TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

TWENTY-SIXTH MEETING

OPEN SESSION

VOLUME I

Pages 1 thru 295

Bethesda, Maryland
March 20, 2000

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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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P A R T I C I P A N T S

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Carole B. Miller, M.D.
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Lynne L. Levitsky, M.D.
Jose Francisco Cara, M.D.
John M. Coffin, Ph.D.
Edith Bloom, Ph.D.

GUEST SPEAKERS:

Robert Goldstein, M.D.
Camillo Ricordi, M.D.
Bernhard J. Hering, M.D.
John O'Neil
Norma Sue Kenyon, Ph.D.
A.M. James Shapiro, M.D., FRCS(C)

GUESTS:

Jeffrey A. Bluestone, Ph.D.
Jonathan Lakey, Ph.D.

FDA PARTICIPANTS:

Gail Dapolito, Executive Secretary
Jay P. Siegel, M.D.
Karen D. Weiss, M.D.
Darin J. Weber, Ph.D.
Philip D. Noguchi, M.D.
Lauren E. Black, Ph.D.
Thomas L. Eggerman, M.D., Ph.D.

C O N T E N T S

P R O C E E D I N G S

Welcome

DR. SALOMON: I would like to go ahead and get started; we have a long day. Just as with the airlines, if you are not going to the Biological Response Modifiers Advisory Committee then you are in the wrong room or the wrong airplane. We have a lot to cover and it may seem like that from time to time today.

Anyway, it is a pleasure to be here with all of you. We will begin with Gail Dapolito reading the official conflict of interest statement, after which I think we will go around the table and have everyone introduce themselves, which has been sort of a tradition on this committee, and then get going with the meeting agenda this morning. Gail?

MS. DAPOLITO: Thank you, Dr. Salomon. This announcement is made part of the record at this meeting of the Biological Response Modifiers Advisory Committee for March 21, 2000. Pursuant to the authority granted under the Committee Charter, the Director of FDA's Center for Biologics Evaluation and Research has appointed the following participants as temporary voting members: Mr. Antonio Benedi, Drs. John Coffin, Joan Harmon, Pamela Hartigan, and Ms. Alice Wolfson. In addition, the Senior Associate Commissioner of FDA has appointed Dr. Jose Cara, Dr. Lynne Levitsky and Dr. Robert Sherwin as temporary

voting members.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all relevant financial interests reported by the meeting participants. In accordance with 18 USC 208, the following participants have been granted a waiver of general applicability which permits them to participate in the committee discussions on human pancreatic islets for the treatment of diabetes: Mr. Benedi and Drs. Auchincloss, Cara, Champlin, Harmon, Hartigan, Levitsky, Miller, Papadopoulos, Ricordi, Salomon, Sausville, Sherwin and Ms. Wolfson. In addition, the agency has approved a waiver for Drs. Hugh Auchincloss and Esperanza Papadopoulos which permits them to participate in the discussions related to the xenotransplantation subcommittee report.

With regard to FDA's invited guests, the agency has determined that the services of these guests are essential and, at the request of the acting chair, they have been invited to participate in the islet transplantation discussions.

The following interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants: Dr. Jeffrey Bluestone reported that he collaborates with the Islet Transplant Center at the University of Minnesota. He

also has received research funding for islet transplant research from the Juvenile Diabetes Foundation and NIH. Dr. Robert Goldstein is employed by the Juvenile Diabetes Foundation International. Dr. Bernhard Hering is employed by the Islet Transplant Program at the University of Minnesota. Dr. Norma Kenyon is employed by the Diabetes Research Institute at the University of Miami. She also received research grants from Biogen and is a consultant on islet transplantation. Dr. Jonathan Lakey is employed by the Islet Isolation Laboratory at the University of Alberta, in Canada, and is the co-director of the Juvenile Diabetes Islet Distribution Center in Edmonton. Mr. John O'Neil is employed by the Joslin Diabetes Center. Mr. James Shapiro is employed by the Clinical Islet and Pancreas Transplant Program at the University of Alberta, in Canada.

In the event that the discussions involve other products or firms not already on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name, affiliation and address any current or previous financial involvement with any firm whose products you wish to comment

upon.

Copies of the waivers addressed in this announcement are available by written request under the Freedom of Information Act. Thank you.

Introductions

DR. SALOMON: I think we are going to go around and introduce ourselves. We will start on the left.

DR. LAKEY: Jonathan Lakey. I am Director of the Clinical Islet Isolation Laboratory in Edmonton, Alberta Canada.

DR. KENYON: Norma Kenyon, Associate Director for Research and Program Development, Diabetes Research Institute in Miami.

MR. O'NEIL: John O'Neil, Manager of the Islet Isolation Laboratory, the Joslin Diabetes Center, and the JD Center for Islet Transplantation at Harvard Medical School.

DR. HERING: I am Bernard Hering. I am Director of the Islet Transplant Program at the University of Minnesota.

DR. SHAPIRO: I am James Shapiro. I am Director of the Clinical Islet Transplant Program at the University of Alberta in Edmonton.

DR. RICORDI: I am Camillo Ricordi, Diabetes Research Institute at the University of Miami.

DR. LEVITSKY: Lynne Levitsky, Chief of Pediatric

Endocrinology at Mass. General Hospital.

DR. SAUSVILLE: Ed Sausville, Developmental Therapeutics Program, National Cancer Institute.

DR. CHAMPLIN: Richard Champlin. I am the Chairman of the Department of Blood and Marrow Transplantation at M.D. Anderson Cancer Center.

DR. SALOMON: Dan Salomon. I am a research scientist, Department of Molecular and Experimental Medicine, the Scripps Research Institute in La Jolla.

MS. DAPOLITO: Gail Dapolito, executive secretary. I would also like to introduce the committee management specialists here today, Ms. Rosanna Harvey and Ms. Denise Royster.

DR. MILLER: Carole Miller, Johns Hopkins Oncology Center.

DR. PAPADOPOULOS: Esperanza Papadopoulos, Allogeneic Bone Marrow Transplant, attending physician at Memorial Sloan-Kettering Cancer Center, in New York.

DR. AUCHINCLOSS: I am Hugh Auchincloss, the Director of Juvenile Diabetes Foundation, Center for Islet Transplantation at Harvard Medical School.

MS. WOLFSON: I am Alice Wolfson, and I am here as the consumer representative, with no medical background of this sort.

MR. BENEDI: My name is Antonio Benedi. I am the

past president of Transplant Recipients International Organization and I am a liver recipient.

DR. HARTIGAN: Pamela Hartigan. I am a statistician at the Department of Veterans Affairs and Yale University.

DR. HARMON: I am Joan Harmon. I am Senior Advisor for Diabetes at the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

DR. BLACK: Lauren Black, pharmacologist in the Division of Clinical Trials, FDA.

DR. WEBER: Darin Weber, a product reviewer in the Division of Cellular and Gene Therapies at the Center of Biologics.

DR. NOGUCHI: Phil Noguchi, Director of the Division of Cell and Gene Therapy.

DR. SIEGEL: Jay Siegel, Director of the Office of Therapeutics at the Center for Biologics.

DR. SALOMON: Everybody passed with 100 percent on this microphone button thing. As I am sure to be one of the major offenders later, we will all leave it at that.

I think that at this point it is appropriate to begin. I just wanted to note that Dr. Goldstein from the Juvenile Diabetes Foundation International, Dr. Sherwin from Yale, and Dr. Jeff Bluestone will be joining us later. So,

they may filter in.

It is my pleasure, and with little introduction needed, to call on Phil Noguchi, from the Division of Cellular and Gene Therapies of the Center for Biologics Evaluation, CBER. Phil?

Topic I - Islet Transplantation

FDA Introduction

DR. NOGUCHI: Thank you very much, Dan, and I apologize for my voice this morning. First of all, we would like to thank the committee for taking their time and effort to both listen and to advise the FDA in this very exciting and old but new field, as I think you will hear today. I would especially like to thank the staff members of the Division of Cell and Gene Therapy and Clinical Trial Design and Analysis for putting together this program, formulating the questions and in general making sure that the upper management, namely Jay and myself, were always kept informed of the progress of this committee meeting.

Over the next two days it will be a discussion of the challenges of clinical islet cell transplantation. You will be hearing presentations on the current clinical reality, on some of the animal models that have been developed and, very importantly, on both the public and the private funding of this area which will give it the ability to actually move forward in a coherent and very active

manner.

We will also be asking for advice for the FDA on islet cell preparation, that is, how best to make them; how to characterize them; how to test them on animals; and on the clinical trial design, such as the best trials of administration and dose, questions of repeat administration; and what might be the most appropriate outcome measures, and not the least, immunosuppressive strategies.

This is what I would very confidently call an extremely ambitious program and, therefore, I will cut my remarks right here and just once again thank you all and welcome you all to our active two days.

DR. SALOMON: Thanks, Phil. The first part of this session today, which will start now and run to our first break at 10:50, will consist of a series of three presentations by three leaders in this field, and I think it is a real treat to have them here and to share this sort of foundation data that I think will be very important in terms of guiding the discussions that will go on this afternoon. The first presentation will be given by Dr. Camillo Ricordi of the Diabetes Research Institute, University of Miami School of Medicine.

Rationale for Islet Cell Transplantation as an Alternative to Whole Organ Pancreas Transplants

DR. RICORDI: There is always a little trepidation

with the first presentation and the projector and the computer, but it appears to be working so we are lucky so far.

[Slide]

I have the job to review briefly the rationale for why we are proposing islet transplantation, and I would not strictly put this as an alternative to organ transplantation but as one of the approaches in biologic replacement that may eventually, in part, replace the need for a whole organ transplant. Many of the comments are more extensively reviewed in a chapter that has been published by Simeon Taylor in Current Reviews of Diabetes of which Dr. Hering and myself are co-authors.

[Slide]

Mainly we consider pancreas and islet cell transplantation as the most physiologic way you can replace the pancreatic endocrine function in patients with Type 1 diabetes. Even though there have been some highly experimental protocols in Type 2 diabetes, Type 1 diabetes remains the main objective and major target for this kind of treatment.

[Slide]

So, the primary objectives of the treatment of transplant procedures are to normalize metabolic control to prevent, halt, or reverse the chronic complications of the

disease. So, in this direction, normal glycemia is the primary endpoint since it has been shown in another study how important it is to obtain normal glucose and metabolic control in the absence of hypoglycemia. So, in this regard, hemoglobin A1c alone may be misleading because you may have reduced hemoglobin A1c and have several episodes of hypoglycemia, but normal glycemia through clamping of glucose levels in the normal range is the more desirable endpoint.

[Slide]

So, even if insulin independence is not the primary endpoint for several trials, freedom from insulin injection and glucose monitoring is, for sure, the first and most desired immediate effect that patients would like to see after an islet cell transplant procedure.

[Slide]

I mention normal glycemia in the absence of hypoglycemia because it has been shown as a limitation that it is a complication. That is, in any regimen trying to increase insulin treatment with multiple injections, going towards very intensive insulin treatments, you see that you have an ideal target to shift A1c levels towards the normal range, or to the left of the curve, but if by any chance you can see that as reduced hemoglobin A1c, reducing the risk of complications -- in this case retinopathy -- you also

increase dramatically the risk of severe episodes of hypoglycemia. This is with intensive insulin therapy. So, this shows, on one side, how important it is to normalize glucose levels and, on the other side, how difficult it is to achieve this in all patients.

[Slide]

This is a slide from Dr. Kenyon's experience. It compares what can be achieved with a functioning islet transplant compared to what can be considered an intensive insulin regimen and its effect on glucose levels. So you see that, despite multiple insulin injections in patients with Type 1 diabetes, it is very difficult to maintain close control of glucose levels. If you have a functioning islet transplant, or in this case several islet transplants in non-human primates, you can really clamp in a close range glucose levels.

