is. That's part of the question.

DR. WILCOX: We've already heard somebody suggest that it would be 100 animals for a year. Is that going to be long enough?

DR. TROJANOWSKI: 100 animals for a year, yes. Show me data to the contrary. 100 animals surviving a year with cells injected, a million, 2 million, 4 million, and do bromodeoxyuridine labeling at various times in between for further backup. But as someone who has worked on tumors for 15 years of the brain, I don't see any animal models of tumorigenesis beyond 365 days when the cells are there, and they're alive of course. They can't be dead cells.

DR. WILCOX: Are you referring to the nude mouse models?

DR. TROJANOWSKI: I'm referring to nude mice, yes.

DR. SALOMON: Dick, Tom, and Mark.

DR. CHAMPLIN: I think biologically there may be a difference between these ES cells and other cells in a steady state. The embryonal cells are programmed to make an embryo. So, they're going to proliferate and make a mass naturally. Whereas, cells that are collected in the steady state situation from even the fetus or an adult are quiescent because of natural controls on their growth. I'm

not aware of any precedent for those cells making tumors in any system. So, I would be very suspicious of ES cells in terms of their tumorigenicity, but I would think it's going to be the exception rather than the rule for these other cells, and I wouldn't make a giant requirement there when there doesn't appear to be a rational need.

DR. FREEMAN: Just to support this number of 100 animals, if you're looking for landmarks, if you use a stem cell that is partially committed such as Evan's and they can migrate all over the brain, including to the contralateral side, and you can deliver them with one needle track, as opposed to cells that are differentiated and stay where they're put -- for example, in our program we're using 16 needle tracks. What's the relative risk surgically? You're talking probably about a one-half to 1 percent risk surgically for all those needle tracks, not to mention cognitive difficulties from multiple tracks through the frontal projections. So, therefore, that gets weighed into the formula, and I think that 1 percent number is probably reasonable.

DR. NOBLE: I'm just a little concerned about the focus on tumorigenicity. We know that the most mutagenic components of the brain are myelin, and in the brain you have lipidic haptene that people worked on for so many years and that you always got an immune response to is

galactocerebroside, the major myelin in glycolipid.

So, I think there's a certain concern that I have that if you are going to do a nonautologous transplant into a patient in situations where you were going to generate oligodendrocytes, that perhaps there is a need to at least be looking for changes in the percentage of T-cells or immunoglobulins that are reactive against the myelin antigens so that we are aware of the potential of these autoimmune disorders.

DR. SALOMON: So, that's actually raising another issue. That may allow us to move on.

In a year or two, when they get rid of me, I still want them to get up and give me a plaque or something.

(Laughter.)

DR. SALOMON: So, I think we've done tumorigenicity. I don't know that anyone wants to tell you it's 100 animals, though we've had an argument for that. But I think in general we agree that there should be information available on any cell line for a clinical trial that includes but doesn't exclude anything specifically, but includes karyotyping, p53 expression, contact inhibition in in vitro growth assays, but certainly also includes data in animal models. Maybe we'll get back to that a little bit about immunodeficient animal models

versus primates. I think that's kind of where I'm wanting to have a little bit of time to talk about next. But it should be both animal tumorigenicity data and in vitro tumorigenicity data. I think that's probably where we ought to hold there. And I'll resist the gene chip comment at this point.

Yes?

DR. JOHE: I'm Karl Johe from NeuralSTEM Biopharmaceuticals.

In terms of tumorigenicity, the nervous system disease does present two unique differences which I would like the committee to consider. One is the lesioned environment, whether the tumorigenicity test should be done in lesioned nude mice or not. Second is the site of the injection. There are different neurogenic sites in the adult brain and I would like the committee to make specific recommendations.

DR. SALOMON: I think certainly with respect to the latter, the committee has already repeated on multiple occasions from multiple people here. So, I think I can speak for the committee, unless you guys disagree, that site is important and lesion is important in terms of the environmental signals. I think everybody agreed with that.

Some of that will come back down to models. I think at some point along the line, if you want to do a

disease X study, you're going to have to provide animal information in a model of it. The intrinsic quality of that model is something that is not easy to predict because there are so many different possible models.

