DR. AUCHINCLOSS: I would actually take a different point of view from Dr. Sherwin in the following sense that you could make the argument, and I think it is a reasonable argument, that the people with proteinuria or elevated creatinines are exactly the wrong population to go for, and the reason for that would be that I think that the major risk associated with islet transplantation alone is sensitization for the subsequent transplant that they may need.

So I would not target the population that you know is heading there. I would take the opposite population.

DR. SALOMON: I would point out that what I was talking about was a patient with microalbuminuria and there is some reasonable hope that, in that early population who has got no elevation in creatinine or any change in creatinine clearance, if anything, they might have actually an increase in creatinine clearance at that point, that a successful islet transplant may prevent the kidney disease.

So I think if you choose that patient correctly, the only argument I would have is that I think you could reverse some of the disease. Certainly, there is evidence of some reversal in kidney disease in pancreas-alone transplantations.

I think that would be a nice hope to the extent that we all believe that there is some reversible component

to the microvascular disease.

DR. HERING: I would like to argue in favor of hypoglycemia unawareness. I understand this is a significant clinical problem in a small group of patients. You are not talking about thousands of people here--in a small group of patients.

The reason why I argue in favor of this subgroup is they will benefit right away. The problem of hypoglycemia unawareness is eliminated right after transplantation to the point that you have a clinical effect obvious to everybody who wants to see it.

If you argue here, now, kidney and maybe neuropathy or whatever, this may take five or ten years before you see a difference in a prospective clinical trial. But, in hypoglycemia unawareness, the patient may benefit immediately from the procedure whether you have complete insulin independence or whether you have some level of islet-graft function.

All the available clinical information clearly supports this point.

DR. SHERWIN: A lot of patients have diminished awareness from hypoglycemia and the reason is that the threshold for releasing counter-regulatory hormones is set downward, but also their function is maintained better during hypoglycemia because the brain metabolism changes as

a result of that.

But I do agree that that, in association with a certain defined number of severe hypoglycemic events would be a reasonable approach. It is just that I think that someone's hypoglycemia unawareness is someone else's not hypoglycemia unawareness. I think that it needs to have some sort of assessment of it from--

MR. SIEGEL: I have a question about an underlying assumption here which I assume is true because it is unspoken but we are all assuming it. Are we comfortable enough that there will be normal homeostatic mechanisms in transplanted islets that, assuming once we have a therapy where there is good tolerance or immunosuppression and good survival of large numbers of islets that there is no concern at all that those islets, themselves, would cause hypoglycemia?

DR. SALOMON: Jay, can we hold that just for a minute until we finish this one on candidates?

MR. SIEGEL: It is quite relevant to whether the hypoglycemic-unaware patient is the best population because if there is any risk that the treatment causes hypoglycemia, that wouldn't be a good population. But it sounds like we are all assuming that we know that that is not a concern.

I just wanted to make sure--

DR. AUCHINCLOSS: The answer to that is yes,

unequivocally yes.

DR. SALOMON: I think the animal data suggests that if it works, it works really well and in the humans, data that works--

DR. SHAPIRO: The clinical data also clearly indicates that that is the case.

MR. SIEGEL: I assume, from the discussion. I just wanted to get that out on the table.

DR. HARLAN: I just wonder what is wrong with the criteria that Hugh Auchincloss proposed. There is a risk associated with this procedure, no doubt, but diabetes is not a benign disease, now matter how well you care for it. It is not a benign disease.

If the patients are aware of the risks of whatever the protocol is that that study is going to do, it is paternalistic for us to say you can't do it, if they understand those risks.

DR. EGGERMAN: A fundamental question is do we know what the risks are that we can tell the patient so they can be truly informed?

DR. HARLAN: They can be quantitated as much as is humanly possible. There are some unknown risks. Whenever you enter into a protocol, you state that to a patient.

DR. EGGERMAN: That needs to be clarified to the patients, too, and it is not an assumption that we know all

the potential risks in a field where there is investigative study.

DR. BLUESTONE: On the immunosuppressive side, we have tremendous amount of information and that seems to be what we are focussing on here is the immunosuppression not the transplant.

DR. RICORDI: So you could establish an independent panel to discuss the informed consent with these patients instead of to decide whether it was a treatment failure of insulin.

MR. SIEGEL: This is an experimental therapy. I think this issue of it being paternalistic not to allow the patient to accept the risk is not an inappropriate standard. I think it is well establish, for example, if you can ask a scientific question in population A or population B, and it is safer to ask it in A than in B, you shouldn't ask patient B to answer that question for you, you should only ask patient A.

If you have a healthy person who is willing to volunteer to accept something very dangerous to advance science, depending on the nature of that, it may well not be appropriate to ask him to do that. So it is not so black and white that informed consent solves all of the problems, in part because of the proviso that you mentioned at first which is there is no such thing as true and perfect informed

consent.

DR. HARLAN: It is very difficult to achieve but true Type-1 diabetes with no demonstrable C-peptide, stimulatable C-peptide, is not a benign disease.

DR. KENYON: Can I just comment on all this? I am agreeing with Hugh and David that partly informed consent--I think where I would draw the line right now is age. I certainly am not ready to go into a child with the protocols that we have available until they are more proven in adults.

But I think that quality of life is really important in the risk-benefit ratio and David is right; it is not a benign disease. It is a full-time job. The hypoglycemia unawareness, when you have it, you have to reset your target levels and then your hemoglobin A1c goes up and your chances for complications go up.

We don't know. Everybody differs so the true risk for the complications of diabetes are maybe just as unknown as what the true long-term risk of some of these drugs are. So the only place that I would really draw the line right now is not to go into children until we have a little more data.

But it is not a disease that is great to live with and the quality of life should clearly be considered. I think each patient, as long as they have been carefully evaluated, is best suited, with good informed consent, to

make that decision.

DR. SALOMON: Can I ask a question? If you take a patient who has some objective viable end-stage organ injury, whether hypoglycemic unawarenss could be included in that or recurrent keto--any of things, microalbuminuria. I can follow that.

If you go back and you say anyone who has had true valid informed consent, who is an insulin-dependent diabetic, should go into the trial then the question I have is if you have 100 insulin-dependent diabetics today, and you come back in thirty years, how much do we know about--are 100 of the 100 that we started with going to be blind and on dialysis at thirty years?

DR. SHERWIN: No. Clearly the kinds of results that can be predicted now from intensified better therapies that we offer today, up until twenty years ago, we didn't even have any way of assessing how things were going. So it was hopeless to manage diabetes. We didn't try to manage it because we couldn't.

But it is likely--the data for renal failure in Scandinavia now long-term are about 9 percent. It is predicted if people can achieve levels similar to the DCCT that that would be--over the course of one's life, renal failure would be about a 9 percent risk as opposed to 30 to 35 percent previously.

The chances of developing blindness is probably a similar percentage, about 8 percent.

DR. SALOMON: I would just point out that if you think about allotransplantation right now, the half-life of an allotransplant, and I am being vague--kidney, heart, liver--maybe liver, I would put on the side for a minute--but certainly kidney and heart--would be fifteen years? Half-life? That is being pretty generous, actually. There are people that could argue that it is less than that.

But, certainly, fifteen years, maybe twenty, if you say these newer therapies are going to impact significantly. So I don't think it is so unreasonable. I think we should be careful that if we take the attitude that, of that 100, all of them should be offered this islet transplant if they get true informed consent, based on the fact that 50 of 100 will have lost their islet allograft by fifteen years, maybe twenty, and then what percentage is left that would have been guaranteed to have complications at thirty?

DR. BLUESTONE: But then there are a couple of points that you want to also make is that the JAMA article that says what happens if you don't get that kidney transplant. And, being on dialysis, you have a eight-year--so there are morbidities associated with not.

DR. SALOMON: If you said the hundred patients all

had kidney failure at the time, then I am quiet. I was talking about a hundred patients with no problems.

DR. BLUESTONE: I understand. But now you are getting to a question--so I am going to re-ask my question earlier because now I am hearing you and Bob say something which I guess I would not have imagined. But it is okay. Bob has already said that short-term immunosuppression, I can live with that. It is this long-term thing that is a real problem.

The islet transplant is okay. There is not a big safety issue there. So I posed the question of if you transplanted a hundred people and, at one year, they were all normoglycemic but all destined, now, to stay on rapamycin in low dose, you guys would actually think that that was a bad outcome because the immunosuppression outweighs the benefit.

If I am understanding what I am hearing correctly, you think that, in the absence of both of those, the islet transplant and the immunosuppression, that person can live a better life because of better management of insulin and stuff like that, because that is what it comes down to. It comes down to a question of whether islet transplantation, if successful under current regimens, is a good therapy.

DR. SHERWIN: You think you are going to get 100 percent?

DR. BLUESTONE: Then we can have discussions about survival.

DR. SHERWIN: Do you know anything about the long-term--we haven't discussed the long-term--

DR. SALOMON: Let's not discuss the long-term yet.

