UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
(CBER)

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE MEETING

OPEN SESSION

8120 Wisconsin Avenue

Bethesda, Maryland

Friday, November 13, 1998

PARTICIPANTS:

MEMBERS

Dr. Julie M. Vose

Dr. Richard A. Goldsby

Dr. Hugh Auchincloss

Dr. Carole B. Miller

Dr. William M. O'Fallon

Dr. W. French Anderson

Dr. Richard E. Champlin

Dr. Daniel R. Salomon

Ms. Abbey S. Meyers

Dr. Virginia C. Broudy

Dr. Esperanza B. Papadopoulos

Dr. Edward A. Sausville

Ms. Gail Dapolito, Executive Secretary

Ms. Rosanna L. Harvey, Committee Management Specialist

CONSULTANTS

Dr. P. Jean Henselee-Downey

Dr. Joanne Kurtzberg

Dr. John E. Wagner

PARTICIPANTS (CONT'D):

GUEST SPEAKER

Dr. Richard J. O'Reilly

FOOD & DRUG ADMINISTRATION (FDA) PARTICIPANTS

Dr. Jay P. Siegel

Dr. Patricia Keegan

Dr. Gerald E. Marti

Dr. Karen D. Weiss

Dr. Stephen D. Litwin

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C O N T E N T S

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P R O C E E D I N G S

(9:05 a.m.)

MS. DAPOLITO: Good morning and welcome to the 24th Meeting of the Biological Response Modifiers Advisory Committee. My name is Gail Dapolito. I am the committee

executive secretary and the designated federal official for today's proceedings.

The committee is meeting today to discuss issues related to allogeneic transplantation with a focus on haplo-identical transplantation and other high-risk transplantations.

I would like to begin by introducing the committee members and other participants of today's discussions.

If I could begin on my left, it is a pleasure to introduce and welcome two new committee members. Dr. Daniel Salomon of the Scripps Research Institute and Dr. Esperanza Papadopoulos, Memorial Sloan- Kettering Cancer Center.

Next is Dr. Carol Miller, the Johns Hopkins Oncology Center. Joining us shortly, Dr. Hugh Auchincloss, Harvard Medical School, Massachusetts General Hospital; Dr. Richard Goldsby. Dr. Goldsby is here somewhere, Amherst College; Dr. French Anderson,

University of Southern California; the Chair Dr. Julie M. Vose, the University of Nebraska; Dr. Michael O'Fallon, the Mayo Clinic.

Now, I have the distinct pleasure of announcing that Dr. O'Fallon has recently been elected to serve next year as the president elect of the American Statistical Association. This is a very prestigious honor and we would like to offer Dr. O'Fallon our sincere congratulations.

And I think I heard something about a Bronx Cheer.

Proceeding around the table. Dr. Jean Henslee-Downey, University of South Carolina, Richland Memorial Hospital; Dr. Richard O'Reilly, Memorial Sloan-Kettering Cancer Center; Dr. Joanne Kurtzberg, Duke University Memorial Center.

The FDA Center for Biologics Evaluation and Research, Office of Therapeutics Research and Review is

represented today by Dr. Stephen Litwin, Dr. Patrician Keegan, Dr. Karen Weiss, and Dr. Jay Siegel.

We would like to request in consideration of the committee that you do not operate cellular phones in the room today and please put your pagers on silent mode.

Dr. Vose, with your permission I'll read the conflict of interest statement.

DR. VOSE: Please.

MS. DAPOLITO: This announcement is made a part of the record at this meeting of the Biological Response Modifiers Advisory Committee on November 13, 1998. Pursuant to the authority granted under the Committee Charter, the Director of the FDA's Center for Biologics Evaluation and Research has appointed Dr. Jean Henslee-Downey and Dr. Joanne Kurtzberg as temporary voting members for the Committee discussions.

Based on the agenda made available and on relevant data reported by

participating members and consultants, it has been determined that all financial interests in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the committee's discussions have been considered.

In accordance with 18 U.S.C. 208, Dr. Esperanza Papadopoulos has been granted a general matters waiver which permits her to participate fully in the committee discussions.

In regards to FDA's invited guest speaker, the Agency has determined that the service of Dr. Richard O'Reilly is essential. At the request of the Chair, Dr. O'Reilly has been invited to participate in the discussion of general scientific issues related to allogeneic transplantation. The following reported interest are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by Dr. O'Reilly.

Dr. O'Reilly is conducting a trial which involves the use of a product provided free of charge by a firm which could be affected by the committee discussions. In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interests the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

Screenings were conducted to prevent any appearance real or apparent of conflict of interest in today's committee's discussions. Copies of the waiver addressed in this announcement are available by a written request under the Freedom of Information Act.

With respect to all other meeting participants we ask in the interest of fairness that they address any current or previous financial involvement with any firm

whose products they wish to comment upon.

Dr. Vose, should I proceed with the open public hearing?

DR. VOSE: Please.

MS. DAPOLITO: We have received no prior requests to provide public comment. At this time is there anyone present who would like to address the committee on matters before it today? Dr. Vose, I see no on. I'll turn it over to you.

DR. VOSE: Okay. Thank you. We'll proceed then with the first item on the agenda, summary of the NIH/CBER Hematopoietic Stem Cell Progenitor Workshop and Dr. Marti.

SUMMARY OF NIH/CBER HEMATOPOIETIC STEM CELL PROGENITOR WORKSHOP

DR. MARTI: Members of the Advisory Committee and staff, FDA, CBER colleagues, guests and press, I've been asked to give a 15 to 20-minute review of the recent meeting on peripheral stem cell and cord blood meeting that was held at the CBER and NIH.

This meeting was essentially chaired and organized by Leanna Harveth who is unable to be here today due to an illness in her family. And therefore I'm going to try and take her place.

The meeting was entitled, Hematopoietic Stem/Progenitor Cell Products and it was a discussion of unrelated allogeneic placental umbilical cord blood and peripheral blood cell banking and transplantation.

Next slide. It was held on September 10th, 1998. Next slide. And it was sponsored by both CBER and NHLBI. Next slide. By the way, you have a set of these overviews in your blue folder. The workshop objectives there were five. The first one was to have an overview of the Federal Register notice which was published January 20th and it was entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood

Hematopoietic Stem/Progenitor Cell Products: Request for Comments."

Next slide. The second and third objectives are listed here. The first was to discuss the current status of related and unrelated allogeneic peripheral blood hematopoietic stem/progenitor cell collection and transplantation.

The third objective, discuss issues regarding the administration of cytokines to normal donors for mobilization of peripheral blood stem cells.

Next slide. And fourth to discuss the current status of unrelated allogeneic cord blood banking and transplantation.

And the final objective was to discuss the status of professional voluntary standard development.

Next slide. There were four sessions. The first session consisted of presentations of the review of the Federal Register notice by Dr. Harvath, and this was

followed by a review of the transplantation registration data by Dr. Mary Horowitz and then the experience with normal donors and cytokine administration in the setting of a blood bank at M.D. Anderson was provided by Dr. Anderlini.

The next slide. Session II consisted of experiences related to related allogeneic stem cell transplants at M.D. Anderson by Dr. Champlin and Washington University by Jon DiPersio.

The unrelated allogeneic stem cell transplants peripheral based on the national marrow donor program, the NMDP experience that was provided by Dr. Dennis Confer.

Next slide. The third session primarily focused on the issues of blood banking of cord blood samples. There was a presentation from Georgetown University on the multi-center cord blood banking and transplantation study. This is an umbrella IMD. Then there was a presentation by Dr.

Pablo Rubinstein from the New York Blood Bank that has the largest experience with cord blood in this country and the world. And there was also a report from Duke University by Dr. Kurtzberg who is here today. And then the more recent experience of the cord blood bank in St. Louis.

The fourth and final session on the next slide was essentially a discussion of professional standards and these discussions emanated from representatives from AABB the American Association of Blood Banks by Dr. Haley, and then representatives from the transplant community, Dr. Shpall, Rowley, and LeMaistre.

The next slide, please. We'll now discuss briefly some of the points from the Federal Review Notice which was essentially a request for comments.

Next slide. For minimally manipulated unrelated allogeneic peripheral and placental/umbilical cord blood

stem/progenitor cells intended for hematopoietic reconstitution, it may be possible -- next slide -- to develop product standards, establishment control and processing controls from existing scientific and clinical data.

For those of you who find these Federal Register notices difficult to read, and it's taken me some 20 -- 15 or 20 years to learn to read them, I will repeat that sentence because I think that is the gold coin, the nugget of that paper to develop product standards, establishment controls and processing controls from existing scientific and clinical data.

Also to issue guidance for establishment controls, processing controls and product standards; and to grant licensure for products certified as meeting issued standards.

Next slide. If the FDA determines that data are available to support the

development of standards, the FDA intends to publicly announce such standards and licensure may be grated for products certified as meeting promulgated standards.

Next slide. If sufficient data are not available to develop standards, after a specified period of time unrelated allogeneic stem cell products would be subjected to IND and marketing application requirements.

Next slide. Now, continuing with peripheral blood stem cells, and I prefer saying "peripheral blood stem cells" to saying "peripheral blood hematopoietic stem/progenitor cells." These are mobilized in normal allogeneic donors who are treated daily for five to six days with G-CSF or GM-CSF prior to the apheresis collections.

Most stem cell collections experienced thus far have occurred with HLA-identical sibling donor/recipient pairs.

Next slide. The reported advantage of peripheral stem cell products when

contrasted to HLA-identical sibling bone marrow donor/recipients during the first 100 days post transplant appear to be the following two items:

There is a decreased time to an absolute neutrophil count of greater than 500 per microliter -- I guess that's a mistake. I don't think it should be "ML -- in four to five days, and there should be a decrease in inpatient days, pharmacy costs and blood products.

Next slide. There does not appear to be -- well, with regards to Graft-verus-Host Disease, the incidence of chronic Graft-versus-Host Disease is increased in peripheral blood stem cell recipients. But the incidence of acute Graft-verus-Host Disease does not appear to be different between the two products.

Next slide. The International Bone Marrow Registry transplant and registry data analysis to one year post- transplant

indicates a trend to 75 percent incidence of peripheral stem cell products compared to 45 percent in bone marrow recipients.

Also, the Washington University data at two years post-transplant indicates a 90 percent actuary incidence in the use of peripheral stem cells compared to 40 to 60 percent with bone in bone marrow recipients.

Next slide, please. The peripheral stem cell grafts mismatched at one Antigen result in 100 percent incidence of chronic Graft-verus-Host Disease; 40 percent of these individuals are of the Grade 3 to 4.

And there is an increased incidence in chronic Graft-verus-Host Disease associated with high CD34 cell counts and lymphocyte doses in these grafts.

Next slide. There are studies in progress to quantify the effects of lower cell doses. It's been suggested that perhaps doses less than 10 to the sixth absolute CD34 cells per kilograms and also different

conditioning regimens. One example being the FK506 prophylaxis on the incidence of Graft-verus-Host Disease.

Next slide. In the setting of unrelated allogeneic peripheral blood stem cell products, the National Marrow Donor Program is conducting a study of peripheral stem cells from unrelated allogeneic donors for a second donation subsequent to an initial bone marrow donation.

So essentially these are going to be individuals who have already received a bone marrow graft from the program, but now are being requested for -- that same donor is being requested for a peripheral sample in the form of a lymphocyte transfusion.

Next slide. To date 119 requests for a second donation have been received. As of August of 1998, 34 donors have received G-CSF and 17 of these donors have had a one apheresis collection.

Next slide. And 15 donors have had

two apheresis collections. One donor had the G-CSF administered, and no peripheral stem cells were collected. And one donor received G-CSF administration and the peripheral stem cells were collected, but they were not infused.

Next slide. In this particular setting the donors and recipients are being extensively studied. These donors tend to develop -- I'm sorry, the National Marrow Donor Program intends to develop a similar study for unrelated peripheral stem cell products in the setting of the first donation.

Next slide. Some of the potential disadvantages of the peripheral stem cell product that's been noted in this program is the more frequent occurrence of the CMV viremia; the unknown risks associated with the increased Chronic Graft-verus-Host Disease; the unknown what the survival agency will be; and, of course, the new risks to

normal donors in this program.

Next slide. Some of the short-term safety issues for donors are bone pain, headache, fatigue, and nausea. There are transient elevations of alkaline phosphatase and LDH and infrequent episodes of chest pain and fluid retention.

Next slide. It does require the placement of a central venus catheter, electrolytes, and fluid shifts are noted. There is obviously a leukocytosis and in some individual a thrombocytopenia. I've been told that there was one incidence of a CVA and one instance of spontaneous rupture of the spleen.

Next slide. Long-term safety issues for normal donors essentially remain unknown to present. Next slide. Some of the areas that were proposed for further research by the speakers at that meeting was to have the development of a normal donor registry to monitor long term. "Long term" meaning ten

years of normal donor receiving cytokines for the mobilization of cell products and also to have further studies of biologic and clinical effects of cytokines and apheresis procedures in normal donors.

Next slide. Also to continue to work on development of approaches to control Graft-verus-Host Disease to assess the stability of the peripheral stem cell engraftment to assess the functional effects of T-cell depletion.

Next slide. And standardization of CD34 positive cell assays. This is primarily thought to be flow cytometrically based and then standardization of tumor assays particularly directed at the presence of breast cancer and acute myelogenous leukemia.

Next slide. The third part of the meeting then turned its attention to the cord blood problem both in terms of banking and transplantation. There is essentially a large umbrella type IND that has been

developed at the FDA in combination with NHLBI. This is multi-centered. The three banks are located at Duke, UCLA, and Georgetown, and the six transplant centers are located at Duke, University of Minnesota, UCLA, Fred Hutchinson, Indiana University, and Dana-Farber.

Next slide. This study is going to entail a five-year extensive study to characterize the cord and blood products and it's also going to measure transplant outcomes, results based upon a uniform protocol.

It's my understanding that these protocols will be published in December 1998 and made available on the NIH web site.

Next slide. The New York Placental Blood Program was the first to be established. It is primarily solely for the use of unrelated allogeneic transplantation. It was established in 1992, has banked more than 7700 units, and has provided 700 units

for transplantation.

Next slide. Results of the first 562 consecutive transplants are in press in the New England Journal of Medicine and the speed of myeloid engraftments is associated primarily with graft cell dose.