[Slide]

So, pancreas transplantation has the advantage, of course, that has resulted in complete insulin independence with normalization of hemoglobin A1c levels in the majority of the successful cases. So, this is an endpoint for the whole organ transplant that is readily achievable today. The penalties are that there are still operative and post-operative risks related to the fact that it is a major surgical procedure, and the need for immunosuppression for

the rest of the patient's life.

[Slide]

But there are some important data emerging from pancreas transplantation, including the fact that a tremendous advantage has been shown for patient survival that was improved by 59 percent at 10 years post-transplant compared to a patient receiving kidney transplant alone in Type 1 diabetes. There is a lot of discussion because these data were not prospective, randomized trials. Some people say, well, maybe the patients receiving pancreas transplantation and kidney were a better patient population, with less risk than the ones who don't qualify for the combined procedures, or those who received the kidney alone may be patients with higher risk but, nevertheless, there is an indication that, hopefully, will be confirmed in prospective trials.

[Slide]

In islet transplantation the advantages are mainly related to the ease of the procedure at the time of the transplant, but it is a rather complex procedure for transplanting in processing and purifying the islets which virtually eliminates the operative risk because it is just like a blood transfusion, currently performed generally in the portal system. The penalty has been that we didn't consistently achieve insulin independence, and the results

have been generally reported as functioning islet transplants, with C-peptide secretion and decreased insulin requirements rather than complete insulin independence.

[Slide]

In addition, in pancreas transplantation we have an organ that is immediately vascularized with the islets that are surrounded by their native matrix. So, they are surrounded by their native microenvironment of the organ where they are supposed to be to begin with. In islet transplantation, the islets have to readapt to a new microenvironment at ectopic sites, such as the liver, increasing the likelihood that a fraction of the transplanted tissue may be lost, in what we call early graft loss, before they are fully revascularized and can adapt to the new ectopic site.

[Slide]

So, the indications for both procedures are currently justified in patients already requiring a simultaneous organ, like a kidney or liver, transplant for islets and mainly in patients that are already treated with chronic immunosuppression so that in the case of the islets the additional islet transplant doesn't represent an increased risk in immunosuppression or drugs that patients have to receive.

[Slide]

In addition, we have other patient categories that have been now targeted for trials of islet transplantation alone, and also in parallel trials from pancreas transplantation alone Those are patients who have already some risks related to hyper-labile diabetes, very difficult to control diabetes for either hyperglycemia or hypoglycemia despite attempts to keep the disease under control, or the development of complications that could justify some form of immunosuppression in a relatively higher risk population.

[Slide]

So, the ideal goal for both procedures, but more achievable by a cellular transplant with no operative risk, is to try to perform the procedure early in the course of the disease without waiting for the development of chronic complications. So, it is much easier to prevent, like retinopathy, to try to reverse end-stage retinopathy or kidney disease. So, as we target a younger recipient population we must also carefully consider all the potential risk introduced by the selected approach, whether it is pancreas versus islets or whether it is immunosuppression versus immunomodulatory strategies.

[Slide]

Now, in islet transplantation we had a lot of promise, a lot of hype and a lot of hope over the decades. It was also the cure around the corner, or something that

was supposed to happen within a couple of years. But, there has been, indeed, some remarkable progress in the field since we started isolating islets from rodent pancreas. Then just to bring the technology to be able to separate islets from the human pancreas has required a tremendous collaborative effort of several institutions, many of them present today.

[Slide]

For the first time in 1990 it was demonstrated in a St. Louis trial that diabetes can be reversed with a transplant at the cellular level even though it was for only a couple of weeks. But, you have to understand that this procedure before 1990 didn't produce insulin independence in any case.

[Slide]

At the same time, with the same islet isolation procedure, it was possible to show in two series that we performed at the University of Pittsburgh how it is possible to achieve insulin independence in a consecutive series of patients with a steroid-free immunosuppressive regimen, but in surgical diabetes without an autoimmune background introduced by Type 1 diabetes. Since then, there has been another wave of optimists thinking that now the job was virtually done, islet transplantation could work and could be transferred easily to Type 1 diabetes recipients.

[Slide]

Between 1990 and 1998 there have been over 250 transplants at several main institutions, and others with less number of transplants, where we learned that insulin independence was confirmed as an achievable target, both at Giessen, Minneapolis, Milan, Miami, St. Louis, Geneva, Edmonton and others. But, what we learned is that this was not the case all the time. It was in the minority of patients transplanted.

[Slide]

What we learned from this series is that when an islet transplant does work, like in this patient in Miami from Dr. Alejandro that has been now over nine years with a functioning islet transplant, you can achieve a remarkable control in terms of hemoglobin A1c levels within a normal range. You see by comparison what you can achieve with conventional insulin treatment and with intensive insulin treatment, but, most remarkably, this level of control has been achieved without severe hypoglycemic events, so without the risks that are associated with intensive insulin treatment.

[Slide]

But the problem is that this kind of result has not been in the majority of patients. There is one concern that we had at the level of the international experience,

that most patients had a loss of function or early graft failure even immediately after transplantation or within the first two months, with an overall experience with a level of 35 percent functioning islet grafts at one year.

[Slide]

So a lot of research has concentrated on how to improve early graft function, and Dr. Hering, with the University of Giessen, developed a very accurate protocol of peri-transplant management that was able to increase this early function from 60 percent at 1 month to 100 percent early graft function with remarkable improvement also in overall results in terms of function at 1 year, and even insulin independence in some cases.

[Slide]

So, one of the concerns that we had is that it was clear that the immunosuppression used in this kind of transplant was inadequate for a cellular transplant such as islets, and imposed a metabolic demand on the transplanted cells that may be damaging the very cell transplant that you are trying to implement. So, there has been evidence from our group and others of, for example, the deleterious effect of steroids given at the early time post-transplant even in autograft when you don't have problems of autoimmunity and rejections, where you can see that the transplant can fail long-term if you treat with steroids in the peri-transplant

period.

[Slide]

So, at the same time we were first doing the transplant associated with the kidney transplant in most of the cases. We didn't have any ability to modify what the standard is of immunosuppression developed for the kidney transplants. So traditionally islet transplants have been developed as an adjunct procedure, as an option that you get your organ transplant, whatever the immunosuppression is for that organ, and then you get the islet transplant on top.

But if we review the literature of the series of islet transplantations that produced consistently insulin independence as a result of an islet transplant, we see that this has been achieved in autografts in the Pittsburgh series, the Pittsburgh-Miami trial in surgical diabetes, and the most recent Miami trial in non-human primates, and in the Edmonton trial that will be briefly discussed by Dr. Shapiro later. But all these situations have in common that they have been steroid free and three of the four were also culture free. The islets were transplanted, infused immediately after they were prepared without introducing any culture. This is related to a lot of information emerging from the fact that when you disrupt islet matrix interruption you may promote apoptosis, and during culture we actually don't increase the number of cells that you have

for transplant but you decrease it. This is something that is for consideration for future discussions.

[Slide]

Finally, a rationale for islet cell transplantation that I think is maybe one of the most pressing is that, based on human organ donations, we will never be able to address the majority of patients that may benefit by this procedure. If we get every single pancreas available from human organ donation, we will be able to treat less than 1 percent, or 0.1 percent of patients with Type 1 diabetes, not to talk about if we want to expand the application to Type 2 diabetes, but just considering Type 1.

[Slide]

So, to be able to treat a majority of patients that may benefit from this procedure, we need to develop strategies to improve availability of insulin producing tissue and, besides human organ donors a little can be expanded through living donors but a lot of this technology will come in possibilities from in vitro expansion of human islets and beta cells as well as genetically engineered non-islets or human cell lines, as well as animal sources and xenotransplantation. So, all these approaches are much more likely to be developed as cellular transplant approaches. All the problems we are studying now with allotransplantation, immunomodulation, tolerance induction

and alternative sites of islet implantation are very much applicable to what will be eventually the large-scale application of this kind of procedure.

[Slide]

I would just like to thank, in conclusion, our collaborators, especially Dr. Alejandro coordinating the clinical trial, and Dr. Kenyon coordinating all the preclinical trials. The islet team that has been collaborating to develop and bring the automated method of islet isolation technology to the next level and all the improvement that we have implemented today, as well as Dr. David Harland and Alan Kirk at NIDDK, with which we are collaborating with the newly constituted branch on transplantation and autoimmunity, and the Immune Tolerance Network, all the collaborators that are trying to bring islet transplant pilot trials and, of course, all the funding organizations without whose support we wouldn't be able to develop any of these approaches, and now also FDA which has been helping us make this procedure even safer for patients and for the potential future of this application. Thank you. I will finish here.

DR. SALOMON: Thank you very much, Camillo. Before we give our next talk, I just want to acknowledge the fact that we have been joined by another member of the committee today, Dr. Jose Cara, from Henry Ford Hospital

Department of Pediatrics. Welcome, Dr. Cara.

DR. AUCHINCLOSS: Can we ask questions?

DR. SALOMON: Actually, he finished quite early. So, we don't usually do that, as you know, Hugh, but if you have a key question or two, sure.

DR. AUCHINCLOSS: Camillo, could you say just a few more words about your prednisone studies in the dogs? The title of the article you showed talked about long-term effects of prednisone and non-survival of islets in the liver. How about short-term effects?

DR. RICORDI: Well, what we thought at the beginning in Pittsburgh, and Dr. Riley is here today also who is the main author of the studies -- the reason we did it is because when we moved from the clustered patients from the surgical diabetes where there was a steroid-free treatment to, now, kidney allotransplant Type 1 where steroids were used, we wanted to make sure that the steroid regimen was not toxic to the islet engraftment. Interestingly enough, we didn't observe any short-term graft failure but it seems that you have failure of this graft within one year or much earlier than what we would expect otherwise. So, at that time we were not sure if this was directly related to the steroids or maybe to the intrahepatic site in a pancreatectomized animal in which we thought there may be chronic exposure of endotoxin in the

portal system. There may have been other reasons for failure but steroids emerge very much as a concern for introduction of induction, especially when you do bolus steroids, high dose steroids as we do in many organ transplantations.

DR. SALOMON: Thank you. When I did my residency in Los Angeles I became aware of a phenomenon called the buzz, which is something that emanates out of Hollywood and is usually a sign of some, you know, breaking star or new movie that is out. But in this case, I must say there is a buzz around the so-called Edmonton protocol. The buzz tells us that the data is really quite remarkable and may be the next major step forward in terms of bringing islet transplantation to clinical practice. So, I am especially interested in what Dr. Shapiro has to say today, from Edmonton, on allogeneic islet transplantation.

Recent Experience in Allogeneic Islet Transplantation: Edmonton Protocol

DR. SHAPIRO: Thank you, Daniel, and thank you committee. Good morning. I hope I won't disappoint you too much in the next few minutes, but thank you very much for giving us the opportunity to talk to you today about islet allograft transplantation. I am ready to echo and reinforce many of the comments that Dr. Ricordi just made regarding that procedure.

[Slide]

Unfortunately, however, our data at the moment, although it is a buzz and an exciting field, is an X-rated movie, and our data is currently under review by The New England Journal of Medicine and as such, according to the Inglefinger rule, I am, unfortunately, in a public auditorium, unable to reveal to you the specific nature of those results and I apologize for that.

DR. SALOMON: This happened in LA all the time.

DR. SHAPIRO: So, I thought I would review for you just briefly some of the background history to where we are today in clinical islet transplantation. We go back really to the beginnings in 1889 when Minkowski and Von Merring discovered the link between the pancreas and diabetes when they surgically removed the pancreas in dogs and induced glycosuria.

