FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

TWENTY-SEVENTH MEETING OF THE

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

8:43 a.m.

Friday, July 14, 2000

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Gaithersburg, Maryland 20877

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C O N T E N T S

P R O C E E D I N G S

(8:43 a.m.)

DR. SALOMON: Good morning to the second of this two-day meeting, the Biological Response Modifiers Advisory Committee. I guess that means if you're here for another Response Modifiers Advisory Committee meeting, this isn't the right one.

(Laughter.)

DR. SALOMON: I don't have a whole lot of introductory comments. I think that today is the opportunity now to get into the questions that the stage was set for yesterday. Again, I want to thank the speakers for really a tremendous contribution. I certainly learned a lot and I think there's a lot to build on today in the discussions. We will get a little bit more into kind of the ground rules for the discussions in a few moments.

There is one thing that is actually not a pleasure at all to do this morning, and that is to introduce the presentation of a certificate for one of the people on the BRMAC that is going off. It's not a pleasure because Dr. Auchincloss has been my evil twin on the BRMAC and on the Xenogeneic Advisory committee.

(Laughter.)

DR. SALOMON: We usually are worried if we agree on anything, and I think I stated once in advisory

committee, yes, I totally agree with Dr. Auchincloss, and went on about what it was I thought I totally agreed with him. He immediately responded, you have got me totally wrong. That's not what I meant at all.

(Laughter.)

DR. SALOMON: So, we are 100 percent.

But I think he knows the depth of my respect for him. He is one of the most intelligent, well-thought, articulate people. I say as a joke that I am just an Auchincloss wannabe as a chairman. I don't think there is anyone who chairs a meeting with more style and competence than Dr. Auchincloss. Anyway, neither the Xeno Advisory Committee or the BRMAC is going to be the same without him.

MS. DAPOLITO: He's still on the Xeno.

DR. SALOMON: Oh, he's still on the Xeno. Excellent.

(Laughter.)

DR. SALOMON: This isn't quite as bittersweet then as I thought. That's really good. But you know, the loss to the BRMAC is really major here so it really isn't a pleasure, except to say what I have said. I really respect you. You're really a tremendous contributor to all this.

Phil, Jay, and Kathy?

DR. ZOON: Well, I just wanted to take a few minutes. I know we have a busy schedule. But when

somebody contributes so much to CBER through the Biological Response Modifiers Committee, and helping us with xeno on so many tough issues over the past several years, I think it's just appropriate, right, and a pleasure to thank you for your service.

In many cases being on our advisory committees, as many of you know, is often met with many challenges. It takes a lot of time. The pay isn't very good, and the issues are always tough, complicated, and often highly political. It takes a real dedication to purpose, a real excellence in science and knowledge, and what they call good common sense to deal with these complex issues so that we move science forward, that we don't become handicapped by our inability to deal with new challenges and new issues, but we have the sense and purpose of making sure that it goes forward with the health and safety of the individual subjects in the trials that these patients will participate in.

I think all those qualities have been contributed by you. We are pleased as punch that you could still be on Xeno. I think that is wonderful.

And I would just like to take a moment to give you a small certificate of appreciation, Hugh, and thank you very much for all your contribution. And just to say, Dan, that he always told me you were the evil twin.

(Applause.)

DR. AUCHINCLOSS: The first thing to say is that it doesn't seem like it ever comes to an end because, in fact, I retired at the end of last meeting and here I am back again for this one. And then I learned that, in fact, I do remain on the FDA Subcommittee for Xenotransplantation.

But I do want to thank a number of people, three of them right here and two of them over here. Gail and Rosanna have been terrific. You've really been a great help. Thank you very much.

(Applause.)

DR. AUCHINCLOSS: But let me just conclude by saying that the most important thing that I've learned over the course of the past several years is the extraordinary contribution that I think that the people who work for the FDA are making on behalf of all of us. I really do believe that the dedication that they bring to their job is everything that I would like to think a public servant brings to his service to the country. And I think this is an extraordinary group of people, not only the three people here, but others further back behind the table. Thank you.

(Applause.)

DR. SIEGEL: I will keep it quick. Just to say, first of all, it's not bittersweet for me at all

because, as you know, when someone does as good a job as you do, you don't get off the hook so easily. You are back. You will be back I am sure in the future, as well as in our Xeno committee, and we much appreciate that. You're now in the core of distinguished alumni.

I also would like to quickly note a couple of things that some folks may not appreciate. One is the amount of time Hugh has spent not just on the topics in these meetings but reviewing our scientific programs and asking the same penetrating questions of our researchers and providing the same insight and advice and help in that setting that he has in dealing with both the sponsors and the FDA through advisory committees.

A second and important issue, Hugh, also is that, regarding those last remarks, I have heard indirectly that you have spoken among colleagues similarly about the importance of this advisory committee and those like it and what the agency does, and that has, I know through the grapevine, significantly facilitated our ability to assemble the types of scientists that we have here today. For that as well, we really appreciate it.

(Applause.)

DR. NOGUCHI: I will keep my remarks really short. I think, Hugh, you have brought to the committee exactly the type of discussion, courage, and debate that we

look for. All of us never agree on anything all the time, but that's what we have advisory committees for. In the old days we used to say, I'm from the FDA and I'm here to help you. But I think today the FDA is on the opposite end, to say really, we are from the FDA, and Hugh, thank you very much.

(Applause.)

DR. SALOMON: So, to start this morning's meeting off, I'd like to introduce Dr. Donald Fink from CBER to give us an introduction.

DR. FINK: Well, as chair of the planning committee for this meeting, on behalf of my colleagues in CBER, and including folks from NIH, we have an interesting group in which we have shared resource to help in the planning of this meeting, which has been going on for about four months. I'd like to welcome you to round two.

As a scientist in training, and for those in the audience who are both scientists and clinical investigators, I think yesterday was almost exhilarating in terms of what we heard and the breadth of the information that was made available, and we just appreciate that opportunity. I think in the audience for those who are not of the scientific community, I think you can get a clear vision for how fast this field is going, how complex it is, and just how fascinating. And I am sure the promise out

there is almost hard to resist.

Now, yesterday was the fun day. Today is the brass tacks day, or the FDA day, in which we'll get about to a little more business at hand in addressing questions that have been crafted by the committee. So, having done that, I would like to also thank the audience for their participation and remind you that, as certainly our most important constituent and consumer, this is your direct access. You can cut out the middle man today, come to the microphone, and share your thoughts. It's a wonderful and dynamic interaction that you can have in addition to these well qualified folks here who we are grateful have been able to participate and share of their talents.

I was contemplating, when I went home last night, a title for today, and I want to borrow my title from a picture that Dr. Mahendra Rao showed, and I'm calling it Bridging the Gap from Thursday to Friday. If you remember that classical picture of things that didn't quite fit together. But I think today hopefully our architecture and our energy and certainly our engineering will be a little bit better. So, I am going to try to use my remarks this morning to bridge the gap from Thursday to Friday and lead us into what I hope we will accomplish.

I was thinking about how should I best do this, and I thought, well, I was sitting at the table and said, I

know, for tomorrow what I'll do is kind of give a reprise of the take-home messages. As I started to collect those take-home messages, I realized it was going to take me two trips to do that, so I changed from that. What I am going to do is just give you some reflections or I think kernels that I can remember that seem to be highlights from all of the talks that went on yesterday and try to bring them to the guise of what hope to get to.

I think we all can recognize the fact that stem cells are complicated. I mean, it was just clear as a bell in its complexity. There are many issues and facts and novel discoveries that need to be considered and addressed as we begin this process together collectively of building a strategy for oversight of this product area.

Single markers, a single identity factor. Not enough. Can't do that. We're going to have to look at a variety of characterizations, establish linkage with donor source perhaps, but certainly keep track of where this material comes from, the cell sourcing. And we need to know not only its lineage but its function. It just isn't enough to know that they have a certain phenotypic expression, that they look like something. They have to do something and perform in a certain way. So, that's going to be also part of the considerations.

We know that now in transplanting these cells,

it may not be that the function we envision for them, based on their phenotype, whether they be neuronal or glial, is perhaps how they are going to actually work. The cells, simply by virtue of being there, may elicit responses or secrete reparative factors that can do the trick. I mean, it may simply be as elegantly simple as that. Perhaps not, but it is certainly something to be considered when we go about our contemplating the regulation and oversight of this product and looking at the preclinical testing.

Location, location, location, particularly in the D.C. area, is extremely important. The influence of the microenvironments may be critical. Putting a cell derived from a certain source into different areas can have a completely different outcome, and so it is clear that we need to be considering the importance of those elements.

And finally, I do remember outcome measures was a conversation we spent some length on in terms of being measurable and meaningful. What is the data that we have, how are we monitoring it, what is it telling us. So, those are things that I think that most struck me as being important that I can recall and would bring back to your attention.

Thank you to Dr. Mahendra Rao for his FDA perspective yesterday. It was quite elegant actually. And we appreciate, I think, the fact that a genesis has come

from outside with this group, with the people who are involved in the research and the characterization and the understanding of these cells, that somebody would be bold enough to go forward and put up a straw figure on which we can all sink our teeth into. That's a great starting point and a great place because it tells us not only what you are thinking but how people that are actively involved on a day-to-day basis with these cells and their possibilities, what are some of the most important aspects to what you would like to see a product be.

But I am not going to just let it go at that, of course. What I am going to do is add around that structure, and we will go through just a brief thing of what it is that the questions that we're going to ask later today, we hope to get at in terms of getting some information, input from our advisory committee through its panel of experts as bringing in additional insights.

Source controls. By source controls we are talking about the cell source itself, be it embryonic, be it fetal, be adult, be it autologous, be it allogeneic. We need to know how to best characterize and qualify the source of that material that is going to be used for the product.

Then once we have done that, we have to manufacture them. They have to be made. They have to be

made consistently, over and over again in a way that people can have confidence in. So, we are going to have some issues that are related to manufacturing of stem cells or derivatives thereof, or neuroprogenitors, if you will, that are going to be used eventually in the clinical setting.

Perhaps one of the more critical aspects will be characterizing your preparations. Once you have made them, you have taken them from the source, you have made them, are they what you want them to be and how do you know what they want to be? What we used to establish that we call specifications or setting specifications. These are criteria whereby you perform your qualification tests and you look at your outcomes, and if in fact you meet your outcomes that you have specified in advance, you say, yes, I have the product I want, this is what I am willing to use. And if not, you need to be willing to discard that and start again. It's as simple as that. So, we're going to talk about how to best characterize them, and a little bit start thinking about ideas for setting what would be appropriate specifications for them.

A real critical aspect using biological materials are what we call potency assays. It's a way to say, we know now what we have, we know where we got it from, we know what it looks like, we know what it sounds like, what it feels like, does it do what we want it to do.

We have to have some functional assessment of that.