Next slide. And transplant-related events are associated with the patient's underlying disease, age, graft cell dose, HLA disparity, and transplant center meaning whether it was done in the U.S. or foreign.

Next slide. The St. Louis Cord Bank is a new member -- a new player. They are community-based, trying to bank unrelated cord blood specimens. It is primarily operated by obstetrician/nurse midwives who perform the collections. However only 30 percent of the samples are banked; 70 percent of the samples are deemed unacceptable for a variety of reasons.

Next slide. Areas proposed for future research include ex-vivo expansion of

cord blood subpopulations, adoptive cellular therapies, haplo-identical, related cord blood transplants and to explore the use of cord blood with gene therapy. Of course, that's already underway. And the immunological vaccine development.

Next slide. The last session of the meeting consisted of a discussion of voluntary standards in this field. The American Association of Blood Banks is an organization that was established in 1947. It currently represents 8500 individuals with 2200 institutional members. It has published standards for hematopoietic cells -- progenitor cells since 1991.

Next slide. And it has invited participation of members of the following societies: The AABB, the American Society of Apheresis, the FDA, the Foundation for Accreditation of Hematopoietic Cell Therapy (FACT), which represents ISHAGE, the International Society for Hematotherapy and

Graft Engineering and also the American Society for Blood and Marrow Transplantation and the National Marrow Donor Program. They all participate for standards development and revision.

This group also includes two public members, an ethicist and a patient who has received hematopoietic progenitor cells as therapy.

Next slide. Basically what the AABB is doing is that they are in the process of revising their 1996 published standards to incorporate the ISO 9000 model for prospective comprehensive quality management program.

That was the first time I heard the presentation of the ISO 9000 rules. For several years now, I've had the occasion to drive through some of the parts of the Silicon Valley and Biotech areas in this country and you'll often see companies that will have a big sign up out in front that

says, "ISO 9000 approved." I think it's a very comprehensive approach to standardization and I predict that we will see more of it.

Next slide. FAHCT, the Foundation for Accreditation of Hematopoietic Cell Therapy was founded in 1996. It has 900 members and also the ISHAGE contributes about 1000 individual members. It's purpose is to establish standards for high-quality medical and laboratory practice, to develop and implement voluntary inspection and accreditation.

Next slide. Their standards committee is composed of individuals from the ASBMT, ISHAGE, and FAHCT. Next slide. They expressed concerns regarding the FDA's proposed rule for facility registration and product listing. Some of their reasons were that registration alone is not -- may not or does not improve safety. The sequelae for registration are unknown and there was some

concern that the FDA's ultimate intentions regarding this area are uncertain and that additional regulations have the potential to impede technological advance and compromise optimal patient care.

Next slide. The FAHCT Collection Center standards will include, or actually do include at this point in time, donor health screening including genetic disease; recording clinical outcome data.

FAHCT has also proposed that the FDA grant deemed status to FAHCT and FAHCT acknowledges that some may choose not to participate in their voluntary accreditation program.

Next slide. This was the final discussion point, the importance of developing a single set of standards which are acceptable to all interested professionals in this field.

FAHCT already has a 400-page document outlining standards in almost all

aspects of hematopoietic stem cell transplantation and I suspect we'll see some move toward that set of standards being combined with the ISO 9000 standards that AABB is proposing. Thank you.

DR. VOSE: Thank you, Dr. Marti. Are there any questions or discussion regarding the workshop?

We'll move on to Dr. Litwin.

FDA INTRODUCTION

DR. LITWIN: There's about a one- or two-minute hiatus while the projector catches up to us.

Good morning. I'm Dr. Stephen Litwin and the subject today as you've already heard are allogeneic transplants which I will present an introduction for CBER. The focus is going to be on high-risk allotransplants in which the high morbidity and the limited availability in the case of many donor/recipient pairs has led to a therapeutic dilemma for many patients. The

presentation will be in four sections. In the first section in the background section I am going to present very briefly some of the comments and recommendations of previous biologic response modifier advisory committees.

The second section will review the approaches, generally the expanding group of approaches to the management of high-risk allotransplants. That will be followed by a brief status report and the expectation is that these three introductory sections will serve as a frame of reference for the posing of a series of regulatory issues which are particularly relevant to allotransplants.

And CBER staff looks forward to the committee's comments and insights and recommendations in this regard.

Next slide, please. The first Advisory Committee comments were actually in December of '94. This slide excerpts them. I'll go through them briefly. There was an

emphasis that the goal of -- forward again -- here we go -- there was an emphasis that the goal of less acute Graft-verus-Host Disease is basically and ultimately to improved survival. Concurrent randomized trials were considered essential. The primary endpoint of less acute Graft-verus-Host Disease measured in the first 100 days post transplant was acceptable, but it was highly contingent on the impact, the possible negative impacts on engraftment, on survival, on later events including infection, lympho-proliferative disease.

It was also emphasized there was a need to collect further data in the 6- to 12-month period that would constitute immunologic sustained hematologic and immunologic engraftment. Including recommendations that immune functions could be measured first by collecting useful and detailed clinical information in this later period and by the use of selective, not

panned, but rather selective groups of patients for immune function testing using the immune function tests that were best and most easily determined at the particular investigational site.

It was also recommended that follow up be for at least one to two years.

It was mentioned at this meeting that there were three randomized, concurrently controlled trials in the pipeline. New trials have been added since then, but of these three trials, one has been closed due to a corporate decision, another has failed to show efficacy in preventing prophylactic -- prophylaxis of GVHD, and the third which was initiated at or about the time or shortly after this meeting is still under way.

May I have the next slide, please? This issue was also discussed at the advisory committee meeting approximately six months ago by Dr. Karen Weiss in a single proposal

which dealt with a haplo-identical allotransplant. Protocol was discussed. That was a closed meeting and cannot be discussed further.

The initial development of transplantation and strategies for transplantation, that is, mobilizing agents methods of separating cell populations and the devices for doing these were focused on autotransplantation. And as the field has matured, it has shifted, it is currently shifting to allotransplantation.

The technical issues for both are almost identical, and in fact, in some ways easier because normal donors are the target of immobilizing agents in allotrans-plantation. However, the regulatory issues are extremely different. I have listed on the slide three of the licensed -- FDA-licensed-related applications to, two mobilizing agents and one for a cell selection device, all in an

autotransplantation setting.

Next slide, please. To pursue this further, the endpoints for autotrans-plantation generally have been the purging of tumor cells and in one case reduced infusional toxicity. A closely comparable engraftment has been required. And late engraftment and even survival data has been collected, but there was no requirement that it be powered.

In contrast in the allotransplant setting, the primary endpoint that has generally been offered is reduction of acute Graft-verus-Host Disease although comparable engraftment is also expected, there's greater latitude because the possibilities of a useful application would be greater. And as far as the collection of later data, we have no current guidelines but simply the information gathered from the experience we've had with autotransplants.

Next slide, please. There is a

serious concern about the limited availability of donors for many transplant, allotransplant recipients who need them. The major sources of donors, the four major sources of donors are shown there. In match-related donors there is only about 25 toward the out most, 30 percent opportunity for a recipient who needs a match-related donor to obtain that.

There's another 5 or 6 percent that can be obtained from related donors who have one antigen mismatch. That would include partially matched -- PMRD, partially matched related donors.

The unrelated donor source, for the most part, has been part of the National Marrow Donor program. In the United States among caucasians the chances of getting a match through the National Marrow Donor program is approximately 50 percent. But the possibilities are much less hopeful for many minorities in the United States.

And, finally, the prospects of haploidentical donors who may be mismatched for two or three antigens and pose a much higher risk of the transplant situation is being actively explored.

The morbidity of allotransplants depends on the increasing disparity of HLA among other factors. This slide was shown actually six months ago. It demonstrates the relationship both for related and unrelated grafts. The major morbidity is acute graft versus host disease and engraftment failure. The relationships to chronic Graft-verus-Host Disease while present are probably a little less discernible.

For related donors who are two antigen mismatched, the possibilities of grades II to IV, acute Graft-verus-Host Disease approaches 60 percent, or III to IV, the more severe categories close to 40 percent.

For comparable, unrelated grafts

the figures are similar. Although it's not shown on the listing haploidentical grafts with three antigen disparities have been reported to have grade II to IV acute Graft-verus-Host Disease incidences of 60 as high as 80 percent.

The serious division in prognosis between matched-related and all other were compared by -- this is allo, I hope I'm pronouncing that right. In the Journal of Clinical Immunology last year this comparison of the match-related -- this dichotomous comparison of the match-related to all of the transplants was for three-year overall transplant related mortality. Among the match-related transplants the three-year mortality, morbidity was an acceptable 21 percent. Among all the other transplants it was over 50 percent.

Next slide, please. Given the limited availability of donors, and the high morbidities that some of these patients face

for many allotransplants what kind of alternative therapeutic strategies are out there? Rather than to try to encompass this which is a very large area, I have two examples. In chronic myelogenous leukemia, the early phases for patients who are eligible the use of allogeneic transplants represents in many centers the primary modality.

The use of the allogeneic transplant is considered by many to be curative. These figures under match-related donors from McGlave and Gratwohl are representative figures. I just tried to take them including the whole range. The Gratwohl figure is somewhat pessimistic compared to many of the others.

For unrelated donors the data is very, very similar. Autologous transplantation has a disadvantage of infusing back tumor cells and is not widely used. The use of biologic agents such as

interferon or interferon/hydroxyurea, although quite promising, lacks long-term data. So we do not know what the long-term results or whether these will be actually curative.

Next slide, please. Turning to salvage therapy for acute myelogenous leukemia a far more grim situation, this is a comparison done in 1989 between different modalities by Keating. This is in the post-transplant situations so that each of the -- and the figures that are given there are in percent, so that each of those horizontal sets of figures will add up to 100 percent.

It can be seen that there are sharp advantage to allogeneic transplants which give among the highest complete response rate. Keating has pointed out that there is a relationship between the overall survival and the initial response rate with the except of high dose ARA-C in which there is somewhat

of a disparity.

It can be seen looking again at the allogeneic transplants that the response rate -- the complete response rate is quite good and better than comparable that the number of deaths are about the same as the other groups and the number of chemo resistant patients who are left is relatively small.

Next slide, please. In summary then, what are the alternatives to high-dose chemotherapy with allotransplantation rescue. First, second and third line standard chemotherapy. Avoid the high transplant-related mortality that have a poor survival, autotransplants also have a lower transplant mortality, but you will reinfuse tumor cells back into the patient and there is a lack of graft versus tumor that is allogeneic effect.

On biologic agents there is limited data. Umbilical cord blood or expanded cells are still in early trials. I will touch on

that in a moment. And we are left very often for many patients with a need for a haploidentical or partially-match-related donor transplant with it's high transplant -related mortality and acute Graft-versus-Host Disease.

Next slide, please. What then are the approaches? This is second section to decreasing the allotransplant morbidity. These strategies can be divided into three major areas from the perspective of CBER. There is the most historic method, that is T-cell depletion which will be abbreviated as TCD in many of the next few slides. Both positive and negative selection which I'll expand on in a moment.

There is the approach by manipulation of the stem cell source either by adding additional cells or by in some way manipulating the cell population. Once again, I'll expand on that and finally ex vivo expansion and the use of cord blood

cells. I've grouped these together because in many protocols they're being tried within the same experimental laboratory.

Next slide, please. I'll start with T-cell depletion, TCD. T-cell depletion has been used now for well over 20 years. It remains very controversial as a therapy. We have several experts here and I think we'll hear some comments later on.

The major questions are really how best to do this, that is, which of the many techniques should be used. Does it provide any overall patient benefit? And I'm talking about survival. And finally, what patient population should it be applied to? And we really are ignorant about most of these area. The conventional wisdom is that T-cell depletion will increase in engraftment failure and will decrease the incidence of acute Graft-versus-Host Disease both severity and incidence, but that the jury is still out on whether T-cell depletion impacts survival

for the patient.

T-cell depletion remains, however, widely used. In this slide which is taken from the data from the International Bone Marrow Transplant Registry, it stashes data.

The percentage of TCD by individual clinical entity is shown for matched-related and for all other. And it can be seen that those higher risk transplants, that is, where there's disparities -- HLA disparities among the other, use TCD in a much higher incidence as would be anticipated. Within the study the range of T- cell depletion used was 16 to 56 percent.

Next slide, please. Kernan in 1993 looked at unrelated donors.

This is data from the National Marrow Donor Program registry. She found -- they found, rather, that TCD was used in 21 percent of cases and they emphasized the high incidence of graft failure, particularly secondary graft failure.

Next slide, please. Preti did a survey in 1993 of transplantation laboratories and he noted that 46 percent of all laboratories surveyed used one or another form of T- cell depletion. The majority used pan-T-cell depletion techniques.

Next slide, please. And finally the consequences or the results of T-cell depletion which I've already summarized are Maramount also from International Bone Marrow Transplant Registry data looked at hazard ratios. The relative risks are shown to the right. The enumerator here are those patients who had T-cell depletion divided through by the denominator and those patients who did not.

These are all match-related allotransplants. As you can see, the relative risk is much higher for graft failure, 9.29, that it is lower -- and that would be lower in the T-cell depleted patients; for acute Graft-verus-Host Disease

0.45 relative risk; and for treatment failure, once again, the results probably mean that the jury is still out.

Next slide, please. What are the ways of doing T-cell depletion?

Most laboratories use pan-T-cell depletion, that is all T-cells are depleted. Selective depletion, there seems to be a lack of enthusiasm at least in the published literature at this point. Selective depletion would be depletion of either the CD8 subset or the CD4 subset.

The evaluation of T-cell depletion remains very problematic. There are a number of different methodologies which I will outline. It is not clear that they are all the same. Peripheral blood transplants are being used more frequently. It has about ten-fold higher number of T-lymphocytes than does bone marrow. I think Jerry Marti has mentioned the potential impact of this.

And finally umbilical cord blood,

UCB, and ex vivo expanded cells may have a very different brand of T cells as compared to bone marrow and peripheral blood. We're uncertain about this, but the simple rule of one citizen, one vote, one T cell, one clinical impact would not seem to hold at this point until we get further information.

Finally, the question of how much T cell depletion must be accomplished from a clinical point of view to have an impact either on the severity or the incidence of Graft-verus-Host Disease is very unclear from the published information. In general, a consensus opinion would be that from 50,000 to 400,000 CD3 positive cells per kilogram of body weight of the recipient would avoid acute Graft-verus-Host Disease, but that's a very wide range.