Well, immunogenicity. I don't want to forget that one because that's certainly not irrelevant at all. It's certainly relevant in a number of different things that we do in terms of transplantation and sensitization. In gene therapy, the idea of immune responses altering therapeutic responses and certainly in cell transplantation like islet transplantation and autoimmune disease destroying the islet. So, that was quite an argument between us last time. So, anyway, I think this immunogenicity issue is very important, Mark. I'm glad you brought that up.

Let's talk a little bit about, in the context of animal models, post-implantation cellular fate. Again, I'm cognizant of the time. So, here I might get a little heavy-handed. Please forgive me.

There are two or three really important things I think we should talk about. One is markers. If you do these studies, it would be a big advance if the cells survived and functioned after transplant even if you might not meet the absolute ideal clinical profile, and a lot of that could then spur further research. I think we'd all

agree.

So, what ways do you guys suggest we have available now to follow cells after transplantation in animal models or in the human situation that would be important to think about now?

DR. RAO: It's pretty much all the standard ways, and you saw some of the evidence. You can use noninvasive radiographic methods to follow cells at least in humans, and at least in specialized cases where you have MRI scans, you do this with mice.

I think a couple of things that we should be considering in creative ways that you can use paramagnetic labels, and we may want to see whether we can use those. We can use labeled antibodies with specialized uptake. Especially if you're doing human cells into mice or rats, we have species-specific antibodies which can bind on the cell surface and one can use them to actually follow cells. And all of those are possible.

DR. SALOMON: So, can I get a little bit more? You guys did some neat PET scanning. Stuff was shown yesterday. Now, can those PET positive markers -- you loaded the cells pretransplant with them. You don't get special uptake if you give them IV to the patient after you do the transplant. Right?

DR. RAO: No.

DR. SALOMON: How long will they last? Usually those kind of things we're talking 48, 72, 96 hours. BrdU may be a few days.

DR. RAO: A short time.

DR. SALOMON: So, in terms of a clinical trial, these are not going to be very satisfactory. Right?

DR. GAGE: One of the clinicians explained what's going on with the PET markers in the fetal tissue grafts. That's what you're talking about. This is bottom line rather than the details.

After the graft is in there, you can give something to the patient and mark the functionality of different aspects of the graft.

DR. KORDOWER: You can give like agonists, give amphetamine and have the graft be activated, and you can see function that way.

DR. GAGE: And you can do it repeatedly. So, there are ways of assessing specific functional aspects of the graft. It's debatable, is that the host or the graft that's doing it?

DR. KOLIATSOS: But this is the product of the graft. The question is if you can use neutral markers to trace the origin of the cells. If there are neutral markers and there are markers of differentiation and fate, I think we need both because you need to show that fates

come from your implant and they're not just an independent event.

DR. GAGE: I was just responding to what his question was.

But what we don't have are what we're looking at. What we'd like to have is some sort of tag that you can put onto a cell that could be read out in vivo repeatedly over time, independently of the fate of the cell, just to know where all the cells went. That would be a terrific thing.

DR. SNYDER: That actually does exist. Ralph Wielander up in Boston with us has actually FDA-approved now ferromagnetic tags that can go into cells such that the transplant itself can be imaged by MRI over time in mice and presumably in primates and humans. So, that kind of technology does exist.

There's some emerging technology on actually being able to image lacZ expressing cells equally as well.

So, the technology exists, but hopefully we would be using in clinical trials if we did transplants to follow in vivo in a living person by MRI the cells that we put in there. Again, it wouldn't tell us what --

DR. KOLIATSOS: Have they used the cells and have they MRIed these brains, Evan?

DR. SNYDER: Yes.

DR. KOLIATSOS: Because there's one issue of feeding them ferromagnetic stuff and the other is for the MRI machine to have the resolution to pick up small collections of neurons. There are two different things.

DR. SNYDER: Yes. There is a resolution, but the resolution it's not bad.

DR. GAGE: But I think we need to be careful about what we're thinking about we want to have in the future and what is standard practice in the field at present. And what is not standard practice in the field at present is being able to track individual cells that are grafted now. There may be a hope for something like that in the future, but that is not standard practice in the field.