Now, these can be broad in their scope. I do not want you to think of it as just simply having to go back into an animal or a model that has a condition. We can talk about surrogates or indices of activity. It can be an association between a marker and a known function that we know the marker shows up as a functional correlate and that can be used to tell us with certitude that, in fact, these cells will perform biologically once we have stuck them into the patient. Now, that may not have an intended effect, or the outcome may be negative, but at least we know that when we put them in, they have an activity. So, it's part of describing the quality of what it is that we are trying to use in the clinic.

I think we also heard that animal models in preclinical testing are important, and they are also very variable. We have bandied about the term "gold standards" for asking whether or not there may be models that are already in place, that are already well characterized. We don't have to reinvent the wheel, that we can rely on in certain disease indications or conditions that will give us the information we want in a preclinical setting.

But it also appears that there are many levels of these models. Some of them may not necessarily be in whole animals. Some of them may be in a different activity

type of paradigm. It may not be a genetic animal. It may be something that's done with a chemical to create a lesion. So, there is modeling, and it is an important preclinical assessment in terms of providing safety information before we enter into the clinic in order to begin those initial trials.

I think a big question that always comes out that I have heard is tumorigenicity, or maybe not tumorigenicity, but the ability to form clustered masses of size in places where you don't want them and to exert influences that aren't desirable. I think we heard that in several points, in several different places, and it may be variable depending on your source of cells, whether they were embryonic in origin or adult in origin. Certainly in number. How compact were they put in, do they coalesce. And I think it's an important aspect with the stem cells with pluripotency and potentiality, and we know the ability to proliferate in order to get a handle on whether or not this is an issue that is going to be of importance and may have an adverse outcome.

And finally then, there's consideration of what we call the post-implantation cellular fate. We have seen, I think, just some outstanding abilities to track cells, to visualize them, to identify cells that have been put into a recipient, be it a model or eventually into a patient, as

to where those cells are, what are they doing, how are they behaving, do they survive, what is their fate. Integration is a word that we've talked about. We've heard that once you put in stem cells they seem to integrate seamlessly, they migrate and locate. What does that mean? How is that established, and is that integration simply structural or is it functional, and are there actually contacts being formed and interactions within the host environment that function in a way that is something that we might be able to predict and assess.

So, these are the lists of things that we'll try to bring out in the questions, and we want you to begin thinking about this morning as we go forward.

To wind up this little presentation, again, I am bridging the gap. Hearing from the public. I think I raised that earlier, is important. We listen with ears wide open when you stand at the microphone. The statements that people make from the public, be they from patients, be they from interested individuals, be they from people in regulated industry, are profound at this point. It's the beginning of a process, a strategy, development, a blueprint formulation of a plan to hopefully, efficiently, as well as effectively, regulate this really dynamic area of a novel biologic therapeutic for the clinic.

Finally, on to the questions. Now, I know that

the community members are saying, but wait, didn't Dr. Gage answer our questions yesterday in his presentation? Well, yes and no. The questions that Dr. Gage answered actually, for those in the audience, was a list of questions that was provided by the working group to help the presenters formulate their ideas around how best to structure their talks, and he did a remarkable job. I can tell you, Dr. Gage, people came clamoring afterwards from the agency and say, oh, my gosh, we've got to get those slides, we have got to have those. So, they were really relevant and very important.

But now for the committee we have their questions, which we hope to delve into deeper detail on the issues that I highlighted in the previous slide.

Finally, so that they can't escape anonymity, I know that they were listed in your program, but this is public acknowledgment of all my collaborators that served with me over the last several months to put together this program, and who suggested the names of these people who have been here today and yesterday, who have made such marvelous presentations and for our participants. And I can tell you from sitting and listening to the depth and the breadth and just the enthused responsiveness of our participants, their expertise is without question of the highest level.

Again, Dr. Salomon, your management of the chemistry here has been excellent and we've had a wonderful debate, even though somebody said it looked like we were setting up the Hatfields and McCoys across-the-river shots here. But you've done an excellent job in addressing issues and in speaking to them.

As I close now, I am going to invite one of our committee members from the NIH, and that is Dr. Arlene Chiu. She, along with Christina Borror from the Office of the Director at NIH, but Arlene herself is from the NINDS, to make a few remarks regarding NIH, its interest in stem cells, and its interest in funding research in this area. With that, Arlene, you may go ahead.

DR. CHIU: Thanks, Don.

Obviously, everybody thinks this is a tremendously exciting meeting. I just want to take a few minutes to, first of all, personally thank Don and the FDA for allowing me the privilege of serving on this committee. It is a great example from you of how different government agencies can come together and cooperate and be productive, as well as having a very enjoyable experience.

Although the responsibilities of these different agencies are very different, we share areas of common interest, and stem cells is clearly one of them.

The mission of NINDS, just to bring this up to

the front, is specifically to reduce the burden of neurological disease and stroke. Stem cells, those that produce neurons and glia, as well as those that can in any way promote the restoration of function, is clearly of the highest interest to us. Our support in this area of research has been strong, and continues to be strong, and will be even stronger in the future as more data, more results come out that could lead to preclinical and clinical trials.

But we also want to remind you that we fund both basic research, the biology of stem cells, all the way to clinical trials, and this is a huge umbrella. And as a member of the panel pointed out yesterday, we need advice of how to spend the money, how to allocate resources. We have been blessed by Congress giving us increases in the last few years, but it is still not enough to fund everything. So, I hope in today's meeting, with the discussions, you will help us identify areas of highest priority so that we can go back to the institutes and then work with you to bring stem cells, the most promising ones, to preclinical and clinical trials.

Just to conclude, I'd like to end with two thoughts. The first is that everybody mentions the important link of preclinical testing. However, I have noticed personally that when these grants go to study

section, they die, and they die because they may be minimally hypothesis testing and they may not be the most creative in terms of approach. I also want to remind people at the table that many of you are the reviewers, and when you put on the reviewers hats, please remember what you have heard at this meeting, that you have very strong impact on what gets funded.

So, when you talk about models and you talk about comparing cell types, those are by themselves maybe not terribly interesting studies to bring to study section, but nevertheless of enormous importance.

The last thought is that in moving toward our common goal, no single agency can do all that needs to be done. So, I want to extend a personal welcome to the possibility of greater interaction. That's even partnerships between the NIH, other government agencies, private patient advocacy groups, and industry so that we can do this together, that we can share information, what we do know, share ideas, and maybe split the task and come back together again.

Thank you very much.

(Applause.)

DR. SALOMON: Thank you very much, Arlene. That was great.

What we are going to do now is go to the open

public hearing portion. There are several people who have asked to speak and I will call them in the order I was given, and no particular order of priority, however, is implied by the order I am going to call people in. I am going to keep it to the point. Five minutes or less, unless there's some compellingly important reason to go longer. The first person would be Valerie Estess, from Project ALS.

MS. ESTESS: Thank you, members of the advisory committee for inviting me to speak to you this morning. My name is Valerie Estess.

On March 26, 1997, a neurologist told my sister Jennifer, who was 35 years old, that she had ALS. He told her that her motor neurons were dying and would never be replaced. He told Jenifer that she would die from ALS, because it is always fatal, probably within two to five years. He told her that ALS is a neurodegenerative disease for which there exists not one effective treatment, not one medicine, not one intervention.

Three years later Project ALS, the nonprofit organization founded by Jenifer, my sister Meredith, and our friend Julianne, has funded research that is yielding exciting pilot data. What the data suggests is the stem cells may indeed replace motor neurons and other support cells destroyed in the ALS disease process. Today Project

ALS is riding herd -- and I mean that -- on a true working partnership between stem cell biologists, experts in motor neuron generation, motor axon biologists, and ALS researchers-clinicians.

On the strength of Project ALS funding, the laboratories of Evan Snyder, Jeffrey Rothstein, Robert Brown, Thomas Jessell, John Gearhart, Marc Tessier-Lavigne, and Steven Goldman comprise a collaboration designed to identify any and all possible roles for stem cells in ALS. Project ALS has launched rigorous investigations at all levels in these laboratories and will not rest until we have thoroughly tested the safety and viability of stem cell replacement in ALS.

It is the ultimate aim of Project ALS to deliver the best stem cells to people who are dying. To that end we will continue to exact best efforts from our scientists, recruit new talent from the research community, and seek a constructive relationship with FDA.

There is no disease more lethal than ALS. It is torture without interruption, a prison camp. It is nature at its worst.

Given their apparently limitless potential to heal, stem cells may represent nature at its best. We urge that the FDA, NIH, Congress, the world's gifted scientists, and all Americans who have been or will be touched by brain

disease and injury work together to free the world from prison.

I believe, Project ALS believes, that ours is a nation of wisdom and compassion. Starting now, let us carry the flag forward with a new dedication, for there will be no help for the sick and dying until we work together to bring the best basic science home.

Thank you.

(Applause.)

DR. SALOMON: Well spoken.

The next person is Dr. Darwin Prockop from Hahnemann University.

DR. PROCKOP: Dr. Ausim Azizi and I came here with several rather specific questions about moving from laboratory experiments to clinical trials. It really kind of addresses several specific problems which I think are of general interest in terms of the very nice discussions we had yesterday about the whole topic of stem cells.

So, just to quickly review what Catherine Verfaillie said yesterday, we're dealing with cells, which the name is a little bit still ambiguous because of the history of them. The cells are isolated in most laboratories by a very simple technique of putting whole bone marrow in a tissue culture flask and washing out the hematopoietic precursors. After one or two passages, these

cells are quite pure, they're free of hematopoietic cells, and they have this potential to differentiate into a wide variety of tissues. This is not new. These data are over 20 years old and repeated in many, many laboratories over the years.

Our own approaches were to look at these cells injected into animals. In one series of experiments, we introduced them intravenously, with two different markers indicated there, and we found in mice 1 to 3 months later, somewhere between 1 and 20 percent of the cells in a variety of tissues were derived from these injected cells. Some of these cells took on the phenotype of the tissues.

Now it's an old concept. A beautiful treatise in 1867 by a German pathologist Cohnheim suggested in wound healing, this is what happens. A subset of cells are mobilized in the marrow and become fibroblasts in wounds. So, we think of it as kind of a vestigial pathway that's been there a long time, of course, but only detectable by the latest techniques.

The second series of experiments prompted by Dr. Ausim Azizi, who is here, we infused the cells in the brain. We have several different markers indicated here. We are certain that some of the cells become astrocytes, and yes, we said here perhaps neurons. We are now more certain some become neurons. So, in response to some of

the questions raised yesterday, this is kind of result that's difficult to believe unless one looks at the data. We've repeated these experiments now for about 3 years and totally convinced ourselves.

In a third series of experiments, we have tried to take these cells and create an animal model for Parkinsonism. We introduced two genes that produce L-dopa using a retrovirus in a standard model for Parkinsonism, a rotational model. We got a good response. We could show synthesis of dopamine in the brain. We can also rescue the phenotype of rotation. We had a flaw in our experiments in that we used a retrovirus that since has been known to call inactivation because of methylation of those sequences.

In pursuing a solution to these problems, in fact two of them, one is to use a self-inactivating retrovirus, and the other is to introduce the genes by electroporation. It turns out the inefficient technique of electroporation is now open to us because we can amplify these cells at an absolutely unbelievable rate. Simply putting these cells in very low density, not 1,000 or 5,000 cells per centimeter squared, but 3 cells per centimeter squared, we can make them grow at arrays indicated here. In 2 months, we readily reach 50 population doublings.