DR. RICORDI: Excuse me. You will have 100 percent because if one fails, stop taking the immunosuppression. So those who will continue immunosuppression are only the ones that are successful. So the risk will be calculated on 100 percent of the surviving grafts.

DR. BLUESTONE: Right; from long-term immunosuppression. You are only worrying about the guys that are out a year, normoglycemic and on their drugs. Would you want to take them off--I asked you before and you said, "I don't know if I wouldn't take them off." That is what I think is the gating issue here because, to me, it never occurred to me that a successful transplant at one year in normal glycemia and normal well-controlled normal glycemia would be a possible bad outcome if it meant immunosuppressive drugs for the long term.

DR. SALOMON: I want to make one thing clear. My last comments were simply to Dr. Harlan and Dr. Auchincloss' concept that anybody with insulin-dependent diabetic, if they had informed consent, was a candidate for this.

DR. RICORDI: Maybe I can expand that criteria staying instead of anyone with diabetes, it should be anyone where insulin treatment has been a failure, failure meaning inability to achieve normal hemoglobin A1c levels in the absence of a hypoglycemic episode. That is treatment failure in diabetes because it doesn't prevent the development of complications.

DR. SHERWIN: I am not arguing that we would like everybody to--I would favor every type-1 diabetic patient getting an allograft. I have no problem with that. I hope that happens. I am just saying, in the very early stages of any trial where you don't really know what you are doing, it seems to me to be very careful in that selection process in the first line--so you don't get caught up in some bad incident like gene therapy.

DR. BLUESTONE: The question was what do we mean by "we don't know what we are doing?" The islet transplant will either work or not work. If it doesn't work, then they go off their immunosuppression. If it works, then we knew what we were doing for that and then you are worried that we don't know what we are doing vis-a-vis the immunosuppression.

I would argue that we already know what we are doing. It is not all good. We know that. It is not going to worse for the islet transplants and all the other people

we give the immunosuppression. So what are you worried--if it failed, then they are off the immunosuppression. We already agreed short-term immunosuppression isn't the gating issue here. So what are we worried about?

DR. SHERWIN: Somebody could die during the procedure. It could happen; right?

DR. SALOMON: As long as you start off with a patient population that has a clear complication of diabetes, not just diabetes on insulin, per se, then, after that, I am okay with the idea.

MR. SIEGEL: Maybe it is time to move on to other questions in the interest of time. There is clearly not consensus here. I guess I did want to explore one underlying assumption. Is it also--or it is not an assumption. I think Dr. Bluestone just stated it explicitly. Is it the general agreement here that the concerns of exposing somebody who is doing well to, say, short-term--so he is only on immunosuppression for four or five months and then he is off of it because the treatment failed, that that is not a significant or worrisome risk?

DR. SALOMON: We have to take the one sobering data that if you take patients who are on dialysis, get a kidney transplant and the kidney transplant fails and they go back to dialysis, they do very much more poorly than a population that stayed on dialysis.

So the idea here that even short-term immunosuppression and a transplant procedure, per se, would have no negative effect on the patient isn't necessarily true.

MR. SIEGEL: So you might affect the underlying cause of the disease.

DR. SALOMON: The first thing, let's make sure--I am making an analogy to patients on dialysis with a kidney transplant and immunosuppression and that may not be fair.

DR. BLUESTONE: Again, that is apples and oranges. Number one, how much of that poor outcome is because they are on immunosuppression versus the consequence of going back on dialysis suddenly, in the metabolic aspect. I think there is no data to suggest that their worse outcome had anything to do with the fact that they were on immunosuppression for four months.

The second thing is that there is no correlation, in my mind, with the surgery that you went under to get the transplant that failed four months later and the injury of islets and the morbidity associated with major surgery and the possible outcome of that.

So, as you always say, I want it on the public record that I would hate that the outcome of whether immunosuppression on the spectrum is bad is based on dialysis in kidney patients who reject it. I think we can

have a more objective view of this of a large cohort of patients, especially in the autoimmunity setting, who have been given short-term immunosuppression in phase I and some phase II trials.

I don't know of any data that says that the outcome of their disease has been negatively impacted by the fact that they have had immunosuppression for that short period of time.

DR. SHERWIN: Do we know anything about outcomes? There have been a couple of hundred islet transplants. Most have failed up until now. What are the results? How are they done?

DR. RICORDI: I think that the consideration of risk has to be weighted on the proposed immunosuppressive regimen and on the alternatives. So here we are not proposing, as has been for several years, to use massive T-cell-depletion agents. We are not proposing to do total infrared radiation or any major--the induction is like with xenapax with an anti-IL2 receptor, there is low dose of K506--what I am afraid is happening is that we are overregulating what we were thinking was the safe alternative to what is going to happen anyway that is the whole-organ pancreas graft with this same immunosuppressive regimen because these patients will not just take the opinion of whoever as an indication and say, "No; you have

to stick with your 14,000 sticks every year to check glucose and get insulin," that they will go and try to get a pancreas transplant which is a non-regulated procedure, easily accessible and performed increasingly at all major institutions.

So I see the potential that we are overkilling what we consider the safe alternative to whole-organ transplantation when we will be using the exact same immunosuppressive regimen. But I agree that it should be weighted, like what are we proposing? Are we proposing lethal radiation reconstitution with islets and life-long important with methotrexate and cyclophosphamide?

No; we are proposing no steroids. That was one of the major concerns. Low-dose tacrolimus, rapamycin and an induction with an anti-IL2 receptor that has been so far the safest induction treatment ever proposed in transplantation.

DR. AUCHINCLOSS: Before you leave the subject, you just need to point out to the FDA that there might be additional patient populations that should be considered; namely, pancreatectomy patients and type-2 diabetics with minimal or no C-peptides who have reasonable insulin requirements.

There are potentially patients who are not type-1 diabetics who could be candidates.

DR. SALOMON: Does anyone have any other comment

directly on the question of what patient population because I would like to summarize and move on. So it is just patient-population selection.

DR. EGGERMAN: I just wanted to know, does anyone have any idea of what risk islet therapy has on subsequent organ transplantation or subsequent islet transplantation? Is that just a theoretical risk or is there something real? I know about the HLA sensitization which you mentioned but, in terms of actual outcome of organ transplantation--

DR. AUCHINCLOSS: If you sensitize some people to HLA, then you are going to prevent some people from getting kidney transplants in the future. It is not a theoretical risk. It is real.

DR. SALOMON: Or at least they would go on these lists looking for a perfect match or something like that, which can happen, but is definitely detrimental in these days of organ shortage.

DR. EGGERMAN: You have had experience with several hundred patients who have been treated with islet therapies. Have any of them gone on to pancreatic transplantation?

DR. RICORDI: Yes. We actually have experience both on the fact that in simultaneous islet and kidney transplant where you have failure of the islet graft within one year because of failure of the immunosuppressive

strategies with that immune component, the kidney transplant maintains 100 percent graft survival and eventually, in the four-year follow up, are still without a sign of chronic rejection.

We also have cases of patients who had an islet transplant that failed who undergo a subsequent organ transplant with no apparent impact on the transplanted organ. But is this the final word? I think these are very anecdotal reports on very few patients.

But the early indication that we have from the transplant surgeons--Dr. Alejandro is here--in pancreas transplantation or kidney transplantation, there has been no reported negative effect.

DR. AUCHINCLOSS: I think that you would have to start with the assumption, however, that the first kidney followed by a second kidney experience probably applies to islet transplantation as a rough approximation. There, the data would say that the outcome of the second transplant statistically is not quite as good as the first and that the waiting time tends to be longer because sensitization has sometimes occurred.

DR. BLUESTONE: The other issue is that there are a subset of patients who historically, when they get monoclonal antibodies, have a reaction to that monoclonal antibody that prevents retreatment with the monoclonal

antibodies. So, low as it may be, there is a possibility that that would happen.

DR. SALOMON: I would also want to point out that I haven't been convinced. I think that if you transplant somebody, immunosuppress them, they go through all the metabolic gyrations of curing their diabetes for a short period of time, then losing their diabetic control possibly getting some anti-rejection therapy and then going back to being diabetics is not a necessarily neutral event.

I don't think the experience with the problems we have had with kidney-transplant patients is absolutely irrelevant--we seem to like analogies to kidney transplantation in some settings. I am just suggesting there is something to be learned there as well.

Are there any other comments on this?

DR. HARLAN: Two real quick comments on risk/benefit analysis. Even if diabetes wasn't the leading cause of blindness and kidney disease and a major risk factor for blood-vessel disease, you know where I am coming from. Even if it wasn't that, it is still a disease that requires daily therapy, very expensive, very disruptive to a happy lifestyle. That is on the risk side.

On the benefit side, we know from the UKPDS that if you help someone control their blood sugar for one year, it has sustained benefit for them down the road. So even if

this is beneficial for only a year or two, that has demonstrated long-term health benefits if type-2 diabetes is a useful model. And I think it is.