So, what we know right now is not where all the cells go in all of the different models that we are dealing with, much less the fates. That information is at best derived postmortem in our sections when we look at the animals, and if you label every cell, you hope that the label stays on long enough so that you can then double-label that marked cell with enough phenotypic markers to determine what they turn into.

But that's the state of it, and it's not bad. Actually that part of it is coming along pretty well. But I think it would be wonderful if we had magnetic markers or

something like that for clinical applications where you actually could track the cells in situ, independently of knowing what they are. Just knowing where they are would be a relief I think to experimenters and clinicians alike.

DR. KOLIATSOS: The problem I see here is that because of the extensive migratory properties of those cells, they're going to disperse themselves quite a bit. It's not like the traditional grafts where you put a big chunk of cells inside of the brain and the machine, the magnet can pick it up. They're going to go all over the place, and they're going to dilute the signal. So, this is a significant technological problem which is ahead of us.

DR. SALOMON: One of the things I think about the migration is that if you have an injury somewhere, they may migrate out, but if the injury is in the site where you just injected the cells, there may not be a specific reason for these cells to migrate. I think it's an important question in each of these models, how much, if any, migration will occur. Of course, it will have to do with the cell type. I don't want to get into that. That's obvious. But also just the situation around it.

Tom?

DR. FREEMAN: In terms of radiologic surrogate markers, obviously with dopamine neurons it's our best characterized surrogate marker using the fluorodopa PET

scan where the test/retest variability is available. But even that even in the best of situations is limited because region of interest is 2 centimeters or a centimeter and a half even in the best of hands for test/retest variability, and many will say it's even larger than that. So, to expect a pharmacologic surrogate marker is just not practical even in the best of situations.

Then once you get into other diseases, what's the pharmacologic outcome you're measuring? Are you looking for GABAergic function or whatever? The markers and the methods for looking for that are just not available.

On the other hand, if one is looking from a safety point of view, just a plain old MRI scan a year and a half out is good, regardless of therapy, for tumorigenicity purposes. That's really what we're looking for primarily, and that's available.

DR. SIEGEL: Tumorigenicity may be a primary concern, but we are interested in, as noted in the bullets in this question, what animal models might tell us about migration, differentiation, phenotype, integration, and survival.

DR. SALOMON: Great. We've got 15 minutes to do all of that.

(Laughter.)

DR. GAGE: Well, I think that there are some answers. Again, in the short time, trying to give some advice or some recommendations, cells can be labeled either with dyes or with bromodeoxyuridine prior to grafting so you can track them, or with viruses in some way so that you can see where their fate is. And then after grafting, in the appropriate model, use that graft-identified marker to determine what the cell fates of all those cells are.

To go back to what we were saying, not just how many tyrosine hydroxylase positive cells develop reliably as a function of the number of cells that you put in, but also how many of the cells that you put in survive -- get some quantitation on it -- and then how many of those cells differentiate into the phenotype that you've determined in your experimental model is causally responsible for the functional recovery that you've seen. You can set that barrier and say, okay, look, we need to get, based on our experiments, this many cells surviving. We've put in this many cells, this percentage of our cells, differentiating the fate, and we get that in some sort of ratio.

I don't think it's unreasonable to ask for those parameters in any experimental model to say what percentage of your cells differentiated in the phenotype that you believe is causally responsible for the function that you have in vitro and in vivo. And that is a

percentage of the total number of cells that you put in.

DR. SALOMON: In the back.

DR. WILCOX: I agree with that, but I think one of the other problems that we face as reviewers is that we're also concerned with what else they may become. If the intention or the desired phenotype is tyrosine hydroxylase positive, what are the risks that the cells might, or a portion of the implanted cells, may assume other phenotypes? And does that matter? Is it going to be clinically relevant? When we ask sponsors for preclinical data at this point, it's often not clear what kind of clinical relevance it's going to have, and it's very difficult sometimes to convince sponsors that we want to know what else these might do.

My feeling is that we should have that information in case there are adverse events which we then can use those data to perhaps evaluate the adverse events. But is it realistic to ask sponsors to put resources into these large preclinical studies where we don't really know even what we're looking for at this point?