The key here is that by plating at low density, we retain the cells you see on the left here at two

different magnifications. Extremely small cells, 7 microns in diameter, almost no cytoplasm. But as those cells deposit in culture, they give rise to clones where you have the larger cells you see on the right. In a way these cells make their own feeder layers, is what we're seeing. They make the large cells to which small cells then grow.

The number of the cells we can make I still find staggering. Three passages over 6 to 8 weeks, from 20 ml of bone marrow aspirate, we can make a total of 10 to the 13th cells, and the key measure here, surrogate measure of multipotentiality stays there. So, we can make 10 to the 13th multipotential cells in these cultures.

So, for those reasons we're optimistic in pursuing these cells with two general strategies. Cells from bone marrow aspirate, expanded, engineered in the laboratory, systemically infused for systemic diseases, particularly diseases of the skeleton, into the central nervous system for diseases of the central nervous system.

Now, I have an updated obsolete technology here I'd like to use.

The advantage of these cells are simple. We can get cells from the same patient. They are multipotential. Our laboratory, Catherine's laboratory, other laboratories are convinced they can differentiate even into astrocytes and some neurons. We can't say all

neurons, we can't say they make connections in the central nervous system, but clearly you see some neurons. And we can rapidly expand them so we can manipulate these cells without the need of a virus.

Now, specific questions that we've come here with. We need the help of the FDA, the panel, and I think the whole scientific community. We tried to say how are we going to go from these results to therapy of disease like Parkinsonism. So, how much do we need to characterize these cells? We certainly don't know all about the nature of these stem-like cells, and we certainly could spend a long time further characterizing them by microchip techniques, a whole bunch of things. We don't know how exactly to differentiate them in many cases. And again, we could spend a long on time on that. How much time? I think we're talking years, many years.

But the real question is whether, from what has been learned about these cells over a 20, almost 30-year period, can we go ahead? Can we do the kinds of procedures I have said to make the cells produce L-dopa, which becomes dopamine in the brain, and then can we go on to toxicity studies and efficacy studies?

As Rusty brought out in his presentation, right here is the major question: Do you use human cells in incomplete or difficult animal situations, or do you use,

say, in rat rat cells and in monkeys monkey cells?

Ausim Azizi has shown that human cells in rat brain do survive, but they obviously don't do as well as rat cells. So, we have a question of how to sort that out.

Toxicity in rats and dogs is reasonable. How much do we need in the way of more elaborate, costly toxicity studies in monkeys? Don't know.

And again, questions from yesterday. What are the assays? There is no indication that these cells make tumors, but maybe what we need to do is extended, many-month, and maybe many-year studies to see if we do get to tumors. No indication of it, but how do you really rule it out?

Then the efficacy. The rat model is a well-accepted model, working well in our hands. Do we go to the monkey models? Well, they have many problems. Extremely. Jeff here knows a great deal about that, in setting up the monkey model. We have had experts give us answers on both sides of that question. Yes, you need extensive monkey model testing, others say no. If it's a serious disease, you don't really need that.

In the end here we are convinced -- certainly I am convinced -- we don't want to deal with mildly affected patients in early stages of the disease. I am very much committed to the idea that you look at the very severe

patient before you try something as new as even this.

In terms of Dr. Sugarman's presentation, we would love to have a consensus on this, how to go about this, and the help of the FDA and the whole scientific community. But I must say I am pessimistic about a consensus because of an experience we have had in using these cells there are different clinical problems. I would like to just take a couple of minutes to tell you that history.

In 1966, we presented data in mice with these cells, showing they were nontoxic and there was some efficacy in a mouse model for brittle bone disease, osteogenesis imperfecta. We made the model of a mutated collagen gene, which we and others had shown produces severe brittle bones in children. Based on those data, Malcolm Brenner at St. Jude's in Memphis suggested we go ahead with this therapy, take a patient with severe OI -- or rather he and his colleague go ahead -- do marrow ablation, and then transfer whole marrow to a matched sibling. Standard bone marrow transplant.

I was sort of involved in providing initial data. I felt very uncomfortable about this because marrow ablation, of course, is a very serious procedure. I called a meeting in Philadelphia, attended by over 100 people, experts in this field. It was the most tumultuous

scientific meeting I've ever attended. Words like "outrageous," "unethical" were bandied about in the air. I could not get a consensus. People from the bone marrow transplant field were on one side of the room, microbiologists were on the other side of the room.

Malcolm Brenner and Ed Horwitz, who began work on this project, went ahead with it anyway. They did 5 patients. They reported last year that all 5 showed a decrease in fractures, increase in growth, and increase in bone mineral. These were extremely severe patients. They had to be propped up in bed with pillows because they would break bones just rolling over in bed. These results were encouraging, but Malcolm presented it at a meeting on OI last summer, and again he was criticized very heavily.

But just at a meeting held two months ago, he presented another series of results. He took the same patients, the same donors, and gave expanded cultures of these cells. So, the patients now had the immune system of the donor. He reported that in 4of 4 patients there were no toxicities. The patients at this stage are 4 to 6 years old. 3 of them stood for the first time, a very rare event in this serious form of this disease, and 2 took their first steps.

I'm not sure that even those data are going to convince everybody in the field and give us a consensus,

but we think they set the basis for this kind of plan, taking cells from the patient, gene-correcting them with the techniques I've talked about briefly, and bringing them back to the same patient, this time without marrow ablation. But it's in that context that we invite help and discussion from the whole community to see if we can reach a consensus as to what's the wise thing to do.

Thank you.

(Applause.)

DR. SALOMON: Thank you, Dr. Prockop. Just one quick question. In addition to representing yourself and your lab at Hahnemann, are you also representing a company when you repeatedly use the word "we"?

DR. PROCKOP: No, I am not representing a company. We have been approached by several companies. I have started a company in a different area, I should say, totally unrelated to this, but I have found it's a very strange, complicated game to deal with companies on these issues.

DR. SALOMON: We're just sensitive. Just wanted to know.

The next person is Richard Garr, from NeuralSTEM Biopharmaceutical.

MR. GARR: Good morning. Thank you for this opportunity to address the committee exploring the status

of stem cell research as it applies to neurological indications. My name is Richard Garr and I am the President and CEO of NeuralSTEM Biopharmaceuticals.

As our name implies, we are a CNS stem cell company and we are in fact the owners of the U.S. patent on the isolation, expansion and culture and differentiation into functional neurons of human CNS stem cells. Obviously, we have a great deal of interest in your topic today.

Briefly I will tell you that our cells are different in many ways than the cells you have been hearing about. Whether or not they are stem cells or progenitors or precursors, while of academic interest, is irrelevant, I think, to the important questions that you are learning about. What our cells do is they turn into functional human neurons all the time, every time, and we can do it in vitro as well as in vivo. We can grow all different types, all different phenotypes, dopaminergic neurons, cholinergic neurons, spinal motor cord neurons, and we do this without inducing the phenotype. This is constituitive from the cells. That technology is also the subject of an issued U.S. patent.

The doubling capacity of our cells without genetic manipulation is roughly about a billion-fold, and we can completely control the expansion phase, as well as

the differentiation phase. The cells are extremely well characterized. We do know all about these cells. We do know how to control the differentiation of these cells.

And I bring this to your attention because I think that in this area, in particular, there is a great deal of expertise and knowledge in the private sector and that you need to reach beyond the usual suspects in academia to really educate yourself as to where this is. In one of your introductory remarks, the gentleman talked about how fast this field is moving. Well, I can assure you it's moving much faster than any of you are aware of.

We have in the past year licensed our technology to major genomics and drug discovery companies. We have chosen not to publish, outside of the patents that have been published, for business reasons. However, several of your presenters here are very familiar with our work. And as the patents are now published, and even as some of the data you saw the other day suggest, there are probably a great number of labs that are actually working with the cells.

Because of the unique focus of our company, and because of the commercial resources that we have had access to because of our genomics and drug discovery deals -- and in fact, I believe we will probably announce the major global transplantation partner, pharmaceutical company,

this summer -- we have already spent a great deal of time and effort on many of the preclinical and product development issues that you all are beginning to consider.

Clearly, the technical questions about models and product efficacy and safety are crucial to even thinking about moving this technology forward into human clinical trials. But I think it's also obvious that the expertise and experience exists to evaluate and create standards which will adequately protect the public's interest. Dr. Gage's insightful and direct consideration of these questions the other day is itself an excellent starting point.

There was also no question that the science will be there. Clearly, within the next 12 to 18 months, in addition to ourselves, there will be companies that will be coming before the FDA that have in their minds worked out the manufacturing GMP issues, worked out the model issues, worked out the efficacy and safety issues, and in their own minds feel that they have compelling evidence to move forward into human clinical trials, at least in the CNS stem cell area.

I think that the most difficult areas for us have been addressing issues of donor privacy, donor consent, and other tissue sourcing issues. There is an extremely fragmented regulatory, legislative, and ethical

framework that exists out there right now with respect to these issues. I think that I would urge you to accelerate a robust public education on and debate about the ethical issues involved in tissue sourcing, and particularly donor privacy. This needs to happen sooner rather than later because again, I think as you're going to find out as you move through this process, as you expand your educational reach out into the private sector, this is much more imminent with respect to CNS stem cells than perhaps your first glimpse is showing you.

I want to thank you again for the opportunity to address the committee.

(Applause.)

DR. SALOMON: Thank you very much.

I guess this is a personal comment, not a comment as the chair of the committee, so please take it as that. My response to that is, if we're calling for a public education, an acceleration of the process toward clinical trials in this area -- and I think most of us would be okay with that process -- the fact that companies are making supposedly major strides in this area but not publishing anything -- again, I provide you my personal comment and not in any way a comment from the chair. But there is some contradiction in that. So, I would urge companies to really step up and do their part of this whole

process, which is critical, I think.

DR. KOLIATSOS: I think we should all say I support you fully in that sentiment.

DR. NOGUCHI: Dr. Salomon, I'd also say that the FDA is always open to interactions with everyone at any stage of the product development cycle. We, in fact, would urge you to come in earlier rather than later, especially as we're talking about issues of product characterization and preclinical studies.

I would say that the FDA does have expertise in the use of autologous and other cellular therapies. We have licensed an autologous therapy. We have a full CMC section for advice on how to do that. It's the details of the more complicated neural stem cells that we're talking about. But rest assured, should anybody have proposals, we're ready to entertain them, but we also want to get as much advice as we can at the very edges of the cutting edge of the science.

DR. SALOMON: The next speaker is Dr. Curt Freed from the University of Colorado. Dr. Freed I have given 10 minutes to because I think he has some really important clinical experience doing cell transplants in patients that I think is important.

DR. FREED: Dr. Salomon, thank you very much for giving me the chance to talk to this committee. I have

enjoyed the discussions and also the individual scientific interactions that I have had with committee members. It is a tight group of folks that do this kind of work, and it's a pleasure to see so many of the people here.