DR. SALOMON: So to summarize this, and I think that the discussion took a while, but I do think that there were some very important points here. I think, with respect to preclinical models of immunosuppression, we all agree that it is a jigsaw. It ought to be based on some preclinical, some clinical, that there is no single model, that probably more than one model ought to be used.

I don't think that is really committing anything that we haven't already discussed in detail.

With respect to the patient selection, per se, that we spent the last half hour discussing, there I think that there are some things that we probably will have to agree to disagree on and the FDA can sort that out their own way.

Clearly, there are those who would say, "Give me a diabetic on insulin and a good informed consent and leave me alone." That has been clearly heard from the committee. There are others who feel that this is pretty reasonable but give us a patient who has clear objective evidence of end-organ, presumably microvascular or neurovascular, disease, microalbuminuria or actually a reduction in renal clearance, early changes in the eye, et cetera.

Then there are those who say that, in addition to that, a very reasonable population to target would be those with hypoglycemia unawareness or those with severe complicating episodes of recurrent ketoacidosis. However, we heard from others on the committee that there it is pretty gray and one has to be concerned about patient compliance, social and psychological factors in deciding that that would be a population to do.

But I think there was general agreement that if you had a process in place that was objective and verifiable that, under those circumstances, it is possible that some of those patients might be candidates.

Am I missing anything? That is kind of what I am coming away with right now.

DR. MILLER: Do you want to answer the first bullet? We still haven't answered the first bullet.

DR. SALOMON: I tried. I really tried. I don't think these guys want to answer that question. I think that the decision here has been there are a number of people sitting here at this table who are ready to go forward. I think the answer is obvious to me that they are ready to go forward.

DR. RICORDI: I can try to summarize what I understand is our consensus here that, in the absence of data emerging from clinical trials in other settings or in

other diseases that prove at least safety of the drugs. If you have a completely new, like, monoclonal antibody untested, that we all agree we would need some data emerging from preclinical testing that shouldn't be limited to small rodents but, potentially, include data from either dogs, pigs or non-human primate and that, in the non-human primates, there is no set preference between total pancreatectomy or streptozotocin-induced diabetes because they both have advantages and limitations.

In one setting, you have a reduced metabolic absorption but a more complete beta-cell exclusion. You may have some residual beta-cell function and you may require additional testing to better define that your islets are actually the ones responsible for the metabolic outcome.

But I think we all agree that some level of preclinical testing is absolutely indicated for agents for which there is no testing available from the clinical experience.

DR. SALOMON: I think we should add in that Dr. Sherwin also made another point and I left it out of my summary. That was, if possible, some data should be provided in an autoimmune model of diabetes because of this outstanding issue of whether or not that is also an impact on survival. I'm sorry I left that one out.

DR. BLACK: I would like to add one more point,

just that, to add to Dr. Ricordi's comments, our criteria for trying the evaluate the risks of a procedure often ask very carefully what is the adequacy of the database, whether it is from in vitro studies, mechanistic studies, mouse models of disease or the clinical field.

Sometimes, the nature of the clinical data makes it very difficult for us to assess a particular combination of agents for whom the other part of the database suggests that there may be concerns. So I think it becomes complex to try to pre-caveat Dr. Ricordi's comments by saying that we can only do preclinical models when we do not have clinical data.

So, sometimes, we will have to supplement the clinical data.

DR. SALOMON: Somewhere along the way, you will have to explain to me the frightening concept that you could pre-caveat something.

DR. PAPADOPOULOS: I just have a question. The one thing that I am still not clear about is we have heard that there is a proposed trial, multicenter trial, to do twenty-some-odd of the these transplants. I still have not heard what the exact eligibility criteria will be for that specific trial.

I presume that that protocol must have been written and there has to be a consensus amongst the experts

as to who will be eligible.

DR. SHAPIRO: I actually presented that in slide form in detail yesterday.

DR. PAPADOPOULOS: Could you just review it?

DR. SHAPIRO: The three patient categories; those with hypoglycemia unawareness, those with metabolic instability and those with early progressive secondary diabetic complications.

DR. PAPADOPOULOS: What are you defining as these early secondary complications? Do you have creatinine cutoffs? What are they?

DR. SHAPIRO: They have got to have a creatinine clearance greater than 60 mls per meter squared per minute.

DR. SALOMON: Speaking as a nephrologist, a creatinine clearance of 60 mls per minute in a 25-year-old person is a terrible creatinine clearance. I certainly would not want any of my children to have that creatinine clearance.

MR. SIEGEL: In diabetics, in particular, with hyperfiltration; yes.

DR. SHERWIN: But it is above; right? There is no limit. It is not below?

DR. BLUESTONE: Correct. They want it at a certain goodness.

DR. SALOMON: I understand. I am just saying that

the range means that you are going to--that's fine. I am just pointing out that it is a very broad range.

We are sort of where we could take a ten-minute break. We are trying to get done by 4 o'clock. What do you guys think? A ten-minute break.

[Break.]

DR. SALOMON: One thing I would like to do is we have got an hour and then this is over. I discussed with the FDA sort of what would be the key couple questions and those we will try and get done now. I would like to spend a relatively short period of time, unless there is just overwhelming dispute is, on this question No. 2 which actually, when it was initially presented to me, I was willing to let go entirely because I agree with something you had said earlier that insisting on HLA typing for pancreatic islet transplantation was to really restrict its future.

But the FDA asked me to put it back on the table and I think that the question I would like to start off with was there was an interesting question from Camillo and that is, given this autoimmunity and some of the data Bernhard came up with with HLA identicals; is there any concern on the part of the group that--not that you would have to HLA match but that, actually, there might be a detriment to even a haplotype match.

DR. AUCHINCLOSS: There is data and it is so controversial that it is not worth even thinking about. The answer is simply unknown, I think. And that extends all the way to the xenotransplant whether the xenotransplant is more resistant or recurrent diabetes. So there is no scientific way to answer your question.

I think the important thing in issue 2 is the issue that is not included. I would probably match for blood group although there is no good evidence there either that that is necessary, but it is just easy and it is prudent. I would not worry about HLA typing.

The question is whether you should do a cross match.

MR. SIEGEL: Both of you have talked about HLA typing. I think what you are saying is you wouldn't worry about HLA matching as an inclusion criteria, I would hope. Or what part of what we are asking the committee on this is that we believe that all of these studies should be collecting HLA data.

DR. AUCHINCLOSS: 100 percent, for sure.

DR. SALOMON: Nobody here would even have thought of that one.

DR. AUCHINCLOSS: But the prospective question that you have not addressed here is whether or not to do a cross match. If the recipient does have antibody against an

HLA antigen of the donor, does that preclude the transplant?

DR. RICORDI: We always do a crossmatch and it is excluded. A positive crossmatch will exclude the islet transplant.

DR. AUCHINCLOSS: I think that would be prudent way to approach it. But maybe you or Bernhard or one of others can actually comment about how good the data is one way or another.

DR. HERING: There are no data, but I guess, in the Edmonton protocol, it may be difficult to do a crossmatch. At the very same time, you can argue if a patient is PRA-negative, has not received any blood transfusion, no pregnancy, no previous transplant, it is completely unlikely that this patient will have a positive crossmatch.

I am not sure whether they actually did weight for the crossmatch. I guess they transplanted right away.

DR. SALOMON: I can't imagine that, by the time they took the organ, by the way, they hadn't finished the crossmatch. But, certainly, by the time they processed the islets--do you guys disagree with that?

DR. LAKEY: It is all being done and it is all done ahead of time before the transplant.

DR. AUCHINCLOSS: So I would do it, but there is no data to indicate that it is actually important, except,

as Bernhard says, where they are PRA-negative, I don't think I would bother to do it.

DR. MILLER: This is a place where animal studies may be of some help in that it won't help you with the autoimmunity question but it will help about whether or not there is any evidence that HLA matching in other species has any effect. So, I don't know.

DR. SALOMON: That is a really good point, actually. One of the things that we talked about was to identify where preclinical models would help. That is possibly a good message to the FDA.

DR. AUCHINCLOSS: I have written that grant twice and not gotten funded.

DR. MILLER: Write it again.

DR. BLUESTONE: I think there is a problem. Number one is that in non-human primates, that is not doable. With rare exceptions, we don't have enough, yet, markers to even do a lot of the matching there; right? Dogs is not doable.

DR. AUCHINCLOSS: This isn't matching. This is a cross match. Sensitize, get an antibody and then see what happens. Does a positive crossmatch cause "hyperacute rejection of islets?" Nobody knows.

DR. SALOMON: You could do A2, for example; isn't that right--in figuring?

DR. AUCHINCLOSS: Nobody knows whether blood group incompatibility is a problem.

DR. BLUESTONE: There have actually been some studies in mice, now, in which presensitization is done. It has been more difficult to suppress rejection. I was always thinking, use the antibody, but you don't get hyperacute. You just can't suppress the regular rejection very well.

DR. SALOMON: I still, though, think all the animal data in tissue transplantation, whether it be skin grafts and, certainly, any organ grafts, that if you are presensitized against an MHC molecule, that you are going to have a detrimental immune reaction.