Next slide, please. Kernan, in a very widely-quoted paper in 1986 looked at 31 patients who had had T-cell depletion and she observed that none of the patients who

received under 100,000 clonable T cells suffered from Graft- verus-Host Disease. As I said, there were 31 patients, there were four who developed acute Graft-verus-Host Disease.

These are Kernan's data taken from the paper, but they're reorganized by the patient group who had no GVHD which is the first vertical column or middle vertical column, that is 27 patients, and those who did, the four patients who did. As you can see from the numbers, there is no -- we cannot make a distinction at this point between the absolute numbers and the relative numbers, the relative numbers being expressed as kilogram of body weight of the recipient. They both seem to show a relationship and a sharp difference.

The average patient, and I'm talking about now the relative numbers, that's per kilogram of body weight received 37,000 T cells and no-GVHD group and close to

240,000 T cells in the GVHD group.

Unfortunately it is hard to determine the border between these two subsets that would help us understand -- first of all, clonable T cells, by the way, were within this study IL2 PHA stimulated and cultured T cells. And it is not clear what the cloning efficiency was.

To determine the border between these two groups, that would help us discern the boundary for a threshold for inducing acute Graft-verus-Host Disease. If one looks at the frequency and the distribution among the no-GVHD group there were 27 persons, but there were four who had well over 100,000 clonable T cells. And among the GVHD group, the four, these figures were very high. They had very high numbers of clonable T cells. So that it is impossible to pick out a border between these two which would be useful.

Next slide, please. And I think finally I should mention in the study that I

had mentioned earlier by Maramount, it was noted that patients who received under a million T- lymphocytes and these were CD3-marked T-lymphocytes had a lower severity of Graft-verus-Host Disease. I don't show the data here.

What kind of processes are involved in T-cell depletion? Basically positive selection or negative selection. Positive selection indicates that another population other than the T-cells are selected for leaving the Infused 8, the transplant Infused 8 at a much lower volume and number of cells and excluding many of the T cells from that selection which then becomes a T cell selection method.

We've talked about the selection devices. Centrifugation has been used, the results are very limited in terms of T-cell depletion, density media, several have been used. The figure of 85 percent reduction has been given, much less than a log.

The two devices which are now being discussed for CD34 cell selection will deplete two and a half to three logs of T cells. Counterflow elutriation centrifugation -based technique will deplete about two and a half logs.

Next slide, please. This is just an example of some published information on T-cell depletion using the separate device. The figures of CD3 count before and after the selection method are shown. You can see that links figure for peripheral blood is three logs; Bensinger two and a half -- 2.8, I'm sorry, for peripheral blood; Cottler-Fox had figures for both peripheral blood which were very similar, 3.1 log and a higher T-cell depletion in bone marrow.

Next slide, please. Negative selection involves the direct removal of T-cells, the most historic of methods is the Sheep Red Cell Rosette Method with or without agglutinin-NV log of T-cell depletion shown

here for the Sheep Rosette Method is without that a agglutinin and it's higher with it or with double rosetting.

Many of the methods used now are antibody mediated. That is antibody in the presence of compliment, antibody present on beads which can be magnetically removed or are dense so that they can be spun down. Antibody covalently linked to toxins panning which means that the antibody is covalently linked to the settling chamber is not widely used anymore.

Let me call your attention to the last -- that is the use of positive and negative selection together which is now being employed in a number of protocols. That will achieve up to four logs of T-cell depletion and is one of the active, though early areas being explored.

Next slide, please. The second approach is the manipulation of stem cells. Examples are given here. They include:

megadosing; highly purified stem cells referred to as HSC; the addition of facilitating cells, stromal cells, expanded stromal or mesenchymal cells; and in earlier times the actual use of mixed bone marrow and peripheral blood.

I'll start with megadosing. Next slide, please. These were first described or popularized essentially by Aversa. These next two slides are on results published in a very recent paper, a '98 paper. He had two groups; one who were transplanted with peripheral blood, and another group who was transplanted with both peripheral blood and bone marrow.

The figures aren't that disparate. There were 43 patients altogether. You can see that the number of CD34 positive cells given and that's per kilogram of recipient body weight is much higher than usually used. It's 10 to 14 million. Although certain centers now are moving up within approaching

these numbers.

There was extensive T-cell depletion during these studies. The number of CD3 positive T cells is 27,000 to 35,000 in these groups.

Next slide. The next slide shows the results from the study of 43 patients. The median ANC, that's a thousand or was 11 days. For platelets reaching 50,000, 29 days. There were two patients who had primary graft failure, both were given secondary Infused 8 of cells and both seemed to engraft, though one did die. And that's the Graft-verus-Host Disease and developed Graft-verus-Host Disease. There was one case out of the 43, and that patient did die. So we can assume that the Graft-verus-Host Disease was severe.

There were 17 deaths, most of them due to infection. Of the 43 there were 13 relapses and 12 patients at a median follow up of 18 months were disease free.

Next slide, please. Highly purified stem cells were first developed in mice. They represent a very small proportion in bone marrow and now have been extended to man and are entering early clinical studies. These cells contain most, probably all of the engrafting cells. Their phenotype is relatively similar in mice and men. Thy-1.1 lo, lineage negative, though there are some differences in antigens. And in the mouse it has been shown that these cells will expand several thousand fold, that is, in the mouse under the appropriate cytokine conditions.

Next slide, please. Facilitating cells were first described by Drs. Sachs and Ildstat and a lot of the work is continuing in Dr. Ildstat's lab. It is once again, a rare cell population. The phenotype is T cell receptor negative, CD3 positive, CD8 positive. Also, these studies are also entering early clinical testing and it should be noted that both of these, both the HSC,

highly-purified stem cells, and the facilitating cells involve very extensive concomitant T-cell depletion.

Next slide, please. Ex vivo expansion, the goals are to increase stem cells in patients who have a very low yield, so to permit them to get transplants. To decrease the number of pheresis and potentially for putting away cells for the future. It is also being applied in very exciting possibilities for expansion of umbilical cord blood cells which will deal with the problem of limited numbers.

And it is also being looked at to increase the number of mature polymorphil nuclear leukocytes post-transplant to decrease that window of infection, that is, the post-transplant neutropenia. The problems are that there are not any defined culture conditions or agreed-upon culture conditions that maximize the results to date, and even more intrinsically there is no

well-define combination of cytokines.

Also the engraftable cell that should be measured as a marker of what is happening is very uncertain. In two of the reports of ex vivo expansion, in the face of a very, very marked increase in the total cell number the number of CD34 positive cells has remained about the same. CFU have expanded, long-term culture initiating cells, LTCIC, have been used, cobblestone assay, it's really an uncertain area.

Next slide, please. Cord blood has the problem of a limited number of engraftable cells. There is reported delay platelet engraftment of 60 days or more. And the biologic potential for both engraftment and complications are unknown, but data is rapidly being obtained and I'm sure we'll know more about this by next year.

Next slide, please. I'd like to provide for you a very short status report. We searched the IND/IDE files using as the

search term "Peripheral Blood Stem Cells, Allogeneic." I think you can see from the simple figures that we have given, these were 51 IND/IDEs that we found. That represents only 3 to 4 percent of the total amount of CBER activity over a period of about three years. But as you can see from these figures the numbers are increasing. Among the staff there is also the same subjective impression, that is, we're seeing a lot more activity in this are.

I should point out that we're -- that the only INDs or IDEs that CBER sees must involve a device or a drug, or an agent, or a monoclonal antibody, or some other experimental agent. CBER essentially does not regulate straightforward allogeneic transplants if no experimental modality is involved.

Next slide, please. The features of the experimental design as interpreted from this group of studies -- of protocols

that we looked at for the last three years were that they were, in general, single-arm studies which would have to be compared to historical data. They were small in size, they were single site, they were individual investigators, and they were early studies.

Next slide, please. The eligibility was determined in general by these studies by the institutional standards of care. And generally a class of hematologic malignancies, that is, five or 6 malignancies all scheduled for allotransplant by institutional protocols were involved in the studies rather than single clinical entities.

Most of the data is from fully-matched, matched-related donor recipient pairs.

Next slide, please. In summary then, with respect to CBER activity direct T-cell depletion remains the major experimental approach to high-risk

allotransplants that we're seeing. T-cell depletion with greater log reduction of the lymphocytes is being actively explored. Selective T-cell depletion to date has not been convincing.

Next slide, please. A broader group of biologic approaches through Graft-verus-Host Disease are also being looked at. They're in early phases and many of the newer techniques also produce very extensive T-cell depletion which is going to make interpretation even more difficult as these cell populations are processed, expanded, cultured, and manipulated.

Next slide, please. To summarize the deficiencies, there are at the present time only two concurrently-controlled late-phase studies that remain open, one, a third, will start recently soon, we hope.

There was a sharp absence of dose finding studies. there is an absence of ability to identify those critical subsets or

subpopulations in the allogeneic and fuseates that underlie biologic activities.

And finally, there's a lack of trials involving high risk haploidentical, partial-match- related transplants.

Next slide, please. The last section deals with a series of regulatory goals, regulatory questions really. Our overall goals remain pretty much the same. That is, the decrease of acute Graft-verus-Host Disease, retain the early engraftment and sustain hematologic function; improve or retain graft versus tumor allogeneic effect and, of course, overall survival.

The first regulatory question deals with the study population. Should the study population to license strategies which improve allogeneic transplants be conducted on relatively healthier subjects or on higher-risk, and less-healthy populations?

Next slide. On the healthier

populations they are often younger and have matched-related donors. There would be less background noise and so adverse events, in particular, but also activity would be easier to determine. Concurrent unprocessed controls would be more available since the standard techniques using as well matched a donor as you can are far more -- far more frequent than would be those for high-risk persons. And so the possibilities of getting controls would be greater.

The ability to collect long-term data would also be improved because the study group would survive much longer than a higher-risk population.

It should also be mentioned that the risks may be unacceptable. That is, in a population of such patients in whom a standard procedure, although risky, offers a substantial promise -- a very risky experimental procedure should be thought about very carefully.

Next slide, please. In terms of the high-risk populations they were often older, they were often HLA mismatched and they often have higher stage disease and a lot of previous treatment.

The reasons to look at such a population, which we already alluded to, would be first of all the dramatic unmet need that we have here. The impact on survival may be more visible though in a shorter term.

Control populations may not be feasible. The number of patients who would be involved in these procedures are being involved in these procedures is quite small. And clinicians and physicians may be very resistant to taking the patient with such a high risk and not offering a modality that at least offers something such as T-cell depletion in a controlled arm, or the possibility of a control arm.

Next slide, please. Also with respect to the study population a second

question: How narrowly focused should the study population be? A single conditioning regimen, a single GVHD prophylaxis regimen, regulations are in concomitant medications.

Should the group be stratified for a narrow Tcell dose range? In general we see a very wide range since all the cells that can be appropriately collected on guidelines are usually infused.

Should it be stratified for unrelated versus related donors, for HLA match?

Next slide, please. Endpoints. In studies with concurrent controls and a primary endpoint of decreased acute Graft-verus-Host Disease or decreased morbidity in the transplant period, must survival and event-free survival data be collected? And if the answer is yes, I hope it is, is similar or superior survival of the treatment arm necessary? If similar survival figures are necessary in any treatment arm,

how similar should it be? How much leeway should there be, how much worse could it possibly be and still be evaluated as a useful procedure.

Next slide. And finally, endpoints, should the primary endpoint be overall survival or event-free survival, and should the study be powered to detect a difference in overall survival or event-free survival. And I'm restating what was really said on the last slide.

Next slide, please. Controls. Are concurrent controls not only desirable but absolutely required? If not, could you please comment on alternative experimental designs that might be available and which could be acceptable.

Thank you.

DR. VOSE: Thank you, Dr. Litwin. Why don't we proceed with a short discussion or maybe questions for Dr. Litwin. Dr. O'Reilly.

DR. O'REILLY: Yeah, just to make one comment, the estimates that you had for Graft-verus- Host Disease for the mismatched circumstance are derived from a series that included both depleted and unmodified. In the unmodified mode, the usual read for a Graft-verus-Host Disease in a two antigen disparate graft is 80 to 85 percent grade II to IV and for a three it's in excess of 90 to 100 percent with very few, if any, long-term survivors. And I think that that's an important point when we're getting into this in the evaluation of these types of transplants because in very real terms a full haplotype unmodified graft is lethal and can be lethal in very few cells administered.

DR. VOSE: Any other comments or questions?

DR. O'REILLY: The source for that is Pat Beatty's study in the New England Journal and there are several other sources on it.

DR. LITWIN: There wasn't a question in that, was there, Richard?

DR. O'REILLY: No, no, but I think that's important because because I think that the barrier is more extreme than the figures that you presented suggested.

DR. HENSLEE-DOWNEY: Although I think it's of interest that even in Pat Beatty's publication in the New England Journal of Medicine in 1985 which clearly showed in unmodified grafts that the incidence of Graft-verus-Host Disease would be in the 80 percent or above range.

When he looked at patients transplanted in remission survival beyond two years was identical, and when one looked at all of the mismatched family donor transplants compared to matched sibling donor transplants. So even then feasibility of performing haploidentical transplant was established if the patient was in good condition and could tolerate the transplant

reasonably well. Yeah, it's true, people forget it.

DR. O'REILLY: As far as I --

DR. VOSE: Can you just speak into the microphone? I'm sorry, it's being recorded.

DR. O'REILLY: As far as I remember, the only ones that are comparable survival to the HLA matches were the one antigen disparate grafts.

DR. HENSLEE-DOWNEY: No. No, actually the whole group as a whole in remission patients -- I have the slide upstairs -- in remission patients only had similar survival as matched-sibling donors.

DR. O'REILLY: Okay.

DR. LITWIN: I think we can all accept the fact that the risks, however, in mismatched transplants are substantial and that's our focus.

DR. HENSLEE-DOWNEY: Absolutely.

DR. VOSE: I think we're scheduled

for a break, but why don't we just go on to our presentations if that's okay with everybody.

We'll just take a couple minute break to get everybody set up and go on with our guest presentations.

(Recess)

INVITED PRESENTATIONS

DR. VOSE: We'll next proceed with the guest presentations and first Dr. Henslee-Downey from the University of South Carolina is going to speak. Jean.

DR. HENSLEE-DOWNEY: Thank you. Well, it is a pleasure to be with you today and to discuss this topic that I've been actually working on for over a decade now. And I thought I would review some of the issues as well as share with you some of our own work in doing the haploidentical transplants.