I'm going to talk to you about this double-blind fetal cell transplant trial which we have just completed with Stanley Fahn of Columbia University in New York and Dave Eidelberg because I think it illustrates -- while not stem cells, it illustrates the use of a cell substitute or alternative to drug therapy. I think you will see the interplay between drugs and cells in this presentation.

We are transplanting embryonic dopamine neurons from week 7 to 8 post-conception abortuses which we recover from elective abortions. In order to put tissue into the brain, you have to have it in a form that can actually be put into a needle. We have chosen to make strands of tissue, and you see this tissue strand being expressed from a glass cannula. This has proven to be a method that provides reliable delivery of tissue.

This is the second patient to receive such a transplant. This was back in 1994, before we actually started doing the NIH protocol, and he actually has four small incisions in his forehead that represent four needle passes into his brain. Parenthetically, I'd like to say

that this man is the first man that we have had get off all medications for Parkinson's. That was a year and a half after transplant. He has been off all medications for 4 and a half years. He received tissue from two embryos, one on each side of the brain, each subdivided in half.

This shows the MR scan with the traces of his needle passes through his frontal lobes, one, two, three, four.

Based on these studies and other work, we proposed a double-blind placebo controlled trial with 40 patients aged 20 to 75. The youngest was actually 34 but the oldest was 75. You had Parkinson's for more than 7 years' duration. As we talk about animal models that mimic human Parkinson's, I don't think anyone would have kept an animal around for 7 years prior to transplant. The typical patient had almost 14 years of Parkinson's.

All patients had to be L-dopa responsive, with fluctuations, namely being frozen and then having excess movements.

20 patients received implants, 20 placebo. In addition, we divided the recruitment roughly equally to patients under age 60 and over age 60, and then we also paid attention to disease severity, age, and sex in distributing the patients.

The patients were evaluated at Columbia and had

fluorodopa PET scans done by Dr. Eidelberg on Long Island.

There were lots of results but I am going to just highlight a couple. Motor UPDRS off scores, a standard measure of Parkinson's; high is bad and low is good. When we looked at the sham patients, we saw no evidence of a placebo effect over the 12 months of this trial. It was a baseline period, then people looked at 4, 8, and 12 months after surgery. For the transplant group, there was a highly significant difference compared to placebo, and I believe that is at about the .01 level.

Very interestingly, when we subdivided the groups into the preassigned under age 60/over age 60, the improvement occurred in the under age 60 group. The over age 60 group as a whole did not improve. 7 out of 10 of these patients improved; 1 out of 10 of these patients did.

We had as a primary endpoint a very subjective variable. It said at 12 months, how do you feel? Are you better than you were before? And much better was plus 3, and much worse was minus 3, with 0 being the same. What we found in this distribution was that, in fact, the young transplant group had the largest change in this value. However, you see all patients on average felt that they had improved. So, this is the only demonstration that we have that there is a placebo effect when you ask a very global, subjective question as opposed to an objective measure of

neurologic condition.

I might add, those data were not significant. However, when we looked at these data at 4, 8, and 12 months after surgery, as you saw the other data, there was a significant difference between the transplant group and the sham group. But again, our decision prior to breaking the blind was to look only at the 12-month data.

What happens in the long run? This is 36 months after transplant. Same scale that you saw before. What some of us had observed almost for a decade is that patients improve over time who have transplants. Transplants are a dynamic process, with fiber outgrowth continuing over a period of years.

So, if we look at the average transplant patient, shown in green, this was the blind phase you saw before, and then by 18 months after transplant, you see a dip here. You say, why is there a sudden dip? Is this a placebo effect with people catching up? Well, there was another important effect. Some of these patients had become dyskinetic, and yet their drugs were kept constant.

At this point drug reduction was allowed, and then, as you'll see in the next slide, drugs were reduced and the overall motor UPDRS off value has improved. Younger patients have done better than older patients, although now as we have more patients -- this is a year-old

graft -- as we have more patients out here at 36 months, we're finding that there's been progressive improvement in the older group as well as the younger group.

The total daily drug doses are shown on this slide. The typical dose is about 1,000 milligrams of L-dopa or equivalent drugs, and by 36 months after transplant, that drug dose has been cut in half. While the drug dose reduction is interesting, it still complicates the use of neurotransplant therapy in that we have drugs playing together with the cell therapy, and it makes juggling the two therapies simultaneously difficult.

Will the transplant survive? This is a fluorodopa PET scan. The red shows the normal dopamine uptake in the striatum, caudate, and putamen. Typical Parkinson's patients have fluorodopa uptake in the caudate but much less in the putamen. Here is a transplanted patient with fluorodopa uptake very closely resembling normal. Sham surgery patients had no change in that signal. 85 percent of transplant patients showed detectable transplant growth by a blinded rater. There was only 1 out of 20 false positives.

This just quantitates that PET scan data, and the point of showing you this is that the implant group had this change, the sham group had, if anything, a reduction. In the sham young patients, that reduction was significant.

So, this is rising. The ability to store L-dopa in the brain is rising and the natural tendency through the natural disease tends to be falling.

Well, you saw that only young patients responded. How did the transplants grow in the elderly? These are the under age 60 group, change in PET scan, significant. Old implant group, change in PET scan, significant. So, the transplants grew equally well regardless of age. This was a striking finding. Namely, the aged Parkinson brain can support fetal dopamine neurons and their outgrowth, a remarkable result of this study, and one that we were perhaps somewhat surprised but still delighted to see.

So, the failure of transplant effects in older patients must have something to do with other kinds of brain disease or downstream events from the transplant.

When we correlated the change, in this case improvement in UPDRS score, with the change in how well the transplant grew -- this is in younger patients -- we saw a significant relationship between the growth of the transplant and the change in neurologic score.

We've had 2 patients who have died of causes unrelated to transplant in the year since surgery. I am going to show you a pathology from a man who died 3 years after a transplant of a heart attack at age 71, one of the

older patients. This is a glial scar in his transplant tract. Here's the caudate, here's the putamen, our only target. No patient was immunosuppressed in this study, so the growth that you're going to see of the transplant is without immunosuppression.

So, this is the transplant that you saw glial scar with. You notice you're not really seeing a central line here, even though this is where all the cells are. But the fiber outgrowth from the transplant is so extensive that you lose the transplant tract, and in fact this man has filled his posterior putamen -- well, his putamen up to here with fiber outgrowth.

The caudate, interestingly, the untransplanted structure, has only a thin rim of tyrosine hydroxylase fibers. He has lost nearly all of his intrinsic nerve terminals. Ordinarily this is preserved and this is lost. So, all he has is the transplant.

Adverse events during the course of the study. We had no surgical complications that required breaking of the blind. There was one asymptomatic hemorrhage. We defined serious adverse events as events that required hospitalization or cause death. There were 8 such events in the real implant group, 1 in the placebo group. Other adverse events, including development of dyskinesia, were not regarded as serious adverse events during the course of

the study, and they were equally distributed between placebo and implant patients, although dyskinesias themselves, excess abnormal movements, were more common in the implant patients but for the most part responded to drugs.

And then this slide just summarizes the specific adverse events to show you what they were. We felt that they were usually not related to surgery. So, the needle track hemorrhage was clearly related to surgery but did not produce symptoms and, thence, was actually not called a serious adverse event in our definition.

There was a subdural hematoma that appeared as confusion 2 months after transplant surgery, and again, in that patient the confusion responded to reductions in drug therapy. A woman died in a motor vehicle accident. A cerebral infarct, myocardial infarction happened in two people within the first year. Wrist fracture from a fall, so forth. The sham patient, only 1 patient, was admitted in that case for a hysterectomy.

There is an elective shoulder surgery here which was made possible by the fact that the transplant produced a reduction in Parkinson dyskinesias, which made it possible for this woman to undergo shoulder surgery. She has since had dyskinesias develop that were at least as bad as before surgery, and she's 1 of 2 patients with

severe late dyskinesias despite elimination of drug doses. There are another 2 patients who have had some dyskinesias following substantial reduction of drug doses. So, 4 of the 34 transplant patients have had long-term development of dyskinesias.

Thank you very much.

(Applause.)

DR. SALOMON: I have one quick question. The graphs that you showed with a significant decrease in drug dose, for example. You didn't show the sham, the placebo control there.

DR. FREED: And the issue was, did the sham patients reduce the drug doses? No.

DR. SAUSVILLE: Also a question related to this, any selection criteria for donors, particularly with respect to matching for transplantation antigens?

DR. FREED: We are transplanting tissue from four embryos per patients. It is still very difficult to acquire human fetal tissue now. When we started doing transplants, we did ABO matches, and then we also inventoried results from HLA matches. In the first patients which we did, the first dozen patients which we did, when we looked at HLA mismatches, there was no relationship between the apparent clinical success of a transplant and the degree of HLA mismatch. We have now had

the opportunity to see 2 patients' brains with randomly ABO matched tissue. There does not seem to be a difference in survival based on ABO mismatch in the transplant tracts that we've looked at.

The immunology of transplants is really a beginning field. The fact that we decided to go ahead without immunosuppression was based on animal studies, and so allogeneic transplants in rats and in monkeys showed generally no transplant rejection. It was based on the monkey data that we decided to go to humans without immunosuppression.

DR. GAGE: Related to the charge of this committee, what did you use to standardize the cell preparations in terms of dopamine content or whatever, between patients and between groups? What were the variables that were used to assess equivalency of each batch, as it were?

DR. FREED: There are several issues with preparing fetal tissue. First of all is the standard for dissection, how big a piece of tissue, what age tissue are you going to work with. So, those are the first issues that were standardized. Namely, you have to be confident that you have an intact mesencephalon to dissect. Embryos are always fragmented, so you have to have someone very skillful actually doing the initial dissection.

I think we're the only group that's actually looking at dopamine production of each tissue fragment prior to transplant, and we're doing that via the measurement of the dopamine metabolite HVA, and so we measure HVA production per day with twice weekly testing. We actually put these strands into tissue culture as strands, and we transplant out of tissue culture from 1 to 4 weeks after these cells go into culture.

Actually over a period of time, namely after 4 weeks, we can see a fall-off in the rate of HVA production. So, HVA production within a window is our measure that we're dealing with a dopamine-producing tissue. It also confirms that our dissection was correct, that we don't have something other than dopamine-producing tissue.

We also screen for fungus, bacterial and viral infections. Herpes simplex and cytomegalovirus are both specifically cultured, and tissues only transplanted if those cultures are negative.

DR. GAGE: This is a serum-free medium that you put them in before this week period of time?

DR. FREED: Oh, no. As a matter of fact, this might be helpful to other people working with human tissue that is going to go into humans. We use human placental serum. We found that human placental serum from cord blood is better than fetal calf serum, is better than horse serum

for keeping dopamine neurons alive, and of course has the advantage of being compatible with human use.