DR. AUCHINCLOSS: It just is not the case. We do not have the data that HLA antibody causes an adverse outcome for islet transplantation.

DR. SALOMON: I would like to officially say that I was not on the study section nor a reviewer of any of your grants. Are we settled on that? I don't think that is even worth summarizing.

Then what I would like to do is turn the page to page 2. I am going to make the executive decision to skip organ quality, as we did discuss that yesterday. I think that is more getting back into product issues. I would like to, again, just setting up priority, look at this route and site of islet product administration as a question.

Is it desirable for islet preparations to be in direct contact with the portal circulation and what data support this determination?

DR. HERING: Insulin independence supports that this is feasible. It may not be the best site but, before you move to a new site, I think here you should demonstrate preclinical data, that this is actual feasible.

DR. SALOMON: The animal studies have all been done by putting islets under--excuse me; many animal studies have been done putting islets under the kidney capsule. There have been attempts in human patients to put islets under the kidney capsule not, I would say anyone would agree, I'm sure, exhaustive studies.

But there have been some trials and they haven't worked very well.

DR. HERING: Every single transplant failed; right.

DR. RICORDI: This is probably also because of mechanical consideration that the kidney capsule in a rodent or a small animal is like a very thin structure. The human kidney capsule is probably one of the worst places we can put islets. But there are other sites like the spleen. It is an issue that is the object of continuous investigation.

The pancreas, itself, is a major target of future potential new sites.

DR. SALOMON: We could say that a serious objective for preclinical studies would be taking the best that we can do now with human islet verification and test at alternative sites. It probably really should be done with human islets for at least some of these studies; right?

DR. RICORDI: Or at least in a large animal where you have the same kind of mechanical consideration or vascularization.

DR. SALOMON: Good point.

DR. BLUESTONE: I would just emphasize that one of the interesting questions is that the thymus is a potential site as well, but we have to be prepared, at some point, then, to think about younger recipients.

DR. SALOMON: Right. Again, there, though, it would be nice particularly to see successful non-human primate models of that.

DR. BLUESTONE: You betcha.

DR. SALOMON: We tried, with a grant from the Juvenile Diabetes Foundation, and did eight animals with human fetal islets--so there is a difference; not adult islets--into the thymus of juvenile rhesus. We tried it with immunosuppression and without immunosuppression and were uniformly unsuccessful in even finding the tissue afterwards so we would find the transplant site where it was marked.

Does that mean that it won't work? No. Does that mean we picked the perfect immunosuppression? No. I am just saying that there has been experience. I also know Eli Naji has tried it as well and has not had much experience. But I do think the animal data is compelling. So I am not saying it is not worth trying. But that is definitely an interesting topic.

DR. SHERWIN: Has the peritoneum been given up as a potential site, the peritoneal cavity?

DR. RICORDI: Not for encapsulated products but the requirement for islet mass varies with the site that you consider so let's say if you need 1,000 islets in the liver, you would need, like, 1,500 in the kidney capsule and maybe 2,500 intraperitonally to achieve the same metabolic results.

So there are considerations also--and the site may affect other variables. That is why you may need data from a large animal or a clinical model for new sites.

DR. BLACK: What about splenic infusion?

DR. SALOMON: I think Camillo mentioned that. Camillo pointed out that that is another site. There is animal data suggesting you can put it in the spleen or, as you mentioned, the pancreas.

DR. RICORDI: The only caution there is that the human spleen is, in that case--it has been used a lot in

dogs, like intrasplenic infusion. The spleen in a dog is probably one of the largest organs in the body. It is a huge spleen compared to humans. So it has been used traditionally when you have unpurified preparation or where you are afraid of intraportal high pressure or portal hypertension.

Then it is rather safer to put an unpurified preparation in the spleen. But that is definitely another potential site of islet implantation that may have the same requirement of mass as the liver.

DR. HERING: But the spleen is a site that needs a lot of attention. Significant complications were noted in clinical settings with intrasplenic transplantation, either autotransplantation and I think, to some extent, with islet allotransplantation because the anatomy is very complex. In a few instances, islets in majority of injected islets were found in the lung.

So it is something that needs attention. The spleen is not the site to go without careful consideration.

DR. RICORDI: Or the patient with cirrhosis because to get to the lung from the spleen, they have to have collateral--

DR. BLUESTONE: So the question I would have, in terms of site, is I think it is pretty safe to say that the liver has been a site that is used a lot and successfully.

So you don't want to necessarily throw out that baby. What I think the critical issue is here is safety.

Of the things that one can identify in the procedure that could have some morbidity associated with the injection sites is going to be one. What has been the experience in terms of problems that have occurred with this kind of route of implant?

DR. RICORDI: Bernard summarized them yesterday.

DR. HERING: I think simply a lack of efficacy. So why would you do a transplant with some sort of immunotherapy or immunosuppression without any evidence--

DR. SALOMON: Bernhard, we are not talking about that. We are talking about the idea of intraportal hypertension, the possibility of infarcting a lobe of the liver, the possibility of it not going to the liver but infarcting something else or embolizing another organ system. That is, I think, what Dr. Bluestone is asking.

DR. HERING: There has been no single case reported to the registry or communicated at any meeting or published with any significant complications resulting from intraportal infusion of purified and unpurified islets in the '90's, to the best of my knowledge.

DR. EGGERMAN: Didn't you say yesterday that some patients died that were associated--

DR. HERING: This was in the early '80's and late

at

'70's when significant volumes were infused into the portal circulation without heparinization, without maybe adequate washing steps as they are now standard.

This is the experience that we have.

DR. SALOMON: Have you had any instances in these where patients will spike a fever? Has there been any evidence for a disseminated intravascular coagulation? I know any kind of cytokine release syndrome, pulmonary leak, pulmonary edema? Hypoxia? Anything?

DR. HERING: The only complications that have been noted are subcapsular hematoma and then there is one reported death resulting from injury to the hepatic artery and one gall-bladder injury requiring cholecystectomy. That is what has been reported.

DR. SALOMON: Camillo, did you have a comment on that?

DR. RICORDI: Actually, Dr. Alejandro has a paper submitted--I don't know if it is accepted, but reviewing the whole--of percutaneous intrahepatic catheterization of the portal vein for islet infusion and complications that affect hypotension. I think there was that one perforated gall bladder was the worst.

DR. SALOMON: Jeff actually asked a question about thymus. That opens up a door into questions of other potentially immunoprivileged sites. I know there has been

some attention given for over a decade now to the testis, for example, as an immunoprivileged site.

I have always thought that was sexist, but there have been some clinical trials proposed for that. Do you guys have any comments about any alternatives for immunoprivileged sites? Let me say, I don't want to get into fast gene--I think that is for another day.

DR. RICORDI: Then I would limit, definitely, the volume that you infuse.

DR. SALOMON: No argument there; right? Well, I am nonplussed, but let me summarize what came out of this again with the idea of making sure that we have some consensus and that the FDA questions have been answered.

I think there is a consensus that the portal circulation--I'm sorry; let me back up before I summarize. Do you have to put it in the portal circulation? I realize we didn't answer that question specifically. We talked about how good it was to put it in the portal circulation because that is way you have done it. I buy that 100 percent. I was getting ready to summarize that.

But then it dawned on me the question that we didn't talk about briefly was is there a metabolic argument for the portal circulation? We all know there is, but how strong is that relative to, let's say, putting it in the forearm?

DR. SHERWIN: It is more theoretical but I think it makes sense. The question I have is whether injection islets into the portal circulation and having them lodge in the liver is the same as having insulin produced by the pancreas and then diluted in the pancreatic circulation because I would suspect that a lot of the insulin has got to leak--much more insulin has got to leak out into the circulation systemically than it would if it was in the pancreas, for example.

DR. HERING: There is more and more evidence now from small animals studies that intraportal islet transplantation actually induces a state of insulin resistance and is really not a physiological site.

But, at the very same time, it is the most accessible site for clinical transplant studies. There is a long list of arguments in favor of other sites with true portal drainage. Simply, we have to develop the sites in preclinical models before we can proceed.

DR. SHERWIN: That is really what I would emphasize for the future is really sites that would allow insulin to be released into the portal vein rather than directly in the liver. I think that this is much closer to being a peripheral site than people think.

DR. SALOMON: Okay; excellent. Let me start again. I think there is consensus here that, at the moment,

the injection of the islets into the portal circulation makes a lot of sense from the basis of the preclinical models, the clinical experience and I think everyone around the table is comfortable with that.

We do acknowledge that the idea of other sites are very critical to consider and that would be an excellent target for studies in the preclinical models; right?

I think that about summarizes it. Amazing.

The next thing I would like to go to again, just because I want to make sure that this gets covered before we have to stop, is, on the next page, No. 8, and that is outcome measures. I think that we have had some discussion of these and I think Dr. Kenyon did a really nice job with her last set of slides in giving us some sense of what things look like in the non-human primate model in terms of what sorts of things correlated.

