take one more comment now and if you are willing to wait we can return to this subject in about a half hour or three-quarters of an hour if you are willing to wait. You may not have the time. We will carry on the discussion ourselves if that is the case.

DR. SAGOFF: I would love to. I have to give a talk at the World Bank at 10:30.

DR. SHAPIRO: Then I will give -- I will just take one more comment now for you and then we are going to have to move on.

Tom?

DR. MURRAY: Thank you. When this commission did its work on human cloning I think one of the greatest contributions we made was not so much in the specific recommendations for policy, although they were relevant, but in an effort to give a clear and sympathetic description of what seemed to be widely

held concerns.

As you know, much of the work, I think, of good philosophy is trying to see what lies behind and try to give a clear statement to it.

DR. SAGOFF: Yes.

DR. MURRAY: Now in some cases when we did that we would say, well, this is simply a mistaken concern. You know, cloning is not xeroxing for example.

DR. SAGOFF: Yes.

DR. MURRAY: I am wondering if we would -- ought to think about our role with respect to gene patenting in a somewhat similar way. It is different in that cloning -- I mean, human cloning more or less burst on the scene with Dolly.

DR. SAGOFF: Yes.

DR. MURRAY: It had been out -- lurking out there but that is when people became aware of it. Gene patenting is the ethical/legal issue that will not die in that every time scholars think it has been put to bed someone -- the religious leaders issue a

statement and everybody says -- lots of people say yes. So there is something going on here in widely held public perception and belief which may not always be well articulated and I am wondering if that is what we ought to address.

So my question to you is do we have a good sense of what it is that most motivates public concern and apprehension about the patenting of genes, especially the patenting of human genes? I mean, I applaud you for your continuing efforts to try to articulate that but is there any good data on what is really lying behind the public concern?

DR. SAGOFF: I do not think there any survey data but the concern has gone -- goes all the way back to Thomas Jefferson who wrote the patent statute and at the time that he wrote the patent statute he wrote a lot of essays about it and he harped on the distinction between nature, which he says was the common heritage of mankind, that kind of language comes from Jefferson, and invention.

The distinction between what we all own in

common because God made it or we all find it, it is in us, and what we create ourselves because of that spark of rationality got has put in us was basic to Jefferson's view of patents. I think that that long intellectual history that separates invention from discovery, creation from finding still gnaws at us and we cannot let that distinction go. It means too much about the structure -- it talks too much to the structure of how we recognize -- realize our relationship to what we could not possibly have created, could not possibly have created or designed.

DR. SHAPIRO: Okay. I know there is other commissioners who wish to speak but we will have to return to this topic later.

I really want to end by thanking you very much for being here, not only for being here today but for your many contributions to the ongoing discussion of this topic. We really are very appreciative.

DR. SAGOFF: It was an honor and a pleasure. Thank you.

DR. SHAPIRO: And we, hopefully, will

continue to be -- our conversations in some other venue in some other time but thank you very, very much.

DR. SAGOFF: I wish I had more time.

DR. SHAPIRO: We very much appreciate it.

DR. SAGOFF: Thank you.

DR. SHAPIRO: I would like now to turn -- obviously we have a guest here with us this morning. I think it is someone -- you all know who is Neal Lane, a distinguished physicist and the President's science advisor and someone who is obviously very important to NBAC as OSTP is really home in some sense -- in one sense or another to us.

So, Neal, I want to welcome you this morning. It is great to have you here. Just -- I do not think -- we all know you but I do not think you know every commissioner here. You may not know. So I will just ask each commissioner to say who they are and any other four word description if you want to go there. Let's start off with David down here.

DR. COX: I am David Cox from Stanford

University and I am a human molecular geneticist.

DR. DUMAS: I am Rhetaugh Dumas from the University of Michigan. I am a nurse and a Ph.D. psychologist.

DR. MIIKE: Larry Miike, private citizen from Hawaii, previously in health policy at National Labs.

DR. SCOTT-JONES: I am Diane Scott-Jones. I am a professor of psychology at Temple University and for this year I am an IPA at the National Science Foundation.

DR. MURRAY: Tom Murray. I write on ethics and am now president of the Hastings Center, formerly a professor at Case Western Reserve University School of Medicine.

DR. GREIDER: Carol Greider. I am a professor at Johns Hopkins University in molecular biology and genetics.

PROF. CAPRON: Alex Capron. I teach law and medicine at the University of Southern California.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Jim Childress. I teach

bioethics at the University of Virginia.

PROF. BACKLAR: Patricia Backlar, a research associate professor of bioethics at Portland State University and assistant director of the Center for Ethics in Health Care at Oregon Health Sciences University.

DR. LO: Bernard Lo, professor of medicine at UCSF in San Francisco.

MR. OLDAKER: Bill Oldaker, the newest member. I am a practicing attorney in Washington, D.C., and I also own a -- founded a small biotech company called Neurostem.

PROF. CHARO: I am Alta Charo. I am a professor at the School of Law and in the History of Medicine Department at the School of Medicine at the University of Wisconsin.

DR. BRITO: I am Arturo Brito, University of Miami School of Medicine and I am an assistant professor there and a practicing pediatrician.

DR. CASSELL: Eric Cassell. I am at Cornell and I am a physician who writes about ethical and

philosophical issues in medicine.

DR. SHAPIRO: Thank you.

Neal, welcome. It is a great pleasure. Thank you very much for taking time to come speak to us today.

Oh, Steve Holtzman is on the phone. Excuse me. This is our colleague who is, I think, in Cambridge.

Steve?

MR. HOLTZMAN: Hello. I am Steve Holtzman, Chief Business Officer at Millennium Pharmaceuticals and a disembodied voice.

(Laughter.)

REMARKS

THE HONORABLE NEAL F. LANE

ASSISTANT TO THE PRESIDENT FOR SCIENCE AND TECHNOLOGY POLICY

EXECUTIVE OFFICE OF THE PRESIDENT

DR. LANE: Hi, Steve. I am glad you are with us.

MR. HOLTZMAN: Thank you.

DR. LANE: I am glad you are all here today. I am delighted to have a chance to meet you. I have known about you in many ways from different perspectives for a long time but I do not know all of you personally and it is a great delight for me to be here today.

I sort of envy Harold for his opportunity to work with you because this is quite an extraordinary group of individuals and professionals, and Americans, and it has just got to be fun. I mean, as much -- as hard as you work, I know that the discussions you have must be incredibly interesting and I know from the work that you have done, which is considerable, that somehow you are able to do this in a way that is efficient and actually moves forward and I know that is a tribute to all of you but also to Harold's leadership so we very much appreciate it.

Jack Gibbons, I know, my predecessor, did an extraordinary job in the White House. He certainly considered the establishment of NBAC one of his great triumphs and he did many outstanding things as science

advisor in the White House but he certainly looks at this particular accomplishment as a special one.

I think Jack opened the first meeting three years ago and had a chance to speak with you about how important these issues are and how much the President was going to rely on and, now we look back, has relied on the excellent advice he has gotten from you so we really appreciate the commission's timely and very important contributions to the national debate on what are clearly some of the most controversial issues in science policy that we face today and certainly your work reflects well on the wisdom of establishing this commission and we know you spent a lot of your time and effort on it.

Twice the President has called upon you to interrupt your deliberations and take up highly charged questions that define the intersection of science and ethics. What happens when scientific breakthroughs challenge our views of nature and humanity? The crux of the challenge is how we can best square our newest technologies with our oldest

values, both cloning as was mentioned a few years ago and stem cell research, both of which came during my relatively short time in the White House, are really good examples of how we have to look at our fundamental values and make some very difficult choices about how we proceed as a society.

So I want to express my personal appreciation and certainly that of the President for the sensitivity and for the scholarship and the wisdom that you brought to your deliberations on both of these topics, and the reports that you write are fascinating as well. They are well-written. They are interesting. They have considerable depth which will make them last, I know -- their impact last well beyond the immediate considerations of policy that they receive in the White House.

When you take on such weighty issues you have to accept in advance that probably not everyone is going to embrace your conclusions in their entirety. I do not know if that has been the case but I could well imagine that it might be given the difficulty of

all these matters but I think it is a testament to your hard work and Harold's leadership that you are lauded for listening and for being especially sensitive to the range of America's views and emotions that accompany these thorny ethical issues that lie at the nexus of humans and technology.

This commission has also submitted two other reports to the President. It is really quite incredible the work that you have done and the products that have come out. I must say I am very -- I remain very impressed.

The two reports, Research Involving Persons with Mental Disorders that May Affect Decision Making Capacity and the second Research Involving Human Biological Materials: Ethical Issues and Policy Guidance, both of these reports make landmark contributions to ongoing discussions regarding human research subject protection. The capacity of the report ably addresses a longstanding need for special measures to protect a particularly vulnerable segment of volunteers in a research enterprise, namely those

with conditions that may reduce their ability to make informed decisions.

The Human Subjects Research Subcommittee of the NSTC Committee in Science has now been tasked to put together a set of policy options that are based on the 21 recommendations of your human report and that is our mechanism for getting your recommendations translated into policy.

The Human Biological Materials Report is significant in that it describes the terms under which it would be ethically permissible to use the more than 300 million human tissue specimens that are currently stored in various repositories throughout the country, some of which have been in storage for 100 years. Well, given the powerful genetic tools that might be used to identify inherited traits, protecting the privacy of the people from whom this tissue was derived and their descendants is particularly important. This report also provides an excellent analysis of the question as to when the source of a biological specimen should be considered to be

identifiable.

The President has just asked NBAC to continue its work for the next two years. No good deed goes unpunished in our business.

(Laughter.)

It makes it a really auspicious time for me to have the opportunity to meet with you.

Instead of coming to you with another quick turn around request -- I cannot, of course, promise that that might not happen again.

(Laughter.)

I wish I could but at least that is not happening today.

I ask you instead to recall the original charge from the President to examine the current federal system of human research subject protections. Several recent events have drawn attention to what is largely a decentralized system with great responsibility placed on individual investigators and their sponsoring institutions.

The Department of Health and Human Services,

and within that department, the NIH, have taken several actions to strengthen their oversight capability and forestall situations in which subjects could potentially be harmed.

Other agencies have also made changes and instituted policies and procedures that address their role in overseeing human subject research. The Department of Veteran Affairs is one example. The Department of Justice is another and I know you are going to have a look at what they are doing.

So while there has been increased attention paid to this area I think it is increasingly clear that a comprehensive examination is in order and I would expect that such a study would include an assessment of the adequacy of the current federal system of protections, a review of the relevant statutes and regulations with particular attention to the effectiveness of the Common Rule and its applicability to the full range of government sponsored research activities involving human subjects, and an examination of the strengths and the

weaknesses of the infrastructure responsible for ensuring the entire system's integrity.

The most important component of this task is to provide detailed recommendations for changes necessary to ensure that our ethics are as good as our science.

You are all aware that it took ten long years to promulgate the Common Rule in 1991 and yet even at that time it was agreed that additional work needed to be done to provide adequate coverage for every research subject, including special populations.

One of the driving forces behind NBAC's establishment was the desire to accelerate progress towards the goal of ensuring such coverage. The Comprehensive Report that you will consider today should be constructed so as to fulfill that desire.

You probably -- you will probably note that I focused solely on federally sponsored research and not research carried out with private funds. I understand that NBAC has passed a resolution recommending that human subject protections be extended to all research

subjects regardless of the source of funding and I fully expect that the bulk, if not all of your recommendations, will have equal relevance for research carried out in the private sector and you might want to make note of that in your report.

However, it is important to recognize that the initial audience of your reports is the National Science and Technology Council chaired by the President and made up of those agencies, at least all agencies, including those that are involved in human subjects research.

These agencies then through the work of the Council are well positioned to take immediate -- to make immediate use of your recommendations through the administrative actions in their respective program areas. I have outlined sort of how that happens. We get the recommendations from you and we put together a working group. We translate your recommendations into policy options and then those get considered at the appropriate policy levels of the President's Council.

So it makes sense for you to focus most of

your energies on the advice that can be incorporated into the government's ongoing efforts to enhance human subjects protection.

When I sought Harold Shapiro's wise counsel earlier this week, as I often do, we talked about this proposal and I conveyed the strong sense of the President and Secretary Shalala that human subject protection is a critical element of our research enterprise. The President has addressed this in the past most notably in his commencement speech at Morgan State University.

The Secretary is currently engaged in efforts to bolster protections including, for example, protecting medical records privacy. These and other ongoing activities make this an opportune time for the commission to take on what is admittedly a very challenging task.