DR. GAGE: Well, if you have markers in the cells and you've used one marker to identify what the fate is that you're searching to, you use other markers to determine the percentage of cells that have gone into other fates. You wouldn't just use a single marker, but you have

to at least get the cells down the lineage that you want or that you're targeting. Then as a corollary, you want to find out as many of the other fates as you can within the cell type. But I wouldn't be satisfied just knowing all the other ones. I'd want to make sure that you've got the fate that you want.

DR. SALOMON: Tom, Jeff, and Vassilis.

DR. FREEMAN: So far with, for example, fetal transplants, no one has had more than, say, 5 to 10 percent of the neurons that are going in being dopaminergic because that's standard within the mesencephalic dissection. So, by definition, our experience has been with the heterogeneous population not with the homogenous population.

There is evidence suggesting that that may actually be good. Say you have your dopamine neurons surrounded by mesencephalic glia. That may not only affect survival rate in vivo, but also the type of outgrowth versus branching is directly related to the surrounding glial milieu around the dopamine neurons.

So, the bottom line is I think that, from my point of view at least, all that matters is that what's going to go into patients is tested from a safety perspective in animals. I think we tacitly have to admit that it may not be possible to characterize to the last

cell exactly what's going on, at least at this stage. That may take 20 years to achieve. But as long as the safety profile for the way it's going to be used clinically is evaluated, I think that should be paramount from the practical point of view.

DR. MACKLIS: A comment to follow up on what Rusty said about markers and prelabels. I don't think this committee can decide, but I think there would be some agreement in the field that there's some prelabeling markers that are not dependable, that can be transferred to endogenous cells by cell lysis, and one would want to use one or multiple markers that are going to be dependable and also ones that are going to show all the cells you put in so you can look at these alternative fate decisions.

DR. KOLIATSOS: I would also vote that we do these experiments with neutral markers and with fate-specific markers both in normals at different ages and in a variety of lesion models, try as many different scenarios as possible. I could envision five or six, and I don't want to lay them out. Because, again, let's remember that in an acute stroke model, the behavior may be different than in a familial ALS transgenic mouse than in a control mouse than in a control rat. So, we may want to have observations along a number of models in terms of fates and differentiation.

DR. SIEGEL: For the most part, I haven't found the issue of uniqueness too important. Every class has its own issues. Every product has its own issues. And we're here to discuss this class and this product whether they're unique or not.

But one thing that has struck me as unique about this that hasn't come up yet, which is that this is the only class I can think of cellular products where we've talked about long-term animal safety studies. We don't put human blood products or pancreas in animals for a year and see what happens.

DR. SALOMON: That was my point to Dr. Prockop.

DR. SIEGEL: Right, and that gets to a particular question. The reason, obviously, that we can talk about that is the immunological barriers presumably. But that raises an important inferential question because the cells exist. They live in animals. They sometimes differentiate. They do things in animals, but we know that all the neurokines and cytokines and different factors and their receptors are not all identical across species. So, then part of the question in animals then is are we likely to learn more by putting human cells into animals or by putting animal homologous cells prepared the same way into a homologous species? Where are we likely to get our important information on these questions?

Do we know, for example, if you do rat into rat versus rat into mouse or dog into mouse with these embryonic cells, that you see major cross-species behavioral differences? Are our findings quite similar when you use homologous species?

DR. SALOMON: Yes. That's actually exactly what I wanted to finish with, so that was perfect.

What we've talked about here have been rodent models, but obviously we're using human cells of various sorts so that one issue here is putting human cells into immunocompetent animals or human cells into immunoincompetent animals like SCIDs or nudes, and then we haven't talked yet about rodent models versus primate models. And now Jay has put one last thing on the table and that is going backwards, I think, to start to model rat cells into rats and then come here and say, well, now I want to put human cells into humans just after Phil got done telling us that the tumorigenicity question just starting from scratch is different.

Ed?

DR. SAUSVILLE: Although I think that highlights that I think you can't make a one-size-fits-all thing. I think you have to be driven ultimately by the biology of the process that you're trying to model. The cytokine experience has shown us that in some cases there's

a very good correspondence between cytokine to cytokine.

In other cases, there aren't. Really they are two sort of different questions. Right? In one case, the tumorigenicity is looking at sort of a gross, space-filling complication that might be addressed best in an immunosuppressed rodent receiving human cells.