Do you want to start, Dr. Kenyon, maybe in saying, in a nutshell in your opinion and experience what should be the best outcome variables?

DR. KENYON: I think it is a series of things. Clearly, blood-glucose monitoring on a daily basis, at least in the first month post-transplant and then you could decrease later on; periodic metabolic assessment by either intravenous glucose-tolerance test or arginine or glucagon stimulation which, I understand, the investigators in the

network are discussing now; what is the best way to test that without stressing the islets; hemoglobin A1c, periodically, clearly.

I think those are the primary ones--reduction of insulin requirement, insulin independence.

DR. SALOMON: One point you made, I wanted you to comment specifically, was you did an IV glucose-tolerance test. Two ways to interpret that--well, actually, there are three ways that you could look at it. Glucose disappearance, KG. You could look at C-peptide stimulation and you could look at insulin levels.

Do you want to comment? Do you need to do all three? Is one superior to the other?

DR. KENYON: I think, clearly, you need to look at all three. It has just been our experience in the monkeys that looking at the glucose release alone, which if you look back at the literature historically, that is what has been shown, that that, alone, really, does not give you a good indication of the functional islet mass.

The glucose response curve can look fairly normal in an animal with partial function whereas if you look at insulin, first-phase insulin release, it correlates fairly well with, in the short term, the number of islets we have transplanted and, in the long term, with whether or not there has been an episode of rejection.

So you can see, in the absence of rejection, a maintenance of first-phase insulin release. Subsequent to a rejection episode, you can see a decrease in that. So I think it gives you a nice measure of graft function. And then C-peptide clearly is important to look at as well.

DR. SALOMON: So, could we say that, again putting this out as something to discuss, that insulin release associated with a glucose stimulation would be more sensitive than looking at the glucose disappearance curve. I guess the reason I bring that up is that, if you look at the experience with islet autotransplants for chronic pancreatitis that I think has been very nicely documented even just recently a follow-up study from David Sutherland and the Minnesota group, many of those patients are insulin independent. I think about 70 percent is the most recent data. Bernhard, you can correct me if I am wrong. But 80 percent of them or more have abnormal IV glucose-tolerance curves.

DR. HERING: This is entirely acceptable.

DR. SALOMON: I was just using it as a check for--if you have a normal IV glucose-tolerance curve, and a normal disappearance, my point was that even without insisting on normal insulin dynamics, that would be quite a great result for an islet transplant.

DR. KENYON: I agree. The slide I showed showed

you that at day 42, the first phase was significantly blunted as compared to pre-pancreatectomy. But that animal was insulin independent and had normal metabolic control. What I am strictly saying is as a measure of functional islet mass, not as a measure of outcome as far as metabolic control.

So, in that case, hemoglobin A1c and the presence of C-peptide and insulin independence.

DR. AUCHINCLOSS: I think there are two issues her, Dan. One is outcome measures and there are dozens of them. And they are relatively easy to list. Norma has even mentioned--and, obviously, you want to get into things like long-term complications, et cetera.

You might want to be thinking about imaging techniques that might be applied to assess islet mass. But all of those are easy. The hard question is which of them turn out to be easy to list.

The question is which outcome represents efficacy. I think the way to frame that argument is to ask the $64,000 question, supposing you got an outcome of measurable C-peptide production but ongoing use of insulin. How good an outcome is that? I think you could make the argument--I would be curious to see what the committee says--that that is a surrogate marker for an acceptable outcome.

DR. HERING: The question, Hugh, is is partial

graft function--let's say C-peptide A1c is normal in the absence of hyperglycemia. Would this justify immunosuppressive treatment long-term?

DR. SHERWIN: Not an easy answer. We don't know the answer. Obviously, it is much easier to manage diabetes if there is some ongoing insulin production, even if it is not adequate to sustain normal glycemia.

So, clearly, there is benefit accrued if you can produce some insulin. On the other hand, we don't know enough about the immunosuppressive--the risk/benefit ratio is really not clear. So I wouldn't want to call it a success. I would think that the outcome would be one for investigation to try to determine whether it was successful or not.

As far as the assessments are concerned, I would propose that there are new methods you might think about. One is now MiniMed has made a glucose sensor that allows you, for three days, to continuously monitor glucose in an ordinary day's circumstances with food.

So it seems to me that hooking these patients up to a MiniMed sensor for three days periodically might give you a nice assessment of their everyday levels of glucose. I think you might learn something from that.

The other thing I might suggest--most of us in the diabetes world are not too enthusiastic about IVGTTs as a

measure of glucose disposal because a lot of glucose is lost in the urine when you give a big glucose load. My sense is if you want to look at glucose levels, you might do a glucose-tolerance test although an alternative approach, which is reasonable, is a frequent sampled IVGTT to look at insulin action and secretion simultaneously.

There are models that have been set up by Bergman that allow one to make an assessment of insulin secretory rate as well as insulin action with using minimal-model techniques. That might be something to do.

DR. HERING: But those are research tools, I guess.

DR. SHERWIN: But you are doing research. I look upon this as a research study, at this point. I am not saying it will be that way forever. I think, because it is a research study, you really want to get as much information as possible to satisfy people that have a metabolic background, like myself.

DR. HERING: We are doing studies like this but I think one other question is is there any assay that can be more or less done at all centers so that we can follow patients using the same assay. I guess here the question is whether this could be an arginine stimulation test which just takes ten or fifteen minutes, can be done on an outpatient basis regardless of blood-glucose concentration.

DR. SHERWIN: Arginine, I wonder about. One of the questions I didn't ask originally is as glucose responsiveness fails, does amino-acid responsiveness fail in concert because, for example, with type-2 diabetes, you lose glucose response of beta-cell function but not amino-acid response of beta-cell function.

So I don't know--if you don't have the answer, then I would not use arginine because it might be a less sensitive measure because people with impaired beta-cell function of type-2 diabetes can have a normal beta-cell response to something like arginine.

DR. KENYON: The reason that I had listed that in the non-human primate studies is there has been a lot of discussion back and forth for a while now on what is the optimal test to use clinically.

We haven't actually looked at that in the monkeys we have done in the past. We are going to be looking at that now, but, really, the use of the test came from interaction with the clinical-transplant people. I think one of them would have to answer, if you have seen a loss of arginine responsiveness in patients who are losing a graft.

DR. AUCHINCLOSS: My impression was that the arginine test became popular because people got so concerned about high glucose loads being toxic to islets. I have to say I have got a lot of doubt about that particular feature

which we will talk about in the moment.

But I think that is really where the arginine test crept into the transplant world in a big way.

DR. HERING: But I think you are right. Whatever you do, you stress islets to release insulin. Whether you use arginine without hyperglycemia or whether you use glucose, I think it is pretty much the same thing you do.

DR. SHERWIN: That is one of the nice things about just getting glucose profiles. You are not doing any stressing to the system. But insulin secretion is obviously a critical measurement. I don't know how useful it might be to do urinary C-peptide over 24 hours as a way of trying to assess integrated insulin secretory levels.

DR. BLUESTONE: I am a little confused because it is a great wish list, but if tomorrow there is, from the FDA's perspective, an IND that goes in from a group of fourteen centers and they have to list the outcome studies that they are going to all be able to do, whether that center is in Edmonton, in the States, in Europe, that they are all going to do the same minimal set that allows the IND to be approved--not all the good research, because that may not be done at all centers, or maybe it will have to be centralized.

What is the subset of these that we agree on has to be done at every center?

DR. HERING: It is a very short list. I think you want to know hemoglobin A1c and you want to know whether C-peptide is present. It basically comes down to very simple measures because we don't want to study efficacy, we don't want to compare whether this approach is now preventing complications or is associated with improved quality of life; not in this trial.

So, basically, we want to identify a protocol that can be utilized in a subsequent prospective study to address this question. But, at this point in time, this would be too much and the Edmonton multicenter trial is not powered to address any of the efficacy questions that could be addressed in subsequent studies.

MR. SIEGEL: Let me suggest something about this issue. This question is, in fact, divided, as you see, into activity measures and efficacy endpoints. While I would not presume to suggest that I know what are the right activity measures, I would urge both the funding bodies and the investigators, in fact, to explore a broad variety of these because to develop this therapy, you are going to need something that is going to give you a faster feedback than whether the patient's kidneys fail.

You take a drug. You may change the dose a little bit but you don't change the molecule a little bit. You do that all the time with transplant procedures. You not only

change the drugs but you make minor changes in how you transplant them. You need some rapid feedback as to some indicator as to whether you are doing something that you think might be better or might be worse.

Similarly, in this case, I think, you are suggesting that you want early indicators of when you can stop exposing the patient to immunosuppression. So there are any of a number of reasons why you would want to have a good measure so that, when you get to the efficacy--so that, A, you can have items that you can optimize to and B, then you can see, in fact, which of them are predictors of efficacy when you are ultimately doing those larger efficacy studies.

They don't have to be done at every center.

DR. SALOMON: It seems to me that what I am hearing now is that there ought to be at least three kinds of tests considered. The first is kind of parameters like how is the patient doing, what is their hemoglobin A1c, what is their glucose doing over periods of time.