So, in conclusion, we are particularly grateful to you not only for your four scholarly valuable reports but also for the stimulating balanced discourse that I commented on earlier, for involving

and educating the American public, extremely important, and for undertaking this challenging assignment even under somewhat constrained time frames.

The President and his Administration, and the American public look forward to receiving the fruits of your labors and I look forward to getting to know all of you better.

I apologize for my laryngitis and whatever it was I caught on my most recent trip.

DR. SHAPIRO: Neal, thank you very much and thank you very much for being here. I hope you have a little time this morning. I do not know what your schedule is because there may be questions. I know I have questions but there may be questions from commissioners as well so let me turn to the commission itself to see what questions it may have regarding what Neal said and perhaps something else that you want to ask him.

Bernie?

DR. LO: First, I want to thank you for

coming and being with us today.

Your visit is very opportune in that as you know we, as a commission, are also trying to think about where to turn our efforts over the next two years. And in addition to the report that -- I think we just lost Steve.

(Laughter.)

DR. LO: In addition to the report on human subjects -- protection of human subjects that you just mentioned, we are also thinking of what other topics might be appropriate for us to address. As we go back to the original charter of NBAC, gene patenting was specifically mentioned in that as one of the issues that we should direct our attention to.

And keeping in mind our role as an advisor to the Office of Science and Technology Policy it would be helpful for us as we try and sort through our priorities to get a sense from you whether some of the issues we are considering particularly in gene patenting ones are ones that you think might be of particular importance for you and the OSTP.

DR. LANE: I think that there is no question that the gene patenting issue is an important one and I enjoyed the opportunity to kibbutz a little bit on your discussion with Dr. Sagoff. I had a discussion with a patent attorney yesterday on an airplane some place about gene patenting and found that stimulating.

There is much about gene patenting I do not know. I would say roughly everything about gene patenting I do not know.

(Laughter.)

And so let me not try to pretend to understand the subtleties and the nuances that we are going to have to deal with but stepping back a little bit it is my sense that in the whole area as we unravel the human genome and start to understand its structure in much more detail and the function and the impact of multiplicity of genes in their complex workings inside the human body and other animals, there are going to be intellectual property issues probably that we cannot anticipate. My sense would be that -- or not easily anticipate. My sense would

be that the technology is simply going to allow us to accelerate at a rate we now do not quite predict the understanding of biological systems and when these biological systems are human systems then all of these hosts of ethical issues that you talk about are going to come up.

And gene patenting can be viewed on one hand as a perfectly straight forward issue of intellectual property and how we do business in a society but when it involves things having to do with humans, especially human biology, then I think it has to be dealt with in a manner that is consistent with the values that we talked about earlier. So I -- as it -- as gene patenting raises these ethical issues it seems to me entirely appropriate. It is an interesting an area of study but entirely appropriate.

But here today what I am wanting to do is to encourage you to pursue this comprehensive study because it clearly is timely and of immediate importance to informing policy.

DR. SHAPIRO: If I could just say, Neal, that

our current agenda has us spending quite a bit of time in the short-term, that is the next months, three or four months, on international issues which you are aware of and we hope to complete that early.

And as Bernie said, we are now looking beyond that and trying to think of what will fill up our agenda for the next two years for the moment.

And even within the comprehensive report, which it is loosely called -- looking at the human subjects protection as a system, we will have to make decisions as to what to include in that. There are all kinds of issues that we could include. We talked about some of them yesterday and so on. And so we are just in the middle now of just sorting these priorities out.

Alta?

PROF. CHARO: Dr. Lane, first let me echo Dr. Lo's thanks for your coming to speak with us today.

You referred in your statement to President Clinton's commencement address at Morgan State University, which I remember well because I read it

in, I believe, it was Science magazine where it was published as an article, and I was struck by the President's statement that no American should be a guinea pig in research without having informedly volunteered. And the President did not caution those remarks by saying, "No American in a federally funded research trial," but simply said, "No American." It was really very straight forward.

Given that the audience for our reports, as you noted, is the NSTC but also given that the President's interest seems to transcend the narrower issue of federally funded research and that we, ourselves, have agreed upon a resolution in favor of the extension of the Common Rule to all Americans, I did not -- I would very much enjoy hearing your thoughts about the best way for us to help move this topic forward constructively, whether it is through specific reports, through hearings, through public testimony, what mechanisms do you think would further both our agenda and the President's on this topic?

DR. LANE: Well, all of the above, I think.

Of course, the reason the President made that statement is because he believes what he says and, as you note, in the policy statements he has made he has always made it a point to say -- these are not his words but, you know, even though I cannot direct the private sector to do A, B or C, I strongly encourage you to do that because it is right for the American people.

I think these issues are -- do go well beyond the Federal Government and what the Federal Government does and that is one of the reasons I commented earlier on how much the President appreciates your public outreach because if the public -- if the American public understand these issues well enough then strictly from a marketing point of view the companies are going to be very careful how they proceed in these directions.

There are other controversial political issues in which business I think has responded in a way that is strongly influenced by public opinion. In fact, generally I think that is true. It is just that

often the American people do not know enough about the issues to be able to make their voice heard and I -- you know, the way our American society works, people's voice is very, very important, and so I cannot think of a better way to influence the private sector on these difficult issues than to just make -- help the American people understand what these issues are all about.

This body can do that in a way that is very hard for other bodies to do. It is hard to find a group that tries to balance the obvious benefits of medical research, for example, and just in general the benefits to people that technology is going to deliver -- science and technology are going to deliver with our fundamental values.

And so it is extremely valuable to have that kind of -- that kind of discussion and that sort of deliberation carefully made available to the American public. I do not know the best mechanisms for that but I do believe that is one of your very important roles.

PROF. CHARO: Thank you.

DR. SHAPIRO: Tom?

DR. MURRAY: I will join in the thanks, Dr. Lane. Thank you for coming today.

Do you have any wisdom to share with us about attention which we regularly experience, and you have already seen some reflections of it even just this morning, and that is between the two aspects of our role. One is as a kind of educative body receiving -- in dialogue with the American public. And the second is as a recommender of specific policy options or interpretations to the White House.

We often try to serve both masters but it is not always easy and, you know, where we devote our efforts is -- between those two is sometimes a difficult choice.

DR. LANE: That is a really hard -- I do not have any wisdom on that very difficult challenge. I would just say you have to be good and fortunately you are. It is a very difficult task but let me do say that the President very much is aware of that kind of

tension and that challenge for a group like this and particularly appreciates thoughtful advice. My sense is when we get recommendations from you, of course you are making the best judgments and the best recommendations given all of the information but you also provide your advice in such a way that you think it can be most useful if I might put it that way, most effectively introduced into policy because otherwise nothing gets done and that requires a considerable amount of savvy about the way our system works and the sensitivity to all of the issues and all the pressures that bear. So I do not have no advice other than, you know, go and do well as you have been doing.

DR. SHAPIRO: Thank you.

Other questions or comments from commissioners?

On the issue, Neal, of the human subjects protection and the request you put before us to encourage us to proceed along the task we had in part at least identified, we call it the Comprehensive Report, and it is just a word which has not really --

it is a phrase I should say that we have not fully filled in yet, that is just what characteristics it is going to have, just what tasks it is going to take on, but I understood you to be saying that you really wanted or encouraged us at least to take a broader look at the system of human subjects protection and make some recommendations regarding its overall structure and functioning, and that is very much in line with the kind of thinking we, ourselves, have had over the last number of months. A number of commissioners here have recommended that and we will certainly give that our very close attention almost right away.

So if it is agreeable to you what we will do -- what I would like the commission to do over the next weeks is really give some more detailed thought to exactly what we would do and over what time frame and what we can deliver over different kinds of time frames because that also may be relevant for your considerations, and be able to give you and OSP some feedback on that and perhaps even get some advice back

from you as to which of those you would find the most useful.

David?

DR. COX: Yes. In that context of the comprehensive human subjects, I -- this is a request for wisdom again, Dr. Lane, so -- see we do not -- we need -- you know, wise people all the time. I have always found it personally quite remarkable that it took ten years for the Common Rule to be embraced. To this day I do not understand the complexities that led to that lengthy time and certainly our society has really changed just over the past few years in terms of how we are thinking about protecting human subjects.

So my question for you is do you think that it is going to take another ten years if we come up with these ideas and what are sort of the mechanisms, what are the things that may have changed in terms of being able to implement general recommendations?

DR. LANE: I do not have any real direct knowledge of all the issues that determine the ten

year period. I think a lot has changed in society. One thing I think that has changed is that the American people really have seen the benefits of research involving human subjects but at the same time the American people have not so substantially changed their system of values that that side of the equation is any different and I actually do not see these as two sides of an equation.

I mean, they all have to do with humans individually and collectively but I would put it that way in any case. So I think the answer is no, not ten years. I sort of have to say that. I have to believe that because that would not be good for our people.

Not commenting on the previous deliberation because I was not there, I do not know, but my sense is that based on what I have seen come out of your deliberations, your recommendations, and the arguments behind them I am quite optimistic that we will have what we need to engage the right kind of discussion and get this put in place in a much shorter period of time.

I am hopeful that we would actually see something in a -- I like your suggestion, Harold, of let's iterate a little bit on this just to see what from our perspective would be useful but it would sure be good if we could kind of get this done in a year. The clock is really ticking away and even if the clock were not ticking away in a way you think I mean --

(Laughter.)

DR. LANE: -- these matters are so important to the American people, especially given the rapid pace at which medical research is advancing, the knowledge and the technologies, that I just think we sort of owe it to society to move along as quickly as we can.

DR. SHAPIRO: Neal has to leave but there are two commissioners whose hands have been up for a little while, if they are very short questions I will recognize Eric and Alex.

Eric?

DR. CASSELL: Dr. Lane, I also appreciate the charge. I appreciate the charge. I think that that

is a help for us and it will move us forward in an area that I think is -- will be a legacy of this commission.

We have persistently in some still small voice talked about education as part of our process. Everything we do requires the education of the American public because science policy is public policy. So I am hoping that this stream of thought that comes from here about educating the public is sympathetically received and enters into the consideration of education in general, that science education about these issues is a centrally important matter for the public and, therefore, for the President.

DR. LANE: Let me just give a very short response. I agree entirely and the other thing that occurs to me is that when you leave the meeting you all go to not totally different communities but you cover quite a broad spectrum of society and the old argument, you know, within six people you know everybody in the world or whatever that argument is.

The impact that you can make taking the product of your collective work and, to use a word, translating it to one or another community because I suspect one of you takes it back to your community and they say, "Why in the world did you write it that way? You know, I would have written it this way."

Well, it is because it is a collective work but translating a very powerful set of recommendations -- document and argument and a set of recommendations to all these communities I think is just extraordinarily powerful and I do not know what your practice is but I know you talk with a lot of people so I encourage that.

DR. SHAPIRO: The last question, Alex?

PROF. CAPRON: My question is in a way related to the one that David Cox asked you but it is different in this fashion: When a previous presidential commission, which I had the privilege of directing, came up with the recommendation that led to the Common Rule in a report written in 1981, we were hopeful that there would be change more swiftly than

there was. And this commission began with a presentation by one of the people who was involved at a staff level during that ten year period and my perception of the deliberations we have had on a number of points have been when we get to the human subjects topic we feel constrained in making certain kinds of fundamental recommendations and are instead likely to say, well, let's try to get an interpretation out of an office because to make a change like this is just impossible. I do not believe it is impossible.

I would like to take your comments here today as the pledge from the National Science and Technology Council and its chair that if recommendations are made which substantively are agreeable that the process will to the extent that direction from the top can affect it move much more swiftly and that we ought not to pull our punches on conclusions that we believe are substantively justified because it cannot be done and it is better to do a small thing that is do-able than the big thing that needs to be done.

Is that the message I should take from your comments today?

DR. LANE: Well, I mean, you can certainly take from my comments a commitment to do whatever I can to move this along. I work pretty closely with all the parts of the National Science Technology Council and these are issues the President definitely cares about.

The only thing I would say to -- along with that is that -- is to refer to the comment I made earlier that the importance of delivering your recommendations to us in such a way that you think they can be most effectively used, I would not want to understate that, these issues are of such sensitivity that any lack of clarity or -- that raises then concerns in the larger public that maybe are unwarranted but then also make the difficult to move policy along.

So I am for getting things done and given how rapid -- how rapid the pace is of scientific and technological change, advancement in these fields, I

just think that we cannot afford to wait a long time.

DR. SHAPIRO: I just want to say just one word again of thank you. We very much appreciate you taking time to be here today and as regards -- I do want to also say a word about what Alex just raised.

It seemed to me that it would be not in our interest or in anybody's interest for us to pull our punches in any way. That is not our job. Our job is to give you the best advice we can.