First slide, please. Or I can do that. And this just again looks at donor

availability which is what has really driven our interests in performing haploidentical transplant. And as previously stated the chance to find a match sibling donor is somewhere in the 25 percent range.

The opportunity to find an unrelated donor through registries whether that be the adult volunteer registry or cord blood registries depends in large part on the HLA haplotypes of the person needing the bone marrow transplant and how frequently those haplotypes are expressed in the registry.

However -- and Joanne Kurtzberg will talk about cord blood more later this morning -- the hope was that one could use more mismatching or tolerate more mismatching with cord bloods and therefore it would be easier to find donors. This bar graph is somewhat complex because it does represent the fact that some individuals with very common HLA haplotypes will have 100 percent chance to find a donor and in fact today with

more than 4 million donor in the registry, when an individual has a donor they often have many donors, even 600, 700, 800 donors, but that doesn't change the fact that there are some individuals who probably will never find a donor in the registry.

And particularly individuals who represent unusual HLA combinations and these often represent people from ethnic groups or minority groups where their chance of finding an unrelated donor can be less than 5 percent. And for that reason many people in the field have continued to concentrate on trying to develop techniques to do haploidentical family donor transplants.

Now, for some time in the field in general people have accepted the fact that one might do one antigen mismatched family member transplant. However, this could still only be available if one did very careful extensive family typing and that is not often done. But this donor may only be available

to anywhere from 10 to maybe 25 percent of patients. If one can tolerate a two antigen barrier, whether that be in the donor or in the patient, then the chance of finding a donor could go up to perhaps even 50 percent. But the donor that truly makes allogeneic marrow transplant readily and immediately available to almost every single patient in need of a transplant would be the haploidentical donor.

Now, you need to understand that when we say that this donor is haploidentical it means that there is at least at three antigen mismatch in either the donor or the recipient, or both. So it does get somewhat complex when we start to think about these haploidentical identical donors because we have to think bidirectionally.

Now, we've already listened to the previous speaker who has very nicely pointed out the significant problems that have stood in the way of successful transplant outcomes

and they include graft failure, acute and chronic Graft-verus-Host Disease and poor immune reconstitution. And, certainly, this is -- these represent the most important early and late endpoints that must be studied in any trial to do mismatched transplants.

Not listed here, but also of great importance, I believe, will be the goal standard and that is survival and disease-free survival.

Now, as previously stated, most people in the field have looked at forms of T-cell depletion as a way of trying to overcome histocompatibility barriers. And in this slide, it is my hope to kind of think about the broad approach to T-cell depletion. And we know that outcomes, particularly these early endpoints engraftment or acute Graft-verus-Host Disease can be linked to the degree of T-cell depletion that is performed so that if one does light T-cell depletion and gives a fairly large T-cell dose, then

one can still see significant Graft-verus-Host Disease but also one often sees engraftment.

As one tries to control acute GVHD through T- cell depletion unfortunately there is usually a loss of successful engraftment. And so a number of investigator have tried to look at trying to get in between on this spectrum of T-cell depletion and then look at other treatment modalities that might help you improve engraftment as well as improve the control of GVHD.

For example, certainly host conditioning can be critical in the success of engraftment and it can even correct, perhaps, graft failure when one is even in this range of T-cell depletion. Donor disparity also has clearly been associated with poor graft engraftment. Some investigators are now exploring what was mentioned, and that is increasing the stem cell dose or using growth factors to enhance

engraftment.

On the flip side, if one uses less T-cell depletion as a part of improving engraftment, you may still deal with a lot of GVHD and so people have looked at adding post-transplant immune suppression. Infection control will probably also help to control the incidence of GVHD, anything to reduce in general regimen-related toxicity can enhance control of GVHD.

Although host disparity is listed here, there is less data to actually show that that is correct.

Now, in some of the work that we began, actually in the late '80s included looking at using a fairly broad conditioning regimen using TBI as the base and then adding multiple anti-toxic drugs or antineoplastic drugs that were commonly used in transplantation. Our intent was to both be immunoblative as well as to try to help respond to the very refractory leukemia that

we often see in the patients that have undergone these types of transplants.

So we used a broad approach but reduced the dose of the drugs compared to the usual dose used when a single chemotherapeutic agent is used in combination with total body irradiation.

Immediately prior to transplant we gave large doses of steroids both to decrease cytotoxic -- the cytotoxic environment in which the cells were going to be infused, and to do the last bit of immunoblation of the host.

In this trial that was published in transplantation in 1996, we tried to look at combining ex vivo with in vivo T-cell depletion with the concept that if you did only partial T-cell depletion of the merrill graft and at that time we were studying the use of T-10, B-9 for that purpose which led to a little less than two log T-cell depletion and combined that with an agent

that could be given post-transplant to do in vivo T-cell depletion just as T cells were starting to proliferate in response to alloantigens that perhaps that sequential approach could help to ease the way to engraftment and control of Graft-verus-Host Disease.

At that time we were studying a CD5 immunotoxin for the treatment of acute GVHD and this drug was explored in this protocol.

In analyzing this pilot trial we compared patients in the study group with patient who had consecutively been transplanted previous to the trial receiving only T10B9 depleted grafts and no transplant in vivo T-cell depletion. As you can see, engraftment was excellent in both of these two arms. And although the study group did have a small number of graft failures, these were primarily seen in children how had metabolic disorders and they represent a more difficult group of patients in which to

achieve engraftment.

What we were pleased with was this really quite remarkable reduction in the incidence of grade II to IV Graft-verus-Host Disease which occurred actually in all patients eventually in the previous control group, the historical control group, and was reduced to approximately 40 percent in patients who are received now ex vivo and in vivo T-cell depletion.

This also --

DR. VOSE: Jean, I'm sorry, could I interrupt you for a second? What are the numbers of patients in those?

DR. HENSLEE-DOWNEY: In the study group?

DR. VOSE: In the study group, yeah.

DR. HENSLEE-DOWNEY: There were 40 patients and in the historical control there were 17 patients.

DR. VOSE: Thank you.

DR. HENSLEE-DOWNEY: This did translate into a trend to improve survival. And it probably also represented one of the first trials to demonstrate survival out to ten years and now beyond for these patients.

We subsequently continue to explore this approach and we reported in bone marrow transplant in 1996 a comparison in patients with acute lymphoblastic leukemia who were transplanted with a matched sibling donor in the same period of time that we were conducting ongoing trials using haploidentical donors.

These patients had fairly advanced disease and certainly proportionately the patients receiving a family donor transplant were more often in frank relapse at time of the transplant. The age groups looked very similar in these two groups and at the time of reporting this data, the median follow up was 6.7 years.

There was no significant difference

in the engraftment between the patients receiving a matched sibling donor or a haploidentical donor. However, there were graft failures. And also of interest there was absolutely no difference in the likelihood of patients developing very mild grade 0 to II Graft- verus-Host Disease and more important grade III to IV disease comparing the matched sibling with the family donor.

Not expected, but of interest to us was the fact that patients who received the family donor transplant had a lower incidence of extensive chronic Graft-verus-Host Disease. We felt that that could best be explained by the fact that all of these patients then did receive T-cell depleted grafts while these patients all received unmodified grafts.

When we looked at disease-free survival and compared matched sibling donors with family donors, there was no difference

in an outcome.

Our reviewers asked us to then look at patients who were transplanted in remission and combined the one antigen mismatch haplo transplant with the matched sibling donor and compare that with the two and three antigen mismatched donor recipient pair. And, again, there was no difference in disease-free survival.

This then led to another large series of haploidentical transplants that were performed at the University of South Carolina and reported in blood in 1997. As we proceeded with this work, we did become somewhat more courageous and we began to offer this type of transplant to even older individuals. And, as you can see, in this group we went up to 50 years of age. But the median age was 16.

Also of interest is the fact that this may represent for American studies the largest proportion of patients who do

represent minority or ethnic groups. Still, even the caucasians that are represented in this study are those individuals who could not find an unrelated donor.

Again, the patients tended to be transplanted for very high-risk disease and in fact almost a third of -- three-fourths of the patients were in states of vlas-crisis or refractory relapse of the underlying disease.

Even when we categorize patients in what we might consider a low-risk group, and because the patient --

In this protocol we did make some changes in our previous approach. We started out with a somewhat lower dose of total body irradiation with a total dose of 1332 and about three-fourths of the way through this number is 26, not 46, we increased the dose to 1500, and I'll explain the reason for that in a moment.

We continued to use this broad approach to chemotherapeutic treatment of the

underlying disease in preparation of the patient for transplant. We again used T10B9 to prepare the bone marrow graft, but we did add additional immune suppression post-transplant in the form of very low-dose cyclosporin maintaining these levels between 100 and 200 which is much lower than what one would tend to see in patients receiving an unrelated graft or a matched sibling donor graft.

We no longer had access to the CD5 immunotoxin for post-transplant in vivo T-cell depletion and we turned to the pharmacy for a drug that would be available as well as looked at other experience that had been published in transplant. And as you may know, the University of Minnesota had also explored the use of a course of ATG early post- transplant as a way to help control Graft-verus-Host Disease with favorable results. So we inserted ATG in the same place during the protocol that we had

previously given patients the immunotoxin. And these patients always get pre-meded with steroids, but after we complete the 12-day course of ATG, we then taper the steroid therapy.

Now, the engraftment in the study was actually somewhat disappointing. In the majority of patients engraftment occurred fairly early. This is a thousand cells for three consecutive -- a thousand white cell count for three consecutive days. And patients tended to engraft at about 18 to 20 days out. However, as you can see, to achieve complete engraftment in the majority of patients, there was a proportion of patients, perhaps about 15 percent who required second transplants. And I think that one always has to see that as a failure particularly since the survival of efforts to try to overcome graft failure and particularly known rejection usually is not successful.

Now, when we examined -- the reason we had increased the dose of TBI was because we did feel that we were having trouble with engraftment. And this is another interesting observation of the importance of host conditioning. So that the kinetics of engraftment are quite clearly improved in patients who received more intensive conditioning prior to transplant compared to TBI.

Also, in this particular study there was a significant difference in engraftment if the donor was three antigen mismatched compared to donors who were less than three antigen mismatches. So this histocompatibility barrier had an important impact on engraftment in this study.

On the other hand, our control of graft versus host disease in this study was excellent with a 16 percent estimate of grade II to IV disease in all patients successfully engrafted with the initial transplant.

Within that only 7 percent of the patients developed severe grade III to IV disease.

Likewise, the incidence of chronic graft versus host disease in eligible patients was within what one might see in a matched sibling donor cohort, although often, particularly in older patients, the likelihood of developing extensive GVHD is even higher in an unmodified matched sibling donor transplant.

Survival and a univariant analysis that compared low-risk patients to high-risk patients was significantly different. This is classical for all types of transplants, even autologous transplants or any type of allogeneic transplant. Furthermore, in analyzing this data in a multi-variant analysis risk status or disease status at the time of transplant was the only feature that altered outcome.

Now, what I want to draw your attention to is that using techniques that

did help us to achieve engraftment in the majority of patients and control Graft-verus-Host Disease led to very good outcome in the first 100 days. Even in these high-risk patients. So if you think about 100 days then the mortality risk within 100 days was in the 25 percent range. And what drops these outcomes primarily becomes infection and relapse. As we look now at the cause of death in patients on the study and relapse in essence became our most significant problem.

Now, you have to remember that three-fourths of these patients went into transplants in frank relapse. So I don't think that one could perceive this as a greater risk of relapse. And I don't think it would be a correct assumption to say that the T-cell depletion contributed to this relapse rate. If one looked at a similar patient population receiving an unmodified match sibling donor transplant you would see

a similar, and perhaps even higher rate of relapse.

Graft failure was still significant in this group of patients and we considered that a very serious problem that we needed to address. In doing all alternative donor transplants I think we have to concentrate a great deal on infection and we must monitor post transplant immune reconstitution.

However, major organ toxicity or EBV lymphoma was infrequently seen even in these -- well, not infrequently seen, because I would rather seen none. But, nonetheless, in very high-risk patients this would be what one would expect.

Now, we did make an interesting observation in this series of patients as we examined the immuno phenotyping of the patients post-transplant and we saw that in the early six months to a year after transplant that a large proportion of these patients had an increased proportion of gama

delta position T-cells circulating in their blood which might have been a result of using T10B9 depletion of the marrow graft since this actually interacts with the alpha beta portion of the T-cell receptor.

The reason this was of interest to us is the fact that if we looked at the patients surviving at least 100 days, the disease free survival was far superior in patients who did maintain a greater than 10 percent proportion of circulating gamma delta positive T-cells compared to those who had a smaller proportion of gamma delta T-cells. And the reason for that is easily shown on this slide that looked at the difference in relapse.

So now we are starting to explore gamma delta cells and particularly trying to do co-culture assays with dendritic cells to see if these particular cells could be important post transplant immunotherapy. And I think that's going to be another very

important part of doing haploidentical transplant since I think for some time we will continue to explore patients with more difficult disease to treat.

DR. SALOMON: Were there correlations such as did you have more graft versus host disease or a higher --

DR. HENSLEE-DOWNEY: No, we did not.

DR. SALOMON: -- host disease in these two populations?

DR. HENSLEE-DOWNEY: No, we did not.

DR. SALOMON: So there was no effect of having circulating gamma delta T-cells?

DR. HENSLEE-DOWNEY: No. Not on GVHD.

DR. SALOMON: What about the circulating alpha beta T-cells in these patients, do they follow the same track as the gamma -- if you had more gamma delta, did

you have more alpha beta?

DR. HENSLEE-DOWNEY: I'm not sure about that. I would have to recheck that. Thanks for the question and I'll look into it.

DR. SALOMON: Maybe it could just be artifactual that you had more alpha beta T-cells than --

DR. HENSLEE-DOWNEY: I don't think so. But I'd have to really look. Thank you.

So at this juncture in our work we felt that sequential immunomodulation could be very effective in helping to control Graft-verus-Host Disease after haploidentical transplant. We at this moment felt that it was very important to achieve consistent engraftment, as close to 100 percent as possible and we knew that advance disease would significantly worsen survival. However, if we could make these transplants safer, then this type of donor being very readily available to patients would make it

so that one would not have to delay transplant and one could perhaps affect more cures.