[Slide]

Four years following that experiment, a remarkable experiment happened in Bristol, in England, in fact at the very hospital where I trained, where a surgeon and a physician colleague, Watson-Williams and Harsend carried out a remarkable experiment when they treated a 13-year old boy with a first xenograft of tissue using a sheep's pancreas. This 13-year old boy who was dying from the ravages of diabetes received three pieces of sheep's pancreas placed

beneath the subcutaneous tissues, and for a few days he had some amelioration in his blood glucose before he died. Quite a remarkable experiment when you think about it, the xenograft. It is four years after the discovery that the pancreas has anything to do with diabetes. It is 27 years before the discovery of insulin, and almost 60 years before the modern advent or, say, early modern advent of immunosuppressive strategies.

[Slide]

Clearly, the discovery of insulin in 1922 had a dramatic impact in improving the well being of patients with diabetes. It prevented acute death. But, unfortunately, it converted this condition into a chronic and incurable illness, with most of our patients developing end-stage complications and representing an enormous cost burden to our healthcare society, 15 percent of our healthcare expenditure.

[Slide]

It is the third commonest disease and fourth leading cause of death, and there are one million Type 1 diabetic patients in North America and 30,000 new cases diagnosed every year, and the incidence is considerably on the rise.

[Slide]

So, what therapeutic choices do we have in the

year 2000 to treat our diabetic patients? Well, clearly we have standard insulin therapy. We have intensification of insulin therapy with more frequent injections. We have the potential to use an implantable insulin-delivering device, a pump, but the technology surrounding that at the moment is somewhat limited. We can carry out a whole pancreas transplantation, either solitary pancreas or along with a kidney. And, now we can consider carrying out an islet transplant.

[Slide]

What are the early studies in terms of islet transplantation? We have to look back to 1911 when Bensley first hand-picked a few islets for a morphological study and then, in 1964, Hellerstrom began microdisecting the pancreas and removing islets, again, for a physiological study. The introduction of collagenase into practice by Moskalewski, in 1965, really was a revolution to the field but also had many, many problems down the road since the variability and enzyme preparation meant that this enzyme was not reliable.

The father of islet transplantation, Paul Lacey, as shown here, developed a technique for ductal injection of the pancreas which led to increased yield of islets from the rat. Then subsequent studies by Webber and then Younoszai showed temporary improvement in glucose control in rats. Again, Bellinger and Lacey showed sustained improvement in

chemical diabetes in 1972.

[Slide]

So here we are, we have an experimental procedure but what is the evidence that it might work or might be helpful in controlling secondary complications of diabetes in humans? Well, we don't have any direct evidence at the moment. As I will show you, the results of the Clinical Islet Transplant Registry leave only a few patients off insulin at the current time.

So, we have implied evidence, implied evidence that islet transplantation will impact secondary complications, that will reverse retinopathy, impact nephropathy and enhance patient survival.

[Slide]

The evidence is clearly indirect. As Dr. Ricordi has also mentioned, it comes from the DCC trials of intensive insulin therapy and from the results of whole pancreas transplantation where over 12,000 of these procedures have been performed worldwide to date.

[Slide]

As Dr. Ricordi showed you, clearly an impact in terms of ultimate glucose control and correction of hemoglobin A1c can reverse retinopathy. But here, using intensive insulin therapy, this does come at a price of increased risk of hypoglycemic coma.

[Slide]

What about correction of nephropathy? Well, we have to look, again, to studies of pancreas transplantation, patients undergoing solitary pancreas transplantation when they are more than ten years out after this procedure. Fioretto published in The New England Journal, two years ago, showing that at ten years this did, indeed, have an impact on secondary complications. So, we presume or we surmise that islet transplant, if it can achieve optimal glycemic control in a patient, will have a similar impact on complications.

[Slide]

Again, this is data Dr. Ricordi showed you in terms of enhanced patient survival, 50 percent at 10 years compared to kidney transplant alone in patients undergoing a pancreas transplant. Again, this is prospective but not randomized data indicating that there may be a benefit to patient survival.

[Slide]

If we turn to the Islet Transplant Registry, there are 405 transplants reported to date. If we look at those specifically in patients undergoing transplantation with Type 1 autoimmune diabetes, there were 267 procedures in the last 10 years. The results, however, have been dismal, we have to say, because only 12 percent of patients overall

achieved insulin independence by 1 week and only 8 percent of patients achieved insulin independence or maintained that beyond 1 year.

[Slide]

Why is that? Dr. Ricordi, again, has already alluded to this, that the drugs used in those studies were virtually in every case -- not all but virtually every case -- a combination of steroids, cyclosporine and Imuran.

[Slide]

Now, we have an opportunity, and we have focused in the last five years in our laboratory in Edmonton on trying to work out what is the optimal immunosuppressive strategy to use for experimental and then clinical islet transplantation. Clearly, now in the year 2000 we have an explosion in the availability of new immunosuppressive drugs and antibodies that we can apply. That means that at last we can consider developing strategies that no longer require corticosteroids.

[Slide]

Using an acute canine model, a canine islet autograft treated for one month -- and this is to also help answer Dr. Auchincloss' question -- we carried out frequent sample glucose tolerance tests. When we did that, we found that the use of cyclosporine on its own had no impact on the KG of the glucose decay constant. Low and high steroids on

their own for a short period of time also had no impact on graft function. But when we combined steroids and cyclosporine together it had a dramatic and permanent effect in terms of damaging autograft function by impairing KG and then, after withdrawal of therapy, these dogs failed to normalize.

[Slide]

When we take our data together, you can see that combinations of cyclosporine or tacrolimus, along with steroids, led to a marked decrease in the glucose decay constant and a marked decrease also in insulin sensitivity. When we used this new drug, sirolimus or rapamycin, we found an increase, in fact, in the KG largely accounted for by a prolongation -- a side effect really, but a prolongation in insulin half-life which we thought would be beneficial.

[Slide]

Following that, we carried experimental islet transplant studies in the laboratory and showed that this drug was efficacious, and also there is a large body of clinical literature now to show that rapamycin or sirolimus is an extremely potent immunosuppressive drug -- discovered by Dr. Seran Segal from the soil samples taken from Easter Island -- really quite remarkable that all these very powerful drugs are found just dangling in the soil.

[Slide]

Our experimental studies suggested that the combination of sirolimus and tacrolimus at low dose might be beneficial for clinical islet transplant but it was always believed, based on in vitro data, that these two drugs could not be used together in combination because they both bind to the FKBP12 and FKBP25 cellular binding proteins.

[Slide]

However, this in vitro interaction clearly does not occur in vivo since Chen and Vu, in heart transplants and small bowel transplants in rodents, showed strong synergistic potentiation of these two drugs when used together.

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Furthermore, in a recent article published in The Lancet and now updated to a total of 56 patients, McAlister and colleagues from Halifax in Nova Scotia, Canada, treated patients undergoing liver, kidney and pancreas transplantation and demonstrated that when they used this combination along with steroids for 3 months, that their rejection rates were extremely small, only 3.6 percent.

[Slide]

In the Edmonton protocol, which I will allude to, we have replaced the need for steroids with an anti-IL2 receptor, daclizamab antibody. Thus, we have attempted to impair the augmentation and amplification of the immune

cascade, preventing signal 2 and signal 3 activation events to have a concertive effect in immunosuppression while avoiding steroids.

[Slide]

So, our protocol is completely steroid free, and along with that we tried to optimize islet function by minimizing the cold ischemic time by carrying out immediate transplantation after a negative gram-stain, by using high quality islet preparations as isolated by Dr. Lakey and his team in our Clinical Islet Transplant Laboratory, and we have avoided the use of xenoproteins, the fetal bovine serum that was traditionally used in all our isolations previously. We have delivered a sufficient islet transplant mass of at least 10,000 islet equivalents per kilogram.

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In so doing, we have attempted to address a number of barriers to insulin independence that Dr. Hering brought to the world's attention in terms of delivering a sufficient islet mass by avoiding drugs that induce insulin resistance or cause diabetogenic effects, and by providing sufficient and adequate immunosuppressive effect that we no longer require an effective marker of islet rejection and we also protect quite powerfully against both autoimmune and alloimmune recurrence.

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Furthermore, we have tried to optimize the donors that we use for pancreas procurement, and this shows our technique for achieving the pancreas. Rather than going through all the details, I will just emphasize to your that the aim of this is to allow the pancreas, as soon as the chilled UW solution is infused through the aorta, to allow the pancreas itself to be rapidly cooled both anteriorly and posteriorly so that it is protected.

[Slide]

So, in Edmonton we also have an active clinical pancreas transplant program, and the islets that we have isolated from our donors have not overlapped particularly with our pancreas transplantation. Indeed, approximately 70 percent of our pancreata could not have been used for pancreas transplantation either in our own center or in other centers across Canada. This clearly shows that while we prefer an optimal donor for islet transplantation, although there is some overlap there is also a distinct separate population of donor pancreata with age greater than 45 years that could be used for successful islet isolation but would, therefore, not completely deplete the pool for pancreas transplantation.

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There have been dramatic improvements in our ability to isolate high quality islets. As Dr. Ricordi,

again, alluded to, there has been a tremendous consortium effort between centers throughout the world to achieve this. Tremendous advance has come from the availability of this new enzyme blend, the liberase enzyme which is low in endotoxin, and has really led to much higher consistent islet yields than achieved previously. The use of the chamber described initially by Dr. Ricordi, and for Dr. Lakey's benefit I have to emphasize that this chamber has been modified in Edmonton, and then the use of the COBE 2991 cell purifying system which has also been a tremendous advance since previously we would spend many hours in the middle of the night layering ficoll tubes and falling asleep while we broke the layers, and now this system allows us, in a matter of five to ten minutes, to isolate islets and minimize the exposure to ficoll.

[Slide]

The system that Dr. Lakey developed in Edmonton along with Dr. Rayotte was a system of perfusion of the pancreas with cold enzyme solution to ensure that the enzyme is delivered to all parts of the pancreas.

[Slide]

Here is Dr. Lakey himself, in the middle of the night, shaking the modified Ricordi chamber to shake the islets out.

[Slide]

This is the impure preparation of approximately 50-60 cc which is really too impure to infuse into a patient. After purification you can see that the entire preparation for infusion into the patient is just 3.5 cc maximum here. Clearly, this is a very safe form of therapy to infuse into patients.

[Slide]

This shows the quality of islets alongside an instrument needle, showing just how pure those islets are for transplantation.

[Slide]

We have modified the procedures in Edmonton. Previously we used to culture our islets. Now we carry out immediate transplantation. We really treat the islet as we would a heart, a liver or kidney transplant, knowing that every minute or every hour of cold ischemia leads to additional potential injury. While this is not proven, we believe at the current time this is an optimal way to proceed with islet transplantation.

[Slide]

So, as soon as the islets are isolated we bring a patient to the radiology department and, under local anesthesia, our radiology colleagues, percutaneously by a transhepatic approach, put a needle in the side, gain access to the portal vein and the islets are embolized up into the

liver where they obtain a new vascular supply.

[Slide]

This shows the portal angiogram obtained immediately prior to islet transplantation.

[Slide]

The transplant procedure is no longer an operation. It is a very simple procedure. The islets are simply drawn up and it is the simplest transplant one could ever carry out. It is simply injection of cells.

[Slide]

This shows one of our patients who works as a lawyer, back at work within 24 hours of his procedure, in his pin-stripe suit.