DR. LANE: Right.

DR. SHAPIRO: And then it is someone else's job, which we will help with, to implement whatever seems sensible to those that have to make those decisions.

So thank you very, very much, Neal.

DR. LANE: Thank you.

DR. SHAPIRO: It was good to see you again.

DR. LANE: Thank everybody.

DR. SHAPIRO: Let me suggest a five minute stretch here and then reassemble so let's try to get back together about 9:30.

(Whereupon, a brief recess was taken at 9:23 a.m.)

PRIORITY SETTING FOR FUTURE PROJECTS

GENE PATENTING

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: I would like to return to the gene patenting issue just to see if there are other comments or questions. Unfortunately, our guest is no longer here and I feel badly that we had to sort of cut that short at the time but that was necessary.

Are there any other comments, questions?

I should say that I, myself, particularly, I guess, appreciated Alex's comment because I think the issue of what we can offer here is really not so straight forward on this very, very controversial issue and just exactly what our contribution could be here I have not been able to articulate very well in my own mind actually and -- nor do I think Professor Sagoff responded to that very -- particularly effectively. There might be an answer but what are the feelings here?

Alta?

PROF. CHARO: Well, you know, I know that on e-mail I was one of the people who was writing extensively about how we really cannot do much on the policy level here. The one thing I heard that I had not heard on e-mail that struck me as having some potential was a comment that Tom had made, which was that if there is a role here it might be focused and limited to the use of this as a platform to gather and reflect the very extensive literature that has already been developed by people who oppose this on, you know, religious or symbolic grounds and to explain not only the nature of their objections but also to explain the responses, many of which have been about the degree to which there has been enormous misinterpretation of the significance of patenting and its relationship to the notions of property and ownership so that if we do continue to consider this topic I would certainly be open to exploring that very narrow kind of focus within the topic as the one thing we might be able to do that is helpful just broadcasting what is

admittedly not new but has not yet been diffused.

DR. SHAPIRO: I could hardly contain myself at one stage when he was trying to express his views of it to ask him if he had ever read what Karl Marx had to say on property as theft.

(Laughter.)

DR. SHAPIRO: He actually gave a very good paraphrase without knowing it, whatever you might think of that source or that analysis.

(Laughter.)

DR. SHAPIRO: Bernie?

DR. LO: Yes. I think as we go through the priority setting the rest of the morning, it seems to me the questions I would like to try and answer are to identify -- put things into one of three categories. One where no matter how good a report it makes we write, it is probably not going to make a whole lot of difference. Things just are not going to happen except maybe that we clarify issues and, thereby, educate the public.

The second categories are topics -- would be

topics that something is going to happen regardless of what we do so that something is in line, it is going to happen, and the fact that we write a report is not going to change that outcome.

I would think we should stay away from those two topics if we can identify them and really focus on the third category, which is where what we do really makes a difference, that without us nothing would happen and with us there is a good chance that something significant will happen. And it really seems that the comprehensive subjects report fits into that third category very nicely.

And I think what I am struggling with is of all these other fascinating intellectual topics that pose a lot of policy dilemmas that we have talked about over the last day, it is hard for me to see which of those clearly fit in the category three. And I think the more we can focus on sort of the potential impact of our reports as part of our priority setting I think it will be better.

We have tended, I think, to focus on the

intellectual excitement as a sort of nifty topic and that is really a different question than what will change on the basis of our report.

DR. SHAPIRO: Eric?

DR. CASSELL: I want to put the protection of subjects front and center also. I think that that is the -- that is of central importance. But I must say I think that when -- when we listen carefully to what is going on in the gene patenting and are able to dissect it out and lay out what the problem really is because when I hear this I do hear a lot of excitement about it and also my interest would be -- there is something going on and I do not understand it and I think that that serves a purpose. I do not think it should be our main focus and I do not think it would occupy that much time but I would like to hear what other people have to say about the subject to get a better idea of whether we have something to offer it or not.

I want to also always keep that human subjects protection right in the center.

DR. SHAPIRO: Trish and then Alex, and then Rhetaugh and David, and Tom.

PROF. BACKLAR: Who is going next?

DR. SHAPIRO: You.

PROF. BACKLAR: Oh.

I would like to add to what Alta just said. I think if I understood what you said correctly, Alta, and that is that I think it would be very useful if we could write a sort of clarifying paper, not a brief report and laying out the issues in gene patenting, not the kind of full reports that we have been writing.

I think that would be a very big service and maybe fall into your category three of being a real service to the public and also address Eric's concerns about education and where we would lay out the differences between ownership property, innovation, the distinctions and so forth because I think people are very confused about this.

DR. SHAPIRO: Alex?

PROF. CAPRON: It seems to me that a number

of the things that we have done and certainly that past commissions have done have combined the two tasks that Tom suggested are difficult to combine from the very first report of the National Commission on Fetal Research. A big part of what they did was to take a topic that was extremely heated and showed the reality behind some of the concerns and the unreality behind other of the concerns.

But I do not think that a report in which they had simply done that would be regarded as having been a major contribution in the end. They had to go on and then see what conclusions were drawn on the policy side from that.

The same is true in the report on gene splicing which the President's Commission wrote, which had at its origin a statement by a group of clerics that human genetic engineering was playing God and was unacceptable, and came in the wake of the Chakrabarty opinion and the National Science Advisor to the President said this would be a topic which the President's Commission should address, and a large

part of what it did there also was to address the topic and take it apart.

Now in the process of both of those efforts and in our own efforts it seems to me that we sometimes draw on existing literature and I do not think there is going to be anything we say clarifying on this patent issue that has not been said before.

The value of it would be in saying it from this body, which has access to national attention in a way that a scholar by herself or himself does not and in linking that then to what conclusions and recommendations follow on the policy side.

So rather than seeing these as incompatible I think these are best when yoked together so I would not favor just a brief monograph in which we would say this term has been used this way and that way, and the better way to use the terms is that, thank you very much.

I want to -- then I was trying to press Professor Sagoff to say where does the real moral, ethical issue arise here, and is not that rather than

arguing over the statutory interpretation of the patent law where we would make a contribution?

As for the Comprehensive Report I just think there is no question -- I mean, the real issue is how much we can get done, how soon, and how comprehensive we can be in this process and can we tie the parts together in a way that has some appeal intellectually so that they do hang together? But there is just no question that this is a topic everybody thinks should be addressed. It was in our original charter.

Dr. Lane has said again today, "Please do it." That is the President telling us, "Please do it." I think we had an invitation, thanks to Alta's question, to him not to ignore the nonfederal side when he says, "The President cannot command that." No, but the Congress can. And clearly there could be a policy recommendation that we would leave in the way that Senator Glenn would have done had his bills gone forward.

So I do not see an incompatibility. Bernie, I guess, at the extremes I agree with your categories

but there are a lot of topics, including the patenting one, which will get addressed by people. They will go on getting addressed.

The question is not will someone else address the topic. The question is are there elements of that topic which we are in a good position to address in a way which would move the debate and the policy discussion.

I suspect that the new OPRR arrangements at HHS will eventually -- could get a lot of the things in the Comprehensive Report but we have a leverage point now where we can perhaps accelerate that process and we are deep into a lot of them.

I mean despite the despairing comments that were made I guess when -- I am not sure the chair was then when Kathy Hanna was making the despairing comments at the last meeting about the state of our data, which would be part of the building block there. We still are deeply into it and I think we are sort of up and running. I just do not think there is a question so I would say let's get on with that and

then as quickly as possible identify our one or two other topics.

DR. SHAPIRO: Thank you. I have a long list of commissioners who want to speak. It is almost a coextensive of the people sitting around the table. They will just be getting on the list. I will just go by the list as I have written them down.

Jim, you are next.

DR. CHILDRESS: I do not think I really have a lot to add. I very much agree with the view and it seems to me part of our original concern from day one that we really get on with the Comprehensive Report and we obviously had some abortive actions along the way and failures to realize the kind of goal we had set out for ourselves in even discharging what was expected of us pretty early on. So I hope that we can really do it now and do it well and I guess I am encouraged as we think about our several projects, though I do not want to be overly optimistic or expansive here, but it seems to me that the staff is in a position right now to be able to -- in the way we

are set up to be able to move forward with some of these things much better than we were in our early days. So I am -- I urge us to move forward with it. I am quite hopeful that we can really accomplish something important there.

I think the gene patenting could be done in ways that Alex suggested and it certainly may be worthwhile for us to move forward and see if we can get an appropriate contract paper to -- that would flush stuff out. We may decide after getting those materials that, no, it is not worth doing but I guess what I am hopeful is that we are at a point as a commission that a lot of things can be done by contract papers as I think they have been done very well on the international level so that we can spend our time then thinking about, well, is this really something that we want to go forward with and provide the kinds of ideas that might help it go forward if we decide to go that way, and what kinds of recommendations might follow.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I think that I would like to see us try to ferret out what would be the moral and ethical issues surrounding this gene patenting but I was wondering whether or not that could be handled within the broader context of the Comprehensive Report that we are planning to do. So it seems to me that there are a number of implications for human subjects protection, rights of people and what have you about property that could be incorporated in that broader report.

I do not think we should ignore it.

DR. SHAPIRO: Tom?

DR. MURRAY: Right. I do not hear any dissent about the priority to be accorded the Comprehensive Report and the protection of human subjects so I am not going to add anything to that since there seems to be no dissent on that.

I want to talk about gene patenting and repro tech briefly. That has not -- reproductive technologies has not come up again this morning.

My question to Neal Lane about the tension

between the two was not to indicate that they were either/or's but to indicate that, you know, how we come out on how to deal with that tension will determine both what subjects we choose to study and the kind of reports that we do.

Gene patenting is probably, I suspect, on the more educative side of the line rather than the side that requires a kind of immediate policy intervention.

Because it is an issue that simply has not died -- this is an issue that every time it comes up there seems to be a great deal of public apprehension and I see ourselves as in a way the -- kind of the voice of the public within the federal policy -- a voice of the public certainly within the White House on science and technology issues.

It is an area -- it is a question -- gene patenting as a question has incredible economic interests behind it. It has tremendous economic consequences for the United States. A failure to communicate well to the American public the basis for gene patenting and whatever limits we might think are

appropriate on gene patents makes it unstable. I mean, that is if there is not good public understanding and good public support behind it we have a potentially unstable situation which could, in fact, be threatening to American interests of all sorts so I think even if we do our report maybe primarily educative there with some perhaps advice for policy I think it may well be worth doing.

With that said, we might also provide some, you know -- our -- if we can reach some clarity about some of the moral underpinnings and I agree that ought to be our focus, that might influence the patent office and that might influence legislators in clarifying patent law so I would be in favor of doing it. That is number one.

Number -- quickly on reproductive technologies -- telephone, Lori.

DR. SHAPIRO: That is Steve.

DR. MURRAY: That is Steve, yes.

Lori Knowles -- Lori Knowles. Lori Knowles works for me and she is -- now she works for the

commission.

Lori Andrews gave a wonderful talk yesterday and I would urge us to try to create room in our agenda to begin to look at the issues of reproductive technologies.

DR. SHAPIRO: David?

DR. COX: Yes. So I would very much like to support Rhetaugh's concept and I think it fit into something that Bernie said, too. Let's do the things that we can have really an impact on but then point out how all of these really hot, you know, flavors of the day topics fit into what our primary agenda is, which is human subjects.

And, Tom, I would suggest that that could be precisely -- would fit in with the reproductive technologies. I was struck by Lori's articulate presentation yesterday about how much the issues really are those of human subjects protection in defining what research is on human subjects and that it has broader implications than just reproductive technologies. That could be an example of a broader

issue that we would deal in terms of dealing with human subjects and defining what research is.

So the -- I think that this is a really nice way. We can stay focused on the human subjects but bring as examples these other things.

Now in my view where does patenting fit into that and it does not because the -- for the -- I think the point that Alex was trying to get at, which is where -- what is the major ethical -- you know, fundamental ethical things that we deal with in this, I am having a hard time finding it and -- but I do believe this is an important problem but it is an important problem with respect to how business is done in this country and I do not see it at so much an important problem about the ethics.

I do see that there is this issue about creation and I do see that as a point but the -- I have a hard time seeing how that is going to fit into our human subjects so by sticking with the concept of let's look fundamentally at how we do research on human subjects I have no problem of seeing how the

reproductive technologies would be like down home plate on that but the patenting I have a harder time with.

DR. SHAPIRO: Larry?

DR. MIIKE: Being the practical one here, we are already under pressure to extend and move even further along on the international project. We just got a charge that it would be very good if our Comprehensive Project is done within the year and I take that to mean not that we deliberate on December 31st but that we deliberate about October so there is time to do something about it by the end of the calendar year and that leaves very little room for anything else.