DR. TROJANOWSKI: Curt, could I ask you -- and I'll just say that Curt and I collaborate, so I am asking a question that I couldn't have asked last night. We had dinner together and I just want to ask him if he thought, having heard the questions that have been posed by Dr. Fink this morning, which I think are very, very good issues to target -- are we in the right ballpark?

I sometimes worry that if Adam and Eve had to provide all the pallet data to go forward with producing their children, we might not be here today because you can't really foresee everything in the future, which doesn't mean you shouldn't, of course, try to be as safe as possible.

Are we in the right ballpark with our questions, having brought something to human trial from animal studies?

DR. FREED: The question that we used, when we decided in 1988 to do a transplant in a person, was would we change anything about the way we are going to do this in the next year based on anything we could discover in a year. And what was the basis for proceeding? The basis for proceeding was about 8 years of successful research in the rat.

Then we had done some studies in monkeys for the issues of scale, what was it like to transplant a bigger brain. That was largely a scale issue rather than a principle issue.

So, the rats have provided essentially all the principles. What I think is exciting is that the rat model, even though not Parkinson's, has predicted accurately what has happened in all other species after transplant. So, I would say that the monkey is not a necessary model. The rat data is explicitly important, and every time we consider a change, we say, what has the rat told us? And the rat has been right all the time.

DR. SALOMON: I am going to allow the discussion to continue because this is so on point, I believe. I know there are some people over here who want to talk. Tom?

DR. FREEMAN: I think the field of fetal transplants has brought up several salient features for this meeting in particular. The first is from the immunologic point of view, as you have pointed out. Your data, as well as the work that Jeff Kordower and I have done, have shown that now about 20 different allografts have survived in the absence of immunosuppression in four different unrelated recipients immunologically. Then there's also PET data on over 20 patients with long-term

survival without immunosuppression. So, the immunologic aspect of neural allografts is looking very favorable from a clinical point of view.

Secondly, the long-term survival on PET data is looking very, very good, as I mentioned.

Thirdly, these cells are dynamic in nature. For example, at autopsy at 18 months, they have synapses on the shafts but not the dendrites, which is more of an embryonic form. So, therefore, when one looks at efficacy results, the clinical outcome in a month when you start to see benefit may be via a mechanism of dopamine storage, and then the secondary improvement that occurs at 18 months may be related to drug manipulation. There are tertiary changes down the road at 3 years that may be related to synaptic morphologic changes and development to a more adult nature. So, therefore, it is a very dynamic pharmaceutical in comparison to drugs, which are static.

Therefore, when one looks at the late onset of dyskinesias in some of these patients -- and this has also been reported from Sweden, and we have seen this in our group of our open label patients from early on as well -- this suggests that from a regulatory point of view these cells are not static and it is a very dynamic process that evolves over time, and therefore the long-term follow-up of any patient receiving a cellular therapy will be necessary.

DR. SALOMON: I would just like to capsulize that, then, that that's a critical thing for us to think about later in terms of outcome parameters, this time frame, and I think that was well articulated, actually by both of you.

David, and then you.

DR. DRACHMAN: These data, these results are very important. This is really one of the few human observations, but I think it would be very important to get it all right out on the table. Would you describe for us the very worst dyskinetic consequences so that we might think a little more about whether the benefits are worth the risk? As we discussed, one of the negative results came my way and Stan Fahn has spoken highly, widely then. Fill us in.

DR. FREED: Yes, there are 2 patients, as Dr. Drachman was alluding to, that actually had a spectacular initial response to transplant. I will describe a man -- not this patient -- I will describe this gentleman first, a man about 43 years of age who had had bad Parkinson's for more than a decade. When he was off, he had dystonic posturing that was quite uncomfortable, so his hands would be strangely postured. He had difficulty walking as well.

Following transplant, I was at a meeting at National Institutes of Health and this man had been

presented at NIH -- we were unaware of that, it was certainly not a part of our program -- during the blind phase. And two senior NIH neurologists, Tom Chase and Mark Hallett, said, we saw your patient presented and he is on no drugs and he looks normal. I said, isn't that terrific. Maybe this is a placebo patient. They said, if that's a placebo, that is a miracle.

So, here we have a person with an extraordinary response to transplant, off drugs and looking normal. Of course, if we could do that in every patient and capture that moment, we would have finished with transplant evolution.

That lasted for a period of about a year and then he began having abnormal movements of his head. At rest, I might add. When he walked, his ability to walk was better than before surgery, but these abnormal movements of his head made it difficult for him to eat. That required a lot of working with drugs. Amantidine seems to be helpful in that situation.

So, that's that gentleman. His weight has been maintained. He continues to walk three miles a day, but the abnormal movements of the head have continued.

The second is a woman in her late 40s, who was wheelchair-bound prior to transplant, largely from her bradykinetic state because when she took drugs, she became

extremely dyskinetic. So, this woman, several months after surgery, got up in the middle of the night and walked to the bathroom. Then she came back and she woke up her husband and said, I walked. I can walk now. I don't want to make this excessively melodramatic because I am also telling you the down side of these things. So, for about 1 year this woman was able to progressively reduce her drugs and come off drugs. Again, a very remarkable response.

Beginning somewhat after the 1-year point, the lady began having generalized dyskinesias of her limbs, and again, more at rest than when she walked. She actually can still walk and her dyskinesias are somewhat less when she walks than when she is at rest.

What can you do about that? The lady is off drugs, she's dyskinetic. In fact, Paul Green, the neurologist who's doing primary care on these folks, actually went so far as to start her on a dopa synthesis inhibitor, alpha methyl paratyrosine. In fact, the alpha methyl paratyrosine was able to shut off the transplant. But then she became very slow again.

Now, it would be possible to pull the transplant out of the picture by giving a drug that inhibits dopa formation by the brain and then give back moderate doses of dopa. In fact, in her, because there is a surgical strategy that seems quite effective for

eliminating the dyskinetic state, namely stimulators into the pallidum, this lady had last week bilateral pallidal stimulators put into the brain, and we hope that in fact the combination of the transplants, plus an operation that will inhibit dyskinesias, will in fact give her a better control of her Parkinson's disease.

I add to this discussion, all of the patients that we have considered for operation are candidates for a surgical intervention. They have failed conventional drug therapy. So, even with the 2 patients who might be candidates for an additional surgery, not only they but the rest of the patients would have been candidates for some sort of surgical procedure.

Now, if we did not want to see any chance of having an excess transplant effect, we could transplant less tissue. We are now modifying, looking at the total results and modifying our thinking about transplants. One of the things that we're going to do is to transplant only tissue from two embryos into the brain instead of four, and it will be in the dorsal rather than the ventral position. The ventral aspects of the putamen are less denervated than the dorsal aspects.

We're also going to start transplanting the substantia nigra as well as the putamen. Why would we do that? Because rat studies said that combination is better.

We are being led by results in rats dating back to 1989.

So, I see the development of transplants as having been made necessary by the lack of good drug therapy for advanced Parkinson patients, and the implementation of transplantation absolutely tracking what we have learned from animals.

DR. DRACHMAN: That I think clinically really does describe well what happened. What I've got to say, though, is something a little bit different. That is, one must be fully aware that cells when transplanted no longer are under our control. The expression "sorcerer's apprentice" and "Frankenstein monster" have been used by people viewing videos of these cases. Those are very dramatic terms. The point is not to raise that specter, but merely to say that some degree of control, some way of shutting down, may be part of what we really want to think of whenever we put in totipotential, pluripotential, multipotential cells whose growth, whose reconnection, whose secretion may not be what we want because the intrinsic regulatory environment may no longer work in this setting. So, it's not whether this lady or these two or four people did well, but what is the principle we want to propound.

DR. FREED: I'd like to add just to your comment because obviously that's a critical one. With stem

cells, where there is the possibility of a malignant cell, or at least a mass growing, I think it could be very important to have a suicide gene or an immunotherapy. Namely, there is value in having a cell be a foreign cell because you could have a pre-existing kit for immunizing a patient and rejecting the cells.

What I described with our patients is that it's possible to use an anti-dopamine synthesis inhibitor to actually shut down the transplant. We have known from the beginning, we published in 1992 that transplants evolve over a period of years. So, that isn't a surprise.

A surprise and, in fact, a result of doing tens of patients instead of a few patients has been that we can now see 10 percent probability events, whereas when people were reporting 2s, 3s, and 4s for patients, you didn't have enough patients to make it likely that you could see the extremes of response as opposed to a more average response. So, the issue of control is important, but I think it has to be in the context of the biology.

The other issue in the transplant patients is we don't see excess absolute dopamine production on PET scan. That's why I think the issue that we don't have balance in the brain, that we need innervation of the region of the substantia nigra is as likely as not to be a participant in this. It could be the persistent

denervation in the nigra as opposed to excess production in the putamen. We have no evidence for excess production in the putamen.

DR. KURTZBERG: I just had a quick question. Did the engrafting tissue express HLA markers?

DR. FREED: We have seen, in different transplant tracts postmortem, HLA class 2 antigens and lymphocytes in some tracts, even though we see lots of surviving dopamine neurons. That's at 7 months after transplant and 36 months after transplant. There was no apparent relationship between the amount of HLA class 2 antigen expressed or the number of lymphocytes and the number of dopamine neurons that survived. My transplant friends have called this minimal inflammation, and it's in the absence of immunosuppression.

DR. AUCHINCLOSS: Somewhere in the introduction to your talk, and I can't remember whether it even came from you -- I thought I heard that we were going to learn about embryonal stem cell treatment for Parkinson's disease, but what I thought I heard actually was about a fetal cell transplant for Parkinson's disease. Where in that sort of spectrum would you actually place this?

DR. FREED: Well, these are embryonic dopamine neurons. At the time that they are transplanted, they are terminally differentiated. The time for transplant is

selected, as shown in rats, at the time that the dopamine neurons have declared themselves, have differentiated, but before they have reached out axons to their targets. So, they are in the embryonic period as opposed to the fetal period, but they are differentiated cells.

DR. MOOS: One of the things that sounds very impressive from listening to you would be how difficult it must have been to design that clinical trial. You are talking about a treatment that changes over a period of time that we don't even understand. What about the non-treated arm of the study? How long could you leave them untreated?

DR. FREED: The contract with the patients, namely the initial consent form, said that the people who have been in the sham arm could have their transplant not at the end of the study but after their 1-year participation followed by unblinding.

Now, there was some disagreement with the performance safety monitoring board, saying, well, wouldn't it be better to wait till the end? The patients insisted that the contract and the consent be lived up to.

So, 34 of the 40 patients have had transplant operation; namely, 14 of the prior shams have had transplant. That was up to the breaking of the blind in January of '99, and at that time the older patients were

advised this may not be such a great idea for them. The younger patients said, well, maybe this is not a cure for Parkinson's. Maybe we will wait to see what happens in the long run before we decide what to do.

DR. MOOS: So, in essence the original study was a 1-year --

DR. FREED: 1-year follow-up.

DR. RAO: A real quick question. Presumably even though it was enriched for dopamine cells, it must have been a mixed population. When you see the dyskinesia, how convinced are you that that can be attributed really to a loss of dopaminergic cells, or not some other aspect of the fetal tissue that was transplanted?