Now, as we turn to our current trial we certainly wanted to concentrate on engraftment, but we also wanted to pay attention to the fact that there might -- there was an increasing requirement that one utilized FDA-approved technologies to perform stem cell transplantation. And, therefore, when we thought about T-cell depletion, we felt that we ought to use an FDA- approved agent although it's not approved for T-cell depletion it is nonetheless approved for human use in renal transplant circumstances. And there was data in the literature that where OKT3 had been used previously in this type of transplant and had been largely abandoned because as an agent by itself it was not sufficient to control GVHD. But you have to remember that our approach is that we don't look at T-cell depletion as the only

part of the protocol that controls GVHD.

We also were not happy with the higher dose of TVI because we did think it perhaps was more toxic and so we decided to go back to a lower dose that we had used previously at 1400 centigrade and we added ATG to the conditioning regimen. And certainly this has been explored a great deal as Sloan Kettering using ATG both prior and after transplant to improve engraftment.

Now, I'd like to show you an analysis that compares then our previous patients who received T10B9 with an ongoing series of patients who have received OKT3 depleted grafts. And let me just point out again the changes that were made in the protocol. We added ATG three doses at 10 milligrams per kilogram during the time that patients received ARC. TBI dose was reduced to 1400. And now we're using OKT3 depleted grafts rather than T10B9. But otherwise we continue to give the low dose cyclosporin and

post transplant ATG.

Now we have 210 patients which is probably one of the largest series in a single center to examine, 75 who received T10B9 depleted grafts and 143 who were in the OKT3 arm. Our age category actually even reached a bit higher to 54 years of age and just for your interest, we have subsequent to this analysis performed transplant in a 58-year-old gentleman who has now over six months post-transplant and doing well. So I think that we are still very cautious about which older patient we would be willing to take through this transplant. It does still seem feasible for adult patients.

Our diseases were very similar in these two series of patients. Unfortunately, if anything, the disease status worsened as we go on. And so that we have a very small proportion of patients in the OKT3 arm who could have been classified in any way in a quasi-low-risk category.

The donors, again, just for your information 30 to 40 percent of donors have been parents and siblings. In fact, probably 75 percent of the time a person would find a sibling who is haploidentical. Children became donors for their parents. And then, of course, occasionally cousins or aunts, uncles, even a grandparent became a donor.

Now, when we retrospectively looked at the graft results in preparing these transplants we might immediately say that we had made a mistake in going from T10B9 to OKT3 because in fact there was a significant decline in the number of nucleated cells per recipient kilogram weight given in this series of patients. We didn't actually have enough patients in the T10B9 group enumerated for CD34 to make a fair comparison. But as you can see, OKT3 was actually a more effective T-cell depleting agent leading to about a two and half log T-cell depletion so that we reduce the number of T-cells

administered to the patients.

But -- and one wouldn't have expected that -- engraftment was fixed. And in this series of patients we have actually experienced a 99 percent successful engraftment rate, and as you can see, these patients reach 1,000 white cells for three consecutive days at about 15, 16, 17 days post transplant.

Now, I don't think that the reason for this is the OKT3. I think the reason for it is because ATG added substantially to host conditioning particularly when one thinks about what we just learned about the grafts between these two approaches.

Now, if we just look at the OKT3 group and we consider engraftment and the kinetics of engraftment based on the nucleated cell dose and we split at the median and look at those patients above the median or below the median, as you can see, the nucleated cell dose at least in this

protocol had no effects on engraftment nor did the CD34 dose. But this is what we are particularly excited about, and that is that the histoincompatibility of the donor or the mismatch, the three antigen mismatch in the donor also had no effect on engraftment for the first time in our hands.

Now, if we look at the entire 210 patients and look at grade II to IV GVHD it remained quite low with no statistically significant difference in engraftment even though there was a slight trend to more disease in the OKT3 group.

Grade III to IV disease was identical in the II series. And GVHD mismatch in the patient had no effect on the likelihood of patients developing grade II to IV GVHD.

Chronic graft versus host disease limited and extensive was very similar to what we had seen in the first series now extended out to both series.

And outcome with regard to relapse and survival did not change significantly and perhaps that's quite a disappointment to us as we finally overcame those engraftment problems. But I think the reason for that is that as long as we continue to primarily transplant high-risk patients with very refractory disease we are going to continue to deal with this high relapse rate that has a marked effect on two-year survival estimates.

DR. KURTZBERG: Is that a -- survival or overall survival?

DR. HENSLEE-DOWNEY: That was survival.

DR. KURTZBERG: Overall --

DR. HENSLEE-DOWNEY: Event pre-survival is very similar.

Now, just in closing, I had recently, for the purpose of a textbook, tried to pull together a number of published results looking at all alternative donors.

And I used for the matched sibling donor cohort, actually Slidlow's paper, so this represents IBMTR data, and tried to think about were the problems in doing alternative donor transplants similar across the different types of alternative donors? And I think several things might be draw just by this casual look at published results. And, of course, there are many more results since this was done, and I'll point out a few of the things that I've missed.

But with regards to engraftment, then I think depending on what techniques are used, engraftment problems can be expected in both haploidentical transplant and unrelated-donor transplant. Engraftment problems have perhaps been a bigger issue in cord blood transplants. Although new techniques maybe helping to improve that. Whether that has done it for all ages yet, I'll leave to Joanne to discuss.

With regards to acute

Graft-verus-Host Disease, again, perhaps the highest GVHD rates have been published actually in unrelated, mismatched -- unrelated transplants and lower -- generally lower acute GVHD rates been published in cord bloods. However, with highly mismatched unrelated cord bloods, it's certainly true that fatal GVHD can occur and is still an issue.

On the other hand with regards to chronic Graft-verus-Host Disease this is where I think that cord bloods sort of stand out, that they truly have across the board shown less chronic Graft-verus-Host Disease. But when we look a leukemia-free survival and what we might consider somewhat low-risk patients versus high-risk patients, then the differences aren't quite as obvious.

Now, you know, one study that is obviously not here with regard to unrelateds is the New England Journal Paper by Hanson from Seattle where he carefully selected

patients both for molecular HLA typing and very, very early disease in CML and produced better results. But I think always the disease status, the patient's condition is going to drive those outcomes more than anything else.

But I think the reason that it is so important for us to develop well-analyzed studies in haploidentical transplant or in any alternative donor transplant is because eventually we may get to the position where we can start to ask the question, are certain patients benefitted more by one type of donor versus another type of donor, and particularly when should you not wait with a patient as you seek one donor versus another donor and turn attention to other available donors for that individual patient. And perhaps some day that we'll -- once we establish techniques that we can some confidence in, we can perhaps do randomized trial in particular diseases where we think

that alternative donors should be used for transplantation. But in the meantime, I think all alternative donors should be considered for patients where it is considered the treatment of choice and that we should extensively type family members, we should obtain molecular typing on patients and donors as quickly as possible to facilitate search -- the search process. But certainly we need to develop the transplant option with a consideration to time and cost.

Now, there are still some patients that would not go down this avenue and I think we still need to do a lot of exploration and autologous transplantation because there is less toxicity there. And some people would add in this group, perhaps CML as they're trying to see if that technology can be used effectively for that disease.

But just in finally closing, there are very compelling reasons to pursue and

study haploidentical transplant. And I would just like to review some of those very quickly.

Probably the lead compelling reason is donor access. These donors are immediately available. I think I see too many posters where the child is being held by the donor who is right now available to them while they search for a donor that may never be available to them. There are no racial or ethnic restrictions when one uses a family donor. Many donors are often available and so one can often select amongst those donors and consider other issues that may change outcome such as sex, age, parity, or infection concerns. Also these donors can be very carefully evaluated.

In addition to that, you have access to that donor at any point in time. And as we do develop the technology that we can use donor cells effectively for immunotherapy, whether it's against the

disease or infections, then this type of donor becomes maybe even more efficient.

There is a lot of cost efficiency in using family donors. There is less HLA typing, the graft acquisition cost is very similar to the use of a matched-sibling donor and there are not registry or banking expenses whatsoever.

In addition there is some efficiency in being able to obtain the graft and to prepare the graft in whatever way may make the transplant more successful. So you can, since these grafts are obtained within the center doing the transplant, you can control cell volumes and you can use fresh cells and manipulate those cells in a variety of different ways that might enhance outcome.

So I'm going to close there. Thank you.

DR. VOSE: Thank you. Any other questions or comments for Dr. Henslee-Downey on that information?

Well, why don't we go ahead and move on to Dr. O'Reilly from Memorial Sloan Kettering and then we'll discuss all the issues.

DR. O'REILLY: I'm very pleased to be here to talk to you. I thought what I would do specifically is also review our experience with T-cell depleted grafts in the context of a haplotype disparate donor. Since we introduced this concept at least in man back in 1980 with the first transplants for immune deficiencies and children with leukemia. And what I would like to do is initially update you on the results of HLA haplotype disparate marrow transplants administered from parents to children affected with different forms of severe combined immune deficiency because I think these have a lot of continuing lessons in terms of what ultimately can be achieved using an haploidentical donor. And then we'll briefly look at the issues of

limitations of grafts in the context of the leukemics as well as what steps have now recently been achieved.

Many of the points I'm going to be raising here are going to be reiterations of what Jean has already told you. Because I think several of the issues that were raised in the initial overview really are now less problems and we are now introducing other alternative issues and are actually looking at new objectives in terms of transplantation.

So overall now this is looking at a series of different approaches to T-cell depletion. And what we have done at our institution was to use limiting dilution analysis to actually look for clonable T-cells in marrow grafts. And this slide demonstrates a series of studies that were initiated at our shop in which marrow -- single marrow aloquats were obtained and then were separated by a variety of different

techniques utilized at that particular time. And suffice it to say that with the lectin, this is a soybean agglutinin and E-rosette depletion. We used the E-rosette because CD2 is constituitively expressed at high levels on T- cells and has been a regularly usable marker for removal of T-lymphocytes.

The lectin separation removes about one and a half logs of T-cells. It also removes most of the mature cells in the marrow such as the B cells, monocytes and neutrophils, and when you do the E- rosette you get an additional -- usually one and a half to two logs -- so normally it's about 2.8 and it can be in excess of three logs in repeated studies now.

Multiple E-rosette depletions can achieve a maximum of two log depletion. Different monochromal antibodies have been used, anti-CD3, anti-CD8, with rapid complement of those have usually yielded no more than a two log depletion. Campath is

the closest to where we're at in comparative trials with about two and a half logs. And then if we use lectin followed by -- of magnetic separation we could get into three logs on a regular basis.

An important point that is comparable in terms of our approach and the campath approach is that both of these remove most of the mature cells in the bone marrow, not only the T-cells, but also the B-cells and mononuclear cells, macrophages as well.

Now, I used to think that in fact most of what we saw in terms of Graft-verus-Host Disease reflected the quantitative alterations in the graft. Unfortunately, I can no longer say that. Because when we have now looked at CD-34 depleted marrow, we can say that in fact we are moving T-cells to about three logs and yet the issue of graft versus host disease has once again come up and made its nasty head known.

So, without further adieu then, I would like to talk about the patients with -- am I going to wrong way?

AUDIENCE: I think so.

DR. O'REILLY: The first I would like to do is to review now 118 patients who have received transplants from haplotype disparate donors for the treatment of severe combined immune deficiency. This is an update as of this week. Looking at recipients that have been transplanted at Memorial Sloan Kettering Cancer Center which is half the series, and the second is using the identical technique of lectin separation to E-rosette depletion at Ülm University under Wilhelm Frederick who was a former fellow of ours. And, in fact, in all aspects of the trial, the studies have been done in the same way so we can really look at this relatively well.

In this particular group where we have all the absolute clear data on this,

there are 67 where you have an allelic -- three alleles unique to the donor which would be for rejection, but in SKD we don't usually talk about that so much, let's focus on GVH.

Sixty-three of the patients were three allele disparate, 41 were two alleles and 10 of these individuals were allele. This is not the whole series, there are a couple of other patients where we're still going to be absolutely sure about the level of genetic disparity before we make the designation.

There's nothing quite so bad as that sound.

You need a nickel.

I think the obvious point here is the fact that in the patients with severe combined immune deficiency you are in a circumstance where you can use a parental donor immediately. There's no waiting whatsoever. And what I'm going to be talking now about really can also now be extended

even to the inter-uterine transplants where again T-depleted grafts are now being explored for inter-uterine correction of severe combined immunal reaction disease.

That was the second worst.

DR. VOSE: Maybe the first worst.

DR. KURTZBERG: Now, you have to shift gears. This picture will help you because I'm going to talk about how to use placental blood which is the baby's blood left over in the placenta after the baby is born and which is nature's example of mobilization to substitute for bone marrow derived stem cells in unrelated transplantation.

Over the last several years as we've been doing this, we've learned some things about these cells. One is that these cells are mobilized throughout pregnancy in the placenta. And they're in the placental blood regardless of the route of delivery when you collect them after the baby is born.

And, in fact, if there was a way to do it, you could collect them in utero as well.

Babies who have had their blood tested for HN compatibility or PUBS for other reasons even at, you know, 17 weeks, 28 weeks, et cetera have mobilized cells there. And so therefore, it's an effective labor and these cells can be collected from placentas delivered after vaginal or C-section deliveries.

In the public banking world, meaning banks like the bank at the New York Blood Center and the other banks funded now by the National Heart, Lung, and Blood Institute, the decision has been made to collect from the delivered placenta. You really could collect from the placenta before the third stage of labor after the baby is delivered, but before the placenta comes out. But because of really a preference not to interfere with the care of the mom and the baby, and also not to have the obstetrical

team be responsible for the collection and also to preserve privacy and confidentiality for an unrelated donor. All of these banks are collecting from the placenta which is delivered, taken into another room and then harvested.

I'll show you a few pictures of how this is done, partially because of the issue of a product. There are a number of instances now where either for directed donation or as part of some other public banking efforts the obstetricians are being asked to collect and this is not a hard thing to do, but it is a hard thing to standardize. And I'll just show you what's going on with the banks currently that are in HLBI funded.

The placenta is placed, fetal-side down in a chuck which is on a stand which is just a plexiglass stand and then the cord is brought down through a hole in the chuck and the platform that the chuck is on. And you can see the vein is the tortuous dark vessel

there. The vein is cleaned with alcohol and betadine and then punctured with an 18-gauge needle that's attached to a standard blood collection bag that goes down to a bag that has CPD anticoagulant in it. And the bag is placed on a rotating scale so that the anticoagulant can mix with the blood. And also so you can tell when blood is flowing because you can see the grams rising as blood comes into the bag.