I do not want -- I think that we are going into the comprehensive project with a fairly defined definition of what we mean by human subjects with the emphasis on human subjects protection and not on comprehensive, not to be comprehensive to include all kinds of other tangentially related things.

I, for one, do not know what we can

contribute to the gene patenting debate and it is nice to hear about various views on it but I -- for the life of me I cannot think of what we can contribute to the dialogue. We have not even begun to discuss priorities and we have already gene patenting and the reproductive technologies but as you know from our e-mail both Alex and I have raised another one which I hope we have time to discuss and which I think fits directly into our charge, which is anticipatory of the kinds of very specific issues that keep arising on a monthly basis.

I am basically talking for want of a better word about all the forthcoming technologies that combine human with nonhuman materials and I think that there is nobody out there that can lay out an ethical pathway that one takes a look at these things that are -- when another one of these specific technologies come along that there would be a document to turn to for a laid out ethical path to look at these kinds of things.

So I think that we are going to have our

hands full just finishing the international project on the comprehensive human subjects project. I would like us to take a look at reproductive technologies but I think the one that I just mentioned from my side is a more direct -- of more direct relevance to our charge to take a bigger look at ethical issues and I do not think we can afford to do more than one or two other than the comprehensive and the international project in the immediate time frame of a year or so.

DR. SHAPIRO: I think Larry has introduced some really very important issues and I was really waiting for this discussion to go on before I raised the issue of priorities and what it is we can fit in given our resource constraints and I think that I agree pretty much with what Larry has said, that is we better be sure we understand what the requirements are of the two projects which we are, in my view, committed to, that is the international and now this comprehensive one.

We may be able within the Comprehensive Report to include some other things depending on how

-- that has to be thought out more carefully. Perhaps something about repro tech or something. I do not know. We would have to think it out carefully. And perhaps the human/nonhuman issues that keep coming up in which part of our e-mail discussions was quite active might also be a part of that. That requires some very detailed thinking and planning and working on, which we have to do over the next few weeks.

On the issue of one year from now, that is what we will be able to deliver October 1, that also needs some careful, careful thought. We will have to work out quite carefully, which is why I told Dr. Lane that we need to continue our discussions on this to find out what is reasonable to deliver by October 1 and what might come February 1, for example, and I am not clear in my mind what that is yet. We will have to decide that but we do have to limit our appetite here somewhat, which I think is what Larry is -- one of the things Larry is suggesting.

The other thing Larry suggested is that really if you had to think about some other topics

that he, himself -- you know, gene patenting does not seem so high to him if I understood you correctly, and other things may be more important but I would be interested in other people's views of these matters.

DR. MURRAY: Just a question really of clarification.

DR. SHAPIRO: Yes?

DR. MURRAY: The Executive Order that founded the commission included gene patenting as one of the things we were specifically requested to --

DR. SHAPIRO: Right.

DR. MURRAY: -- study. I do not know if that Executive Order has been supplanted by something else or whether we should regard that -- that is one reason why -- I mean I think we were instructed to look at it and that -- to me, that counts for something. But if, in fact, it has been supplanted or outmoded by some later documents or other developments that would affect my own view of what priority --

DR. SHAPIRO: I think what I could say about that -- I do not know whether -- I cannot really say

it has been formally supplanted but I do know what they think is most important right now. It was pretty clear from what we heard this morning. But to say that it is formally supplanted I could not say that. I could not say that.

Alta, and then Bernie.

DR. CASSELL: It is dated two days ago.

PROF. CHARO: I absolutely agree with the notion of prioritization and with the clear idea that the human subjects field is the first priority. I think I sense some hunger occasionally on the part of commissioners and more often on the part of people who tell us what we should be doing for something that transcends obvious linkages to particular policy recommendations. Something that is more abstract, something that is more noble, something that is more profound and thematic.

And in the area of gene patenting I feel like I sense one expression of a thematic hunger and it may be that it is what links some of the reactions to a variety of technologies ranging from cloning to

genetic screening to patenting of genes and it is the notion of playing God. It comes up here in the language of creation. It comes up in other contexts that we have heard.

I feel like what is linking some of these issues for people is the idea that there is a change in the relationship that is perceived as appropriate between what we do, both in terms of physical manipulations and in terms of commercial applications, and what is best left to forces that are beyond definition. And I feel like we even could take that theme and we could actually understand what happens within it.

For example, there are -- in the area of gene patenting I think there are fundamental misconstructions of what it means to patent something in terms of its implications for asserting that you created or intellectually authored as well as misconstructions of the concepts of owning property.

I think another area is there are generally different views. In the area of genetic screening

some people have an image of God as somebody who determines fate so that genetic screening and choice by humans is playing God whereas for other people -- Mangus Dewark (?) has a wonderful novel in point -- playing God means actually leaving things to chance in which case genetic screening and determinations is playing humans as opposed to playing God.

In other cases there are different views on what man's role should be and I think the cloning hearings with the religious views about the role of humanity as partners versus as kind of accepting limitations was profound on that point.

I do not think we are well situated to write something on this because I think authorship by a kind of collection of staff and 18 editors for a document that attempts something of this kind of intellectual subtlety is unlikely to be successful.

I do hope that we can consider whether there are ways to look at this outside of a report context that may satisfy this hunger in a less resource demanding fashion to sponsor some process by which

people who are interested in this and are thoughtful about this actually prepare a collection of papers or presentations and to help facilitate that discussion may be an appropriate role for a national body even when a report is not.

On the other hand in terms of actual priorities even given the comprehensive report, to the extent that there are further priorities down the line that are kept on the list, in addition to Larry's, I would like to once again tout the notion that the issue of the body as property is one that has enormous real policy implications and it cuts across multiple issues, whether it is genes and patenting or the sale of -- sale and use of tissue or it is the sale of organs or it is financial incentives for organs, and not only organs but also for other kinds of body tissue that, in fact, now exist in a kind of mixed nonprofit and for profit world like tendons and bone, et cetera.

This is something, I think, that is an underlying area of legal confusion that has profound

market implications nationally and internationally, and I would like to make sure that it stays on the list as a potential actual report topic.

DR. SHAPIRO: Thank you.

Carol and Diane?

DR. GREIDER: I just wanted to respond briefly to the issue of the gene patenting. I absolutely agree that we need to stay focused at least in the short term to reports that we are, as you said, probably committed to.

When I came here, having read the background material on the gene patenting, I thought that this was really going to be a useful thing and something that we clearly would be doing as a topic. And I was enthusiastic about that in part because I understand what genes are and so I thought I could actually understand this report.

But having heard the discussion this morning I had a hard time finding where the ethical issue was that we would be addressing here and I think some of the other commissioners have said this as well. And

so I am willing to be convinced by other commissioners but at this point I do not really feel like that would be a productive use of our time because it sounds to me like it is a legal technical business issue in heart and that the component of it which -- of it which is a bioethical issue is a very small component.

DR. SHAPIRO: Diane, and then Bill?

DR. SCOTT-JONES: The question that I had has already been asked by Tom but I do not think it was really answered so I will ask it again. In thinking about the issue of gene patenting I was just wondering whether we are bound by our initial charge because it is repeated in the Federal Register October 8th. Are we bound by that to consider gene patenting?

DR. SHAPIRO: Well, Rachel? I have not an answer myself. Rachel, do you want to --

DR. LEVINSON: There were reasons at the time that the Executive Order was written that made that a concern. The issue itself since that time, and that has been really several years now, has evolved to the point that there are, I guess, two questions. It

needs to be separated into two questions. What is patentable and what ought to be patented?

And on the issue of what is patentable there has been a considerable body of case law that has developed as well as discussion focused by the Patent and Trademark Office. They are in the process of preparing written guidelines for applicants and for patent examiners so that that will be clarified and that will be clarified, I hope, in a very short period of time.

On the issue of what ought to be patented, that has evolved also but the focus right now -- and it has come to a point where that is really more of a business issue, a business strategy issue, a market driven issue. So I think that if you were to look at it and come to that conclusion that would be sufficient in discharging that responsibility that was in the Executive Order.

And the Federal Register notice and the new charter pick that up only because it picks up all of that language verbatim from the original Executive

Order.

DR. SHAPIRO: Bill?

MR. OLDAKER: The issue of patenting genes, I think, is a legal question and I think that, as others have said, it is difficult to discern where the actual ethical line is. I think they are probably correct.

I think that -- if I understand where the national science advisor to the President wants to go in listening to him talk about several cases is the broader implications of dealing with the human genome and genes and what is done with the information once it is obtained and what impact that that will have.

The questions -- and I think patenting of genes has a certain subset in that but it -- at least in my mind the real ethical issue is once we move into this brave new world, which we keep hearing we are just about ready to embark upon where you basically can get a print out -- take a drop of blood and get a printout of your human genome -- what are the impacts of that and how should that be used? Should that be -- should insurance companies be able to use that to

make determinations? Should they not? I mean it is in some ways a privacy issue. It is in some ways an intellectual property issue as to how do you compare if it is masses of data that are going to be out there.

And I think, you know -- I think that along with having that as kind of a subset -- and that is how I kind of read Donna Shalala's memo of the 20th, too, is a way to frame the charge and I think if the charge were framed that way there are innumerable ethical parts to be dealt with and a number of social policy issues which, you know, the country has not even thought to come to grips with but I could see how they could become enormous political issues. You know, are insurance companies going to be able to look and say that you have a high propensity to have breast cancer, testicular cancer, is that information going to be in the public domain or should it not be? Can people just go by and take a bit of your body parts and saliva and then go run your human genome? And, you know, what rights do you have? What property

rights, if any, in that? You know, so I think that is true.

And then I think the whole question which I think that -- the ethical part of the patent side is I think what we are going to see is that a number of genes are quite unique and although it is a very small percentage of genes that really differentiate various species and human beings that we are going to find a number of unique genes, you know, hundreds, if not thousands, between each individual and, you know, right now theoretically those would be patentable.

Is that what we want to say? That all of the patenting right now has been basically on -- I think on the ability to use those genes for a short period of time. I do not -- I have no idea. I do not think anyone has ever contemplated those issues so I think a lot of it depends on how you frame it.

If it is just we want to look at gene patenting and how the patent departments handle that I think that is -- there are not many ethical issues there.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: Well, just briefly. I think that we have seen a number of areas in medicine, for example, where something that was in the moral realm in relationship between physician and patient moved into the marketplace. The issue in gene patenting is -- the moral issue is, is it a business and legal issue or is it, in fact, something that belongs by inheritance to humans in general, and that is the question. It was settled one way in the past from what I heard this morning and it is now settled another way now. And that is not because some brilliant legal minds suddenly decided it is this now and it was that before. It is because there has been a change in the position of the moral and that is all right. I am not making this as an argument for pushing it way ahead of anything else. I just want to point out that the moral issue is there, make no mistake about it.

DR. SHAPIRO: Bernie?

DR. LO: I want to try and get back to a more pragmatic level that we were at a while ago. It seems to me we have some constraints and some opportunities. One of the things that struck me as Dr. Lane talked is that being a presidential commission we really have sort of an opportunity to impact through our recommendations to him to the council and to the President in ways that other groups do not.

I would really like to sort of try and take advantage of that and I guess it seems to me given his commitment and I think the President commitment to human subjects that that ought to be sort of not just something we are committed to doing but sort of a rush top priority because it seems to me given all that is going to happen in the next two years the sooner we can get a report the more time they have to act upon it and I guess I have a sense of urgency that here is a real opportunity to finish the job that, you know, Alex, your commission really started a long time ago, and to try and take another crack at getting something done without ten years elapsing.

So I guess I am concerned that as we talk about four projects, is that really too much for us to handle and maybe we should just say let's do the international one because it is well under way, let's really throw our attention to this comprehensive human subjects protection, really gear up, really do it, and then if we have time left over there are these very interesting topics that we can come back to later.

I am also very concerned about constraints. I guess, you know, we are really allocating the scarce resources of time and staffing. I guess I would like a sense from you, Eric, as to are we stretching the staff too thin trying to do the international report, trying to get geared up to the human subjects, big, big report, and also doing these backgrounders and sort of on three or four different projects. That is a lot of people going in different directions.

I guess I am concerned that maybe we should just be focused at least for the short term on your -- all your staff effort on really getting this human subject protection clarified, a work plan, check it

out with the Executive Branch, and really sort of jump into it. I mean this is -- we have talked about it but we -- and, you know, this is a good start but we really have an awful lot of work to do and I would really like -- I mean, I think all of us sense that it is not just something we were asked to do it, it is something we care about. It needs to be done and, you know, I would hate to sort of tackle a third or fourth report at the expense of this report.