DR. FREED: Well, the general assumption is that dyskinesias are caused by an excessive dopamine effect, as they are with drugs. It could be some other neurologic regulatory event, though, in that you could say that dyskinesias are allowed to appear when dopamine is present. You see that there could be a difference between those two.

The transplants that have been done in rats, on which all of this is developed, has been the whole ventral mesencephalon. This is a fragment of tissue from human brain that's perhaps 4 milligrams in volume. It's a small transplant. Each of those 4 milligram individual embryo

fragments was put into each of four separate holes. It is simply following the technique. Efforts to isolate dopamine neurons and transplant pure dopamine neurons have failed. There is no way to isolate dopamine neurons without losing the tissue. So, you are transplanting the tissue as it existed in ventral mesencephalon.

There are also studies of survival, of which tissue elements survive. The dopamine neurons do a very good job of surviving in striatum, as do serotonergic neurons. There are a few serotonergic neurons that survive as well. If you transplant cells that would not ordinarily innervate the striatum, they tend to die off, at least the neuronal populations do.

DR. SNYDER: I just briefly wanted to reiterate Tom's point about how important it's going to be for us to really understand the immunobiology of transplantation. Particularly for us in the stem cell field, it's an issue we haven't talked a lot about. But whether or not stem cells are well tolerated may very well influence how we decide to harness this biology for therapy. It will be important for deciding, do we need to do autologous transplants, in other words, adults donating their own cells for reimplantation, or can we really have universal donor cells prepared under GMP.

Much of that issue rests on our understanding

of whether cells will or will not be rejected, which gets down to the immunobiology. The work that Curt and Tom and Jeff have talked about suggests that grafts may be better tolerated, at least if they're young, than we ever might have imagined. Some very early pilot work that we have suggests that immature stem cells, in the state in which we do the transplantation, do not express MHC class 2, and can be tolerated without immunosuppression across strains, at least in rodent recipients.

So, this is a very, very important point that I think will need to be explored very, very carefully and hasn't been as explored in the stem cell field as much as it's going to need to be.

DR. KORDOWER: Unlike a drug trial where you can get uniform delivery of a compound across centers, transplantation trials are dramatically different in terms of parameters chosen, techniques used from one center to another. I spoke with Olle Lindvall recently about dyskinesias in his patients. He said to me that he doesn't see them in his patients. I know he does suspension grafts while you do solid grafts and Tom and our group does solid grafts.

I was wondering whether there are any parameters that you can think of in, let's say, Olle's trial than your trial or Tom's trial that might explain why

you see what Stan is calling runaway dyskinesias.

I think it's also important, when we evaluate stem cell trials, that we understand that it's likely that it's going to be done very differently in very different centers. We've got to think about that as we proceed toward clinical trials.

DR. FREED: Starting with our first graft, our first report in 1990 in Archives of Neurology and continuing to a New England Journal paper in 1992, we said that all patients, or 6 out of 7 patients, developed increased abnormal movements in the months after transplant. Now, that was with transplant of tissue from a single embryo initially on one side of brain, so roughly half the dose that we used in the double-blind study. That responded to reductions in drug dose.

What I think is going on here is the number of patients that we have transplanted. In the double-blind study, there are 34 patients. I think with Lindvall, the total number of patients he's transplanted over the years has only been 10 or 12. So, if you have something with an incidence of about 10 percent, you may not see that with 10 or 12 patients, although I think everyone has seen the tendency for increased abnormal movements if drug doses are kept the same. Some people say those go away if you keep the drug doses constant. We have found generally the drugs

have to be reduced.

But you're absolutely right that there are a variety of techniques. I think that the variety of techniques is helpful to the field because it gives us a range of looks at this physiology without saying this is the way. If we had a doctrinaire philosophy that said this is the only way to do transplants, we would have a much less rich understanding of this field.

DR. KORDOWER: Let me just respond. I agree with you for the most part, although I think the people who are not in this field, they see a paper on transplants and they say, this is what happens when you get a transplant, not appreciating the differences in technique across different trials, which may dramatically impact upon both the positive and the negative aspects that follow the graft.

DR. AUCHINCLOSS: Sorry. The question that I had, I wanted to talk more with Don Fink about the original FDA perspective on this. I think we ought to come back to that.

DR. REID: This is a general question to the panel and to the speakers. Obviously the issue that keeps coming up again and again and is of concern to all of us in the stem cell field is the sourcing issue. What I'm curious about -- certainly we've been facing a lot in the

liver stem cell field, but I am curious about what you imagine being your source in the future for the patient. Is it all going to be fetal brains, or do you have some hope for being able to isolate out the relevant cells from either cadavers or from pediatric or adult sources?

DR. SALOMON: When we come back from break, we will take that up at that time.

Jay, and then Tom.

DR. SIEGEL: Yes, I just wanted to comment on the point of two or three speakers ago, that I would agree both that there is a lot of value in diversity of approaches, but also point out that when you reach the point of doing multi-center trials, there is significant value to come into consensus approaches. We have seen a number in the field of hematopoietic stem cells. There are people who can speak better to that than I can, but suffice it to say, in some of them where there was less investigator consensus, not just about how to handle the cells but how to use platelets, how to use antibiotics, whatever, it's a lot harder to make sense and interpret the results than where there is more consensus.

DR. FREEMAN: A response to a few of the comments that have been made. First of all, the dyskinesias. Olle Lindvall has reported 2 patients, in writing, actually, that have developed increased

dyskinesias. So, it's something that I think everybody has seen in a subset of their patients.

Secondly, it can be related to anatomic issues such as uniformity of distribution throughout the putamen. For example, in Huntington's disease, chorea is not present early, then it develops, and then as there is more burn-out of the putamen, it disappears. So, non-uniform anatomic issues can be involved, such as transplants in the post-commissural putamen rather than the anterior putamen.

Finally, it raises the issues of dosing being critically important for the cells. And for example, our prospective randomized trial has a dose escalation arm. It is these types of systematic base hits I guess has been the analogy du jour. I think we have to look for incremental changes in the field before the therapy is optimized.

I think the paradigm that is relevant is the kidney transplants that were incrementally improved over a 30-year period. And even if you look at success rates around the era of cyclosporine introduction, there was no giant 20 or 30 percent increment. It was still a 2 or 3 percent increment every year over a 30-year period. So, I don't think we should look for these types of home runs right off the bat.

Secondly, from the evidence point of view, from the allograft versus isograft point of view, obviously if

allografts are beneficial there are tremendous advantages from the corporate point of view and the production point of view and the safety point of view. You can use good manufacturing practices on large batches of tissue rather than having individually produced cells.

Secondly, as many of these neurodegenerative diseases are genetic in nature. If you can obviously have a cell source without the aberrant gene expressed, or without the need to do gene therapy with the cells, that is tremendously important.

For example, in our transplants with Parkinson's disease, there was no evidence of Lewy bodies in any of the transplants in our autopsies studied. In a patient with Huntington's disease there was no abnormal expression of the aberrant Huntington protein in any of the grafts as well. So, that would be another important issue.

Finally, from the trial design point of view with the crossover, that is actually not a trivial point. In our study, I think if I was to point to a flaw, we had a crossover at two years, but when you take into account also the time to actually perform the study with recruitment, it is not a simple recruitment. It's a surgical trial, it's not a drug trial. It does not tend to progress as quickly. Particularly in early studies, that can be a burden on patients. I think alternative trial designs need to be

considered earlier on, such as delayed start trial designs so the burden on patients is not as high.

DR. SALOMON: Last two questions.

DR. KARLIN: My name is Dr. Helene Karlin. I'm the President of the Canavan Research Foundation, which was originally started with my husband, Dr. Roger Karlin, after my daughter Lindsey was diagnosed at 3 months of age with a leukodystrophy called Canavan disease. We're a nonprofit foundation. We currently fund research in gene transfer and stem cell approaches to be used clinically.

I would like to thank the FDA and all the scientists for their wonderful presentations and the education it provided me about the current state of stem cell research. Now I do understand that stem cells are not simple. Clearly there is much research that needs to be done in order to completely understand stem cells and their therapeutic possibilities.

I would, however, urge the scientists here in considering regulations to keep avenues open for clinical applications to develop in tandem with basic research. My daughter Lindsey has the distinction of being the first person in the world to be treated with gene transfer. This, amidst a scientific controversy over whether gene transfer was ready to be used in the clinic, in spite of the fact that safety had been demonstrated and efficacy was

a real possibility. Lindsey, who was then 2 years old, improved dramatically on clinical measures, as well as objective measures such as MRI. Eight months after the gene transfer she developed new myelin, which children with Canavan disease do not do.

In spite of this clear improvement, we needed to wait 2 years for a virtually identical trial to be approved in this country. During this time, we had to watch our daughter decline, when we knew that she had already received something that had helped her. When she received gene transfer again in this country at age 4 and 4 and a half, she again improved.

We have now waited over 2 years waiting for a new technology in gene transfer to be approved. Once again, we have watched our daughter decline to the point where the window of opportunity, in terms of the degenerative route of this disease, is just about closed. We've basically stabilized her, we've improved her, but it's a degenerative course, and after 2 years of not having the gene, she's starting to deteriorate again.

As Dr. Noble mentioned yesterday, some patients resort to crazy treatments in nonregulated environments. We're not interested in this. We're interested in good research with safety as our foremost concern. However, we're also interested in the recognition that people with

devastating fatal illnesses have the ethical right to potential clinical treatments in a timely manner. The safety and efficacy guidelines for devastating diseases may not be the same as the guidelines for non-life-threatening disease. In addition, science for the clinic cannot tolerate bureaucratic delays that have to do with such things as people's vacations and the intermittent scheduling of review meetings.

Valerie Estess mentioned the collaborative scientific efforts that private funding is encouraging. We believe that privately funded research, such as the research that we were also funding, can only expand on the science and present opportunities that limited public funding cannot offer. I will mention that Canavan research has received no public funding. Zero. It's all coming from families, and it's quite a lot of money.

I urge scientists to consider the notion that not all the patients out there are dummies. We are educated. We are informed consumers. We know what is going on. We are looking for good research. We are not looking for snake oil, as Jordana mentioned yesterday. I hope that people will consider that in considering regulations and review. I thank you very much.

(Applause.)

DR. SALOMON: That was a little off track, not

that it wasn't perfectly appreciated. I thought it was a question for Dr. Freed.

I think at this point we'll end Dr. Freed's presentation. I really appreciate that you brought another dimension and very on point to the discussion this morning, Dr. Freed. Thank you.

DR. FREED: Thank you, Dr. Salomon.

(Applause.)

DR. SALOMON: I'd like to bring this part of the open public hearing to a close and go to a break. However, I do offer, is there anyone else in the audience who'd like to get up and make a brief comment?

(No response.)

DR. SALOMON: No? Then I certainly invite the audience to participate the rest of the day as we have before, and see you in 10 minutes.

(Recess.)