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So, how do we know that these islets are safe to infuse? Well, in Edmonton we carry out post hoc quality control analysis. Obviously, we carry out detailed culture for bacterial, fungal, viral and endotoxin. We carry out a Gram stain prior to transplantation. Then, Dr. Korbutt in our group carries out detailed immunohistochemical analysis to determine the exact cellular composition of each of the preparations, indicating what percentage of beta cells, alpha cells, delta cells, pp cells and ductal elements are transplanted. We, therefore, have a very good index of how pure our preparations are; what their insulin content is;

and we carry out in vitro viability studies, using static incubation assays in low and high glucose media to show that our islets really are viable and they are able to respond appropriately to a glucose environment. We also carry out SCID mouse transplants to confirm in vivo viability. Again I emphasize these are post hoc quality control assessments since islet transplants, in order to minimize cold ischemia, are already transplanted into the patient.

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So, what criteria do we use for transplantation? We take an islet transplant mass of more than 4000 islet equivalents per kilo for the initial transplant, or a total of 10,000 islet equivalents per kilo in a packed cell volume which is usually 3.5 cc but is always less than 10 cc, and we have a negative Gram stain. We avoid the use of xenoproteins. We use a percutaneous route for portal access. We measure portal pressure before and after the islet infusion. We give systemic heparin at a relatively low dose of 1000 units to an adult, and we use a plug of gel foam to the peripheral tract before we remove the catheter from the liver to try to minimize the risk of bleeding.

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These are the immunosuppressive strategies that we use, zenopax, tacrolimus and sirolimus at the doses shown, and we don't use any steroids. We use prophylactic

antibiotics initially, imipenen and vancomycin. We use ganciclovir for the first three months to minimize the risk of CMV infection, and we use PCP prophylaxis for the first year.

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These are our indications for islet transplantation, solitary islet transplantation. Patients have to have Type 1 diabetes for more than five years. They have to have evidence of hypoglycemic unawareness; metabolic lability of instability; evidence of progressive secondary complications despite being on an optimal insulin regime; and they must have evidence of failure of intensive insulin as judged by an independent endocrinologist from our program.

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We have a number of contraindications too for patients that we will not accept at the current time. We won't accept patients with severe cardiac disease, active alcoholics, those with major psychiatric illness, or those with a history of non-adherence., those who have an active infection, malignancy, obese patients, and those patients who have evidence of positive C-peptide prior to transplantation -- they do not undergo transplantation.

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At the current time we are avoiding transplanting

patients with evidence of severe renal dysfunction with a creatinine clearance of less than 60 ml/minute/m^2 or evidence of macroalbuminuria but, clearly, in the near future this may be a group that we should be considering targeting based on the evidence from whole pancreas transplant literature. If a patient has gall stones or angioma in the liver, that might increase the risk of complication either related to the needle puncture itself or from systemic immunosuppression. So, these patients are excluded on a baseline ultrasound.

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Clearly, a number of other contraindications are listed there, the least of which is inability to reach the hospital in time, within two hours for notification for that transplant.

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So, how do we work out the risk-benefit ratio for this procedure? Well, if we just look at patients on insulin alone -- I have emphasized to you before that this is a chronic progressive illness and when patients are on insulin this is not a cure -- so the risk-benefit ratio falls severely down for the patient just on insulin. It is clear they have a relative risk of renal failure, 25 times the normal population; 20 times the risk of blindness; 40 times the risk of amputation; 3 times the risk of stroke;

and 5 times the risk of myocardial infarct; and at least a 10-year shortening in life span as reported by Nathan and colleagues, in 1993, demonstrating that insulin alone is not a satisfactory treatment for the majority of Type 1 diabetic patients.

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When we put the equation this way, solitary pancreas versus solitary islet transplantation we don't know. We have never done a prospective study; we hope to do that eventually to show what the benefit of islet transplant will be, but we believe that the equation will be largely in favor of benefit for islet transplantation because pancreas transplantation remains an invasive procedure, associated with significant morbidity in some cases, although the results have improved considerably over the last five years or so.

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Now, if we try and equate the risk-benefit ratio for insulin versus solitary islet transplantation in a patient with no secondary complications but where we have to use systemic immunosuppressive drugs along with the transplant, we don't know what the true risk-benefit ratio is currently but we believe in this situation, when there are no secondary complications, at the current time probably the balance is in favor of continued insulin therapy since

these drug therapies clearly have potential side effects, increased risk of infection and increased risk of malignancy.

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When we take a population of patients with potentially life-threatening secondary complications the balance is changed. With the presence of hypoglycemic unawareness, coma, metabolic lability, recurrent ketoacidosis, frequent hospital admissions, etc., and evidence of early but progressive secondary complications, then the balance falls in favor of the islet transplant plus systemic immunosuppressive therapy. We believe. There is no hard evidence for this at the current time. Only prospective detailed studies will be able to prove that this is the case.

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What if we take a patient and go back again, a patient with no secondary complications, in that situation the risk-benefit ratio is only going to fall in favor of islet transplantation if we can really achieve long-term stable tolerance and achieve a strategy that will not only prevent both autoimmune but alloimmune recurrence.

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So, why do we need tolerance for islet transplantation? We need to avoid the long-term risk of

immunosuppression. We would like to be able to extend the risk-benefit ratio so we can treat newly diagnosed children. We would like to apply the islet transplantation to the earliest sign of diabetes so that we can really have maximum impact on prevention of secondary complications. Furthermore, for islet transplantation, if the strategy fails the risk must be low.

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So, the playground of tolerance will not be in heart or in liver transplantation where there is a risk that the patient might die, or potentially in kidney transplantation where scarce results may be lost, but we believe will be in islet transplantation in the near future where, if the graft fails, the patient simply returns to insulin.

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Dr. Norma Kenyon has shown recently, last year, that the advent of newer co-stimulatory blocking antibodies, the anti-CD154 monotherapy, clearly was able to prevent rejection in primate islet allograft when continued long term.

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It is hoped that this and other co-stimulatory blocking strategies used in the very near future will allow us to achieve the true goal of tolerance, either through

costimulatorty blockade, non-depletional or depletional antibodies, or anti-adhesion therapies, donor bone marrow transplantation or a number of potential anti-inflammatory strategies that might allow enhanced early islet function and survival after transplantation.

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In conclusion, intensive insulin therapy fails at the moment to normalize hemoglobin A1c. Solitary pancreas transplantation can achieve that. It achieves excellent glycemic control but it remains invasive. And, for islet transplantation it is now imperative for us to establish in a multi-center trial the true benefit of this therapy in terms of minimizing risk; in terms of achieving excellent metabolic control; in terms of complete correction hemoglobin A1c and in terms of sustained freedom from insulin.

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As such, the Immune Tolerance Network, with a number of centers fished out by Dr. Ricordi from centers in the world, will address this in a true multi-center trial in the very near future.

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Clearly, our ultimate goal is to carry out islet transplantation as a cure at the time of diagnosis. Thank you very much.

DR. SALOMON: Thank you, Jim. Actually, I have two quick questions. I see Hugh shaking his head; he may have one as well. Can you clarify two things for me? One, we will get to this later in detail but you raised an interesting question that there was a percentage of pancreata that were harvested that would not be suitable for whole organ pancreas transplantation but would be a source for islet preparation. We will return to that because that is a real issue in the field. What percentage of that is the case in your experience in Edmonton? And, what are exact criteria that you have for accepting a pancreas for islet purification?

DR. SHAPIRO: We will accept any pancreas for islet purification provided that it cannot be used either at the local center or our own center for whole pancreas transplantation. We have fairly stringent criteria for what we will accept for whole pancreas transplantation, and these are, I think, fairly standard in North America. Most centers use an age cutoff for whole pancreas transplantation of 45. Some extend that up to 55. But, clearly, where there is evidence of early atherosclerosis in the vessels to the pancreas or where there is evidence of trauma, damage, edema, etc., then that graft cannot be used for a whole pancreas transplantation but may be ideal in that situation for islet isolation. So, we will use any pancreas that

cannot be used for whole pancreas transplantation provided there is no other contraindication to use of that organ in terms of infection, malignancy, etc. We will accept organs from most age ranges. In our series we have used a donor up to age 71 with satisfactory outcome. Clearly, therefore, although there is overlap in terms of organ usage, there is a disparate population of pancreas that might be ideal for islet isolation also.

DR. LEVITSKY: Actually, I have two questions for you. The first is probably a little bit out of your field because I know you are doing islet transplants but apropos of the experience some years ago using cyclosporine early on, immediately after diagnosis of diabetes, it would seem to me that it might be even more logical if we now have a set of anti-rejection drugs that can suppress the immune response to try those primarily, rather than even need to do the islet transplant early in diabetes.

DR. SHAPIRO: You raise a very important point. Clearly, the strategies that we are using for islet transplant in Edmonton currently are being seriously considered for those immune intervention trials. But, to my mind, I don't think I would want to be on those drugs if I wasn't going to be completely off insulin and if they weren't going to have a serious impact in terms of preventing the secondary complications. We will know over

time whether or not that can be achieved.

DR. LEVITSKY: The second question I have for you is that I am a little concerned about your criteria for patient selection. At least, we pediatric endocrinologists believe that recurrent ketoacidosis is not a biologic condition but is, rather, the effect of recurrent lapses in insulin administration. So, I wonder whether by selecting out patients who may be at higher risk for lapses in medical behavior you are actually handicapping your outcomes, and also because this may be such a wonderful outcome why should only that group of patients who seem to be not biologically determined to have these episodes be part of your selection criteria?

DR. SHAPIRO: Well, I think that is very true in children. The patients that we transplant in Edmonton clearly are a very, very highly selected group of patients who have clearly failed exogenous insulin therapy as assessed by a number of endocrinologists who have worked very hard, and where we have clear evidence that those patients have complied. But I accept that every patient that comes through the door with ketoacidosis is not necessarily a candidate for islet transplantation.

DR. LEVITSKY: Well, maybe we can discuss the biology of ketoacidosis at some later point.

DR. AUCHINCLOSS: It is unfortunate that we can't

see the actual data but I have seen it and I will just assure the committee that it is very, very impressive.

James, I want to play out a conversation that we have had before in private. Your extraordinary success could be attributed to, (a) you make better islets or they are fresher islets than anybody else has. It could be, (b) because you have the best immunosuppressive protocol -- steroid free, etc., or, (c) because you give more islets than anybody else because your patients have had in general two, and in some cases more, pancreas-worth of islets. Can you tell which, (a), (b) or (c) is really responsible for the success?

DR. SHAPIRO: Right now we don't know. It could be (a), (b) or (c), or could even be (d). We are carrying out sequential islet transplantation. Maybe that in itself has some benefit. But as Dr. Hering really pointed out during that conversation, the whole thing is like an orchestra and everything has to be in tune.

DR. AUCHINCLOSS: I guess my point would be we don't know whether everything needs to be in tune. We really don't know what the crucial variables are, and that is really the point. We are all learning. You have a combination where "in tune" is certainly working but it is not clear that you couldn't drop the cello and still have it work.

DR. SHAPIRO: I totally agree.

DR. AUCHINCLOSS: And one thing you do not have that people have for a long time believed is critical is tight glucose control in the early post-transplant phase. Is that correct? You don't make any effort?

DR. SHAPIRO: Absolutely not, no.

DR. SALOMON: Dr. Ricordi?

DR. RICORDI: I just wanted to comment on Dr. Levitsky's question. That is, indeed, it is the strategies that we are implementing and studying. If you can induce tolerance or if you have an effective immunomodulatory or immunosuppressive mixture it will, indeed constitute a unique opportunity for intervention trials early on in the course of the disease, and islet transplant will still need to become available for those who don't have any beta cell function but it will be ideal to be able to intervene early and maybe block the immune response or reeducate the immune system and have the native islets regenerate or just continue to function.

DR. SALOMON: Dr. Cara?

DR. CARA: Could you tell me how you establish islet equivalent units?

DR. SHAPIRO: Dr. Lakey could probably describe this better than I can -- go ahead. Why don't you do it?