DR. MESLIN: From the staff side, our hope is that we have the ability to complete the international project by the early spring. The schedule that Alice and Ruth have laid out, I think, is a very well organized schedule that will get drafts of that report, you know, in the coming months.

My sense on the staff side is, as you have seen, we have been reorganizing our staff and we still have a number of slots that we can still fill. My view is that we should be able to complete the international project undisturbed along the same path that we have and that we can begin a process of both

planning for and initiating the conduct of components of this comprehensive report immediately. Some of those can be done with outside folks and some of those can be done with people that we still intend to recruit but I would just remind the commission that we need input from you as to what are the priorities.

The proposal that we put on the table for some immediate response on what federal agencies have done and continue to do, whether there can be a Common Rule project standing alone or in concert with an IRB project, this is entirely within our capability at this point.

Could it all be done one year from today? No, probably not.

Could good portions of it be done in pieces over the next eight, ten, twelve, fourteen months? Absolutely. Part of it is a scope issue but, yes, we have the ability to expand our staff as needed up to certain budget constraints and other priorities.

DR. LO: If I could just follow up. If we also start to explore a third report or a fourth

report, even the extent of doing these background papers, to what extent is that a trade off with our ability to do the comprehensive report?

DR. MESLIN: I do not think that the -- we had planned for preparing background papers. We stopped commissioning or hiring staff to do background papers after we hired Stu and Andrea. They are members of the research staff. Their tasks are not limited only to those background papers. That is why they are here, to principally get those on the table for you by about December. That is their -- that is their schedule to have thorough background papers by about the December meeting. If not, then the January meeting.

If you wished other background papers we would have to appoint or identify other people to do those because that would be stretching the staff.

DR. SHAPIRO: Well, Bernie, I have a really pretty clear idea in my own mind that relates to your question and it seems to me that in the short run, meaning next month, until we meet next time, that we

ought to use whatever resources we have to do two things. Bring the international report along as fast as we can and, two, to clarify, plan and initiate activities dealing with the comprehensive report. And until I am satisfied that we have our hands around that and that we have a plan that feels good to us and that feels, yes, if we can do this, this is something we can be proud of, I would be very wary of getting -- of using resources for anything else.

Now part of that clarification and planning involves things that have been suggested around this table and whether they will be put in the plan in the end or not I do not know, whether it is Larry's suggestion that really certain kinds of important issues fit into human subjects protection and ought to be part of that, that is entirely possible.

But it seems to me that if we do not come back to the December meeting with a really -- as well worked out plan as we can develop with -- give us enough confidence that we can really deliver this in a timely way and whether it is reports one, two and

three or just one grand report four or whatever it is, I would feel very, very uncomfortable. I think all of these other issues are -- as many have said -- extremely interesting and I hope that when we come to the December meeting it may even be true that we feel comfortable moving in some other directions at least whether it is for something of the kind that Alta suggested or other suggestions here regarding how we might have documents or products that are not reports in the full sense of the word.

They are all worth very careful consideration but I am very worried about in the short-term getting distracted here. This is going to be -- we have a lot of work to do to get a plan which really feels good and say, oh, yes, that is the plan we want and let's get on. That is no mean task and, you know, we have been at this a while, that is true, but we have not really focused our efforts in some sustained way.

In my own view this includes things which we have touched upon over and over again. How well are the federal agencies doing? We just absolutely must

complete that if we want to take this report seriously it seems to me.

IRB, how are the IRB's functioning? How should they function? How should they be held accountable? Should we go to accreditation? Should we go to audit? Should we go to some -- I mean, I do not know. I am not trying to write the report now. It seems to me an absolutely essential part of that.

The Common Rule, is its scope and impact sufficient and where -- and I mean I think we know some of the reasons why it took ten years. It was not all bureaucratic delays although bureaucratic delays were part of it. In some part it is because it fits well for some huge part of this and it does not fit very well for other parts of the human subjects. We know that now and it would have been very hard to anticipate that before. We know that now so I think all these things have just got a formal part.

Now you just began articulating these and I have not given you the full list by any means. The breadth of what we are calling upon ourselves to do or

are being called upon to do is really quite substantial and so my proposal would be that in the short-run, that is between now and the next meeting, that we really focus our resources on those two programs and particularly on bringing here a credible and satisfactory plan for how we will proceed.

Now that may help us and then we will say, "Gosh, this is so overwhelming, we better not do one other thing" but we may say, "Gosh, we can do this in seven months. Let's start thinking about A, B and C." And so that is my own sense of where we should be going now.

DR. LO: If I could just follow-up? I think that is really right on target and I would actually suggest that for the rest of the time we have at this meeting we kind of table the priorities discussion really to look at the proposal --

DR. SHAPIRO: That is what I am going to be turning to in a few minutes.

DR. LO: -- to really give you some --

DR. SHAPIRO: Alta?

PROF. CHARO: And actually, well, in some ways it is kind of the thing because first I was never suggesting that any of these other things that --

DR. SHAPIRO: I understand. No, I do not think anyone --

PROF. CHARO: You know, we have had so many different outlines for the so-called comprehensive project. It must be at least a dozen. We have had so many background documents of one sort or another. I actually personally feel ready to take it down to the lesson of our Capacity Report and from the discussion yesterday on international, would it be so terrible to have a stab at actually writing up some findings and recommendations and then focusing the discussion and debate around them?

It is remarkable how that has forced everybody to hone in, in the past.

DR. SHAPIRO: I think the strategies we use to get from here to there are still an open issue and that is helpful.

PROF. CHARO: It is just the idea of trying

to once again outline and -- we could write a book about the human subjects protection system in the United States and yet 60 percent of what is in there may not be turn out to be directly pertinent to what we ultimately say and starting with findings and recommendations may help us to limit the scope of what is written to a manageable size.

DR. SHAPIRO: I think that is possible. Larry, and then Alex.

DR. MIIKE: For the next meeting I agree totally with that but I would add one other thing, and this would put the burden on the commissioners who really want some other studies done. I would suggest that the commissioners who are thinking of other projects, such as myself and Tom, I think, write up what they think the project should be and very short. Very short. Sort of like what Stu wrote about gene patent, one or two pages. And if you want to take a crack at it, try to estimate what -- how much resources you would need to do it. And I think that if we shared that by e-mail and other people are

interested they could tag on and expand on the idea.

But I think that would take the burden off the staff and instead of us coming here and trying to discuss de novo each of these projects that we want to push we would have a better idea of that and we could set aside maybe an hour at the next December meeting to discuss that.

DR. SHAPIRO: No. I would be glad to do that. It is a useful suggestion.

Alex? I think you are on my list. Are you still --

PROF. CAPRON: I wanted to make the point that you have made and Bernie, I think we should get on with trying to figure out today what we are going to do on the comprehensive report. I think we ought to also stop referring to it as the comprehensive report.

DR. SHAPIRO: Yes, that is a good idea.

(Laughter.)

PROF. CAPRON: It is the human subjects umbrella.

(Laughter.)

PROF. CHARO: Microphone, Alex. Microphone.

PROF. CAPRON: In all likelihood there are going to be several reports in this area and it is really under the umbrella of human subjects protections that we are talking about.

DR. SHAPIRO: If you could figure out a good acronym of one kind or another. It does not occur to me right away. There are not enough vowels in this subject.

Why don't we turn, as Alta has pointed out, to the latest proposal that you received.

Eric, do you want to just describe that and take us through that and see what kind of reaction we get from commissioners?

COMPREHENSIVE PROJECT ON HUMAN SUBJECTS PROTECTIONS

DISCUSSION OF PROPOSED PROJECT

DR. MESLIN: As commissioners know, there have been a number of versions of proposals for how to deal with this. At the September meeting where only a few of you were in attendance due to the hurricane,

Jonathan Moreno and I put on the table a document which was essentially a proposal for NBAC producing a number of status reports on the system of human subjects protections in various forms.

There was some feeling about the value of that, that it was of some value but not the best use of time, and it evolved into this proposal before you which can be seen in a couple of ways. I will just briefly outline the three components to this proposal.

The first component is to return to and make use of information gathered over the past couple of years on the extent to which the Common Rule is being understood and implemented by federal agencies. Just so that you are clear, for those who were not at the meeting, there was some discussion about what we have referred to as the federal agency survey, a series of interviews and other interventions by previous staff of agency representatives, which were collected in various forms and through working through Rachel and OSTP there have been a number of conversations with agencies about the quality of that data and its

usefulness.

Not to debate the quality which you heard at the last meeting has a variety of interpretations, some of the quality is good, some less good, it is still quite important using this proposal to return to the agencies with two purposes in mind. One is to ask them again to review the summary data itself, bearing in mind that this is now old and is essentially cold data.

But more importantly perhaps to also give then the opportunity to both update what has happened since then because many agencies have been writing to the commission informing us of policies or procedures that they put in place, best practices models that they think they would like to share with others and the like.

That is -- that component of this three-part proposal is something that I think can be accomplished obviously with hopefully the kind cooperation of the agencies to whom we would have to return in a relatively short period of time on the order of three

or four months, including, you know, starting now and including conversations, writing and follow-up.

It is not a data collection activity or a new data collection activity, something that had been put on the table at the September meeting to resurvey everyone yet again. This proposal does not involve gathering more data from what they were doing before but to provide to them summaries of what had been reported and give the opportunity to update, expand and offer suggestions for reform and improvement.

Commissioners will recall at the June meeting when we had several agency representatives here, many of them spent some of their time commenting on how they thought the system could be improved, what structures could be in place, what interpretations of the guidelines and regulations they felt were problematic, and it would be in that spirit that component one would be prepared.

I can go through each of the components unless you want to offer comments or questions about them.

The next two components can be really read in either order depending on the methodology and what you want to get out of it. The two components relate to IRB's and to the regulatory framework in place so if you think about this in the order that it is presented it is quite possible to now start -- to now -- and start to gather both quantitative and qualitative data about the IRB system and to make specific recommendations about any reforms that may be necessary.

This, of course, would involve not duplicating previous studies that have been done by a number of government bodies but involve our careful reading through and analysis of those but to supplement that where necessary. This would be an empirical project of some import with, I think, a hefty amount of input from the principal consumers so to speak of the regulations. The IRB's themselves, investigators, research administrators, institutions and even subjects. It would probably do more for -- in my view -- NBAC's credibility on looking at the

system if it could demonstrate that it has gone as far and wide as it can in this country to solicit the views of those who have to read the regulations.

This proposal or this component of the proposal really is a -- it depends in terms of time line, depending on the scope, depending on whether we conduct this in small focus groups at already scheduled commission meetings or separately convened meetings is a methodologic question that once the staff fully worked it out with you, you would know how long it would take to get this done.

It would be a very pragmatic and practical proposal in that there would be specific recommendations regarding IRB reform not limited to federal or publicly funded institutional IRB's but as you have seen in the outline questions about private IRB's and even national oversight and review, something that the commission has addressed in at least two of its previous reports, HP Capacity and Stem Cell."

The third component here affectionately

titled the reach of the federal policy for the protection of human subjects is the so-called Common Rule portion of this that could be as large or as small as one saw fit. You heard from Alta and Neal Lane that this is an issue of great opportunity.

The Commission can both address interpretations of the Common Rule, its reach beyond simply the biomedical paradigm and, a side comment here, this might be the place where, for example, issues about public health research or population research or outcomes research that are not well addressed in the current regs could be easily and I think very appropriately included as part of the reach of that activity.

Issues of whether or not it should be -- one goes in the incrementalist approach proposed by Tina Gonzales in her paper commissioned by NBAC, starting with the signatories to the Common Rule, recommending expanding that to all government agencies, extending that beyond the reach of the Federal Government to the private sector, that would be the locus or the set of

questions for that.

And I think the idea here, whether this is in Alta's mind something profound and dramatic -- you did not use the word "dramatic" but you did use the word "profound." This --

DR. SHAPIRO: That would be dramatic.

DR. MESLIN: It would be very --

(Laughter.)

DR. MESLIN: This would be the opportunity where the commission, I think, has the chance to not simply ask how should we reform the current regs but is the system that has been in place adequate and up to the task? Do we need a new regulatory framework? This is the one time when the commission could literally, if not figuratively, ask whether the Common Rule is the best mechanism of ensuring human subjects protections. Whether some other regulatory framework or format should be in place.

Now the only other thing I will say is I have given you that outline in its chronological order. One could easily reverse component two and three and

say let's get started on the big picture questions about the regulatory framework because that is going to take a lot of working through and I cannot -- I will not give -- I have given you some rough deadlines for this which are just approximate deadlines of the amount of time it will take to do these things.