As far as the efficacy issue and whether there are long-term toxicities associated with these cells operating in their normal milieu, I could imagine that you'd want to see supporting data of the species to species. But you have to look at each situation in and of itself.

DR. REID: One technical issue. At least of the data that I've heard from some of the investigators here and elsewhere, I think the lowest efficiency I've heard about in any kind of transplantation phenomenon has been in the neural stem cell field. That is, when they're injecting cells, at least from human cells, into the brains, they're having to use, I think, extraordinary amounts of starting material in order to get some type of efficacy.

So, one of the things in the inoculation procedure, which you have on your list to be concerned with, is the implanted cell survival. So, I think you're getting exceedingly low cell survival based on some of that

data, and at least some of the known conditions that might improve that might, in fact, dramatically improve not only your model systems, but even some of the effects that you're worrying about in studies of transplants into one species into another.

DR. SALOMON: The problem here, though, is that cell transplantation per se is troubled by the number of cells surviving. In islet transplantation, everybody was jumping around with press releases yesterday about a tremendous step forward in islet transplantation, but it's two whole pancreata worth of islets to cure a patient, realizing that we can probably take out two-thirds of a pancreas from any one of us and have a normal glucose. And I can give other examples. Cell survival in any cell transplantation experiment is a big issue.

In the few minutes that we have left here, where do you feel in your field are primate model experiments? How far are you willing to go on rodent experiments?

DR. KORDOWER: Are you talking in terms of safety or in terms of efficacy?

DR. SALOMON: I think just in general. In terms of efficacy perhaps is better put, but safety too.

DR. KORDOWER: I'm going to kind of limit my remarks, because we don't have much time, to Parkinson's

disease. My opinion is that we need to do more nonhuman primate studies.

Now, I think, first of all, the rodent studies are too much dependent upon rotational behavior alone, so people who do rodent Parkinsonian studies I want to encourage to do more complex motor tasks because there are lots of things that will reduce rotation.

Curt Freed said that fetal grafts in rodents were totally predictive of the human studies, and that's true. But there are a lot of other manipulations where that's not true. You can reduce rotations in rats with adrenal cell transplants, or the success that Marty Bohn has had with the adenovirus GDNF in rats she has not been able to replicate in nonhuman primates.

I think with regard to stem cells, there have been reports from Ron McKay's group and Tim Collier and Paul Carvey from our group have demonstrated you can put dopaminergic progeny from stem cells into rodent models and get reductions in rotation, but that's because the striatum is so small. What happens, though, if you look at these grafts, is they don't innervate. They don't send out processes like our primary cells do, and if you had those grafts in a monkey, I doubt that you'd see efficacy.

DR. SALOMON: How about safety? I got a dirty look from the back table when I said efficacy, which just

reflects my bias. I apologize.

(Laughter.)

DR. KORDOWER: With regard to safety, I think you have a problem in that you're going to be doing a xenograft. Now, there is some evidence that dopaminergic cells can be grafted into monkeys without cyclosporine. If stem cells can similarly survive under those conditions, I think you can learn a lot. But if you have to immunosuppress just to get the cells to survive, then the rules change, and I'm not sure that that's going to be particularly beneficial.

DR. SALOMON: So then, let me just broaden it a little bit. Whereas I tease Jay about the idea that I thought it was going backwards to start doing rat to rat to prove what you'd want to do in a human, I might put out on the table for discussion the idea that I don't think you'd be moving backwards if you had to do primate to primate as a model for humans.

DR. SNYDER: Or even human to primate.

DR. SALOMON: No, no. The human to primate was fine. I was sliding that by. That would be the best. But I'm just saying that if you felt that there was an issue of xeno that you could do primate to primate if you have pretty good models. I'm suggesting.

DR. FREEMAN: A few things. As a clinician

that went from rat to humans, there are a few issues wrapped up in this.

Clearly volumetric issues are better answered in primates. So, therefore, degree of outgrowth, if outgrowth is an issue, degree of migration, or Rusty's point which I think was very important, if the dose is much larger than what can be tested in a rat and if the differentiation of the cell is dependent on the environment, then really that needs to be looked at in the species that is quite close. These volumetric issues clearly need to be addressed in primates.