I thought the idea Dr. Sherwin had of doing close monitoring for maybe three days in, let's say, a GCRC setting would be useful in some centers. Then there should be a second class of studies that ask the question, is there functioning islet tissue there. Those studies could be a rather simple measurement of circulating C-peptide,

post-prandial bump, maybe an oral glucose challenge.

And then the third would be real functional tests of an integrated nature such as a graded multi-step IV glucose tolerance measuring C-peptide insulin and glucose disappearance. I think, Bernhard, we don't need to worry about whether your trial decides to do all three levels of tests the first time through. We don't have to be that specific.

But, do you agree that that is sort of the general idea?

DR. HERING: I agree that detailed metabolic studies should be done in a selected group of recipients. This is an independent study but cannot be done in the majority of islet-transplant recipients.

DR. MILLER: Why not? It is only 28 patients.

DR. KENYON: These are simple.

DR. HERING: If you are talking about a stepped hyperglycemia clamp assay, if you are talking about a frequently sampled IVGTT, if you are talking about euglycemic clamp studies and if you want to do it at intervals, the people cannot leave the CRC in the first year, more or less.

DR. SHERWIN: We are not talking about that at all--not at all. In fact, if you want to assess insulin secretion, you could do it in ten minutes with an

intravenous bolus of glucose, if that is what you want to do. But everything I said was outpatient. Nothing is inpatient. I don't want people in the hospital. They should be out of the hospital in their ordinary environment.

Even the glucose-monitoring system is an outpatient procedure. Even that.

DR. AUCHINCLOSS: Bob, tell me about the twenty-four hour C-peptide in the urine because, to me, it seems to me the surrogate maker ought to stay focussed on C-peptide. Is the 24-hour C-peptide in the urine a pretty good marker of sort of total production?

DR. SHERWIN: Renal function is reasonable; yes. Not bad. Fasting C-peptide is fine, too. But it is something that should be considered. It is not that hard to do. It is an easy measurement, basically.

DR. HERING: I think you will learn so much by looking at insulin requirements before and after transplantation, A1c levels, basic C-peptide and stimulated C-peptide. I agree, the MiniMed approach should probably be added. I guess the Edmonton protocol is proposing mean amplitude of glycemic excursion which, basically, gives you the same kind of information.

I would limit it. And then you have studies, detailed metabolic studies, that can address an endless list of other questions. But that will not help us right now at

this level. Basically, we want to assess the proportion of patients with full or partial islet-graft function.

This is what we need. Once we have a protocol, then we may want to proceed to the next level of complexity and compare to intensified insulin treatment or pancreas transplantation and then efficacy measures will be completely different.

DR. CARA: I might be coming out of left field asking this, but there is reason to believe, whether you believe it or not is a different issue, but there is reason to believe that insulin might "protect" the pancreas or at least the islet-cell functions of the pancreas and may serve some immunomodulatory role.

Do you know if concomitant insulin treatment post-transplant actually improves ultimate outcome? Is it something that should be considered?

You indicated the need to evaluate the actual function of the transplanted tissue but I am wondering whether it would make sense, in the beginning, to at least maintain some sort of insulin there or whether or not it should. I don't know.

DR. HERING: More or less every single experimental study suggests that insulin administration in the peri-transplant period improves islet engraftment. Insulin can put beta cells at rest. That was the first

hypothesis. Insulin is a growth factor. Insulin is antiapoptotic. Insulin blocks macrophage NO production.

But the question is at what levels. The Edmonton protocol did not administer insulin in a routine manner after transplantation, only if blood-glucose levels, I guess, exceeded 180 milligram per deciliter.

But, at the very same time, the question was not addressed whether peri-transplant insulin administration would have been helpful. So I think you should prevent, definitely, hyperglycemia in the peri-transplant period and the question is what is the threshold that you would like to see.

DR. SHAPIRO: Some people believe that it may actually stimulate the growth and function of the islets. So it is not truly known.

DR. AUCHINCLOSS: To put your question in context, for a period of time, it was sort of the lore that you couldn't do islet transplantation unless you maintained absolutely rigid tight glucose control for weeks after the procedure. But the fact of the matter is that the successful islet transplants that have been done on people generally have been done without tight glucose control.

I don't know about Norma, but I suspect you probably give no insulin after you do islet transplants in monkeys. We don't. We don't bother at all. None of the

whole-organ pancreas-transplant programs worry about glucose control postoperative. None of the small-animal studies maintain--so the lore is a little bit hyped, I think.

DR. HERING: But, Hugh, the point is what is the number of islets required to restore insulin independence. This number may depend on the degree of metabolic control post-transplant. I guess you would agree with this.

In some of the experimental studies where you transplant a very good number of islets, yes; you may see normoglycemia and insulin independence and you may not want to overtreat the recipient.

DR. AUCHINCLOSS: I like James' approach. Just keep giving islets until they come off of insulin.

DR. RICORDI: Actually, one of the debatable issues like whether do you need systemic, like, insulin, exogenous insulin injection, to have metabolic control in the post-transplant period or whether a mild hyperglycemia can stimulate more insulin secreted at the site of implantation in the microenvironment where you really need the growth factor and the antigenic factor of the antiapoptotic.

So I think there is still a little controversy whether you should clamp very closely or whether a mild hyperglycemia may be acceptable. But I would like to echo Dr. Siegel's point that we need to find out markers that can

define good outcome in terms of what is good for the patients.

I think that these endpoints that we are defining are exactly doing that because if you measure C-peptide and hemoglobin A1c, if you assume that you have two levels of success in a cellular graft, it is not like an organ transplant where partial function virtually does not exist.

But, in islet transplantation, you can either achieve complete failure, partial function or complete insulin independence. The measure to assess partial function is C-peptide and whether your normalize hemoglobin A1c levels, because those are outcome measurements that have been, thanks to the studies of the DCCT and others that have been correlated with positive endpoints for patients because, even within the cohort of patients of the DCCT, it has been shown that those patients with type-1 diabetes that have residual C-peptide secretion do better in terms of complication development than other patients.

There have been urine studies in Europe on C-peptide treatment showing that even if you have a C-peptide secretion around 1 nanogram, it may be something beneficial for patients.

So I think C-peptide hemoglobin A1c does not just give us an immediate assessment of how much the islets are working, whether they are working or not, but they also can

be related to some kind of outcome long-term predictions.

DR. SALOMON: Camillo, can I ask you a question, following up on that--well, to everyone, but to you--what criteria should be used to determine the loss of graft function? I guess my question is can you use any of these criteria to diagnose rejection?

DR. RICORDI: It depends if you have partial function or complete insulin independence. But I would say that the first--if you have partial function, the first index that you may have is hyperglycemia and higher insulin requirement compared to what was your baseline when the transplant was functioning. Absence of stimulated C-peptide production, basal and post-prandial, are clear signs for when you lose completely a graft.

You can do a glucagon test and have confirmation of stimulated C-peptide test and have confirmation that there is no more C-peptide production.

DR. SHERWIN: I would bet, although I am not sure, that the best way of testing whether you are beginning to lose function is insulin's response to intravenous glucose over a ten-minute period. If you knew that and could follow it, if you began to lose islet mass, that response would begin to fall off.

DR. RICORDI: The reason I am saying depending on the graft function, because we know from the preclinical

study when we did these monkeys with normal, that if your baseline is insulin independence with an extremely well-regulated glucose level and basal in the 80's range, even suspect rejection when basal or post-prandial--when you have just a little blip in post-prandial, it is already an indication--when you have a partial function, it is more complex because you may have more variable baseline or post-prandial glucoses.

Then unless you do very frequent IVGTT, it may be very difficult to catch at an early time.

DR. HERING: There is one important question in this context; should islet-transplant rejection be treated.

DR. SALOMON: You sort of anticipated my next question. What is the answer?

DR. HERING: This depends on the availability of early markers of rejection, I think.

DR. AUCHINCLOSS: That's right.

DR. KENYON: I would say yes if we have an agent that can effectively reverse it. I agree with Camillo, what he is saying. It is so much cleaner if the animals are clearly insulin independence. Using the loss of first phase or a blunting in it as a predictor of rejection is difficult because you would have to do it fairly often.

We have, retrospectively, seen animals that had a rejection episode and, just serendipitously, we had done an

IVGTT the week before and there was clearly a loss of first phase. But, especially, depending on the initial mass transplanted, they can be having some kind of an ongoing rejection for a while, I think, without us detecting hyperglycemia.

Just like when you are getting diabetes, you can lose a lot of cells before you actually detect hyperglycemia. With regards to treating them with insulin post-transplant, when we have done it, Hugh, is when the animals have been hyperglycemic. So usually that is associated with the marginal islet mass and then we will treat them to keep them below 200 post-prandial and around 100 fasting.

I have had monkeys that actually required significant amounts of insulin that got a marginal mass and actually came off insulin after the first 100 days. But as far using that as a marker, it is difficult to say--if the animal has partial function, I think it is important to give insulin because they may come off and it keeps their general health status.