One could then do the IRB project second so to speak once we learned more about what the reach of the rules might be.

DR. SHAPIRO: Thank you.

Let's see what comments. Jim, then Alex, and then Alta.

DR. CHILDRESS: Well, thanks very much to Eric and the staff for working this up. I think this really helps moves us forward. Since the Human Subjects Subcommittee was involved a lot in the early process of trying to get at federal agency compliance I very much like what you are doing in sort of incorporating whatever is useful from those early materials but also getting the further feedback and review, and that seems to me to be appropriate.

Where my major question comes, though, and where I think that you suggested perhaps chronologically reversing two and three, I am really worried on page four about another study of IRB's.

On the one hand I think -- yes, it is important but what I would urge is not even waiting until January but if there is a way -- if we have staff who can do it -- that we can actually pull together sort of what is present in the McKay study, the IG report and hearings and so forth, and just see really where the gaps are to see whether we really think there are important questions that could be addressed by yet another study and then talk about design and so forth.

That it seems to me to be something that we really need to have some work done on immediately if we think such a study is important but I think the preliminary work is going to be necessary probably before we could even decide whether it would be important to have a study especially if we want to get something on this available that we can actually

incorporate and use in time to get something in, in a reasonable period, to the White House.

DR. MESLIN: The only thing I would say just as a reminder, in the document that was distributed at the September meeting that Jonathan was the principal author of, there was a section there, a relatively well flushed out section but by no means comprehensive -- I will have to pick a different word -- by no means exhaustive because it did attempt to summarize that past work. More needs to be done but there has already been a very good start made on summarizing that material.

DR. CHILDRESS: Yes, you are right.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: I concur with Jim's sense of some urgency on bringing us up to speed with what has been done and I agree with you that some of that came before us in September. I suppose that the narrow part of the project, which is simply reporting on what the status not of implementation -- to me that is too

strong a word -- but the federal agencies' activity in the area of human subjects protection.

The only reason I worry about implementation is I think in common use that would suggest what happens on the ground and what we are still talking about is what happens in Washington and having that as a separate report would have the advantage simply of getting that out of the way.

Your timetable here is one which I wish I could believe. I hope you are right about it because I do think we should get it out of the way.

Beyond that, however, I am not quite sure that I agree with the way that the other topics are divided and then lumped. It seems to me that a big part of the IRB question is the resource issue for IRB's. We know the criticism from the Inspector General report. What we do not really know and what you would need, I think, fairly rapidly to get a contractor studying is what kinds of resources IRB's have available to them, how do they come to get those resources, how would greater resources be used, how

would they be earmarked for them, et cetera, within the context of different kinds of research sponsors?

Secondly, I do not see -- I probably missed it here but I do not see anything that really goes into the issue that Harold mentioned in passing, which is the oversight accreditation monitoring of IRB's. And if there is one thing that the recent activity of OSTP has made clear in having the kinds of institutions, the quality of the institutions, which it has singled out for halting of research, UCLA and Duke and so forth, we have to assume it seems to me that these problems are not isolated problems and yet for them to be bubbling up at this point -- I mean, I am glad to see OPRR attending to them in this way but I do worry that any critique of the system would be why hasn't there been an ongoing regular mechanism. I mean if hospitals in the United States, we waited for HHS and HCFA to suddenly say, "Oh, my God, this hospital has not been doing a good job and we are going to shut it down," don't you have some ongoing process. Well, we do in the case of hospitals and we

do in the case of universities, and we do in other cases but we do not as to IRB's. And I think what that would mean could be a substantial contribution.

The President's Commission made its recommendations because they were -- in one of its last reports there was no follow-up.

The issue -- the other issue that I find oddly -- the two other issues, excuse me, that I find oddly placed here are calling the issues of the level of regulatory oversight -- this whole thing that we formally adopted a couple of years ago on my motion that we consider the placement of the overall federal structure here, and whether in response to that or in response to their own internal concerns HHS has of course announced that OPRR is being moved up in the structure into the Secretary's office, and that was one of the options that was before us.

I gather from the fact that you continue to mention here that we do not feel that that move takes it off our table. We are just now going to be examining as to HHS a slightly different placement. I

do not think that that is a matter of the strengths and weaknesses of the Common Rule, which is the section you have it in. Your third section. That is not the Common Rule issue. That is how do -- that has much more to do with that first report.

Now I do not favor, I think, holding up the first report here until we can resolve that issue but certainly it flows from that. Here is the structure. Here is what has happened in a decade with the Common Rule and the many years before that with our own agency policies. Is there some reason to think that we would get better results if we had a higher level or is the present arrangement basically the correct one and just needs encouragement?

Likewise, in a certain way the issue of all Americans being protected is not an issue of the interpretation of the Common Rule and its strengths and weaknesses.

I think it is a basic issue about whether there is a -- in a way a right or an obligation, put it the other way, that we have towards everyone to

ensure that the kinds of things that have come to attention in the private sector that are scandalous do not happen anymore and that there is an oversight mechanism to ensure that everyone understands when you do research you have to go through a process which delivers, as I think our language is, the twin protections of IRB review and informed consent at the minimum. And that is not an issue of the interpretation and the strengths and weaknesses of the Common Rule.

The one way that it does, however, relate to the other topics is if the Federal Government is doing a lousy job of protecting subjects in federally sponsored research, we gain very little by saying the Federal Government will now "protect" people in privately sponsored research if it cannot do a good job -- so that the topics are linked but they -- but it is not, I think, a strength and weakness of the Common Rule as such. It is much more the implementation issue.

Also, I do not think I see in here one aspect

which is a Common Rule substantive issue. Is there anything in here that I missed about compensation of injured subjects? That -- is that in there and I just missed it?

DR. MESLIN: It is a very small point.

PROF. CAPRON: It is a very small point. Well, I looked over it.

That issue has also been on the table. At our last meeting it was discussed again. It seems to me it fits right in here in some fashion. I am not sure where. So I am not -- I -- after the first couple of pages where you talk about the agency status report sort of thing, I do not find this particular organization at least -- I mean, not the idea that there will be several reports but where you put the subtopics. I am not yet convinced by this -- for the reasons I have given.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO: I must say I was gratified to see how much is in here that reflects previous work

but nonetheless find myself agreeing with Alex about the dilemmas of organizational approaches.

On the other hand, as my previous comment may have indicated, I dread the notion of another exercise and going through three more different versions of an outline.

One of the things about this area, I think, is that one could legitimately come up with five perfectly good ways to organize it thematically and the problem is if you try to compromise among the five you get a mush that does not work for anybody. Any one of them would be adequate to the task, which is why in some ways I am terribly tempted again to push the point to bypass the outlining process for the moment, move right to the guts, finally talk about it as opposed to talking about how we are going to do it.

I mean, on the federal agency stuff, I would be -- I would be nervous at the notion that we were going to walk down a path that leads us towards doing a GAO type of report in which between the old data and the survey and the agency updates we kind of do a

report card on an agency by agency basis. GAO is very good at that. We are not.

Interestingly enough, one of the reasons we are not and even GAO have trouble is something that would flow out of a very sensible set of findings and recommendations that we could write today. All right. Based on all that has been done and that very helpful meeting with the agency reps. Finding: Most of the agencies are okay but there are some problems. Here is a list of examples.

Two: Oversight is hard because of the lack of internal monitoring systems that let us know basic things like how much research is being done, how many protocols, how many -- what happened to them, who reviewed them, how many subjects, what were the outcomes.

Three: There is no set of language you could put into any rule that could completely prevent these problems from arising.

Recommendation: The agencies have to have a reporting mechanism that permits something of an audit

and oversight because no system is no perfect.

Right? Easy. And it would have to cover those things.

You know, findings: The agencies frequently expressed frustration at the use of the Common Rule in nonbiomedical settings.

Agencies frequently, you know, are frustrated by the lack of an easy means for cross agency collaborations.

Third: Agencies often wish that they had a place to go for advice that was completely separated from the place that actually enforces against them so that there is a kind of safe haven. They want to have a -- you know, a penitent kind of confidentiality guarantee. Some place they can go to the confessional.

You know, recommendation: We can talk about that. All right.

Findings that the diffusion of responsibility for interpretation of key terms among departments, secretaries and agency heads has resulted in confusion

and actually in conflict on interpretation of key terms that cover very basic things like who is protected and from what.

Second that OPRR's move within HHS may handle some internal conflict of interest issues but it does not touch this problem.

Recommendation -- you know, we could write that today.

PROF. CAPRON: Second.

PROF. CHARO: With regard to the second half of this, though, and that is interesting -- and interestingly it looks directly to that last recommendation about the issue of confusion of responsibility, right. That is the one where the debate is then going to focus on, well, should it be one department that takes the lead or should it be something outside the department structures and, if so, where. Is it OMB? Is it -- what is it? You know, and the political whims of support and -- well, that dovetails very nicely with the question or whether or not the system is going to be aimed only at

federally sponsored or at all research. That will be important in the debate about the appropriate recommendation to follow from that finding.

At which point -- as I think Alex said -- the question of the adequacy of the current system and its definitions and its presumptions is tightly tied to the scope of the research that it is reviewing, increase the scope of the research and you must pay even more attention to the ability to implement the system efficiently and effectively.

Again there I think between the Gonzales report and the other reports that have been delivered -- and maybe we can have a new kind of mailing that just collects the key documents that are now scattered in all of our offices in various unorganized piles into one mailing so we have it all in one place for those of us that are not particularly good at this and do not have secretaries, we can actually sit down and say, "Okay. What do we really want basically?" And if we do not know because there is an empirical fact missing like we do not know the scale of private

research and we do not know the number of private IRB's, we can then stop and say, "All right. You always make policy based on imperfect information." Can we make policy now already or do we really need information here for this recommendation and, if so, now we will know exactly what we need to get.

I guess -- I guess I am just frustrated.

DR. CASSELL: Well, you should get frustrated more often.

PROF. CHARO: I am restless.

(Laughter.)

DR. CASSELL: You should get frustrated more often.

DR. SHAPIRO: Trish, and then Bernie.

PROF. BACKLAR: Well, there are two things. One is I actually think some of the work we are going to do on the international project is actually going to be -- I actually think that some of the work we are going to do on the international project may be very helpful for us here as well so we are not necessarily wasting our time over there in terms of this report.

The other thing that I am concerned that nobody has mentioned, and I wanted to make sure we have it on the table, and that is the issue of conflict of interest, which is the oversight, hopefully, as one -- I do not see it mentioned anywhere in this report and I think it is a major problem for the IRB's and I am presuming that if we come up with some creative way of oversight and so forth like JCHO that that would be a way of -- one of the ways that one could deal with that.

DR. SHAPIRO: Could you just help me, Trish, by which conflict of interest are you focusing on?

PROF. BACKLAR: I am talking about the institution's conflict of interest within the --

DR. SHAPIRO: I see.

PROF. BACKLAR: -- IRB, which is reviewing its own -- I do not need to spell it all out. We all -- everybody knows what I am talking about.

DR. SHAPIRO: No, I just wanted to be sure that --

PROF. BACKLAR: Right?

DR. SHAPIRO: -- I know exactly what.

PROF. BACKLAR: Yes.

DR. SHAPIRO: Okay. Bernie, and then Larry?

DR. LO: You know, in the spirit of trying to move us on, I think, it would be useful for the second big section interpretation and implementation where there have been a number of reports to really delve into what is known and what is missing and I -- being probably the most disorganized person on the panel I think it would be really helpful --

DR. SHAPIRO: Let's not start any conflicts of interest.

(Laughter.)

PROF. CHARO: Because you will not win, Bernie.

DR. LO: You should see -- you have not seen my office.

PROF. CHARO: All right.

DR. LO: To get --

PROF. CAPRON: The two of you --

DR. LO: To get a packet with the relevant

reports but even more important to ask the staff to prepare all these wonderful master charts, you know, report A, B, C, D, what do they identify, what do they recommend for resources, issues where there is confusion. To really start filling that in.

I would also suggest there is some -- I guess that rows cutting across the -- my impression from the reports as I recall them -- are missing. One is how much do we know about the experience of lay members -- outside members on these panels? Are they really adequate if there only one or two of them? Are there holes there? Are they sort of token appointments? How effective are they?

The second has to do with private IRB --

PROF. CAPRON: Yes and no I think is the answer.

DR. LO: Yes. But again to document that and to try and identify IRB's that have done that well.

The second issue has to do with private IRB's. As I recall, you know, when you try and go out to talk to them it is hard to do that. If that is

missing maybe we could try and invite some of those people to testify in front of us as a way of getting some of that knowledge.