DR. LAKEY: Samples are removed from a preparation

and they are counted in duplicate by two independent investigators, and the islets are categorized into 50 micron categories and, using an established protocol that was first published by Dr. Ricordi in 1990, they are equal rated to an equivalent volume of 150 microns in diameter.

DR. CARA: And is that an internationally accepted --

DR. LAKEY: Means of quantifying? Yes.

DR. CARA: Another question is have you done any sort of formal post-transplant quality of life assessments in the patients that you have actually done these treatments in?

DR. SHAPIRO: Those studies are actually under way at the current time. The difficulty has been what is the ideal way of assessing that. Clearly, most of the questionnaires are not necessarily ideal or ideally tuned to islet transplantation. The ultimate goal is to compare islet with whole pancreas to, in a prospective way, determine what the benefits in terms of quality of life are for those two procedures versus patients on insulin.

DR. CARA: It is a critical issue because whereas survival of the graft or insulin-free time intervals after transplantation are very important, I think it is important to also to think about at what patient cost. I think the quality of life issue is an important factor in all that.

DR. SALOMON: Thanks. Dr. Sausville?

DR. SAUSVILLE: So, returning to this issue of quantifying the islet equivalence, I take it then you don't really use measures of insulin content or insulin secretability, and do you foresee the suitability, shall we say, of the morphology only criteria for ultimate use in contrast to developing some rapid means of assessing actually insulin content or function?

DR. LAKEY: Samples are removed at the conclusion of the isolation for quantification. In addition, samples are removed for post hoc insulin DNA, and also samples are removed for functional viability testing. That is all post hoc. Camillo, perhaps you would like to comment.

DR. SALOMON: Can I interrupt? This is exactly where we want to go this afternoon, and I think that was a great question and a good answer and, Camillo, I know you will be here this afternoon and will participate. So, just rather than get into an area where we really should take it in detail, because I think that is a major interest on the part of the FDA in terms of starting this whole area off right as a well-characterized product, I think this is so important, if you will forgive me, I would like to kind of steer us away from it right now.

I think that was great. Is there anyone else who has a question that would take off in a different direction

because we are running a little bit ahead so we do have that flexibility?

[No response]

Thank you very much. I think that was excellent. The next and final speaker of this first session is Bernhard Hering, from the University of Minnesota, Diabetes Institute. It is a pleasure to welcome Bernhard here.

Lessons from the International Islet Transplantation Registry and Recommended Quality Standards for Islet Preparations

DR. HERING: I would like to thank the FDA for inviting me to this important meeting in the history of islet cell transplantation.

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My assignment today is to review lessons from the International Islet Transplantation Registry and to discuss recommended quality standards for islet preparations.

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We haven't discussed fetal and neonatal islet tissue transplantation and reports on at least 3000 fetal and neonatal islet allografts and xenografts performed at about 80 institutions from 1977 to 1996, the majority performed in China and the former Soviet Union. Communicated safety and efficacy data are very incomplete, and insulin independence has yet to be documented.

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Then, we also know of results in islet autotransplantation in patients undergoing pancreatic resection, and at least 239 procedures have been performed at 33 institutions from 1977 to 1999. Initially, in the early phase of islet autotransplantation, in the late '70s and early '80s, serious adverse event reports including hepatic infarction, portal hypertension, disseminated intravascular coagulation and systemic hypertension were communicated, including two deaths in the early '80s and one in 1996.

Long-term insulin independence has been documented in approximately 50 percent of totally pancreatectomized recipients. The longest documented follow up is now exceeding 13 years.

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Islet allografts, adult islet allografts, 405 procedures at 38 center from '74 to '98, including 357 in people with Type 1 diabetes. As mentioned earlier by Dr. Ricordi, transplants have been done in patients with surgical diabetes at the University of Pittsburgh, in the early '90s, a remarkable series, and also in insulin-requiring patients undergoing liver transplantation with presence of diabetes at the time of transplantation. One-year patient rates exceeded 95 percent, and only one death

likely or definitely related to islet transplantation. Serious adverse events have rarely been observed following intraportal islet infusion, which is the most common implant site. I just want to mention the serious adverse events that have been communicated -- liver capsular hematoma requiring transfusion in four cases; gall bladder perforation in one; portal hypertension requiring splenectomy in one case; and liver transplantation in another case, this was a patient receiving a simultaneous liver and islet transplant; bacteremia due to contaminated cryopreserved islet preparation in one patient; and injury to hepatic artery leading to death in one patient, the only patient who likely or definitely died related to the islet transplant procedure. Then, HLA sensitization has been documented in patients with rejecting islet allografts.

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Results in patients with Type 1 diabetes -- almost all transplants in conjunction with kidney transplantation simply because kidney transplant recipients are immunosuppressed anyway -- survival rate based on C-peptide, 35 percent and about 10 percent of the patients became insulin-free after transplantation. At 1 year 8 percent remained insulin free. Duration of insulin independence, however, on average was 450 days and the range is from 7 days to 5 years. In 1995, as mentioned before, the success

rate in terms of insulin independence at 1 year increased up to 33 percent and, as just reported by Dr. Shapiro, in 1999 there has been a significant improvement of the success rate with the new protocol developed at University of Alberta.

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What are basically the lessons if we summarize what has been learned so far? I think it is fair to say that adult islet allograft, at least based on the available information, is associated with low morbidity and mortality. The success rate is much lower, however, compared to preclinical studies, human islet autografts, human islet allografts in surgical diabetes, and pancreas allotransplants despite 35 protocol modifications between 1974 and 1998, as detailed in the review paper that is in your information material.

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One obvious question, of course, is what are the determinants of success? A number of factors have been discussed -- donor factors, pancreas procurement, islet processing and characterization, viability, islet dose, islet engraftment, autoimmunity rejection, and recipient factors, to name a few.

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The recipient category, as indicated before, seems to be very important. Here you see percent insulin

independence during the first year post-transplant in people with Type 1 diabetes receiving allografts, patients receiving allografts, patients with surgical diabetes and islet autograft recipients. So the recipient category is of significant importance. If you compare pancreatectomy induced diabetes and autografts, allografts and Type 1 diabetes, we understand that in the latter category there are a number of barriers that may interfere with the restoration of insulin independence -- inflammation, alloimmunity, drug toxicity, chronic diabetes and insulin independence at the time of transplantation and autoimmunity.

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Among the two variables affecting outcome, we have to consider the engrafted islet mass and the metabolic demand, and the protocol that was developed at the University of Alberta seemed to support this hypothesis that the metabolic demand and the presence of insulin resistance are critical determinants of success. The question is whether islet engraftment or the available insulin secretory capacity are important factors as well. This is a very complex issue and if we are going to discuss islet dose this afternoon, what is the right islet dose, I think it is a very difficult question because many factors may determine the dose.

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So, first of all, hypoxia at the time of transplantation, the presence of brain death, cold storage and preservation; then the ability of a given islet preparation to repair injury; anoikis, that is, the disruption of the cell matrix interactions, the susceptibility of a given islet preparation to oxidant stress or insulin resistance present at the time of transplantation. This injury and stress may trigger inflammation. Inflammation may trigger immune responses. Established autoimmunity, of course, augments inflammation and also immune responses, and then islets are transplanted in an environment where islets face toxic substrate concentrations. Also if it is an intravascular site, like the intraportal circulation, activation of cascade systems is another important factors. So it is not an easy task to determine islet dose necessary to reverse diabetes consistently.

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If we compare again the outcome in different recipient categories -- surgical diabetes, islet transplantation, immediate insulin independence. The time to insulin independence is usually very, very short, a few days. As well as in patients with surgical diabetes that receive islet allografts, immediate insulin independence has

been reported in the majority of cases, in sharp contrast to Type 1 diabetes where we see early islet graft loss, complete loss, in about 30-40 percent of the recipients. It is conceivable that some 30-50 or even 70 percent of islets are lost in the immediate post-transplant period in patients with Type 1 diabetes.

There have been two case reports, patients undergoing pancreas transplantation, one patient undergoing solitary pancreas transplantation for the treatment of hypoglycemia unawareness, and a few months after transplantation a graft pancreatectomy was performed because of graft pancreatitis. Islets were isolated from the previously transplanted pancreas and transplanted back into the patient and immediate insulin independence was noted despite the presence of diabetogenic drugs. This is a very important observation and it is difficult to understand why the outcome is so strikingly different in this category.

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If we compare the different recipient categories, there are questions, questions like living donors like in islet autotransplantation versus cadaver donors, is this an important determinant? Or purified versus unpurified islets because islet autograft recipients more or less receive the unpurified islet tissue? Or Mantle versus cleaved islets? Or is the presence of diabetes at the time of

transplantation important, or the presence of insulin resistance because islet autograft recipients, or totally pancreatectomized islet allograft recipients, or this latter case that I alluded to, patients that received islets from a previously transplanted pancreas -- were all normal glycemic and insulin independence at the time of transplantation and the success rate is remarkably different, or combined transplant or solitary islet transplantation, or the presence of autoimmunity, or immunologically naive patients or the presence of diabetogenic drugs.

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Well, we don't know. We only know based on the available information that this procedure seems to be associated with low morbidity and mortality. Determinants of success are unknown, and better approaches are necessary to identify parameters necessary to restore insulin independence in Type 1 diabetes.

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Future directives are obvious. We need to identify testable hypotheses. Carefully designed, prospective clinical trials are required. We need clinical trial design expertise. I guess we should limit variables. We should use the highest quality of donor pancreata available. Short cold storage periods; controlled islet manufacturing processes; validated batch product release

criteria using experimental studies. Clinical site monitoring and training is a point of discussion. And, we need an infrastructure for the collection, storage, management, quality assurance, reporting, and analysis of study data and adverse events.

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In this context, we should reconsider how to develop an islet transplant registry that can serve the purpose to assist FDA and Canada in safeguarding the public health while promoting development of islet cell transplantation; or provide UNOS and the Canadian organ replacement registry with donor pancreas utilization data, transplant statistics and waiting time; or assist NIDDK, NIAID and JDFI in the scientific advancement of islet cell transplantation; or healthcare payer providers and professionals with data on metabolic control, complications, patient satisfaction, healthcare dollars per quality adjusted life years saved.

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I think we could discuss different approaches but I think one approach would be to follow the example of a North American pediatric renal transplant cooperative study which is coordinated mainly through Emmes Corporation. So, four organizational bodies are key for the success of this registry: a clinical coordinating center, data coordinating

center, scientific advisory committee and, of course, participating clinical centers. Such a registry with four organizational bodies could interface with FDA, NIH, JDF, UNOS and healthcare payers, providers and professionals.

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There are a number of aims: register and follow islet transplant recipients; identify, characterize and follow current practices and trends; characterize patient survival, graft survival and patient morbidity and effects of the procedure on secondary complications, and correlate these measures with an outcome with donor data, islet quality control data, patient demographics and clinical protocols; and interact with federal agencies, the International Islet Transplant Registry and other institutions.

[Slide]

I guess we have to simplify data submission utilizing web-based data entry and capture; disseminate information in a timely fashion; conduct prospective studies; compare the data obtained with information on intensified insulin management and pancreas transplantation; and also serve as a resource to investigators, patients and healthcare insurance industry, providers and colleagues.

[Slide]

Now let me turn to the second part of this

presentation. Let me discuss recommended quality standards for islet product testing. We need to address safety issues, identity, purity, potency, viability and cell number.

[Slide]

Just a few general considerations: Sampling is a very important factor, and we need to review our approaches to obtaining samples. Timing of islet isolation and transplantation, of course, will determine the choice of islet product release criteria and post-release criteria. If islet transplants are performed immediately after isolation, then a number of assays can only be done and assessed in retrospect. On-site versus reference laboratory testing -- do we need preclinical studies? Do we need site monitoring and training? What type of oversight and coordination will be necessary to identify factors that are predictive?