But, as far as protecting the islets, post-transplant, we don't have any data to support it one way or the other. It is just a matter of metabolic control.

DR. AUCHINCLOSS: I would say two things. One is, I think, I buy the point that probably glucose control

matters somewhat but probably not to the degree of religion that we had about five years ago. But I was actually prompting you to point out that you believe you have treated rejection episodes and reversed them an maintained islet mass sufficient to maintain normal glycemia.

DR. KENYON: We have; with anti-CD154, multiple episodes of rejection in the monkeys.

DR. MILLER: What is the registry data about treating rejection? Has that been captured in the registry, because I think when we are looking at risk to patients, I think that the protocol should very much standardize what gets done and how soon you stop, the less immunosuppression, so that there are clear-cut answers when the pilot is done how you manage rejection.

DR. HERING: There is only anecdotal data, and I am not aware of any protocol that consistently reverses rejection. So, hyperglycemia is a very late marker. We know this. It is conceivable that 80 percent of the islet mass is gone by the time you see hyperglycemia, or 50 percent, you can argue.

OKT3, ATG, steroids have been tested, but anecdotal data, at best, are available.

DR. SALOMON: I have to say, it sounds like a 24-hour urine for C-peptide that was quantitative might actually be--

DR. HERING: If you look at the normal range of C-peptide in the urine, it is anything, I guess, from 5 to 200 microunits or whatever. I don't know. But it is a wide, wide range. There is one paper in the literature, The Pitfalls of Urinary C-Peptide Analysis. This was published by Ken Polonski. If you really want to study C-peptide, then you have to study the C-peptide kinetics of a person. So you have to use radioactive C-peptide and have to go into a lot of details if you really want to develop a sensitive assay.

DR. SHERWIN: That's correct. The other thing I would emphasize again, and you are right about glucose being a late marker, but one thing that I have been struck by with the glucose monitoring is that, in people with normal A1c's that we aggressively treat, let's say, with pumps, once you put them on a continuous monitor, there are a lot of abnormalities because you are getting--the immediate rise and fall is much more abnormal than we suspected by getting a continuous readout.

So I think you may detect subtle abnormalities in post-prandial glucose metabolism with that kind of an assessment. I surely would try it as a trial in your study, in not necessarily every patient, as a way of trying to pick up early rejection because, obviously, that would be critical.

DR. HERING: There is, now, I guess, some software some mathematical modeling software, so it could address the question whether a given glycemic profile could be an early marker of rejection; right.

DR. SALOMON: We are getting a little bit toward the end here. I just want to make sure that we get the highlights. One thing that we haven't--we have sort of been talking about 8a up until now, of course, on purpose. Can we just spend the last couple of minutes here on 8b, the idea here being what kind of efficacy parameters would be reasonable for really judging an outcome.

What would you accept as a good outcome? What is the range of things? Obviously, everyone understands that perfect islet function is a good outcome, but what about the intermediates there?

DR. HERING: One outcome measure is healthcare dollars per quality-adjusted life years saved.

DR. SALOMON: Anything else?

DR. RICORDI: I think C-peptide secretion with normalization of hemoglobin A1c levels in the absence of severe hypoglycemia would be a gold standard of treatment now.

DR. SALOMON: Even if the patient was still on insulin.

DR. RICORDI: Yes. I am saying intermediate

outcomes, not--

DR. SALOMON: I understand.

DR. AUCHINCLOSS: Are we sure we agree on that? I even saw you, Bob, nodding your head yes.

DR. SHERWIN: Yes.

DR. AUCHINCLOSS: I think that is a very fundamental point for this committee if it really agrees that C-peptide, normalization of hemoglobin and A1c is a surrogate marker for a good outcome in a trial even if you are on long-term immunosuppression.

DR. SHERWIN: I think--would you say "good?" It is an intermediate outcome that I would accept as acceptable from an experimental perspective. I don't know whether it is a good outcome or not because I have no way of assessing the long-term effects of immunosuppression.

But I think it is something that is a reasonable one to look at. It would be not an unacceptable outcome. Let's put it that way.

DR. BLUESTONE: I guess the question I have--this is my earlier question, now, an hour later. If at one year, somebody had a partial functional islet graft but was on severe immunosuppression with this protocol, would you leave him on the immunosuppression?

DR. RICORDI: You give him another informed consent.

DR. AUCHINCLOSS: You would actually give him more islets.

DR. SHERWIN: I would go on. I think I would go on. I need to know more--hopefully, I would have learned some more as I went along. I am not saying that it is inappropriate therapy, really; no. And I don't know the answer to it. It is an experiment that, as long as it is conformed consent and we are getting a good outcome from A1c, I think it is an experiment worth seeing, if the patient is informed.

MR. SIEGEL: I guess more of what we are getting to with this question, though, would be what outcome would be convincing that you have a favorable risk/benefit, either a measure of benefit or reasonably likely to predict clinical benefit, to the extent that you would feel this is what you need to know to say yes, this is an effective treatment.

DR. SALOMON: Give us another minute. We are getting there.

DR. AUCHINCLOSS: Jay is asking the right question because I was trying to phrase it that this was a surrogate marker for a good clinical outcome. Bob answered the question, I think, by saying, yes; you ought to go ahead and study that.

DR. CHAMPLIN: But the long-term outcome is,

obviously, reducing the end-organ damage and that, at least right now, correlates with the hemoglobin A1c the best and, at least for a surrogate, in the short term, that would be the gold standard.

I guess the other aspect is is the patient suffering from their immunosuppressive treatment. If they are doing well without infection, without renal failure or any toxicity from those drugs, then there is little harm in continuing it. So that has to be considered as well.

DR. CARA: I have a couple of comments. One is that, regardless of whether or not the glycohemoglobin has been improved or normalized, I think one of the important issues is to sort of continue the ongoing monitoring that we routinely provide to individuals with diabetes to make sure that we are, in fact, reducing the incidence of kidney disease, eye disease, and so on and so forth.

I think another important issue is the quality-of-life issue. We may not necessarily "cure" individuals with diabetes, but if we can improve their quality of life, either by reducing hypoglycemia or frequent episodes of ketoacidosis or hospitalizations or whatever, I think that is of clear benefit.

MR. SIEGEL: I would infer from that, though, that when--and I heard that the studies that are being planning now are not at that stage of proving clinical benefit, when

we are looking at that, then, those comments would also relate to what sorts of patients you would want to study.

If you want to show you are preventing complications, you want to study a patient population in which you know you have a reasonable incidence of what complication to expect.

Or if you want to improve quality of life, you want to study patients whose quality of life needs improvement.

DR. CARA: But there are a couple of different ways that you could, obviously, do that. But I think the historical data that we have, thanks to the DCCT, provides us with fairly substantial information as to the natural history of diabetes.

If we can impact that in any positive way, I think that is a very important issue.

DR. SHERWIN: There is one issue, actually, revolving around that question. Again, I don't know enough about transplantation; most people with diabetes die of heart disease and macrovascular complications. My impression is that people who get transplants have a high rate of macrovascular complications.

So the one issue that we have not focused on and I am sorry I didn't really focus on it before is what do we know about transplantation in general with respect to

macrovascular disease and could we be accelerating macrovascular disease in this patient population.

That might be one of the things we monitor.

DR. LEVITSKY: I thought most of that was due to the glucocorticoid but maybe I am wrong about that, in renal-transplant people, people who are not too controlled. My question, actually, related to, as we were discussing the previous scenario with the patient who was sort of a half-way patient, it seemed to me that we were discussing an N of 1, not an N of however many patients are going to go into a study.

I think I would like people to refocus the question in terms of if the outcome of this study is that everyone enrolled in it, or a certain percentage of people enrolled in it, has that same scenario, that they are all sort of halfway there but not completely off insulin, not if one single patient is in the study is there and you are making an individual patient decision, what kind of outcome do we want for the entire study.

Does 50 percent of the population have to be completely off insulin? If 50 percent of the population if on insulin but has a better hemoglobin A1c, is that an effective outcome?

DR. SALOMON: I think that is a good way of posing the question. I don't know that we need to come up with an

answer to that, but I think that--

MR. SIEGEL: Dr. Bluestone has argued, I think, that the argument for posing it in terms of the individual patient is that it is only the individual patient who is experiencing that benefit who is also experiencing the risks of prolonged immunosuppression. So, if that is the main risk you are wanting to counterbalance, you can look at it that way.

DR. CHAMPLIN: I would argue that if you can be successful in some patients, some meaningful fraction of the patients, that would give you promise that improvements upon the procedure, giving more islets, optimizing immunosuppression, doing things better, could get you up to 100 percent.

So the part-way solution, I would view, is good for a step that would justify carrying on.

DR. SALOMON: We are near the end here, so what I would like to do is try summarizing this last question of the two days.

DR. CARA: Could I make one more point? That is the issue that--I think we sort of agree on the things that we know we would need to be looking at from the point of view of diabetes, but I am not so sure that we have a good sense of what we routinely don't look for that we probably should be looking for in a population of individuals that

are undergoing islet-cell transplantation.