Third, one of the reports started to talk about what are some of the burdens of IRB's that are excessive. Are there situations -- are we just going to sort of do more and more, saying you have to do this, this and that, and we will try and get you more resources? Or do we also address concerns that maybe in some areas the regulations are overkill, that we should try and cut back.

So I think to really push us ahead by critically reviewing what is already known would be extremely helpful and I would suggest where you see an obvious gap maybe start to schedule speakers to come in and help us.

The second thing I think is this: All of us in the interim should go and talk to someone we know who works on an IRB and say what is going on, what are the things you have trouble with, what are the problems you face, what would make a difference to you

in terms of resources, what is really needed, how do you educate each other, how do you -- where do you turn to if you have a stumper or a question?

I mean to the extent that we are all connected in some way, I think, with institutions that do some research that it would be at least helpful for us to get a personal sort of, you know, qualitatively information on what is going on out there.

But I think, you know, what I am hearing is that there is a lot out there and we need to sort of bring it together, and I think whatever we can do to kind of move that along would be helpful.

DR. SHAPIRO: I think that is very helpful. Obviously in the -- any time one does quantitative studies we do not have to do one twice. If there is some information out there you ought to accept it. Second, you ought to know what you are going to do with the results if you go out and get them. You ought to test yourself and say, "Well, if I had this information would it make any difference?" Both those things are really important as we go ahead.

Larry?

DR. MIIKE: Yes. Just several comments. I think on the discussion we had at the last meeting about how to update the agency information that it was for the purpose of what you would like, Alta, which was really not to -- there might have been elements of finger pointing early on in the collection of it all but it was basically to supplement and make sure that the information we got is agreeable to the agencies that that is what they said they are doing.
And the panel that we had -- you could combine both of those things and I think you would come out with a fairly good list of things that need improvement. So that is all I have just on that point.

I think I agree also with Alta that -- let's not decide at this moment where things fit because that -- we are going to change that to the very nth degree, to the very last day, but let's be clear about the areas in which we really need the information and as soon as we can get clarity on that I would strongly recommend that if not formally we all think about,

okay, what are the findings we expect out of this and what kinds of recommendations follow because it is a good focusing effort and I think that when we do that -- especially since there are many commissioners here who have very in depth knowledge about this field, and I think that from our past experience we soon find that we are in collective agreement in a lot of these areas and so we can dispense with the areas where they are not controversial or in disagreement among the commissioners and we can focus on those areas where we really need to get some agreement on.

DR. SHAPIRO: Let me ask a question to commissioners on an issue that has come up before and is mentioned here in this outline. I believe it is at least mentioned on four and Alex referred to it before.

And that is the question of the ongoing monitoring of IRB's. I actually think that is really quite an important and central issue regardless of what we find out what resources and all kinds of other issues which are also important, and I agree with

Bernie if we could find some way to make their work effective but less burdensome we ought to identify that. We ought not just to pile on more work and so -- but as I recall our discussions, two different models were mentioned at least explicitly regarding how one might monitor IRB performance.

One was the accreditation model, which I think Alex talked about quite persuasively at one of our meetings, and the other we have talked about less often and that is the question of some kind of audit procedure which is similar objective, different methodology.

The question I have is twofold for the commissioners.

One, as you have thought about this has either of these methodologies recommended themselves to you or do you have any other ideas about sort of a broad methodology one might consider moving in here and defining because I think it is going to be quite an important part of what we do.

Eric?

DR. CASSELL: Well, just on the face of it, the fact of the need is there because we all know that something goes to the IRB and from then on once it has gone through its process we forget it. So we have agreed generally on the business of some kind of educational process for people who are members of IRB's and whether that leads to accreditation or not.

But it would be very difficult to have an audit method in there unless they get more resources because we will end up giving them, you know, auditing without the ability to repair. So I think anything we do in the way of audit has to have -- has to be coupled with the idea that they are going to need more resources.

DR. SHAPIRO: Alta?

DR. CASSELL: Who pays for it?

PROF. CHARO: First, I absolutely agree with Eric and everybody I think needs to keep in mind that the issue of resources for IRB's is embedded in a more general issue of how medical schools, hospitals and other institutions finance these days, and how rapidly

that is changing.

More directly in answer to your question, Harold, I think actually this is extremely important because it is a genuinely different mode of addressing the question and it also offers up opportunities to do things we have never tried to do until now. As it stands we have one se of rules for everybody regardless of how frequently they oversee research and how good they are at it.

When it comes to driving a car we recognize differing degrees of licensing freedom to your license. You have got learner's permits and you have got regular licenses, and then some people have special licenses to drive motorcycles and heavy trucks and others do not. A system like that actually offers a great deal of flexibility that does not exist in the current system.

Right now we have got administrative rules that are aimed quite centrally at substantive issues like what is acceptable risk/benefit balance, others that are aimed at trying to ensure that the IRB

actually thinks through the problem completely such as checklists over factors regarding children and others that are purely there so that we can, in fact, do audits in the future.

So recording votes and recording the minutes are really about allowing oversight in the future and it is possible that with a system of some kind of accreditation, something like the CLIA model with which laboratories are tested for competency and then are permitted to pursue things subject to periodic retesting and reauthorizations and such. We could actually change the particular sets of administrative rules that govern IRB's in a way that facilitates review for those that have shown they are competent and maintains a very heavy handed level of oversight on those that are still proving themselves and are still in training. This is a whole new way of balancing people's interest that has never been available to us before.

DR. SHAPIRO: Jim?

DR. CHILDRESS: In response to your question

this is an area that if we have general agreement that is well worth exploring, as I think we probably do these, I would be helped by having actually some arguments developed and some indication of how these might work so that as we move toward some recommendation we would have already some of that in place rather than having to come up with it at the last minute.

PROF. CAPRON: In that regard if I could just put a request in. One place to start would be in the materials in the 1983 so-called second biennial report on human subjects report from the President's Commission because an exploratory study had been done actually implementing a process which was like an accreditation sort of process involving peers and so forth. And the other thing would obviously be to look both at the implementation of the Clinical Laboratory Improvement Act, CLIA, that was mentioned by Alta and how that is done under a federal mandate and the rule of federal agencies in that, and that some of the private accreditation bodies, which I think would have

a whole lot on the philosophy of accreditation, and then going to the Price Waterhouse's of the world for the auditing process as they do in the corporate area.

So it should be very quick, Jim, to pull that together.

DR. SHAPIRO: Yes. One of the -- I do not have any position on which of these might be the most effective. I have not thought it through carefully enough in this case but one of the things that has happened in, for example, higher education accreditation is the agencies are loathe to withdraw accreditation from anyone under any circumstances because it immediately gets them into a lawsuit and that is very aversive to most of the people who run these organizations, and so that is really hardly even an option they considered seriously even in some very serious cases.

And whatever we design, whether it is audit, accreditation, whatever it is, and I do not have any particular view right now, we want to make sure that somehow we do not get into that kind of situation and

I think one of the things that we should think about and I think Jim's request is entirely reasonable that we should start outlining the pluses and minuses and characteristics here. That is very helpful. I have always thought and still think that some kind of public disclosure here is an enormous benefit, regardless of whether you are doing it through accreditation or audit or whatever else you do because that gives you strength to actually go ahead and stick to your guns on the issue.

Bernie?

DR. LO: Yes. I just want to reenforce that this is incredibly important and there is a lot being done out there. I would just like to sort of pick up on Alex's suggestion that we look at some of what is going on with voluntary accreditation in health care delivery so the problem you addressed, Harold, of sort of once you are accredited no one wants to take it away. In health care NCQA accredits health maintenance organizations and physician groups on a time limited basis so that you have to come back and

get, you know, reaccredited and people do flunk.

But I also think we need to be very careful to sort of -- the underlying philosophy of what we are trying to do. I mean, the advocates of an NCQA type approach say that it is -- the audit and quality improvement are meld -- they try and meld it together. So that rather than saying we are going to come in and judge you and you better shape up, it is we want you to set in place something where you, yourself, review what you are doing and have a system in place to assure improvement in certain key areas.

They feel that that is a much more constructive way of sort of starting a system where none had existed before but they have a lot of experience with this and a lot of experience dealing with the concerns that, gee, you are making us do this, it is incredibly expensive, it is burdensome, it takes resources and time away from our real task, and is it really worth it. So those are the issues that if we can get people really to deal with that it would be very useful.

DR. SHAPIRO: David and Larry?

DR. COX: Yes. I would just like to second what Bernie said because if it can happen in the medical profession, it can happen anywhere and that is a fairly recent thing. I mean, this idea of getting recertified has happened, you know, probably in the past 15 years and it did not happen at all and then it happened everywhere so it is the expectation, Harold. If there is the expectation that people will fail but not very many because everyone is trying to work so that they do not then it is not lithogenous. I mean, probably some doctors do sue but I think the idea is that no one is going to pay attention to them because this is accepted in the field.

PROF. CAPRON: You are referring now to board certification?

DR. SHAPIRO: Board certification of individuals, yes.

DR. COX: Yes.

DR. LO: I was referring to certification of HMO's.

DR. COX: Yes. But it is the same. But actually --

PROF. CHARO: You can have both.

DR. LO: Absolutely.

DR. SHAPIRO: Larry?

DR. MIIKE: Well, the NCQA is an imperfect model because it is more a marketing tool than anything else. There is really no consequence if you are not accredited. It is to be able to say I am an NCQA member. I have done really well, look at how great my return rates are, and those kinds of things. So it is an accrediting model that does not really have the kind of teeth that we would need.

DR. COX: In medicine it does. You do not get -- you cannot practice.

PROF. CAPRON: Yes. It is not true of hospitals because the absence of accreditation --

DR. MIIKE: I understand it. What I am just saying is the NCQA one about the HMO -- also really if we are talking about specialty organizations and being board certified, I doubt that there are very many

physicians who get their board certification revoked except for if they do not continue paying their dues and things like that, you know.

PROF. CAPRON: But they have time limited certificates now I think was the point.

DR. SHAPIRO: Okay.

(Simultaneous discussion.)

DR. CASSELL: -- if I thought to complain about it.

DR. SHAPIRO: What is that?

PROF. CAPRON: You still it, though, didn't you?

DR. CASSELL: Yes, I got it. I did it. I wanted to complain. I thought it was a lousy idea but you could not complain unless you did it, see.

DR. SHAPIRO: You did it in order to get the right to complain?

DR. CASSELL: That is right.

DR. SHAPIRO: I see. That is all right. Well, there you are. Some positive outcome.

DR. CASSELL: That is right.

DR. SHAPIRO: Both the complaint and the recertification.

I think when we come to look at these various models of audit, accreditation, whatever we are going to do that there will be some trade off between the resource intensity and various characteristics here. Some of these I think will turn out to be cheaper and some better and then we will have to make some decisions of that.

PROF. CAPRON: Yes. I wanted to underline at the last meeting I brought up the notion of the percentage that would -- one percent, two percent of a budget that ought to be assigned to the human subjects protection function and I want to underline what Alta said which is we really need to understand the financing of the human subjects protections as they now work on an institutional level, which will be quite varied but have an understanding of that range because obviously in some circumstances with institutions that may be doing a very good job within their own distribution of overhead, they may be

supporting at a level above that.

And the last thing we would want to do is to turn around and say, well, actually you only should be spending two percent of the research budget on this function if an institution has discovered that it takes three or four percent to write a good IRB that is well staffed, et cetera.

What we are really concerned about is the indications that IRB's in many circumstances are resource poor and that some of the problems that arise seem to originate there and this is an example where if we sort of had a tentative idea where we wanted to go that the resource problem is -- then we can kind of ask the kinds of questions that Alta was pressing. What data would lead us to one kind of conclusion or another in our specific recommendations? I think we ought to -- frankly, I think we ought to take the transcript pages in which Alta went through half a dozen recommendations on things and just sort of have those slightly spruced up because they were off the cuff but they were very good and have that on our

December agenda just the way yesterday we looked at some of the tentative recommendations on the informed consent issue rather than putting them off until we "do all the research," which often just leads us hither and yon.

DR. SHAPIRO: The issue of cost and cost reimbursement I think is going to turn out to be a complicated one.

PROF. CAPRON: I am sure.

DR. SHAPIRO: At least to the extent that these are reimbursed to institutions through indirect cost rates because there already are caps on the administrative side of indirect costs and they cannot go anywhere in most institutions. And so depending on what we discover, and we will have to look at it carefully, this may be a fairly sort of complex administrative matter to deal with.

PROF. CAPRON: Then again the point of whether we are talking only about federal dollars --

DR. SHAPIRO: Right.