[Slide]

Safety studies are listed here: Gram stain on site, and additional studies to be performed in reference labs -- cultures, endotoxin and mycoplasma studies.

[Slide]

Identity -- the assays that are currently utilized, DT zone staining or cellular composition determined by immunohistochemistry as mentioned by Dr.

Shapiro and as developed in Brussels and the University of Alberta, including staining for insulin, glucagon, somatostatin, PP, amylase and CK 19.

[Slide]

Purity, assessments of purity -- percentage of red-stained cellular particles in DT zone-stained aliquots; total immunoreactive insulin content divided by total DNA content; and percentage of beta cells as determined by immunohistochemistry.

[Slide]

Potency, again, a number of assays -- glucose-stimulated insulin release in vitro either as static or dynamic incubation assay, insulin biosynthesis as a measure of the insulin secretory capacity of a preparation, or in vivo using a diabetic nude of SCID mouse bioassay.

[Slide]

Is it easy to determine the potency of a given preparation? I think it is fair to say that quality standards for human islet preparations have yet to be identified, validated and implemented. Rigorous preclinical studies are lacking, and adequate models have yet to be developed, or are not available to assess and to study the predictive value of potency assays. It is important to note that the lack of insulin independence following single-donor islet transplantation virtually eliminates the possibility

for validation of quality control assays being predictive for insulin independence. Measures of clinical efficacy beyond insulin independence are ill defined.

[Slide]

Viability -- most centers are using fluorescent dye inclusion/exclusion assays. Images should probably be stored for later analysis. Flow-cytometric assays of dispersed islet cells to measure the percentage of necrotic and/or apoptotic cells; single islet real time calcium imaging in response to glucose or NAD(P)H fluorescence measurements in response to glucose, or islet nucleotide profiles have been proposed.

[Slide]

Here is one example. This is a negative or a poor example of a porcine islet preparation and insulin stained in red, and apoptotic nuclei stained in green and glucagon in blue, studies performed by Vincenzo Ciruli.

[Slide]

Here is another preparation showing apoptotic nuclei in green.

[Slide]

Now, cell number, and I discussed before how difficult it is to assess the islet dose necessary. Assays that are utilized are islet enumeration using islet count and islet equivalents, preferably with image analysis

systems to be developed and standardized; insulin content, to be determined based on secretory capacity, probably a much more predictive assay than the determination of insulin content; DNA content; and calculated beta cell number as practiced at the University of Alberta in Brussels, and the calculation is possible based on total DNA content and determination of the percentage of insulin-positive cells based on immunohistochemistry.

[Slide]

There are a number of assays that I discussed. Currently we are discussing the following product release criteria because not every single assay has been available, and some of the assays may be mandatary and some may be optional. The current practice is more or less as follows: Potency is determined by glucose-stimulated insulin release in vitro, and here is the specification range. So, a stimulation index greater than 1 is considered acceptable. Others -- viability, viability must be 50 percent and we also discussed 70 percent. So, this needs to be determined. Purity, cultured islets before resuspending in transplant media, islet enumeration, 5-20,000 islet equivalents per kilogram; total volume of islet preparation must be 10 g or less. Again, we don't know whether this is the right approach. And, safety studies at the time of transplantation, documentation of a negative Gram stain is

considered the approach to go.

Then, there are product post-release criteria, mainly addressing safety. Aerobic, anaerobic and fungal cultures ought to be negative; endotoxin equal to or less than 0.5 units/ml, and then mycoplasma samples, negative. So, this is one possible approach to a situation in which you isolate islets one or two days before transplantation. Again, as I said, the islet protocol determines the choice of criteria.

[Slide]

Based on what we have heard this morning, I think it is fair to say that this year may mark the turning point in islet transplantation. Now, for the very first time, significant funding is available through NIH and the Juvenile Diabetes Foundation to do clinical trials. For the very first time, non-diabetogenic protocols are available and strategies are discussed. For this reason, transplant trials are open to recipients before complications set in or before complications become severe. I guess another very important point is that for the very first time we are discussing carefully designed prospective trials that may help address all the questions that we have, and this may lead to a consistent success in contrast to the sporadic success in the past.

[Slide]

I would like to thank the Juvenile Diabetes Foundation for supporting the registry, and for supporting efforts in the area of islet quality control, and for supporting our institution, participating islet transplant centers, and Drs. Bretzel and Brendel at the International Islet Transplant Registry, and Drs. Ricordi, Alejandro, Lakey, Shapiro, Korbutt, Rayotte, O'Neil and Weir for discussing islet quality control related questions, and colleagues at our institution at the University of Minnesota. Thank you so much for your attention.

DR. SALOMON: Thank you, Bernhard. Before we go into the break I would like to acknowledge that two more members of the committee have joined us since this first phase started, Dr. Robert Goldstein from the Juvenile Diabetes Foundation -- welcome, Bob -- and, Dr. Jeff Bluestone from the University of Chicago. Welcome, Jeff. Yes?

DR. AUCHINCLOSS: Bernhard, first off, could you put up that slide that I was mentioning to you?

DR. HERING: Yes.

DR. AUCHINCLOSS: This has to do with the question of whether recurrent autoimmunity leads to the destruction of allogeneic islets in patients with Type 1 diabetes. Nobody has spent more time than I have in the past several years trying to make that case but, I must say, I sometimes

stop and say what is the evidence for that, particularly when we saw some animal model studies that led me to wonder about that issue. If you put up your slide of the survival of islet transplants in allo situations where Type 1 diabetes is involved versus no Type 1 diabetes, surgical pancreatectomy, my impression is that this is the strongest evidence in the clinical situation to demonstrate that recurrent autoimmunity is important.

[Slide]

That is the slide, right there. Can you point out to the group the difference that is involved there?

DR. HERING: Yes, let me just show this again. What is shown on the slide is insulin independence following islet transplantation, and here you see percent insulin independent patients, and this is the Type 1 diabetic recipient category. Here you are talking about islet allotransplantation in surgical diabetes and islet autotransplantation in patients undergoing total pancreatectomy. There are two very important issues to be discussed. One is not only the difference at one year, but also the time to insulin independence. The data seem to suggest that autoimmunity is a very important factor. I would agree entirely, but I guess we cannot exclude the possibility of other crucial factors, such as the presence of diabetes at the time of transplantation because here

there was no diabetes present at the time of transplantation --

DR. AUCHINCLOSS: There is really only one point I want to make about that slide. I use your slide, that one, all the time to make the same case. But the point I want to make is that the 40 percent survival at the end of 1 year in the allotransplants for non-Type 1 diabetic patients involves 15 patients total. So, the survival there involves 6 patients out of 15 instead of an expected 1 patient out of 15.

DR. HERING: Yes.

DR. AUCHINCLOSS: The numbers that we are using to make the statement that recurrent autoimmunity is a crucial factor in islet transplantation lack of success are very tiny. The fact of the matter is that when you do a whole organ pancreas transplantation it is vanishingly rare to report recurrent autoimmunity as a cause of islet destruction, and I think that is a much stronger statement from the literature than the statement we have here. It is not that I think it might not be true; I just want us to remember that the data is precious small.

DR. HERING: I think the only point that I can make is that the data seem to support the hypothesis, and we have a testable hypothesis and we can test it in the clinical setting now. So, we can do transplants

prospectively in patients with surgical diabetes and Type 1 diabetes to address this very specific question.

DR. AUCHINCLOSS: I couldn't agree more. Bernhard, you mentioned HLA sensitization has occurred after islet transplantation. How frequent is it?

DR. HERING: I think Barbara Olack is in the audience, and the Washington University in St. Louis was the first to document sensitization following islet transplantation in patients with rejecting islet transplants. Do you want to comment on this, on your experience?

DR. OLACK: All I can say is --

DR. SALOMON: Sorry, microphone, and identify yourself, please.

DR. OLACK: Sorry. It is Barbara Olack from Washington University. All I can say is that the criteria we used to measure the HLA sensitization -- we took 6 patients that we felt had had good C-peptide levels after 6 months of transplantation, and those were the patients that we looked at because that at least gave us a baseline to start with, with rejection, and of those 6 patients, 5 of the patients had rising HLA sensitization exactly at the time of their C-peptide decline.

DR. AUCHINCLOSS: And these were patients who had not had kidney transplants?

DR. OLACK: They had all had kidney transplants.

DR. AUCHINCLOSS: So, they have another explanation potentially.

DR. OLACK: We saw no sign of creatinine change at the time of the islet rejection. Also, looking back at specific alleles, we found that there was a number -- and I don't remember the exact numbers at the time, but there was a number of patients that the alleles that were positive with the antibody did not occur in the kidney. It was only in the islet transplants.

DR. AUCHINCLOSS: That sounds like pretty strong evidence, although you would agree that you could have a kidney transplant in place with a creatinine that doesn't change and it still develops an antibody.

DR. OLACK: Sure, and the thing of it is that when we did the transplants with the islets we were trying at the time -- and, of course, HLA matching with islet transplant is very difficult, and which way to go is still in question, but most of our islet transplants also had matching alleles from the kidneys. But, we could identify specific alleles that were not in the kidneys and were only in the islets that came up positive for antibody.

DR. AUCHINCLOSS: That will be an important question for this afternoon's discussion. A very last question for Bernhard, this issue of how to judge whether an

islet is a good islet or a bad islet and what things to measure is frustrating to all of us, and you made the suggestion that there needed to be a lot more animal study work to determine that. But I think we also have the impression that different animals are different, different species of animals are different and not all of them represent human beings. Will we learn what we want to learn from doing animal studies, say monkey studies, of what is a good islet versus a bad islet?

DR. HERING: Well, this will be a very difficult task, and the number of studies that could be done is more or less endless. I think another approach could also be, now that it seems possible to reverse diabetes on a more or less consistent basis, maybe in the foreseeable future with a single-donor islet transplant and then we can address prospectively the predictive value of assays. I think this is an opportunity that was not present in the past. As we all know, for autoimmunity there is no large animal model or brain death. Do we have brain dead organ donors in large animal settings? Nobody has ever done this. Do we have recipients with long-term diabetes for clinical models? It has never been studied. So, the models available are not suitable to address the questions that we face in the clinical setting. That is why I like the approach of using highest quality organs, documenting the feasibility of islet

transplantation, and establishing criteria that have predictive value in the clinical setting as long as this is a safe procedure.

DR. SALOMON: Thank you, Bernhard. Just to give you a little of the lay of the land, tomorrow the committee is going to take up sort of this transition from product to preclinical models, and I think this is a very apropos beginning, to begin thinking about it. My personal opinion is that I am excited for the idea that we can now perhaps, in the next couple of years, move forward into more clinical trials with higher levels of success. I am disappointed that we didn't get to see the data but I will look forward to it coming out soon. But, at the same time, my personal sense is that we are going to need good, strong preclinical models behind these pioneering attempts in human studies but we will get into some of that tomorrow.

I am going to say we will have a ten-minute break because it is never ten minutes; it is always fifteen. Then we will get started with the second part of the morning.

[Brief recess]

DR. SALOMON: I think we will go ahead and get started, and forgive those getting their last bit of coffee -- I can relate to that.

So, the second session of this morning's program consists of two presentations. It is my real pleasure to

introduce Joan Harmon, from the Division of Diabetes, Endocrinology and Metabolic Diseases at the National Institutes of Health. Joan Harmon has really been a tireless organizer and supporter of research in diabetes and specific research in islet transplantation, and many, many of us in the field owe her a lot.

NIH Support for Islet Transplantation

DR. HARMON: I thank you very much for that introduction.