The sort of thoughts that occur are should we be looking at issues like bone integrity as a result of continued chemotherapy. Should we be looking at a variety of other issues related to either the treatment of the concomitant therapy?

DR. AUCHINCLOSS: The answer is yes, we need the long-term data.

DR. CARA: And, if so, what?

DR. AUCHINCLOSS: The question is what is the short-term surrogate endpoint. I just wanted to come back to that and say I don't personally agree with the statement that I made about partial function.

I believe that an acceptable surrogate marker is insulin independence. I think if you had people insulin independent, you could call that a success. I would actually agree with Dr. Sherwin. I would not feel comfortable accepting, at this point, partial function as demonstration of benefit.

I understand that, in both cases, you go ahead and get long-term data to verify the surrogate endpoint. But I think, at this moment, I would have to say that insulin independence is the surrogate marker I would take.

MR. SIEGEL: Can I ask--I am enjoying this discussion, but I hope we won't leave Dr. Sherwin's question

hanging because I would like to hear more before we go home as to whether are there specific concerns about making macrovascular disease worse or should it be looked at--can you look at it as an endpoint for making it better and how would you look at it.

DR. SALOMON: I think that the point is, and I think that is sort of what Hugh is getting at, is that, within a twelve-month time frame, that is not so very easy to do, frankly, in any objective way. The fact that a risk is there, however, which was alluded to by Dr. Levitsky, Dr. Cara and Dr. Sherwin, is real.

Steroids, alone, are not the only cause for accelerated atherosclerotic vascular disease in transplants. In terms of bone disease, it is known cyclosporine and FK506 do increase bone turnover and decrease bone deposition which is something that has not often been made a big deal of, but it is actually a very real thing.

So I think that there are some potential deficits. But, again, I don't think that you could do bone densitometry in a twelve-month time frame and significantly see differences that would be relevant.

DR. SHERWIN: But you want to do it baseline, then. You are telling me you want to do it baseline because you might continue this trial for five years. It would be good to have that baseline information.

I also think you should do, then, carotid-artery ultrasound. Then the issue is, in other transplants that people do, they do coronary angiography. I am not trying to say that is what I--

DR. SALOMON: I think there is a lot of interest in kidney and heart and liver transplantation with these cardiovascular risks. Let's face it. It is the most common cause of death in vascularized organ allografting, more common than dying because of the loss of your graft which is sobering for all of us.

But we are very frustrated by the fact that there are very few and very poor measures of it. You could spend millions of dollars trying to do quantitative coronary angiography or what they call IVUS, intravascular ultrasound. I don't think anybody wants to go there yet with the first few islet transplants.

DR. SHERWIN: But doppler ultrasound of the carotid artery seems to correlate reasonably well with macrovascular disease. It is surely being used by the DPP as a surrogate marker. It is not very difficult to do.

DR. SALOMON: Again, this is not meant as an argument. I do want to end at 4 o'clock because we are going to lose people on the committee. I thought, before we walk away, that we should try and summarize this last part.

For 8a, my sense of the committee is that there

are four kinds of tests that you go from simple measures such as their insulin dose, their daily glucose levels, to more complicated tests such as the stimulated secretion of C-peptide, the glucose-disappearance curve.

Then the third level would be more complicated integrated tests which would include stimulated glucose, stimulated insulin, release, stimulated C-peptide release and then, finally, a fourth level that I think Dr. Sherwin made me aware of that would even require a hospital admission where you start getting into glucose clamping.

I know, Dr. Sherwin, you were not suggesting that we do any of those things, but there is a fourth level of testing out there that could be done in a metabolic unit. I think Dr. Hering made the point that he thought you had to keep that in mind, not to get completely carried away.

I think that the idea would that, at this point, it is probably too early to say what criteria would be used to determine the loss of graft function short of someone completely off of insulin who suddenly is back on their maintenance dose of insulin, something really obvious with no detectable C-peptide. You don't need to get hit over the head with a two-by-four to pick that one up, but more subtle changes and, particularly in patients who might have partial responses, this could be very difficult.

In terms of 8b, the idea of--

MR. SIEGEL: Before we leave that, am I not correct in having heard the committee say that, in fact, it would be a very important goal to identify early measures of dysfunction for any of a variety of reasons but, notably, to treat rejection but potentially other reasons as well?

DR. SALOMON: Yes; I think the committee agrees.

MR. SIEGEL: That there are potential markers out there and that, for the most part, the only argument against those potential markers was that, in some cases, they might be inconvenient or costly to do.

DR. SALOMON: I think that, overall, what we are trying--I think what the committee is telling you is that, right now, having not had much of an experience with successful islet transplantations, certainly under this particular circumstance and protocol, that it would be premature to tell you what measures, that they should be measured and that that one of the major objectives of the trial should be to answer that question with real data.

In terms of 8b, that, of course, is the idea of what would be the endpoint benefits of a trial like this. There, I think, there was a little bit of lack of clarity on the part of the committee. I think concerns were raised that it is easy, if everybody is off of insulin with great insulin and glucose metabolism.

It is not quite so easy to decide on patients,

let's say, who are still on insulin but have measures that clearly would suggest that they have a stability of their diabetes.

However, I think that, for example, the Edmonton group would say if these are patients who had really severe hypoglycemic episodes or had severe ketoacidosis, complicated ketoacidosis, episodes that those patients really would be getting a significant benefit from this study and probably would justify that.

I think we are all clear about the fact that we don't know what the long-term consequences of this particular immunosuppressive regimen is in this particular group of patients and that that makes this determination a little bit more complicated.

DR. MILLER: Could I just add something to what you are saying. It is not really clear that, if they are under better control--i.e., no DKA or hypoglycemia--that that is an effect of the graft, itself. I mean, these patients will then be changed into a very intensive monitoring roll and so it could be an epiphenomenon.

I disagree that that is an endpoint, especially in these early trials. I really think that, in the earliest trial, the goal is to get as much information as possible to determine the safety and the preliminary efficacy.

This question about how to determine what is for a

phase III trial, I think, is very premature at this time. Let's get some data you can get these in before you start planning a phase III trial.

MR. SIEGEL: I would agree. By the way, I think that point is very well taken. There is a lot of data out there which suggests that, in almost all diseases, that patients who enter clinical trials do better on their trial than they did in the period proceeding the trial.

Given what we have heard about the issues of poor management and whether that represents optimization, one might expect that here. I will toss out something that I am sure nobody will think is a good idea, at least nobody is actually doing the experiments, which is, at some point, and I agree with you entirely, Carole, that this is not the point, but at some point where one were studying this, an interesting way to get at that question, although possibly not feasible, would be to take brittle diabetics and, actually, to randomize them and have some of them in an intensive management program.

Once you had a therapy that you knew was reasonably effective, you could answer some important questions.

DR. SALOMON: I think Carole's point is excellent. The point I was making was simply that, if the Edmonton group puts forward the idea that those are suitable patients

for entry into such a trial, accepting the significant implications, risk, et cetera, to that patient, I didn't think it was unreasonable to put it in the list of things that would be reasonable outcome measures.

However, the potential that that might be a clouded outcome measure is well taken.

Then, lastly, but I don't at all unimportant, is the point brought up at the end by Drs. Sherwin and Cara and Levitsy that the potential of cardiovascular risk factors, bone and other somatic complications of the therapy, really are significant and they are clearly factors in allograft experience with these immunosuppressive drugs and will have to be a parameter.

I think that kind of summarizes it.

DR. RICORDI: May I make on brief comment. I completely agree that hemoglobin A1c alone could be a marker of better management of the patient. That is why you capolate with C-peptide that cannot obviously emerge out from nothing just because of management. But it is very important also that as soon as these patients enter in the candidate list, they start--they are treated with intensive insulin management.

We, indeed, are using this Teledox system that Dr. Alejandro has been using with patients entering the candidate list which manage very closely glucose levels that

you can, indeed, improve even the insulin requirement before transplant. You have to make sure that your baseline is what you can achieve with close monitoring and ideal patient treatment and then judge what is the additional component of the transplant.

MR. SIEGEL: If you enter somebody because of asymptomatic hypoglycemia or brittleness, you put them on the candidate list, and you have this intensive monitoring, do you then confirm that they remain brittle despite this intensive therapy before you actually transplant them?

DR. RICORDI: Yes, because you have to have tried to optimize treatment before.

DR. SALOMON: I think, again, a couple of different times, we have made the point that the baseline, and establishing the baseline of these patients before enrolling in the trial for any one of these parameters is going to be critical. I think that is true. It is true of the cardiovascular and the bone diseases, et cetera.

I would like to end here. I want to thank everyone on the committee, all the speakers who joined us today, the FDA, Gail Depolito, her staff at the FDA and everyone else for their participation today.

Thank you again.

MR. SIEGEL: Thank you all; a very informative and interesting discussion.

[Whereupon, at 4:50 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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