Usually a collection takes about ten minutes and I don't know of anyone who has figured out a way to get more blood than simply using gravity. Methods that people have thought about to squeeze the placenta or vacuum extract the placenta or perfuse the placenta are not better and bring up risk of contaminating maternal cells in the unit which would be bad for the recipient of the transplant.

At the beginning of the days when Hal Broxmeyer wrote in the 1980s about

comparing progenitor cells derived from cord blood and from bone marrow he felt that any manipulation of cord blood would lose progenitors. And so for the first several years of banking for related donors there was no volume reduction and nothing done to manipulate the unit. We now know that volume reduction is possible and along with the volume reduction red cell depletion can be accomplished with a hetastarch sedimentation and then cryopreservation can be done by standard methodology and 10 part-time DNA. So a couple of the banks now through the NHLBI contractor using this freezer which can store about 3600 units and it's in 25 mil bags that are compartmentalized so that later if the need for ex vivo expansion, gene manipulation or T-cell depletion, we don't really know, but it gives you two ways to access the unit, a 20 percent portion and an 80 percent portion.

This is a control-rate freezing arm

which can freeze now in 11 minutes one unit. And since everything is bar coded you don't have to go stick your head down in this freezer to find one of 3600, you just click on a bar code and the robotic arm does it for you which is quite nice.

In the current banks the informed consent process for the donor mom begins with her first visit to the OB group and she just receives literature in the packet of stuff that she gets from them. We also give talks at lamaze classes and have posters and videos in strategically located places. At 36 weeks if the mom has expressed interest and she's sometimes asked again by the OB nursing staff in the clinic, she can then meet with a collection nurse who works for the bank, not for the OB group, and the consenting process is explained to her. If she gives her consent, a detailed medical history is taken and plans are made for collection when she delivers.

This process takes about 90 minutes in our hands, so it's not a short session. Mom comes into labor and delivery labeled as a cord blood donor and when the placenta is delivered it's handed off to the team and then the team goes back to the mom a day or so later and says, well, are you sure it's okay to keep the cord blood.

Mom is also given out-clause card that says -- it's addressed to us, it has a stamp on it and it says, "I change my mind", and she doesn't have to say why.

And that's similar to what the Red Cross does in terms of people maybe not wanting to disclose some high-risk behaviors et cetera. But then later are feeling like it would be a better idea not to keep the unit.

The elements of the informed consent which is a seven-page document are listed here. One is that this is a voluntary donation, that there's no guarantee that the

unit, if collected, will be there in the bank for that family. And we so not notify families if the unit is used for an unrelated donor.

We also know that there are reasons why the unit may be deemed unbankable either because of infectious disease serologies or some problem with processing, et cetera, so that we don't guarantee that the unit will there even though the moms agreed to be a donor.

Mom has to agree to give a sample of her blood which is used for infectious disease serologies and she has to agree to have feedback if those tests are positive. If mom says no she doesn't want to know, then she's excluded as a donor. So that's also considered a high risk behavior.

Mom's chart and the baby's charts are reviewed around the time of delivery. The mom's OB chart is also reviewed. And in each bank there's a subsetted feasibility

pilot for look forward to see if it makes sense either economically or in terms of the workload to look at these babies later over the first couple of years of life to see if they develop a disease that would be transmittable and expressed in the stem cells from the cord blood that would be relevant to the recipient.

In our program we're doing that with chart reviews at two months, six months, and two years post- transplant.

The consent form also specifically states that everything is confidential, that the unit and all the testing is identified by a bar code label, not by name and demographic information. There's only one piece of paper which is locked up linking the mom's demographics to the bar code that's used for all the labeling of the unit.

There also is a clause that says if the mom -- or the family wants to remove the unit and transfer to a private bank at a

later time that they can do that.

I think the issue of this being a product that can be regulated is an important one and I'm not against it at all, but I don't think that all the things we know how to do are enough to guarantee a successful transplant. I think really when you look back on it, you think you had a good product if you have a successful transplant. And, of course, there are many other things that can lead into that. But these are the things we are doing to try to guarantee a good product -- is cultured for sterility and in the public banking system, if units are positive for bacterial cultures they are not maintained in the bank. And in the private donation setting we have had units contaminated with vaginal flow bacteria transplanted without incident -- have the opportunity to exclude anything that might be of a theoretical risk.

We are counting nucleated cells,

mononuclear cells, progenitor cells, CFUGMs, and CD34 cells. And I'll show you some data that makes -- that will make this look important, but I don't think we have really all the knowledge we need to know what the best thing to measure is yet. Obviously we need to measure blood type, HLA type which is done by molecular methods, but at a serologic level for class one, and at a higher resolution level for class two just DR beta one.

In each state hemoglobin electrophoresis is done on the babies as part of neonatal screening programs so those results are obtained four units that were banked to exclude hemoglobin opathaties, the viral serologies are done on the mom, again, because IGG crosses the placenta and measuring and the babies blood really doesn't give you any new information. The detection of CMV which if viremia was present it would obviously be of importance to the transplant

and the transplant recipient as a little bit harder. If the mom is IGG positive, it does not mean there is virus in the blood.

At the New York Blood Center they are culturing the infants saliva and have, I think, a four per thousand positivity rate. For the public banks right now we've decided to look at maternal IGM which does identify all the virus positive babies, but also excludes a series of moms who had recent CNV but are not viremic. But it was cheaper and less invasive. And then a very detailed family history is taken looking for unexplained early deaths in the family, a series of young adults getting gall bladder surgery or splenectomies suggesting hemolytic anemias that might have been undiagnosed in looking for diseases that would be genetic, and not easily testable.

Another thing to consider is contamination with maternal cells and this is just some DNA blots showing how you can tell

the difference between a mother, a donor and a patient. We know there are maternal cells in the cord blood. The more sophisticated the tests become the easier these cells are to find and they're certainly the one in 100,000 level and the one in 50,000 level. What we don't know is what's a significant dose or when that cel inoculant could contribute to GVHD from the maternal cells in the recipient of the transplant.

We now have two children who have had documented engraftment in maternal cells in the liver post-transplant. Both were picked up about four months post-transplant and confirmed on liver biopsy because of elevated trans-aminesses. In both cases these kids were removed from immuno suppression and in both cases the maternal cells went away and the children are well. One child is out a year now and the other child is out almost four years. But we know that this can occur.

I'm going to spend some time making some points with a data set that was put together with the two largest centers in the United States doing cord blood transplants right now and all the units I'll describe were obtained from the bank at the New York Blood Center. At Duke there are about 100 and I think 30 -- or I'm sorry 120 patients represented and from Minnesota 33 for a total now of almost 160. And in this analysis the median age of the patients was 7 years, the oldest being 58 years. Twenty-five of these patients were over 18 and the median age in that group was 43. The rest are children.

Median weight, almost 22 kilos with the largest patient 92 kilos. Sex distribution the same as you would expect for these diseases. And 50/50 split on CMB serology in the patients. No CMB positive units were transplanted.

Two-thirds of the patients had malignant conditions and similar to what Jean

mentioned, these were all high-risk patients either in relapse or in late remissions because of the nature of -- really phase one nature of this work and there were a couple of children with nerve blastoma as well.

And then one-third of the patients had non- malignant diseases and that included congenital marrow failure, fanconi, black fandimon, some in-born errors in metabolism including osteopetrosis, crabase, hurlers, MLD and ALD and leshnihan and then a small group with immune deficiency which my center has an unusual culture that's usually a patient who failed T- depleted haplograft from a parent without any preparative regimen and then needed ablation to get a second transplant.

This just gives you some demographics about the units. Median volume was 84 mils and the range was 40 to 214. Looking at the banks that are collecting right now and also Dr. Rubenstein's bank, the

average collection is in a well-greased banking system between 80 and 90 mils. But you can get units as large as a couple hundred mils when the placenta is big.

The average cell dose per kilo and this is nucleated cells dose, and this is the pre-cryout count was 3.6 times ten to the 7th cells per kilo. That's roughly a lot less than the traditional bone marrow transplant. Average CD-34 cell dose per kilo was 7.6 times ten to the 5th, and you can see there are wide ranges here. Average CFUGM dose per kilo 1.3 times ten to the 4th. And average CD-3 dose as a measure of T- cell dosing was nine times ten to the 6th cells per kilo. So although that's lower than what one would give with bone marrow, that is above the range where one would be protecting someone from GVHD. That is a range where you would expect to see GVHD.

The patients were prepared either with TBI and melflan and ATG which was give

day minus three, minus two, and minus one. At Duke TBI cytoxan and ATG at Minnesota if they had a malignant condition and if they were over two years of age. Patients who were under two at Duke got busulfan in place of TBI because of concerns about late toxicity and patients with genetic conditions pretty much got busulfan cytoxan ATG unless they had cardiomyopathy in which case they got -- we did a few busulfan melflan patients just to avoid exposure to cytoxan.

I need to stress that this is labor- intensive, non-managed care, friendly transplant.

And it costs money. The supportive care is really important. I come from an institution where there was a big adult autologous program that was quote/unquote "outpatient." In fact, the patient got chemo and was discharged on day zero so they could ceremoniously have their transplant in the clinic. But you can't do that with this

transplant. These patients need much too much support and they really need a lot of parental therapy for the first month. They all are supported with IVIG which we now treat for low levels ganciclovir pre-transplants if they were CMV positive, acyclovir post-transplant. If they were any herpes viro serology positive the obvious transfusions and IV feeding, low-dose amphoterous and for fungal prophylaxis, nerve stem hepafiltration. At Duke everyone got G-CSF from day zero just to standardize care. And at Minnesota no one got G-CSF and I'll show you some data about that later.

And we've now brought about eight patients through supporting them with irradiated G-CSF mobilized granule cites that we harvested from their parents twice a week and divided into three doses each if they came to us infected. And, again, in this skid population that's not an uncommon occurrence and you really can't always clear

the infections.

We've also now gotten three leukemic patients through with active aspergillus doing this.

Just to highlight some differences between Duke and Minnesota. I mentioned that at Duke we standardized a G-CSF approach and that was as much because I didn't trust our group not to use it at some point and we wanted everybody to be as closely matched as we could. At Minnesota they did not use it initially. TBI was always given at Minnesota regardless of the disease or the age of the patient when it was a malignant condition. And at Duke if the patient was under two, they did not get TBI. Of if they had had prior mediastinal radiation they didn't get TBI.

At Duke we used high-dose steroids for GVH prophylaxis and at Minnesota they used an intermediate dose. And I'll come back to this, but we both used cyclosporin

for nine months post-transplant.

At Duke we performed more haplo mismatched grafts than a the Minnesota and also the adult population came from Duke.

And again I mentioned that in the leukemic population we used a melphalan-based regimen while Minnesota used the cytoxan-based regimen.

Donor selection evolved over time which I think influences some of our results. At the beginning when we started to do this, we looked for the best matching unit. And we knew we weren't going to get full matches, but we still took the closest matching unit regardless of any other considerations. As we went along though, and this was really based on what we knew about bone marrow -- as we went along we started to prioritize allelic matching at DR beta one and we only do serologic matching for A and B at class one.

Then as we started to see the data

come out, then I'm going to show you we began to prioritize cell dose overmatch. And that means that we'll insist that we reach a minimum cell dose and then look for DR beta one matching and then third look for class one matching. And we will pick a larger four of six over a smaller five of six in order to meet this criteria.

We don't look at HLAC for the other DR DPQ proteins or alleles.

By those criteria the patients are pretty much a group of five of six or four of six matched grafts. You can see 10 percent or six of six, and that's 6 percent or three of six. And this is, again, serologic typing class I and molecular typing of DR beta one.

We all pretty much believed that if we did molecular typing at class I we would have obviously a lot more mismatching.

And now I'm going to show you some outcomes. We defined engraftment as the first of three days to reach an ANC of 500.

And graft failure as failure to reach an ANC of 500 by day 42. And I already mentioned matching.

Engraftment. This looks at neutrophil engraftment; 87 percent of the patients engrafted by day 42 with a median day to ANC of 500 of 25 days. You can see of all engrafting patients which was 93 percent the range was out to 59 days which functionally we think is really too long. We take it if we get it, but that's not really what we're aiming for.

When we looked at what impacted engraftment HLA disparity between the donor and recipient did not impact engraftment. These are the -- green is the two antigen and yellow is the one antigen and, of course, those are the biggest groups. But the three and the zero antigen match did not come out as statistically different.

G-CSF in this not randomized, not controlled, but just as kind of simultaneous

comparison did look like it influenced engraftment and there was a nine-day difference in the median day to ANC of 500 between the Duke Group and the Minnesota group. And so without any randomized trial the Minnesota group has switched over to using G in everyone.

We were concerned at Duke that if we withheld TBI because of the fact that these were mismatched grafts we might see more graft failure. And this just shows you that we didn't -- this is a univariant analysis and it's a little bit misleading because the children in this group overall are younger, smaller, and got a higher cell dose. But at least we could say that there was no negative effect of not giving TBI to that group.

DR. ANDERSON: If you took the pediatric age group out of that and just -- what do you see?

DR. KURTZBERG: The same thing. We

have had -- we've done a number of adults. It's about 11 or 12 true adults over 18 and then another 15 kids who were between 12 and 18 with bumel or busi and none of them have had graft failure. So in fact our adult group which is led by Nelson Chow would prefer to leave the TBI out now for other reasons. So we can't see any negative influence of withholding TBI.

And in multi-variant analysis the only thing that impacted neutrophil engraftment was cell dose. And now this is shown here measured as CD-34 cell dose. I could show you similar data with mononuclear cell dose or nucleated cell dose or CFUGM dose. And when you do the statistics they all correlate with each other. So people like CD-34 and I made this slide, but it's not the only thing that correlates.

A CD-34 dose less than three times ten to the 5th cells per kilo which is a log less than we would give with bone marrow or

peripheral blood progenitor cells is associated with delayed engraftment and inferior engraftment over all. And so that now when we select units we are deliberately avoiding getting this low. In the other three groups, looking at three to six, seven to 16 or greater than 16 times ten to 5th per kilo we couldn't really see any difference in engraftment.

Likewise for platelet engraftment the group getting less than three times ten to the fifth, 34 per kilo had very inferior platelet engraftment. In fact, only half engrafted platelets at all. So that this is raising a red flag as a surrogate for cell dose of where our limitations with this kind of product may be.