[Slide]

Clearly, the NIH has a great deal of enthusiasm and support for islet and beta cell transplantation. A number of you are participating in these programs or will be in the future.

This first slide includes a picture of islets, which was generously provided to me by Bernhard Hering, who is here today. I understand that this is what we would like to see all islet preparations look like.

The recent increase in support for islet transplantation has occurred for several reasons. Clearly, our understanding of the role of costimulatory pathway in transplant rejection has been a major driving force. But equally important, as has already been mentioned this morning, has been a realization as a result of the DCCT, or Diabetes Control and Complications Trial, that tight control

of blood glucose levels is critical in preventing the devastating complications of diabetes, such as retinopathy leading to blindness; nephropathy leading to kidney failure; and cardiovascular disease leading to death. In 1998 Congress established a diabetes research working group to develop a strategic research plan for diabetes funding and the NIH.

[Slide]

This slide presents the recommendations from this plan with regard to islet transplantation and beta cell biology. These recommendations were establishment of centers for islet transplantation; expanding the system for national collection of human pancreata; increasing basic research on islet cell differentiation for growth and development; and creating interdisciplinary centers for beta cell biology. This is an ambitious plan and it is highly unlikely that any one institute could perform all of these recommendations alone.

[Slide]

Thus, this slide presents the institutes and centers that are presently working together to address various aspects of these recommendations. These institutes include the National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK, the National Institute of Allergy and Infectious Diseases, NIAID, and the National Center for

Research Resources, NCRR.

[Slide]

So, what have we been doing with regard to islet transplantation? This slide tries to give you a flavor of what is happening. With the first islet transplant done in rodents by Paul Lacey in the early 70's, there have been a number of preclinical research projects supported by the NIH. Support for such studies has expanded in the past few years and additional areas of research have begun. I will go back to some of these areas later. However, recently a new NIDDK intramural branch was initiated, a Transplantation and Autoimmunity Branch of the NIDDK under the direction of David Harland, who is in the audience, and in collaboration with Alan Kirk at the Navy. To date, this branch has established a human islet isolation facility and prepared islets from 12 human pancreata.

These investigators will be taking part in the Immune Tolerance Network, using the Edmonton protocol, through support by the NIDDK. By this summer, they anticipate initiating non-human primate islet transplantation. Many of you are very familiar with the Immune Tolerance Network which was initiated by the NIAID and co-sponsored by the NIDDK and the Juvenile Diabetes Foundation International. This is a very ambitious project which I will return to in a moment.

A little over a year ago the NIDDK, again in collaboration with the NIAID and the Juvenile Diabetes Foundation International, released a request for applications, entitled, Human Islet Transplantation into Humans. We are presently in the process of funding six of these applications submitted to this RFA. All six applications propose clinical trials in islet transplantation. The NIDDK is also about to release a proposal for an islet or beta cell registry for North America. We believe that this registry will enable the rapid and complete analysis of the many parameters related to islet transplantation. Such analysis may allow us to understand which parameters are most important for successful islet transplant, requiring the least number of islets and immune modulatory intervention.

There is another RFA or Request for Application, for which applications are due in mid-April, entitled, New Strategies for the Treatment of Type 1 Diabetes. This request for applications is supported by funds from the Balanced Budget Act of 1997 for research into Type 1 diabetes. While we have envisioned this RFA to solicit applications for the treatment of new onset or newly diagnosed Type 1 individuals, applications may also be submitted relating to the use of islet transplantation.

Finally, the National Center for Research

Resources, or the NCRR, is presently considering a request for applications to establish islet isolation centers or facilities in several places throughout the United States.

[Slide]

Now let me turn to the Immune Tolerance Network to try to give you a feeling for what this network is about and what it will try to accomplish with regard to islet transplantation. As I said before, this network was initiated by the National Institute of Allergy and Infectious Diseases with sponsorship from the National Institute of Diabetes, Digestive and Kidney Diseases and the Juvenile Diabetes Foundation International. Anyone wanting more complete information on the network can obtain this information on the website at www.immunetolerance.org.

[Slide]

This slide briefly describes the network which was, or is, officially called the Collaborative Network for Clinical Research on Immune Tolerance. The funding mechanism for this network is a seven-year contract which has been awarded to the University of Chicago, and the project director is Jeff Bluestone who is, of course, in this room.

As it is presently configured, the network is composed of 40 research institutions located around the world and up to approximately 70 researchers. As the title

conveys, the objective of the network is to test immune tolerance protocols. These protocols will be tested in an organ transplant situation, the kidney, and in a tissue transplant situation, the islet. They will also be tested in a number of autoimmune diseases in the hope of inducing tolerance to the autoantigen. As part of this network, a component will be challenged to develop assays to measure induction of tolerance. This is perhaps the most essential component of the network and we look forward to their results. The final component of the network will be clinical trials for the treatment of asthma and allergic diseases.

[Slide]

The component of the network which is particularly interesting to us today is the islet transplantation subgroup. On this slide are listed the participants of this subgroup. Many of these participants are, of course, in the audience today, including Camillo Ricordi, Bernhard Hering, Hugh Auchincloss, Kevin Harold, Dave Harland and, if I have missed anybody, forgive me.

[Slide]

On this slide is the present plan of this group. I hope you can read this in the back of the room. It appears to have come out rather light. This group has been approved and funded to test the Edmonton protocol in

multiple centers. As this protocol has already been described to you, I will only reiterate that what was believed to be the critical change in this protocol is the complete removal of steroids as a means to induce immune suppression. It is well known that islets -- including islets in situ in the pancreas -- do not respond well to such steroid treatments. While this protocol is not an immune tolerance intervention, it may well be a protocol that can be reproduced in multiple centers. This would give us an intervention against which immune tolerance protocols can be judged. This will be the first protocol to be undertaken by the Immune Tolerance Network. However, as you can see, this group is very interested in additional protocols, shown at the bottom of the slide.

[Slide]

On this slide is shown the website for the Immune Tolerance Network. While there are 70 investigators in approximately 40 institutions within the network, others from outside the network may also apply for support by the network. The instructions for this are given on the web page. Basically, the review is a two-step process. The first step is the submission of a very short application, equivalent to a letter of intent. These are reviewed and the most promising are requested to submit a more complete application, roughly about ten pages. After review of these

applications a funding decision is made and the real work begins. Unlike the NIH system which requires roughly 9-12 months for funding, this mechanism can be activated within 3-6 months.

[Slide]

As mentioned in the very first talk by Dr. Ricordi, we have a long way to go before we are able to achieve euglycemia. As I have already given you the present status of initiatives supported by the NIH for islet transplantation, I would like to conclude at this point by mentioning several additional avenues that may be required if we hope to treat all insulin-dependent individuals with an islet-like therapy.

This slide lists six approaches to achieving euglycemia or normal blood glucose levels. As has already been mentioned, only a pancreas transplant is effective today for achieving euglycemia. We hope that in the near future islet transplants will also be shown to yield euglycemia for extended periods of time. But we are all aware that there are insufficient pancreata for either pancreas or islet therapies to be applied to all individuals needing such therapies. Therefore, we must consider the use of xeno-islets or islets from different species that my have to be encapsulated within a membrane to prevent xenorejection. We may have to use surrogate beta cells that

may be developed through genetic engineering or non-beta cells to respond to human physiological levels of glucose and secrete insulin.

Recently thee has been considerable interest and speculation about the use of stem cells to produce beta cells, or the identification of beta cell precursors or progenitors that may be used to produce large quantities of beta cells or islets in culture. This little pair of glasses here is supposed to be a beta.

[Laughter]

Finally, there is the anticipation that with the slow development of glucose sensors we may be able to conceive of an actual mechanical device or close-loop system for achieving euglycemia. As we are discussing parameters to predict the success of an islet transplant, perhaps we should begin to think about the parameters which may be necessary in the future to predict the success of these alternative islet or beta cell sources.

Thank you. Are there any questions?

DR. SALOMON: Thank you, Joan. I guess we have a question back here. Can you identify yourself?

DR. HARLAND: Sure. My name is David Harland, and Joan mentioned me as the head of this new NIDDK branch. I just wanted to publicly acknowledge that it is also a partnership with the University of Miami who has helped us

develop this islet isolation facility, and it is a full intellectual partnership there. Thanks.

DR. SALOMON: Thank you. Hugh?

DR. AUCHINCLOSS: Joan, in the conversations of the Immune Tolerance Network and the islet clinical subgroup and in other parts of the Immune Tolerance Network, at least three bottlenecks to trials of tolerance-inducing protocols have been identified -- resources for preclinical non-human primate trials; availability of reagents that might be toleragenic; and, in particular in the world of diabetes, the development, if it is conceivable to do so, of a non-human primate model of Type 1 diabetes. Can the NIH do anything to help in those road blocks?

DR. HARMON: We already have several -- let me try to remember, the first you mentioned was islet --

DR. AUCHINCLOSS: Funding for non-human primate research.

DR. HARMON: Okay, we are funding several institutions. Both NIDDK and the NIAID have support for such facilities. Obviously, if additional applications are submitted and compete well in the peer-review system we would gladly look forward to supporting more of those.

The second one you requested information on was the reagents. Quite often these reagents are available through a commercial enterprise. If these are going to be

forward into a clinical trial setting -- we try to work very carefully and in collaboration with these companies, and in many cases they have been very generous in being willing to provide such reagents for initial clinical trials.

DR. AUCHINCLOSS: And then the last was a Type 1 model in monkeys.

DR. HARMON: We, in fact, are presently supporting one attempt to produce such a model. We would look forward, if that is not successful, for others to come forward and offer potential development of such a model. Clearly, that is very important.

DR. SALOMON: Joan, when do you anticipate some data on that model would be available, because that is an interesting question?

DR. HARMON: I haven't spoken recently to the person who is trying to develop the model. I can only say that their funding, I believe, was started a little less than a year ago and, so, we wouldn't expect something to be forthcoming quite yet.

DR. SALOMON: Yes?

DR. CARA: Can you give us an idea of the price tag on all this?

DR. HARMON: That is a very difficult one to give to you off the top of my head. I believe the Immune Tolerance Network is supporting the islet transplants at

roughly five million. Additional support will be coming from NIDDK to add to that a little bit. Also, we are, of course, supporting the intramural group. The registry will probably be -- I am making up a number here -- about half a million a year to get started. Of course, we have a large portfolio of preclinical studies already ongoing, and ongoing for many years. I would have to guess -- I am afraid to think of it -- it is quite a bit of money that we have had in the area for a long time but I don't have any exact amount for you. I could perhaps give this information to the committee at a later date.

DR. SALOMON: Thank you very much, Joan. The next speaker of this session is Dr. Robert Goldstein, who has formerly supported many of us in his role at the National Institutes of Health, in allergy and immunology, and has now joined the Juvenile Diabetes Foundation International and has really brought this institution forward in a remarkable way in terms of supporting the research in the area of diabetes.

JFD: Introduction of Islet Transplant Programs

DR. GOLDSTEIN: Thank you. I really have a few minutes worth of things and then I will be happy to answer questions.

[Slide]

I am representing children with this disease who

would like to get cured.

[Slide]

For those of you who are unaware, the Juvenile Diabetes Foundation is unique in its passion and its focus, and we actually live, breathe and eat this mission statement. We really want to cure this disease.

[Slide]

This year we will actually spend between 85-90 million dollars funding research compared to about 24-28 million in 1997.

[Slide]

Those of you who are unaware of www.jdf.org, the only real point I wanted to mention here is that we will fund a group effort in an amount up to five million a year for up to five years. That represents an extraordinary opportunity to investigators worldwide to bring us very focused and targeted applications to help us actually accomplish our mission. I was just counting up the review cycle -- we get your application on this day; five months later we will tell you whether you have the money or not, sometimes sooner, seldom later.