PROF. CAPRON: -- or pharmaceutical,

biotechnology dollars as well --

DR. SHAPIRO: Right.

PROF. CAPRON: -- comes in here.

DR. SHAPIRO: Correct. Absolutely.

Bernie, I am sorry.

DR. LO: I wanted to add one more issue to our issues that we have sort of talked about but want to make sure to get it into the outline somewhere, and it is related to the accreditation, and in a sense it also deals with quality control but I think it is separate and it is the education of IRB members and the continuing education of IRB members.

I think the experience of most IRB's is you get the letter in the mail appointing you and you go to your first meeting and that is your introduction. And I think in terms of what should be the best practices for bringing people up to speed before they join, and then the people who have been on the board for -- IRB for five, ten, fifteen years, things change and again there is no kind of assumption that they are going to sort of keep themselves up-to-date. And to

the extent that that needs -- may need to be a part of our report, I think we -- you know, as Alex did so and others, we just need to make sure it is in there in the outline in a clear place eventually.

DR. SHAPIRO: Tom?

DR. MURRAY: This has been a very useful discussion and I sense it is drawing to a close. Let me raise one additional dimension of it. I know Alta is a member of a very active IRB that probably other people sitting around this table who either are or have been members or served on IRB's, it ranks fairly high on the list of relative -- of thank you -- thankless tasks in most universities.

PROF. CHARO: That is why I was grateful to rotate off as of August 31st.

DR. MURRAY: Congratulations.

Now that -- we cannot change institutional norms, internal institutional norms by fiat. That cannot happen. But I think more attention -- we ought to be giving some attention to whatever we can do to alter the way IRB's are sort of thought of within

institutions although I am not sure how to do that.

And the second dimension of this is to ask -- and this may -- you know, we should at least contemplate recommending changes in the rules about composition of IRB's. Other countries have a much greater balance between institutionally affiliated and public members. New Zealand, for example, requires that either an equal number or a majority of members of all research ethics committees be from the general public. I would like that at least to be on our agenda to talk about.

DR. SHAPIRO: Incidently, I think the -- I think those are very good points, Tom, and I think also that while we certainly cannot change the status of IRB's by any, you know, exhortation or statement that we say here, I think, you know, people's thinking, for example, at Duke about IRB's changed overnight about their importance and they are not going to think the same way again for a long time.

And so it is related to this monitoring and so on. It is a very important issue but it is related

to how seriously rules and regulations that are appropriate are actually implemented and taken seriously and so we cannot -- you are quite right. I mean, I accept your point but we can do something in that sort of indirect way on those issues.

PROF. CAPRON: The Presidential Medallion for Service in the Protection of Human Subjects given to IRB members nationally.

(Laughter.)

DR. SHAPIRO: Bernie?

DR. LO: I want to go back to an issue that Alta raised that struck home with me in terms of beginning to think about learner's permits for kids and in my own case sort of geriatric driver's license certification.

DR. SHAPIRO: Bernie, you do not look that old.

DR. LO: You should see me drive.

(Laughter.)

PROF. CHARO: Revved that Buick Skylark up to 35 yesterday, right?

(Laughter.)

PROF. CAPRON: Do you have one of those restricted licenses, no driving on hills?

(Laughter.)

DR. LO: We noted in the outline that different kinds of research raise different sorts of issues and so research on DNA testing of stored tissue samples raises different issues than research on children, research on patients with mental illness, and at our institution a big issue is clinical trials research.

Sometimes -- you know, sometimes it is unrealistic to expect the same IRB to be equally adept at all kinds of research so that within a large institution, many institutions, including mine, have started to split IRB's into sort of more differentiated IRB's.

And, again, as an option for, Alta, the high volume research institutions maybe there is something to be said for kind of having them match their IRB's to the types of studies they are doing and at least

demonstrate that for the types of protocols that come before them frequently they should be sure they have adequate expertise on their IRB's and experience to deal with those.

We sort of said that with regard to our research on patients with mental disorders that may impair decision making capacity, if you do that a lot you have got to have extra members and so forth and so on. And I think to the extent that that is a useful principle for areas that are known to have special problems we maybe need to have IRB's target that.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, allowing the complexity of the issue, each one of these points that have raised up is associated also with compensation to the IRB for the costs involved because every one of those things certainly outside -- increasing the number of civilians is going to increase the cost and changing the number of IRB's is going to increase the cost and also their prominence in their institution will be greatly helped by a budget -- independent budget that

makes them seem more important to the people who serve on them and so forth and so forth and so forth.

DR. SHAPIRO: Trish, and then Alta?

PROF. BACKLAR: Bernie brought up a very important point which I also want for us to remember and that is the one size does not fit all and one of the errors we fell into with the capacity report at one point was we had completely forgotten about a certain kind of research which was more demographic and so forth, and we had included all kinds of strictures and so forth into that loop so we want to make very sure just as we are thinking about the international research that the context are going to be very important.

DR. SHAPIRO: Alta?

PROF. CHARO: I wanted to also respond to Bernie because I think that the observation about the growing number of seemingly special cases is also linked to the question of governance of the system and the degree to which certain governance options offer flexibility.

For example, if you had a central governing authority that transcended the departments but actually controlled all the departments simultaneously as well as in theory the private sector if we got them included, and it had the ability to do things like, for example, issue annual lists of topics that are on this year's list of special topics that have special rules, whether it is this is the topic that requires a national review or this is a topic that requires special consultations by special groups. It would permit IRB's to operate without having to find some way to create all these different special bodies themselves and it would also permit the IRB's to respond consistently to these special topics instead of having the special topics -- for example, research with children, be governed by one set of rules if it is NIH funded and another set of rules if it is FDA funded, rules that sometimes actually have conflicting policy directions so that the -- the question of what we choose on the national level is intimately linked to what can be accomplished efficiently on the local

level with the resources that we have or the resources that we advocate they should have.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: Just from what I have learned about IRB's over the time that I have been with this commission and even in our past reports where we have just loaded more tasks on to an IRB, it seems to me that the most straight forward way of dealing with all of the complexities around the IRB issue is to make their job simpler and I have heard suggestions along those lines but I think that would solve a lot of the problems about whether audit or accreditation is better or not because I do not think they have bad motives but it is probably they are confused about what their responsibilities are or there is so much stuff that you sort of rubber stamp kinds of things.

So I think what we need to really do is take a look at what the original and current purposes of those are and match that up against the piling on of responsibilities that has happened and try to cull it

back down to something real simple.

DR. SHAPIRO: Okay. Well, let me try to articulate where we are now. One, I think two suggestions, in particular, are very helpful for us to follow up immediately. We will be doing a lot of things immediately.

But, one, I think -- I do not remember whose suggestion it was but I think the idea that we should try to get the so-called federal agency part of this thing done and finished is a good idea. I do not see why that has to be part of our larger report. It is a finite subject and it can be handled effectively, and we ought to get it finished and done with --

PROF. CAPRON: Post haste.

DR. SHAPIRO: Yes. As soon as we can, whatever that turns out to mean, and that is one of the things we will ask the staff to get on with and hopefully we can finish quickly.

Another suggestion is that as we go ahead and start planning what we want to do we should simultaneously produce something that is analogous to

findings and recommendations to begin getting a sense of where it is we might go, what issues are important and just see how we feel about it rather than waiting until the end. I think that is also an effective thing to do and Alta or someone else made that suggestion, and I think we ought to do this.

Now there is going to be a good deal of intensive work to follow up the various suggestions here and I think it is going to be necessary in the next six weeks -- you might get a call from Eric or myself to see if we cannot meet somewhere to hammer out certain aspects of this and get some suggestions from you because I think we are going to need -- sometimes e-mail will be quite sufficient, other times we may just need to sit down and hammer something out because it is very difficult to do just by e-mail.

So we will be imposing on your time somewhat in the next few weeks really to get this in some kind of shape where we feel better about where we are going in December and we will try to devote our December meeting. First of all continuing on the international

side. We will then spend a good deal of time on this although we have not worked out the agenda yet. And depending on how that looks there may be, of course, other items, people we want to hear from and so on, which will be scheduled for that time.

So I think that we are sort of inaugurating today -- it is hard to say inaugurating since we have been dealing with this subject in one way or another for -- throughout our whole existence as a commission but maybe we are inaugurating the determination to bring this to some kind of conclusion and I think it will be an important product to this commission so it is an exceedingly important thing. I am not going to really devote resources to other things until we have a clear idea of exactly where we are going and, therefore, how much time it will take and what resources it will take. At that time we will be able to decide whether we have other issues of interest to the commission that we are able to take on or not but I am going to hold that up for a couple months before we pursue anything along that line.

Does that seem reasonable to people?

DR. MURRAY: Yes.

PROF. CAPRON: Yes.

PROF. CHARO: Yes.

DR. CASSELL: Could I just ask a simple question?

DR. SHAPIRO: Yes.

DR. CASSELL: How many people on the commission -- how many commissioners have ever served on an IRB?

(A show of hands was seen.)

DR. CASSELL: That is what I thought. We have a lot of expertise about this subject.

DR. SHAPIRO: I actually thought that -- someone made a suggestion, I think it was Bernie who made this suggestion that in the interim for those of us that are either currently associated with or have easy access to a local IRB might want to not only use our experience but to sit down with that IRB and find out what is going on today with them, what is bothering them and so on. Certainly I am going to do

that since my experience in the IRB is sort of ten years old and I do not know if it is even relevant any more and if we can do that that could be very helpful.

PROF. CAPRON: I wanted to just ask you a question about your last comment before the IRB that is, I had thought a little earlier in the discussion that we were still thinking that at the December meeting we would be visiting some of these tryout candidates for topics and in light of -- either at the December or January meeting.

In light of where we stand on this umbrella topic of human subjects protection, we would be saying in terms of the finances and the staff time, will be able to look at gene patenting, assisted reproduction technologies, human-animal hybrids, et cetera, with, I think, the clear understanding that it is likely that those topics will during the following nine or ten months always be a little bit further back on our stove -- on the back burner but working along so that if this commission goes out of existence on January 20, 2001, we will have been able to complete the human

subjects package but we may have other reports in the works which we are not going to get through.

If we wait until June -- May-June when by then the international report should be under our belt and so forth and say now what do we have time for, it seems to me highly unlikely that we would get very far, if at all, on those reports.

I had thought from our earlier discussion, as we said -- well, today, in this time between 10:30 and noon, let's do exactly what we have done, which is to figure out how we want to flesh out the human subjects report, that we also began that discussion by saying the other stuff -- and Eric represented at that time, as he was asked a question, the staff without a lot of additional effort is going to be doing these backgrounders on the three or four topics that have been high on the list.

DR. SHAPIRO: Well, my own --

PROF. CAPRON: Are you taking that off the table, I guess, is what I am asking?

DR. SHAPIRO: Well, my own view of that is

that -- and I was thinking of the time period not between now and next summer but now and December.

PROF. CAPRON: Okay.

DR. SHAPIRO: That is the time period I had my focus on. That we would only take up those things if we thought there was some possibility that they might, in fact, be part of this umbrella report in some way. So, for example, someone suggested repro tech, if that is a word that is used, really could be used as an example of what we mean in certain areas of human subject protection and so on.

And I do not want to be rigid about it because, you know, let's see how much time we take. If we have staff and they have time, you know, and it is not needed, that is fine but we should not be too rigid.

I was only referring to between now and December. I agree with you that we could not go as far as next June.

Larry?

DR. MIIKE: Well, my suggestion was that the

commissioners who are interested take on that burden and that I only ask that you set aside maybe an hour or so in the December meeting.

DR. SHAPIRO: Yes. We will be glad to do that.

Any commissioner who feels strongly about something, strong enough to write something, a few pages, we certainly will discuss it.

Jim?

DR. CHILDRESS: Also, I am sure that the staff already has this recorded but Bernie and I and some others had asked for -- to get as much as we can on the IRB discussion --

DR. SHAPIRO: Absolutely. There have been a whole series of very useful suggestions and I did not --

DR. CHILDRESS: Okay. I just wanted to make sure that the --

(Simultaneous discussion.)

DR. CHILDRESS: -- early ones did not get lost.

DR. SHAPIRO: I did not mean to miss them all. I did not remember them all.

PROF. CAPRON: That is the work between now and the December meeting.

DR. CHILDRESS: That is a lot of work.

PROF. CAPRON: Part of it.

DR. SHAPIRO: Okay. Anything else to come before us today?

(No response.)

DR. SHAPIRO: If not, we are adjourned. Thank you very much.

(Whereupon, the proceedings were concluded at 11:30 a.m.)

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