DR. SALOMON: What I'd like to do now is begin now the most serious working part of the meeting. We've divided the questions that the FDA wants us to address specifically into two parts. The first question is related to product development, and that will be introduced now by Malcolm. Then we won't break for lunch at 1 o'clock. We have got to be done by 3:00 because there is one direct flight out of Washington Dulles a day to San Diego and I am

not going via Chicago.

(Laughter.)

DR. SALOMON: I think I have tried very hard to be very freewheeling in terms of the discussions up until now, but now we have to really focus. I apologize to everyone in advance if I cut you off or move ahead. I only feel like the whole reason that we are here, and tremendous amounts of effort on anybody's part, not to diminish the investment on the part of the government to get us here as well -- they have some questions and we do need to address them. I promise to be fair, and it is nothing personal.

For that particularly, if we can keep our answers on point and ask yourself while you are giving answers. There are lots of fascinating biological and scientific questions that the experts here would want to discuss, and all I am asking is that in the midst of thinking about them, if they are not on point any longer to the questions, it does not mean they are not interesting, it just means that we probably should not be wasting time discussing them now.

With that introduction, Malcolm.

DR. MOOS: Thanks, Dan.

Those of you who have long memories may perceive that I have redrawn this slide slightly and there may be a perceptible alteration in the proportions between

the upper two and the lower two quadrants, based on the discussions yesterday. Notwithstanding this, as Don has pointed out, we now have to get down to brass tacks. Basically when somebody comes to us with a proposal, we have 30 days to make a determination as to whether it represents an unreasonable risk to human subjects or not. And the default position is that the IND goes into effect.

One ground upon which we can place something on hold is what we call insufficient information. So, I would like to enjoin as many of you as possible not to throw up your hands in despair, but to try to come to some considered suggestions that we can use.

Parenthetically, since it was touched on earlier this morning, I'd like to just mention the quadrant that is not really shown up here, which is the quadrant of secret competence. Now, the Founding Fathers considered the protection of intellectual property so important, that it's actually framed in the Constitution. The establishment of the Patent and Trademark Office is there, not in statute or regulation. I didn't really realize this until just a couple of years ago, but we also consider proprietary secrets very seriously indeed.

On the other hand, there are certain matters which are often kept confidential by companies for which an ethical and even a legal argument that they should be is

difficult to maintain. I would like to simply make the statement here that it has been our experience that fields where information is exchanged relatively freely advance more quickly. The old phrase about a rising tide floating all boats definitely obtains here. We not only see everyone's successes, which become public, but we see everyone's failures, which do not. At least not immediately.

If the FDA suddenly starts asking for a particular type of experiment and you can't figure out why, you might start to put two and two together. There are constraints upon what we can say and what we cannot say, but nevertheless there is an eventual percolation of private data into the public domain at various paces, especially as they relate to data involving safety. In certain particular fields -- and perhaps Dr. Siegel and Noguchi can speak to this at greater length -- there are different considerations about what is confidential and what is not.

With that out of the way, I would like to return to the point that Dr. Drachman made with a slightly different analogy yesterday, in talking about the confidence that we have of things being represented as clay, molding themselves however they want. The paradigm I like is that articulated by that a brilliant American

cartoonist, Al Capp, a half century ago. These are the schmoo. These were organisms that were so delighted that anybody might find them of utility, that they would turn into whatever you wanted to eat, like magic, and in unlimited, self-renewing supply.

(Laughter.)

DR. MOOS: So, I think the analogy and the whole concept here is exactly on point.

We need to establish how far we can take this, and more importantly, what we can use to place limits on our confidence or lack of confidence. That brings us to some of the basics, which Don alluded to and I am going to focus on in just a little bit more detail, of how we regulate biologics. And these were the basics that Don mentioned. Source control, process control, and specifications. I am simplifying a little bit too much here, but I want to get through this quite quickly so that we can start addressing the questions.

Source control involves things like who, how old, history and habits if we are talking allogeneic donors. There was some discussion, and we will have more of it, I think, about whether or not there should be constraints on who can donate and whether there might need to be genetic testing of them. Various types of testing, not just the standard microbiology screening that we have

talked about, but HLA matching, other types of tissue matching. And most importantly of all, things that didn't make it to our list that we should be thinking about that didn't occur to us.

Next is process control. For those of you not familiar with our paradigm, this is perhaps one of the most unfamiliar ideas. But really it relates to a very common experience. The analogy I like is candy-making in the mid-19th century, where you could use qualitative tests called hard ball stage, soft ball stage, hard crack stage, depending on whether you were making brownies or peanut brittle, and you would not have to understand chemistry or carbohydrates and caramelization to make use of these tests, but if you followed a consistent recipe, if you were an experienced confectioner, if you knew what your raw materials were, who they came from, you trusted your suppliers, you qualified your supplies, and you used these sorts of what we call in-process tests appropriately, you could generate a consistent product. If you became the sort of a confectioner that everybody might want to emulate, eventually you kept careful records and you might have even made an extra buck by publishing them.

And finally, there are elements of process control that we're beginning to hear about. For example, Dr. Gearhart has mentioned magic lots of fetal serum that

work for some things and not for other things and variability in starting materials. And how you qualify the starting materials? Maybe the tests that you use to qualify the starting materials have their own problems. Or alternatively, what are strategies for getting away from starting materials that are difficult to control. I think this is a technically quite knotty issue that we'd like to hear as much advice about as possible.

Finally, what we call specifications. Some things are very basic. We need things to be sterile. We need the endotoxin levels to be low. We don't like them to be growing mycoplasma and so forth. We know all about that. But beyond that there are some special difficulties with these products that we often don't have as much trouble with with other classes of biologics.

One of the most nettlesome that confronts us I think in this arena is how do you identify your product. It's continuing to evolve in culture with time. It may be heterogeneous. The characteristics which define it unambiguously I submit we probably do not know. Certainly we have been thinking about gene profiling and microarray technology and FACS scanning with as many different antibodies as we can find, and looking at function and so forth, but this is just a start. We heard the number of three markers yesterday, and I am willing to bet a large

portion of my personal assets that it will only be in rare cases that that will suffice to define the identity of a product. I know other examples where 18 markers is not enough, as judged by evaluation and stringent in vivo models.

So, the idea that some people think that you can identify something just by its morphology, even when there are fairly good characteristics, this structure here usually identifies a witch, but it's important to determine whether or not what you're looking at is artifactual as just one example, is really quite premature and inadequate.

We heard about functional testing, which I think is a very interesting and difficult area. One could imagine doing patch-clamp electrophysiology, but then if you are looking at a dish or a lot of cells, what is your sampling paradigm? How many, what kind of standard deviations, what actually is your number, what is your specification? Do you say plus-minus, action potentials, yes-no? Do you place a number on it? Calvin told us that science is measurement. Was it Rutherford who said if you can't reduce it to numbers, I am not interested? I think that is a terrible paraphrase. But nevertheless, that issue needs to confronted.

Dr. Gage mentioned a very interesting idea, that there may be windows of competence during which, or

states of competence during which a product may adopt its eventual fate, or not, depending on what you have done to the cells, how they have been treated, how old they are, how many passages, and who knows what. The importance of this may depend on where you're intending to implant them. Could one envision functional tests to evaluate competence, whether in vivo, or perhaps maybe one could figure out some magic growth factor or combination or sequence of growth factors, and then look at immediate early response genes. One kind of idea.

And finally, the most difficult issue which, like Dr. Salomon, I will refrain from going too far overboard with. I guess I've kind of talked about this already, but then the thought of developing surrogates for potency is something that we'd like to hear a lot about if, indeed, there are rational ways for doing it.

So, with that I will yield the floor to you folks so that we can hear as much as we can about what we need to know.

DR. SALOMON: Thank you, Malcolm.

I know you had wanted to make a set of questions.

DR. AUCHINCLOSS: I guess it's a question for both Malcolm and for Don Fink. It's really a generic issue. This is a generic discussion. The question that I

think you are asking us today is what special regulatory issues are associated with stem cell therapy. But when you put up your list of considerations, both your list, Don, and what we just heard there from Malcolm, they're precisely the same issues that you address in any other form of cell transplantation, or indeed, precisely the same issues that you would address if you were approving a new cytokine or monoclonal antibody, et cetera. There is nothing unique in any of the questions at least in the broad categories of any of the questions that you put to us, and you know how to do that kind of regulation.

So, my first question for you is, what do you feel is really special about "stem cell therapy" that you want us to try and help you with?

DR. FINK: Well, let me take a first shot, and Malcolm, you can follow up if you need. I think probably the one point that we focused in on as a group or a committee is the rather unique and intrinsic capacity of these cells, presumably stem cells with pluripotentiality, to actually become perhaps something different, or maturate following placement within a patient, whereas in many contexts when we're evaluating cells for therapy and characterizing them, we know what they are prior to implantation. We probably have a fairly good idea what they are going to do.

But in this context what we're interested in finding out as much as we can about what we might anticipate, either positively or negatively, to be the case following placement of the cells within the patient, that we cannot perhaps necessarily get a handle on up front, although we can use tests to qualify or characterize them as derived from the source to get some indication that at least this primordial or this prior to implanting formulation will lead to, in fact, what it is we hope to find. I think that's probably the difference or the intrinsically different nature of this product compared to other cellular therapies.

DR. AUCHINCLOSS: Well, I don't think so, if I can comment further on that. It seems to me that it's fully apparent to you that you have been regulating adult stem cell therapy for a long time in the form of bone marrow transplantation. In bone marrow transplantation, you put in cells that are going to differentiate into other cells than the ones you put in, and you're perfectly comfortable with that at this point. Indeed, as I go through bone marrow transplantation, it seems to me -- and I guess I am now going to put this as a question to everybody -- why isn't bone marrow transplantation a paradigm for all of the issues that you are dealing with?

Bone marrow transplantation brings up the

immunogenicity of stem cells. There is no question that outside of the CNS they are exquisitely sensitive to rejection. Bone marrow transplantation involves adult stem cells at least at the multipotent level, probably at the pluripotent level, and yet we don't talk about teratomas in bone marrow transplantation. We don't worry about over-doing it. We don't worry about too much bone marrow production when we do bone marrow transplantation. We have recognized, when we do bone marrow transplantation, that there are different recipient populations, some of which can respond to stem cell therapy, some of which can't. We recognize, when we do bone marrow transplantation, that the population that we're putting in is heterogeneous and inherently so.

So, many of the issues that have popped up in the questions that we're going to be supposedly addressing are ones that you're perfectly comfortable with at this point. So, my question, I guess, would come down to, what's different between the stem cell therapy that you've been regulating for a long time, bone marrow transplantation, and your worry about stem cell therapy in a larger context?

DR. MOOS: Well, there continue to be, I think, both some scientific and historical differences. For quite some time, there was a lot of activity with bone marrow

transplantation, before it occurred to anybody that the practice should be regulated, and there was a sort of a grandfather effect -- go ahead.

DR. SIEGEL: Just as a quick technicality. Bone marrow transplantation per se is not under FDA regulation. With peripheral stem cell regulation, transplantation is, and many other devices and growth factors that are used with bone marrow transplants are. So, from a scientific perspective --

DR. AUCHINCLOSS: You're very comfortable with regulating bone marrow transplantation, is all I am suggesting.