[Slide]

In the spring of 1998 the Juvenile Diabetes Foundation announced its research agenda. That followed deliberations of a lot of people trying to focus the

research agenda onto a small group of areas that we thought would accomplish the goal. The number one goal was to restore normal metabolism, and the number one version of how to accomplish that was to take what was perceived as individual laboratory efforts here and there and create the possibility for a group effort, and then to scale it up because it was perceived that the thing that we could accomplish first in the near-term, that is, three to five years, would be to accomplish the task of transplanting human islets. When I say near-term, that is to be contrasted with something like supporting stem cells which we knew was not going to provide anything clinical for a decade of so. The parents of our children would like something today. They would rather not wait. There were other research emphasis areas. They are not important for this.

[Slide]

What we next did was to say what was missing from the equation, what was really needed to make human islet transplantation a reality. By the way, our obvious desire is to have that occur without immunosuppression so children can receive islet transplantation. It is not very interesting to us if you have to have a kidney transplant, islet transplant and receive toxic drugs. But we knew you had to start somewhere and an obvious place in our minds a

couple of years ago was the simple inability to have very high quality, uniformly controlled, prepared, available human islets for research and other things. Realizing that it is very hard to send an RO1 to NIH and say something like "you are going to take pancreases and prepare islets" -- that really falls out of the hypothesis-driven category, and that really wasn't being done. So, nobody should be surprised that that was not being accomplished at a high rate of speed.

So, we took the opposite position and said it is obvious that people need resources to do that. This is a list of groups. We call this distribution centers. What we mean is as follows, we funded people and anybody from this group may be receiving as much as half a million dollars a year, and the mission for people identified was to prepare human islets in the best possible manner to begin the process of quality control, etc., and to make those islets available for research, basic research studies. Our logic at that time was fairly simple. We really had no idea how we could create a list of specifications of what would be required for clinical transplant. So, we thought we needed to start somewhere so we restricted the initial phase to, you know, get started; begin distributing islets. There must be a lot of people out there who ordinarily would not even be able to study them. And, we will begin to

accumulate data and information. I will come back to how we are transiting from that.

For the purposes of this conversation this morning -- Joan told you about the Immune Tolerance Network. Groups will be conducting clinical trials. And, we are at the present time are about to shift those resources that we originally provided for basic research or non-human trials into human trials. The money on this slide is about two and a half to three million dollars a year. So, we think that is a significant amount of money for that particular purpose.

Secondly, we committed to work with the Immune Tolerance Network group to be the source of islets because we had had more experience. They just started out this past fall, and we have been doing this at least for a year and a half or two. So, we wanted to take advantage of that as a platform and so we are committed to providing the resources necessary to produce high quality islets, and we are delighted and pleased to know that the NIH appears to be, in the next year or so, interested, willing and able to launch an effort to make this even better on a national basis so that quality control, good manufacture, and all those things that are intrinsically important to this will be able to occur.

A rough translation of everything I said --

accomplishing high quality preparation of islets should no longer be limited by resources. There should be enough resources available to accomplish that. What is probably relevant is how to go about that and in what context to make it work really well. The sub-text is that we continue to support groups to do other things -- beta cell biology and a whole bunch of other issues that are also important but even groups that don't prepare human islets from pancreata in the usual standard fashion. For example, a group in Brussels, Danny Pipeleers, extracts beta cells from human pancreases, cultures them for a week or two, actually brings excessive numbers from several pancreases, accomplishes transplant in a particular protocol, puts some away in a freezer to find out if we can make them last longer so we don't have to have them as hurriedly as a typical organ transplant.

[Slide]

In addition to simply providing resources to people and saying please get pancreases and prepare islets, we said please send us group applications to accomplish clinical transplant and/or other scientific aspects related to the topic. This is not really a complete list but we are really funding eight or ten groups with significant enough resources so they should be able to be in the business of doing this.

[Slide]

You can't read this -- this is not current and up to date but I just use it to make a point. When I got to JDF in the middle of '97 if we counted all the research we were funding for either beta cell biology, human islets or islet transplant the total was four million dollars. Today, as I am standing here, that total is twenty-five million and is growing. The reason it is growing is that, in a sense, what has happened is that the hints of success, the hints of production, the hints of this and that have gotten us excited and even more interested. So, working with the Immune Tolerance Network and separately funding groups to do it has gotten us excited. We would like to see this happen. We want to make sure that nothing stands in the way, and our constituents want to provide resources to do that.

A couple of side bars -- can I answer your question here before you ask it?

[Laughter]

JDF actually currently funds the current historical registry, which if you look from '97 and earlier, approximately tells you what you would expect a historical register to show you -- the numbers and hard to compare things. So, we applaud the notion of a prospective approach to acquiring and accumulating information. We would welcome non-human primate research grants to accomplish specific purposes, whether they are add-ons or tie-ins, and we have

made that publicly known. We would actually be willing to participate in the development of molecules or reagents if necessary to proceed scientifically. And, we have an ability to do that in a non-standard review cycle. That is, there is no specific requirement that you have to wait for our next grant deadline. We actually review twelve months a year, and we fund monthly. So, a large proportion of our resources is funded following an ad hoc scientific review. Whoever has the Type 1 monkeys, we would certainly like to see them, spread them around.

Let me stop here. My hope is to simply share with you our wild enthusiasm to accomplish this task without necessarily guaranteeing success. I mean, we realize there are some aspects that are still research, but there is a unique moment here in the year 2000 where you have collaboration among major NIH institutes and Juvenile Diabetes Foundation, which is a major funding source worldwide, to accomplish a variety of activities and we are willing, therefore, and able, with think, to make that happen, except that in my office in New York we don't do much research actually. So, we just send out the money and so we need all of the groups here.

So, on behalf of my constituents, I would like to thank the panel members and the FDA for proceeding and making this happen, and you will find us willing workers.

Thank you very much.

DR. SALOMON: Thank you, Bob. Did he answer all your questions?

[Dr. Auchincloss nods in agreement]

Excellent.

DR. AUCHINCLOSS: Bob, I don't have a question for you; I do have a comment and that is, the last two speakers, it seems to me, have done a very important job of placing this issue of regulating islet transplantation by the FDA in context. There are, obviously, a large number of other groups that are involved in the development of an islet transplantation program, including the Immune Tolerance Network funded in part by the NIH and in part by the Juvenile Diabetes Foundation. You have the NIDDK in its own right. You have the Juvenile Diabetes Foundation which is fostering islet transplantation trials. It seems to me that the whole point of this two-day meeting is to figure out where the FDA enters into the regulation of islet transplantation to further that big collaborative effort rather than to make it more complicated than it needs to be.

DR. GOLDSTEIN: I want to add one thing to his comment. The most common question that I have been asked in the past three or four months is since the Immune Tolerance Network which has lots of resources and lots of people is establishing a method of doing collaborative work, is the

Juvenile Diabetes Foundation going to stop accepting applications do things? And, in case anyone hasn't heard or doesn't know, all we have said is we are up and running, and we are in business, and we encourage applications. They have to go through our peer-review system. In a sense, we have made the judgment that this is not enough; we need more, and we need more of high quality, and we want to encourage people to do this.

DR. SALOMON: I think what is raised here is a very good question. I don't know if you have quite got what the FDA has in mind here what they want to do. We have seen it here in a very, very positive way now, organizations, all of which have been mentioned so I won't go over it again, who really stepped up to the plate, as it is, to support research in islet and diabetes. And, I don't think that is the FDA's job, and I don't think that is why we are here today.

From discussions with the FDA though to try and define why we are here for the next two days, is that the FDA realizes that this is now cell transplant and we are going to treat cells provided for such transplantions as a product. We are going to move from a product, which the FDA does have significant interest in defining, in defining quality, in defining its ability to ship, in defining its reproducibility, and in the parameters by which you judge

the quality of the product in the recipient of the product, obviously, post-transplantation. That requires consideration of what are appropriate preclinical studies upon which to base a decision to take a product of sufficient quality, in the minds of the FDA, in the minds of a regulatory agency, and put it in a human being, and how to judge the quality of the responses after transplantation as a product in these humans. I think that is why we are here for the next two days.

DR. AUCHINCLOSS: Actually, I would like a clarification on that, maybe from the FDA in particular. The FDA does not regulate whole organ pancreas transplantation. The FDA is interested to a degree in the regulation of allogeneic cell transplantation. We recognize that the FDA is very interested in xenogeneic transplantation of all forms -- a different subject. But my understanding of the 1997 guidelines for how you are going to regulate allogeneic somatic cell transplantation was that minimum manipulation of the cells meant that you would ensure that the procedure or product was up to snuff but that you weren't going to get further involved in the regulation of the procedure of the cell transplant. Now, am I mischaracterizing that, and is that in fact the issue that we are addressing?

DR. SIEGEL: Well, I don't know that that is what

we are addressing at this meeting, although it is certainly important groundwork in terms of what we are discussing at this meeting. The 1997 proposed approach to the regulation of cellular and tissue-related products does utilize the extent of manipulation as one of the standards for determination of what is the extent, and type and nature of regulatory authorities that will be described. But it is one of a group, and for a cellular product that is allogeneic and metabolic in its function and systemic in its action, independent of the extent of manipulation, that proposed approach would include a significant amount of regulatory oversight and we would regulate it as a regulated product.

I should point out here that although there was some suggestion that this is a novel area for FDA regulation and, indeed, obviously this is a novel area of products in general, some may not be aware that whole blood products are regulated by the FDA. They are approved and the blood banking industry is regulated and the agency has substantial experience, in our Center for Biologics, in regulation of the blood supply and plays, I think, a very important role in ensuring its safety. So, we see a role here, hopefully a role that, exactly in accord with your initial statement, will not impede the development of these products but, in fact, will promote their development by ensuring appropriate

quality control and testing, both clinical and laboratory.

DR. AUCHINCLOSS: I am very interested in this. The FDA has not, in fact, regulated any of the previous 405 islet transplants that have been performed, or felt that it was their responsibility to do so. Does the FDA regulate bone marrow transplantation in the United States? In other words, I am testing you to find out to what extent is this an extension of the FDA's regulatory interest into areas in which you have not traditionally been.

DR. SIEGEL: The question of whether the cellular product is considered a product, in some sense, has been in many cases a rather minor component of that larger question of what we are regulating in terms of these areas. If you look at an area such as hematopoietic stem cell or bone marrow transplantation, for example, there are many devices that have been in use in selecting out stem cells or in removing tumor cells, or many growth factors that have been used in vitro in cells and much more commonly in vivo on both the donors as mobilizing agents and on the recipients. That has been true in many or most areas of development of cellular therapy so that the FDA has been long involved in many areas of cellular therapy development independently of the specific question of whether the cellular product itself is considered a regulated product.

In the case of hematopoietic stem cells, we have

under the proposed rule in 1997 a specific approach for how they will be regulated. That is probably not worth going into in great detail here and if I tried to do it I would probably make a mistake or two, but I can answer specific questions if relevant. But we have been very actively involved in those areas, and we would consider a significant proportion of those products, particularly those products that are allogeneic or those products that are expanded ex vivo or that are genetically modified to be regulated products. Does that address your question?

DR. SALOMON: Can we move along and then we will come back to that? Do you have a key follow up?

DR. AUCHINCLOSS: Just for the context for the committee members who haven't been here before, Jay and I have had this conversation almost every time we have regulated one of these products where I keep saying the FDA should regulate the process, the device, etc., but leave it to the transplant community to figure out where the cell product is best applied.

DR. SALOMON: I think that is something that has to come up in the next two days to put that in context. Today we are going to talk about product preclinical, and I will get back into that again when we come from lunch. Tomorrow, from preclinical to clinical. So there will be several times in which this sort of theme can come up in