Immune reconstitution, I know this is a busy slide, and I'm going to explain more on the next slide, but it just shows you kind of how many time points we have on each patient and where this is just PHA responses

of lymphocytes and culture, every three months for the first year post-transplant and then at varying time points after that. And you can see that in the first three months more than half the patients are not having their lymphocytes proliferate and even the ones who do have so few lymphocytes that I don't think it matters. Between three and six months about half the patients start to recover and it isn't until a year that the patients are consistently at normal ranges.

Now cyclosporin has stopped around nine months, so that also may influence some of this recovery. If you look at other parameters of immune reconstitution and these reflect studies done in Rebecca Buckley's lab at Duke through the pediatric immunology group, all patients were profoundly lymphopenic meaning lymphocytes counted less than 500 for the first six months and less than 800 until mostly -- almost out to 12 months. We can demonstrate normal and K cell

function at three months. T-cell proliferation begins to recover at six months and is normal in everyone after 12 months. T-cell proliferation N numbers increase between six and nine months and then settle out to normal ranges after that. And we haven't seen any BV lymphomas in our two groups of patients, although I think there are one or two in the whole series of -- collected in about 600 patients now.

CD-4 counts recover between nine and 12 months. That means to over 200. And we see a persistence of increased naive T-cells, CD-4 to 5 RA cells even out as long as three years in patients that we've been able to follow that long.

Despite that though, there are normal responses to immunizations after one year. And now in 90 kids who are out more than a year we've only had one case of pneumococcal sepsis. Or we have had one case of pneumococcal sepsis reported to us, but

the other kids are back to normal performance status, normal activity and not on any kind of prophylaxis.

Acute Graft-verus-Host Disease moderate to severe grades two to four occurred in 37 percent of patients and the subset that were three to four is 14 percent. That was not influenced by HLA disparity. And that's also true, this is now a grade three to four subset for HLA disparity. But we couldn't see an effective mismatching on the incidence of acute GVHD.

And, in fact, in multi-variant analysis the only thing that did impact on incidence of acute GVHD was CD3 dose. And if it got to be above 1.6 times ten to the -- sorry -- 1.6 times ten to the 7th cells per kilo, then there was a statistically significant increase in acute GVHD at the .03 level.

Interestingly and I think importantly, chronic GVHD has occurred at a

very low rate. This is held up. This is a probability of 11 percent overall. None of this has been extensive. It's all been either skin rash or some poor weight gain which corrects with steroids and no one is on long-term immunosuppression for chronic GVHD at this point.

Relapse has a probability of occurring in 25 percent of patients and to me given the nature of the high-risk criteria of the patients we transplanted, I think we are seeing a preserved graft versus leukemia effect, but obviously we need to look at that more carefully. We do have one patient now who had a three of six antigen matching graft for very refractory CD7 positive immature leukemia who when it was in relapse at the time of transplant went into remission post-transplant. Relapse six months post-transplant was taken off immunosuppression and is now a 100 percent donor again in the marrow and the blood and

has no clinical evidence of leukemia. So again, that suggests to me and that's a highly mismatched graft, but at least in that setting we did document a GVL effect.

Interestingly and I don't know how to explain this, the patients getting G-CSF have a lower probability of relapse than those not getting G-CSF. Now, you could argue well, remember I said, Duke gets G and Minnesota doesn't. Duke gets melphalan and Minnesota doesn't. But we went back and did those analyses and there was no effect of melphalan in this.

Minnesota went back and did a small series of patients where they randomized between G and no G and also saw the same result where the G patients were relapsing at a lower frequency than the non-G patients. But I don't know how to explain this. G means that they continued out to 100 days on G-CSF support and their white count was maintained at around 20,000.

The overall event free survival of the whole group is 44 percent at two years. Things that did or did not impact survival I will go over now. These are uni-varied analyses and I'll show you multi-varied at the end.

HLA did not appear to impact survival. The green is the two antigen mismatches. The yellow is the one, the three and the zero on the bottom, again these are smaller groups and we may not have enough patients to reach statistical power for these two groups, but this is the data that we have so far.

If you looked at whether a single class one antigen mismatch versus a single class two antigen mismatched impact survival the answer was no. And if we looked at whether in the two antigen mismatched patients whether the mismatch was at two class one or one class one and one class two impacted survival the answer was also no.

And the survival is the same in the group of three antigen mismatched patients as it is in the zero.

I think you need to think about it for a minute though and realize that these are not haplo in the sense of Jean's haplos. These are people where we can pick and choose which antigen we match and mismatch and so we can have one class -- you know, two B-loca mismatches and complete matching at ANDR. Vice versa we can have molecular mismatching at DR, but serologic mismatching at class one, it's not going in pairs of ABDR like you would if you were in the matched or related setting.

Diagnosis in uni-varied analysis did impact survival. The kids with non-malignant conditions had an improved survival over those with malignant conditions.

And age impacted survival so that the group under two has about an 80 percent

event-free survival and the older groups are down around 40 percent. There is not a difference in the greater than 18 and 2- to 17-year-old group in our hands. The kids under one have a 90 percent event-free survival.

But the thing in multi-variant analysis that impacted survival was again cell dose here shown as CD- 34 and there was an 80 percent non-relapse mortality in the group getting less than three times ten to the fifth per kilo.

If you want to look at total nucleated cells this translated into 1.5 times ten to the seventh total nucleated cells per kilo.

The early non-relapse mortality seems to be related to cell dose. And in that group infections were the major reason for failure. And it wasn't one kind of infection. We had a number of patients, particularly on the adult side die of grand

negative sepsis. Some patients die of either adenovirus or CMV although the CMV deaths are at about 2 percent and the incidence of CMV disease is 8 percent overall.

And then some patients dying of fungal infections and these are all patients who came with a history of fungal infections in their past life, leukemic life. Why might that be? One is -- these are just theories. One possibility is that we're recapitulating neonatal neutrophil maturation. We know that neonatal neutrophils are not as efficient at killing as adult neutrophils. "Adult" meaning taking an older baby. And it's possible that we're seeing that process again and that could be overcome by cytokine or maybe by ex vivo expansion.

I'm sure there's delayed immune reconstitution secondary to the HLA mismatching, but I'm encouraged by the fact that after a year there really appears to be full reconstitution. And it's a question of

supporting the patients through that early transplant period so that they can get to that point. And that may also relate to transplantation of more naive T-cells.

Another thing just looking back at our own practice was that we found that comparing the patients who got intermediate or high-dose methylpred with cyclosporin for GVH prophylaxis, there was no difference in the incidence or severity of acute GVHD. But when we looked at the incidence of infection or non-relapse mortality, the group getting the higher dose steroids had twice the non-relapse mortality as the group getting the lower dose steroids. And we now have cut back to the lower dose steroids because we don't need to push this to have an impact on GVHD.

Another approach we're taking is ex vivo expansion and we have just finished a trial of 28 patients getting ex vivo expanded cells as a supplement on day 12

post-transplant. And one of the obstacles to this study was that all the units that we had were frozen in one bag. And so we couldn't compartmentalize or do any expansion pre-transplant. And so we took the unit on day zero and actually divided the patients into two subgroups of the fixed dose of unmanipulated cells that they received expanded whatever was remaining in conditions that were really derived for bone marrow, but included three ligand pixie and epo.

The expansion was a 12-day process and on the 12th day the cells were harvested and then infused without any other preparation. We didn't change anything else about the kind of care the patients were receiving.

This just shows you the lab data about what expanded under these conditions total cell count expanded about two and a half to threefold. CFUGM expanded on average 150 fold. CD34 -- negative cells did not

expand at all, 34-38 positive cells did expand, but those were really just maturing myeloid precursors.

And this does really represent a form of T- cell depletion because the T-cells go away under these conditions. There's hydrocortisone in the media and so that you take away part of the dose you would have given in the unmanipulated graft.

We are also looking in the laboratory at other factors that can enhance expansion and this just shows you that if we take placenta and we expose the cells -- this is a control in blue, and then placenta in the well in pink, we can get more expansion with placenta and we are considering using irradiated placenta from the actual cord blood donor as a possible source of cytokine expansion. We can get increased expansion with stem cell factor as well, but that requires corporate cooperation which is a bigger obstacle right now than some of the

scientific ones.

This shows you 100-day survival in the group getting expanded cells compared to two groups getting those lower cell doses of unexpended cells, but no boost. And these are historical controls.

The reason I'm showing you survival is because we don't have any impact at all on engraftment. The data on engraftment is the same for platelets and neutrophils and the proportion of patients engrafting is exactly the same. But the 100-day event-free survival looks different. And this is a nice picture, but I can also show you that if you look at just -- at cord blood transplant survival over the past four years, you can see that we've been increasing our success, I think, because we've learned how to do this better or we're selecting units differently. We have changed our GVH prophylaxis et cetera. So when the issue of controls comes up, this is really important because you know

the company was really happy with the first graft, and I'm not unhappy with it. But I can be sure that it was because of ex vivo expansion or it was just because we're doing a lot of things hopefully better as we go along.

So in summary what do we know about cord blood transplant right now? We know that it increases donor availability, and at the 4 of 6 level we can find donors for 86 percent of the patients who come to us who haven't found traditional donors in other settings taking away the haplorelated donor.

We know that we see less acute and chronic GVHD than we would expect with mature adult cells that were better matched from either bone marrow or stem cells and we believe that the GVL effect is preserved. The obstacles we're still seeing are that there's delayed engraftment and if nothing else it makes it more expensive which makes the whole procedure more challenging in the

current reimbursement environment.

There's delayed immune reconstitution although it does occur and that leads to increased morbidity and mortality from early infections.

I want to end by just mentioning a couple of things. This little boy has thalassemia major and had a haplorelated cord blood from his sister's cord blood 100 days before this picture was taken. And he's two years out now fully engrafted with donor cells. And we've done four other children this way. And I think the haplorelated cord blood setting may turn out to be valuable for kids with hemoglobinopathy, sickle cell -- and some of the other rare genetic diseases. And that may be the one place where family banking or directed donor banking makes sense.

And also just to say what's the state of the art in a pediatric transplant unit that does -- you know, we do about 90

transplants a year. I'll illustrate this kindred of kids from Alabama who all have fanconi. They're all cousins and they have many relatives who are inbred. This little boy is two years out from matched sibling transplant. He's one year out from a matched transplant from his HLA identical mom. She's three and a half years out from a three of six unrelated cord blood transplant and she is a few months out from a five of six related cord blood transplant from her aunt. And she had some acute GVH and that's why she's cushingoid, but she's six months past this picture and doing well.

And I guess my point here is that I don't think there's one kind of transplant that we ought to be doing. I think there are going to be settings where we will use a haplorelative and there will be other settings where we need to move faster and we might use cord blood. There are a lot of unanswered questions and I think we need to

collect the data in a way that we can interpret it and then make the best decisions. And I'll stop there and see if people have questions.

DR. VOSE: Thank you, any questions or comments for Dr. Kurtzberg? Please, can you also identify yourself.

MS. RIM: Ilana Rim from Genetics Institute. I wanted to ask you a question related to both your presentation and Dr. Henslee-Downey's which was clear from the confluence of them which is that your data showed a lot of variation with relapse on G-CSF and your showed it with gamma delta cells and I wondered if either of you had data on the opposite experiment. Whether you had looked at gamma delta cells and whether you had looked at time of engraftment.

DR. HENSLEE-DOWNEY: I haven't, no.

DR. KURTZBERG: We have the data, but I don't have it analyzed. We could look at it.

MS. RIM: I just wonder if it's a marker of the same event of early engraftment that is relevant for relapse?

DR. KURTZBERG: I will say though that in our own experience and I didn't have time to make slides, we've done 47 related haplo transplants, 17 of which were five of six and the others were four of six and three of six mismatches. And our event-free survival in that group for all is 43 percent. If you subset it out to the patients who were T-cell depleted and who were not T-cell depleted, the T-cell depleted group has a survival of 35 percent and the not T-cell depleted group has a survival of 53 percent. But if you take out the SBA or the soybean lectin in ER method of T- cell depletion and just look at the T10B9 or we used a chemical purge with the -- formycin which is a lesser purge in terms of logs of T-cell removal. Those groups have 53 percent event-free survival and are the same as the non-T

depletive five of six antigen matched group.

And the only reason I share that is because it's one center that's doing two different kinds of alternative donors and realizing pretty much similar results.

DR. O'FALLEN: You described a very complicated consenting process, but I don't think you told us what percent of the mothers actually consent.

DR. KURTZBERG: It's about 95. But I think I'm in a unique setting. Not unique, but it's different than being in the middle of New York City which is kind of what I'm comparing it to because of Pablo's experience. And we have a community that gets fairly consistent prenatal care and is very interested in participating in these kinds of studies. And so our biggest refusal was one intensive care nursery nurse who decided that she didn't -- you know, she was our only obvious refusal in over -- I think we've consented about 700 women right now.

DR. PAPADOPOULOS: Joanne, could you please clarify your immuno constitution data? Do you have a difference in the adults versus the children?

DR. KURTZBERG: I don't think so. And I'm being hesitant because I have more of the data on the kids. The data I've seen on the adults is not different, but they haven't been as good about getting some of the time points. But, no, the adults are lymphopenic and, you know, they have all the abnormalities that the kids have for the same time period and seem --

DR. PAPADOPOULOS: But do they recover at a later time point than the children?

DR. KURTZBERG: I don't think so. But I can't be as clear about the group that the adults in my group transplanted. We've done some adults ourselves, and those adults I know exactly how they're doing and they're not different than the kids. But there's may

15 more that I have incomplete data on.

There is, though -- there are at least three adults who had later bacterial sepsis than we've ever seen in the kids and this was between nine and 12 months post-transplant. And we haven't seen that in the kids. So there may be something different in the adults that I can't quantitate for you now.

DR. VOSE: I think that does bring up an important point that we need to think when we're talking about study design is that you can't directly compare pediatric populations and adult populations, they may need to have different study designs. So I think that's important when we think about that later.

Any other questions or comments?

Why don't we try again, Dr. O'Reilly?

DR. O'REILLY: I'm hoping that the slides get through. What I would like to do

is then discuss haplotype disparate grafts. I think it's important for the committee to recognize one thing that is different about this approach to T-cell depletion and that is that the studies I'm talking about at the present time utilize T-cell depletion alone.