On the other hand, a lot of basic biological issues like reproducibility, dosing, cell-cell interactions in terms of pathways where migration occurs. Where does neuritic outgrowth stop? Does it stop at appropriate somatotopic targets? Those answers can be addressed very safely and appropriately in a rodent.

On the other hand, one doesn't want to slow research to the point where it's inappropriate. If we had waited for the primate data for nigral transplants, we still would not have started our programs after 13 years or 14 years of waiting for primate data.

DR. KORDOWER: I don't agree with that at all.

DR. FREEMAN: There are many issues that the primate programs have not answered in the fetal arena. The

human data was literally 5 to 8 years ahead of any primate experiment. Almost every primate experiment followed a clinical experiment, and they were happy to be able to reproduce what was done clinically.

DR. SALOMON: We are near done here, but I don't want to leave it on that. To what extent is that an historical truth based on the way people moved forward in those days, which was let's just go do it, as opposed to some fundamental barrier raised for primate research?

DR. KORDOWER: Well, what's the down side to doing primate research? I wouldn't say that it was difficult. It's not difficult. What it is is uncommon, so people can't set up their own infrastructure. But if someone has a real good cell that makes dopamine and they get it to function in rats, I guarantee you we'll be lined up to try and get the cells to try them in our primate model.

They're expensive, but they're not as expensive as a failed clinical trial.

DR. GAGE: Can I say one more thing about the rat-to-rat stuff? Because I agree with you about the importance of primates.

DR. SALOMON: Are you done with your comment?

DR. KORDOWER: I think where people are hesitating going to primate trials, it kind of slowed them

down in getting to be first or close to being first into the clinic. I think we have to realize with Parkinson's patients, these patients have a lot of options. They can get DBS, they can get pallidotomies, they can get transplants. We don't need to rush with a technology that has an excellent clinical model for use. It's an excellent model and it should be used in that regard.

DR. SALOMON: Two more comments. Rusty and then Tom wanted to follow up.

DR. GAGE: I wanted to disagree or bring in the idea of this intraspecies evaluation as being an adequate approach towards clinical applications. So, a rat-rat or monkey-monkey. I think that I personally would feel much safer if you used the cell that you're going to use in patients. That strikes me that that has to be the -- and how you grow it, how you ever plan to use that cell in the patient is exactly how you ought to test it in your animal model. Now, you may use other cells to get to the point where you're testing yourself, but ultimately it strikes me that you really have to look at that particular cell in the best model that you can. And if you don't have a model that can test your cell, you should find one to test your model in and not make assumptions based on how rat cells function or how monkey cells function in some other model.

DR. SALOMON: I agree with that, but you have

to accept the fact then that taking human cells into any model but a human adds another layer of confusion. I know you're well aware of that. In mouse models, for example, there are endogenous and exogenous retroviruses that can enhance the whole tumorigenicity thing. That's one point that hasn't been made yet.

DR. KOLIATSOS: It's not only immunological. If you stick human cells into rats, it's not only the immunological compatibility, it's the cell cycle, the differentiation, the time encoded factors, which are totally different.

DR. SALOMON: Again, I don't think that we are going to answer anything, but I think that your point is well taken, that if you're going to do a clinical trial, as much as possible you want to do your studies with the final product. So, we totally agree.

Of course, there are methodologic questions, so I'm suggesting that in some cases if you have this whole methodology, I'm going to do this, this, this, and this, and after that set of steps, put it into a human patient, I could say to you, you should probably be able to go to a nonhuman primate and do this exact set of steps and get it to work. And if you can't, it's possible I could still get my head around that, but it would worry me at least. If you had a process that was biologically relevant and well-

described, it would bother me that you could tell me, oh, it works great in humans, let me do it, but I can't reproduce it in a primate. But that would have to be discussed.

Tom?

DR. FREEMAN: I don't want to give the impression that I'm saying primate research should not be done. It absolutely does have to be done, particularly right before you have your final formulation, your final protocol, and go into patients. Clearly it's relevant.

The issue is that many of the scientific questions can be adequately answered in rodents and to require that every question be addressed in a primate would be an unnecessary burden that would slow the progress of research.

DR. SALOMON: I don't think any of us who have rodent models and primate models, including myself, would bother that one. That's a good point.

I don't think we answered every question, but I'd like to think that we answered quite a few questions. At this point before absolutely closing, I'd like to ask the FDA if there are any comments, last minute, we just can't leave without answering this question kind of thing.