DR. MOOS: Well, with technologies that grew directly from bone marrow transplantation and have many analogies to it. It's also worth noting that even stem cells derived from bone marrow or peripheral blood are naturally occurring, and in only a few cases is it contemplated to manipulate them extensively, and if they are manipulated extensively, that triggers some of our concerns.

There are, I think, to expound on what Don has said, significant technical differences. While we grant that there is substantial overlap between some of the difficulties with other types of cellular therapies, we think that they are enhanced here.

One is that they have a biology that we don't have a lot of experience with. For example, there is a lot of experience with blood-derived cells, which suggests that tumorigenicity is not a serious safety concern, or at least is a manageable one. There is experimental evidence, some of which we heard about yesterday, that suggests that this is an issue that needs to be studied more carefully.

The other one that Don mentioned is that in more than one aspect, therapies based on stem cells represent sort of a moving target. Often with other types of cellular therapies what we are putting into the patient is very similar, perhaps all the way differentiated to what is going to be there, that we can test the terminal function, if you will. Whereas with many types of stem cell-based therapies, varying levels of further differentiation are anticipated, up to the level suggested by Evan Snyder, where you might use extensively manipulated stem cells rather than stem cell-derived products as tumoricidal killer bees.

The other issue is that there are behaviors of some of these cells that, although there is some precedent in other types of cell therapies, perhaps are more dramatic here. One thing that makes us very nervous is the issue of migration of cells, which especially with relatively immature cells seems to be quite extensive. We don't know

yet if this is a problem or if it's just a concern. This is something that we need advice to deal with intelligently.

DR. AUCHINCLOSS: I wrote down what is unique about stem cells on my list yesterday, and I was putting down different things. I had cell migration down there at one point, and I had differentiation down there at another point. And I don't think those are actually the fundamental features that make this a subject for special concern to the FDA.

We know perfectly well that hepatocytes and islets actually migrate all over the place to different places. Migration in and of itself, and indeed differentiation in and of itself, is not a unique feature of stem cells or a unique concern from a regulatory point of view.

To me -- to answer now my own question, what is unique -- what is unique is your concern of unlimited proliferative capacity. I think that's what's unique in the stem cell therapy.

Now, here I am going to now split between embryonal stem cells, where I think we have heard lots about how the unlimited proliferative capacity is a major potential problem, and adult stem cell therapy, where I haven't heard so far any evidence of overdoing it with

adult stem cell therapy.

But then you say to me, as you did yesterday at lunch, well, that is not the point. The point is that what really makes these stem cell therapies different is they're going to take them out and culture them, and they're going to leave them there for 6 months, and a transformation event might take place. Then we might take an adult stem cell and turn it back into a cell with unlimited proliferative capacity. And I think that's exactly the right concern

But my suggestion to you would be that that is equally true if you take islet cells and put them in culture for 6 months, as people may eventually do. There is the potential for a transformation event that becomes a special regulatory concern to the FDA.

My point in all of this conversation is that I think the FDA wants to try and struggle to say, what's special about stem cells? The conclusion I come to is, what's special about embryonal stem cells is a good topic, but what's special about adult stem cells isn't about adult stem cells. It's about any tissue in which you do something that potentially gives it unlimited proliferative potential.

DR. SIEGEL: I think here you're not addressing the question we need to answer. Because the question is

not what is unique. That is a straw man. It is how to regulate these cells. These cells are not bone marrow cells. They are not pancreas cells. We have experience with cells. We need to know what are the right specifications. You're not going to tell us, like some people told us 3 months ago, that insulin secretion is the right specification for this type of cell --

DR. AUCHINCLOSS: Jay, but you know we can't answer that question in a generic form.

DR. SIEGEL: Well, absolutely.

DR. AUCHINCLOSS: How can we possibly sit here and tell you how to regulate these cells when there are going to be 150 different --

DR. SIEGEL: Well, that is right, and that is why we've been talking about what the various issues are for various types of cells. That's what here for, but we're not here just to focus on what is absolutely unique or different.

DR. AUCHINCLOSS: Yes, I think you basically asked us to talk to you about what's inherently different, what's generically different about the regulatory issues associated with stem cells. I don't know how to have a generic conversation any other way.

DR. SALOMON: This is typical of Hugh and I not agreeing. I totally disagree.

(Laughter.)

DR. SALOMON: And that is fine. This is a dynamic we're used to.

I agree actually with what you just said now, but I do not agree that that is what we are supposed to be doing this morning. What I see us doing this morning is focusing in on what is unique about neural diseases and neural stem cells and neural models that the FDA should be aware of in regulation. I think if we find ourselves discussing something that is generically cell regulation, like measuring endotoxin levels at 3 weeks in culture, I am perfectly happy to give that short shrift.

But if we are talking about going in and taking adult stem cells by taking a piece of brain and dissolving it, or we are talking about taking fetal stem cells or embryonic stem cells and using specific growth factors that are not common to any other field to differentiate, and then come up with an assay and put that into a specific disease, then we're talking about something unique to neural stem cell transplantation, or neural cells transplantation. It doesn't always have to be a stem cell. So, I think that is where I would like to see us focus.

DR. DINSMORE: If I could just make a comment from the floor. John Dinsmore from Diacrin. I just wanted to speak to Dr. Auchincloss' comment about what is unique

about these stem cells.

I would agree with him, the one defining feature is they're expanded in vitro extensively prior to their utilization, and there are events that could occur during that expansion. So, therefore, it is a very useful area, unique area, that isn't normally regulated because other types of cell therapies deal with transplantation into the central nervous system, or putting cells to replace insulin function or liver function. So, in some ways it does come down to an issue of the uniqueness of the stem cell. One of the things is that they're expanded extensively.

DR. SALOMON: Well, that point is taken, but Dr. Auchincloss made the point that other fields are talking about longer-term culture, and so I think that that is not -- I do not think the FDA is hung up on this unique thing anyway.

I know there are some questions. Dick had asked me initially, and then we'll go on.

DR. CHAMPLIN: Just reflecting again on the paradigm of hematopoietic transplants, there is a possibility, at least, of overdoing the requirements for characterization, potency, et cetera because right now we cannot characterize hematopoietic stem cells. There's no assay for potency. So, some of these things are impossible

to achieve, at least at our current level of understanding, yet we have been doing hematopoietic transplants for 30 years and curing a lot of patients.

There is sort of a happy middle ground here where one has a body of information that is sufficient to go forward with human experimentation with clinical trials that isn't necessarily the desired set of knowledge that we all would like to have in terms of fully understanding the biology of these cells.

I think the general principles that apply to other forms of cell therapy apply here as well. We have heard a range of types of cell transplants. The Parkinson's disease study really was a tissue transplant of fetal, dopaminergic tissue into an adult brain without much manipulation. They just take it out and put it in, sort of a minimally manipulated transplant in the vernacular.

Then we've heard about extensively manipulated cells that are grown for long periods of time in vitro, and potentially even genetically modified. That is another category that obviously wouldn't need much more critical characterization of the cell populations involved.

In some cases it's probably a good idea not to have purified cell populations. In hematopoietic transplants, for example, there is a range of things that we have put in the stem cell or progenitor cell category,

some that have short-term proliferative potential, that give rise to cells very quickly and rapid engraftment for the patient, but that can't be sustained forever. Then there are probably true stem cells that may take 6 months to show progeny. If you just gave those cells, the patients would die before they'd recover. So, basically it is a mixture of cells that we actually give to the patients is probably optimal, so that one can't sort of pre-judge necessarily -- at least I couldn't foresee pre-judging in the neural sense -- which nerve cell a priori would be what you would want to be transplanting in any given situation.

So, I could envision being able to go forward, in a spinal cord injury, for example, with a poorly characterized population as was described yesterday, without necessarily needing to have extensive characterization data. On the other hand, if one is genetically modifying and expanding cells in vitro, then that's a totally different situation that would call for a much more stringent description of the source material.

DR. SALOMON: I know there's a number of people who want to make comments. Again, just trying to do my chair's job here. We've got about an hour and in that period of time I need to get through these questions. So, if you could think about what comments you want to make, if it will get us toward talking about human stem cell

sources, then I'm happy to yield you the floor. If not, then can we just keep the comment and bring it in at the right moment? I know there were some comments here. Go ahead.

DR. MACKLIS: I'll try to take 30 second and then you can decide as the chair whether they're on point. But just to give very short answers from a very neurocentric point of view to Dr. Auchincloss' questions, and these may sound exceptionally naive because I do not know that much about hematologic system anymore.

But two central differences may be that when one replaces blood cells, there's a whole range on a CBC with DIF of what's normal. In the nervous system, at least we believe that there are very, very, very perfect, careful controls during setting up of the circuitry of the exact complement. So, that's one.

The second is that we as a field, I think, in general believe that, with the exception of the olfactory bulb in the dentate gyrus of the hippocampus that we heard about yesterday, that the developmental signals to guide proliferation, control, stopping, differentiation, and integration are gone in the adult CNS, and that microenvironment is so important that what we're really talking about in this field is releasing cells from those controls and making them do something on their own or

reactivating those.

And I don't know, those might be two ways in which it's different from the hematologic system.

DR. SALOMON: David and then Tom.

DR. DRACHMAN: Very simply stated, the brain is not a liver. That's very important to remember. Because of that, it is protected by the skull. The cells you put in you may never get back. That's the first thing.

The second thing is that stem cells are not drugs. We give cumadin and we check the INR every other day until we get it right. Once we put the stem cells in, they're gone. These are the two things that to me make this very different.

The gypsy moth issue is another one that you will always worry about, or kudzu. These were things that were brought into this country with the idea that we would have tons of silk as a result of the gypsy moth. It started right there in Massachusetts. Kudzu is going to be a way of solving our problems of eating. It grew a little more than one would want.

This is probably not generally the issue, but rather the brain is not a liver, one, and two, these cells are not drugs and we can't regulate them once they get into the brain.

DR. AUCHINCLOSS: Well, I do not think the

brain is the liver, and that is a very important point, that all of these trials need ordinary regulations specific to their particular cells. Nobody has any doubt about that. The issue is, in a generic conversation about stem cells, what do we really want to concentrate on about stem cells.

Secondly, islets are not drugs either. The FDA is very used to regulating cellular transplantation, and this is cellular transplantation. About 80 percent of what I heard yesterday was cellular transplantation. I didn't hear a stem cell component to it.

DR. FREEMAN: Very quickly, I think there are cellular biologic issues and then there are neurologic issues. First of all, with, for example, bone marrow transplants or pancreas, you're dealing with systemic effects versus local effects in the brain.

Secondly, there's no way to biopsy these cells, and we're relying completely on surrogate, noninvasive markers for monitoring effectiveness.

From the neurologic perspective, also what's unique is that the cells do not do what they are primarily designed to do. They are transplanted heterotemporally, and heterotopically. You don't complete the normal neural circuit. You don't have the same objectives. You have a much more limited set of objectives than you do with