MS. SERABIAN: The only other question I have -- and again, it opens another a whole can of worms -- is

behavioral data. Again, we are talking functional, meaningful, measurable observations. Well, you can get cell migration, you can have an aberrant phenotype expression, but behaviorally what do you see? Do you see changes? Again, like I said, it's whole other can of worms because there are numerous different behavioral testing and controls, and some of that was mentioned yesterday.

DR. SALOMON: Particularly the dirty looks I got when I went "efficacy" and drifted back to safety, so now you want efficacy.

MS. SERABIAN: Not efficacy. For safety. If there's aberrant behavior --

DR. SALOMON: Oh, you're talking about behavioral. I'm sorry. Excuse me.

MS. SERABIAN: -- some motor dysfunction or something.

DR. SALOMON: Well, I think that point is well taken, and I think also, as Ed just whispered, some of that is going to also be more relevant when we get down to specific diseases. Someone wants to do a trial in this and that.

MS. SERABIAN: Right, and again the question from that is talking with sponsors, they're extensive, expensive, time consuming tests. So, you don't want to just say FDA says you have to do this and there's really

not an appropriate reason for doing it or it's not the appropriate test.

DR. SAUSVILLE: Well, that I would underscore. Just watching how well they withdraw a paw or do something doesn't have a clear tie to the pathophysiology that you're trying to fix, I think I would agree. I don't see any particular reason to do that and would discourage sponsors from doing that.

DR. SALOMON: I think one of the things that came out in today's discussion that I think has a lot of merit is that there are, as we admitted early on -- Mehandra got a lot of grief about his Harrison list, but then Rusty saved him by having a worst list.

(Laughter.)

DR. SALOMON: I think that there are a lot of interest groups here that are coming together that are interested in this area, and I think that working groups probably should go out from here and begin to address some of these issues and deal with the FDA early. I think that's one of the points Phil and Jay were making. This idea that all of a sudden, after everything is all done and everything is settled and it's perfectly done and there's nothing else left to do and we all get to go home, now we're going to come to the FDA and we're going to have a clinical trial, and then the sponsor gets frustrated. I

don't think that's the model that we're trying to communicate.

I think what we're trying to say is that the sponsor shouldn't be frustrated, Mercedes. The sponsor should be talking to you very early in the developmental process. I just don't have a whole lot of sympathy anymore for sponsors on that score.

Anyway, again I'd turn to Jay and Phil, Malcom. Are there any last comments you want to make? And then I'll close.

DR. SIEGEL: Just not more questions, but as a comment, I for one have learned a tremendous amount over the last couple of days. I've learned, based on Malcom's model, that there's a great deal that I don't know, but I feel a lot better knowing I don't know it than not knowing what I didn't know.

(Laughter.)

DR. SIEGEL: Those of you who have worked with us, hopefully when we're at our best, we appreciate how much we don't know and what is and isn't possible and try to work and try to work and try to expect you to work within the realm of the possible. This field is moving quickly, and I'm sure that we'll have many future discussions. But I think this has been a great foundation for moving ahead.

I would like to second your remark, Dan, and other remarks we've heard about the scientific community getting together and developing consensus when that's helpful and when we've reached those stages, whether it's about use of reagents, use of animal models, whatever. The agency is very interested in those areas and will find it very helpful.

I just ask everyone to remember that even though we're dealing with a science that isn't -- as many have pointed out, we don't have all the answers yet. We don't know all the things we need to know. We don't know the best ways to test. We're also dealing with an area which is, as suggested by some, rapidly approaching a time for human experimentation. So, we do need to make the best decisions based on what we know now of the right ways to proceed. In that regard, I think this has been a very useful meeting for us.

DR. SALOMON: Then I'd like to close the meeting.

I'd like to thank Gail Dapolito and Rosanna Harvey, Bill Freas, and the rest of the FDA staff for all the kindness and organization. I don't know how I ever get here and back without these guys, but I do. I appreciate it. Thank you.

(Applause.)

DR. SALOMON: Thanks to all the speakers and to the audience that actively participated and see you at the next meeting.

(Whereupon, at 3:10 p.m., the committee was adjourned.)