There is no post-transplant prophylaxis against Graft-verus-Host Disease administered in any of these patients. It's a critical variable in terms of this. So this is what T-cell depletion can do on its own. And this is particularly germane to the study of the kids with severe combined immune deficiency.

So I mentioned the fact that the -- as you see in this particular group over 100 of these 118 individuals are in fact in the context of two or three antigen disparate donor recipient pairing with transplants from the parent to a child.

Now, this is a summary of these results and I'm going to go over this slide

relatively carefully, but I have a lot of background data vis-a-vis immune reconstitution should the committee want it.

Of that total patients there are 118 patients of whom five died early of intercurrent infections and anti-data to the transplant. And remember this is a consecutive series since the initial transplant was done in 1980. So it's every child with severe combined immune deficiency who has received a haplotype disparate graft at these two institutions.

There are 96 of these patients who achieved durable engraftment. The issue of engraftment not being achieved was principally a focus or an issue that we encountered early on when we thought that children with severe combined immune deficiency that is these are children who do not have functional T-cells or B- cells would not be capable of resisting a graft. And I'll talk about that in a bit. But there are

17 who failed to achieve engraftment. Yet of these individuals who did engraft 72 achieved full reconstitution of T-cell function, 20 were partial at the time we analyzed these and there are 10 patients who are still early in recovery of immunologic function of the T-cells. The important point is that of the 42 patients who achieved engraftment of donor B cells 35 of the 42 are full functional reconstitutions in terms of B cells, in terms of production of antibodies in all classes of immunoglobulins.

In contrast, if we failed to engraft donor B cells only four of 64 patients have achieved durable engraftment.

Now, remember a large proportion of this population are recipients of severe -- of these T- depleted transplants without any sign of reduction whatsoever. Okay.

So there is no sign of reductions. In the absence of sign of reductions routinely we will engraft T-cells of donor

origin and have full immunologic recovery of the T-cell function, but we will not engraft donor B cells. If on the other hand you myeloblate this individuals with even low doses of busulfan and cyclophosphamide you consistently engraft the T-cells and the B cells of donor you will have either a split chimeric state in terms of the B cells or full donor chimerism and in all instances we see evidence of immunologic recovery.

The other important point to be raised is that among these 118 patients and the 96 durably engrafted there are only seven patients developed any evidence of Graft-verus-Host Disease and as you see this included six patients with grade two disease. This is in the absence of any Graft-verus-Host Disease prophylaxis. Each of these instances resolved with therapy.

Of the patients who died and there were 40, the causes of death were principally infection. Most of these antecedent to the

transplant. There were two patients who died of Graft-verus-Host Disease that had maternal fetal Graft-verus-Host Disease at the time they were initially admitted. That is, they received an inter-uterine infusion of cells they came in chimeric with maternal cells with overt Graft-verus- Host Disease and went on to die of that complication. But the overall long-term disease-free survival, the 78 out of 118 patients or 66 percent.

If you now ask the question how does a T-cell depletion depleted graft actually grow up? This is a transplant that is conferring to these individuals doses of T-cells ranging between two and eight times ten to the fourth T-cells per kilogram body weight. What we observed in these patients long-term is that these populations of T-cells that grow up within the child actually grow from early progenitors. We have had autopsies on those patients who have died and can demonstrate that the thymus

wasn't brinell is now basically filled in with T-cells. These are of donor type T-cells and you will see development of hassles corpuscles and you can also demonstrate as shown here in the study that was done by Neal Phomenberg some time ago if you compare the response of the mother who is haplotype disparate with the child, if this mother is challenged with paternal cells and this is the sensitizing determinants, you can see that mom's T- cells are clearly capable of killing the father at 68 percent cytotoxicity and killing the cells of the child. This is a B cell line at 69 percent cytotoxicity and also kills the DR-3 homozygous population that bears the DR-3 conferred by the father at 69 percent.

If you now look at this patient, this patient is now -- at this time he was about 18 months post- transplant, was full engrafted. All of his T-cells were of maternal origin and these maternal T-cells

are now challenged with the father in vitro and they are asked what did they do. And they can still kill the father cells by virtue of the unshared haplotype but they have no reactivity whatsoever against the patient or against the homozygous line.

When we have done limiting dilution analyses or when we have done mixing experiments to determine whether this is based on the suppressor cell, what we can say is that there is no effect of the mixing of the patients. That is maternal T-cells with the mom's own cells. These engrafted populations exert no inhibitory effect on the cytotoxicity of the mother's cells either in the time of sensitization or in the time of their effector function.

Thus, from what we are able to see in these patients who received these lectin separated T-depleted grafts, the primary basis of the tolerance observed is actually a deletion of T-cells capable of reacting

against host. And in further studies that we've now done looking at viruses -- and I don't have time to show this -- we can in fact show that the T-cells that emerge that are of donor type have the capacity to engage virus infected cells in the context of the HLA that is unique to the host. So they learn and they are capable of recognizing influenza, epstein bar virus, and other antigens in the context of both helper-based T-cell responses documented by proliferation as well as cytotoxic responses looking at CD-8 reacted populations of cells.

The long-term disease-free survival for this particular group on all patients is 64 percent, but I think it's important also to recognize the fact that this reflects in part the early series from 1980 to approximately 1986 when we were doing a prospective study to try and analyze which patients would or would not engraft. And suffice it to say that two coeruleus were

associated with non-engraftment of these T-depleted transplants. One was the presence of AD-8 deficiency which precluded engraftment in a significant proportion. But the major correlate in fact was the presence of natural killer cells. Almost all of these patients who were NK deficient engrafted. The only ones who engrafted who still had NK activity are intriguingly individuals who presented with disseminated BCG ossis.

And certain members of this team will be smiling because in fact when Gusipuovich initially described the phenomena of what is called F-1 hybrid resistance which has been shown to be an NK mediated resistance against hematopoietic cells, the one way that you could overcome that resistance was to give BCG to the mouse or induce, for example, an RE blockade with carageen in it. So it is an intriguing reiteration of history that in fact in the human condition this appears to be the case

as well.

If we now look at the patients who come to us early in life that is before they really obtain severe infections like GGVS or CMD, the long-term survival since the start of the group is 81 percent and the long-term disease-free survival in patients who are older is about 56 percent reflecting, in fact, the problems with infections prior to the time they come to our shop.

If we look at the different types of severe combined immune deficiency the vast majority of X- linked disease have not required cytoreduction before the transplant and 90 percent of them are long-term survivors. Autosomal recessive now is 78 percent of these and these have now been looked at specifically at a genetic level. The ADA deficients are now approaching about 60 percent and I think that result is a very, very positive one as well.

But the most important thing yet --

DR. ANDERSON: Have you ever determined after this 15, 20 years why ADA -- is so much different from other --

DR. O'REILLY: The basic data that we think is going on is basically what happens is the same thing that happens when you give peg ADA. That is if you give an ADA positive graft that can confer enzymatic capacities on the host which would allow that individual to generate some T-cells that may reject the graft. And we think that that's the strongest feature of it. However, it should also be noted that every one of the ADA deficients has been strongly NK positive. Every single one of them.

Now, the other important point is that time also helps and once we actually became clear on what were the correlates of resistance, that is, patients with NK positive forms of SCID or kids with ADA deficient SCID would then automatically go to busulfan and cyclophosfide for the primary

graft. Whereas those who were NK negative and ADA normal could go to graft without cytoreduction. And as you can see here, since 1986 through to the present, 39 patients in our series, 82 percent of those patients are long-term survivors.

Now, the critical point to be raised here, and this is -- it could be particularly nice if we had a group of them here since many of these kids are now in college. The key point is that they are immunologically intact in terms of their T-cell function. If they have not engrafted with B-cells, their B-cell function has been supplemented by immunoglobulin. But increasingly what we are now doing is looking to secondary grafts to in fact induce the B-cell function as well. And this may require immunoglacian, or transoimmunoglacian with fluderapine in the secondary T-depleted graft from the same donor. But the vast majority of these patients they are basically living

normal lives at home at the present time.

So these results basically showed that one could engraft endurably reconstitute T-cell immunity of the key point is that the donor T-cells recognize antigens from the context of host-unique HLA determinants. The engraftment gives rise to consistent reconstitution of B-cell immunity if you engraft donor B cells.

The critical point is that the incidence of Graft-verus-Host Disease has been extremely low in the absence of any other drug prophylaxis and the high proportion of long-term disease-free survivors that we're recording here has also been iterated, for example at Duke, at LA Children's at San Francisco, at several centers throughout Europe, Australia, China, and Japan. In ever instance in which they have used this approach to T-cell depletion without any prophylaxis the same results has been observed.

Now, when we've looked at this in the context of patients with leukemia the key point is, can you overcome Graft-verus-Host Disease? And this slide is looking at a large series of individuals and they principally are looking at individuals who got no prophylaxis against rejection either pre- or post- transplant, because one of the key points that we have used to actually ensure engraftment was the introduction of antithymocyte globulin back in the early 80s. And this is the important point because these patients again received nothing except a lectin separated graft.

And as you can see among these individuals who engrafted 121 patients had no TVH, five had grade one, and five had grade two. The overall incidence of grade two Graft-verus-Host Disease then was 3.8 percent. This is a group of individuals ranging in the age from 18 to 53. The median age of this group of patients is 40. And

there is no grade three and there is no grade four Graft-verus-Host Disease in this particular grouping.

Looking at overall prophylaxis either giving ATG pre or post, again, the same features will out. Thus, again, T-cell depletion alone can in fact obviate the problem of Graft-verus-Host reactions.

Now, when we initially tried these studies in the early 80s we also were interested in the unrelated and clearly what we were also able to show in this circumstance, again, was that the incidence of Graft- verus-Host Disease is low. If there's no genetic disparity documented between the donor recipient and the unrelated circumstance that you can see is a 7 percent grade two to four. The only incidence where we have had a significant incidence has been in the context of a major class two disparity where it's about 25 percent of the patients have developed some evidence of

Graft-verus-Host Disease.

This is specifically an update on the early Kernan experience because I now -- and I'd be happy to give this to you, but this is looking at 168 prospectively evaluated HLA matched recipients of lectin separated marrow transplants, again, administered without prophylaxis. And what we have looked here at is the number of T-cells demonstrated by limiting dilution analysis. And what you can see is that the vast majority of these individuals received doses ranging between approximately ten to the fourth, and up to about eight times ten to the fourth T-cells.

These are the patients who developed any evidence of GVH. There are two patients who developed grade two GVH and the rest of these patients had grade one Graft-verus-Host Disease. Thus, when we initially published that, in fact, ten to the fifth clonable T- cells per kilogram body

weight was an indicator of, as it were, threshold dosing for Graft-verus-Host Disease. The fact is that that is held over time with the context of HLA-matched sibling. It still holds as a very clear indicator of the risks in terms of quantification.

Over here what we have is over 100 individuals who have received unrelated marrow transplants studied by exactly the same type of analysis. And, again, as would be expected the levels of T-cells administered are pretty much the same. But what you observe in this circumstance and this likely reflect that there are subtle molecular disparities between donor recipient. You can see in a fraction of these individuals grade one, or as you see in black, grade two Graft-verus-Host Disease even at doses down to ten to the fourth T-cells per kilogram.

Most groups now as they're using this technique in mismatched marrow

transplants are attempting to give less than five times ten to the fourth T-cells and in general the issue of Graft-verus- Host Disease has been relatively limited. And, again, as I note here, this is grade two Graft-verus-Host Disease in this series.

DR. MILLER: Rick?

DR. O'REILLY: Yeah.

DR. MILLER: So far in your leukemia studies are you showing us matched-sibling donor data for the relateds or are they a mixture of haplos and matched siblings?

DR. O'REILLY: No, right now what I want to just be sure of is that I get the biology of the circumstance. This is looking at now -- these are related HLA-matched donor recipients or related -- or unrelated donor or recipients who are up to one antigen disparity between donor recipient.

This is the other key that is important and that is in the context of these

patients, a chronic Graft-verus-Host Disease has also been low. It's .8 percent in recipients of matched-related grafts and as you can see 9 percent among the unrelated grafts that we have looked at. That is again in the absence of drug prophylaxis. So clearly T cell depletion can prevent both acute and chronic graft versus host reactions.

When we initially applied this in the early 80s we expected to see significant benefits. But actually in this prospective analysis we curtailed it because of the fact, in fact, there was no difference in T-depleted and unmodified.

The advantages in terms of getting rid of graft versus host disease were countermanded by a very significant incidence of graft failure. But it's an important point for this particular group to understand that the issue of graft failure is now something of an historical issue rather than

something that is present. This was a major problem before and is becoming less of a problem as we go along.

We did several studies and I can show this, but basically in HLA disparate grafts the predominant populations that we observed emerging at the time of graft rejection early after transplant were host-type CD-8 positive T cells that would exhibit selected reactivity usually directed against a single HLA class I determinant, usually HLA B. And the discriminatory capacity of these cells in an unrelated circumstance could be such as to discriminate molecular microvariants of HLA B or HLA A that are single amino acid different. Okay. So that discriminatory power is very clear.

We have found in rare instances the emergence of CD-4 cells that are selected for class two. In the matched circumstance they are invariably CD-8, they are HLA class one restricted populations of cells and the

actual determinants that are expressed on the surface of the donor marrow cells that give rise to the emergence of these cells inducing rejection is still not very clear. Although at least in one instance HY has been implicated.

And this just shows you how we would do these types of analysis. We would take blood from the peripheral blood of the individual and basically look at these populations of T cells. And in this circumstance we have a donor who is unique determinants are A3, B7 and DR2 an what we do is to test these against either the donor populations which you can see can be killed by these host T cells in the circulation and then test them against a series of homozygous cells that share one or another of the alleles with the donor. And in this particular instance we had a CD-8 population of T cells of host origin that were selectively reactive against cells that bore

the B7. They were reactive against the B7 determinant unique to the donor.

Now, recognizing the T cells were a critical variable and this was basically where we were in around 1987-88 we basically then went on to try to develop approaches which would allow us to overcome this. And we explored initially more intensive preparatory cyto reduction but mostly the depletion of residual host T cells with antithymocyte globulin. And in fact the protocols in this series of protocols with rigid stopping rules we determined that if we gave ATG between day five and day 19 post-grafting we could, in fact, obviate the problem of immune rejection. And the subsequent alteration was to administer thiotepa in a an attempt to ensure a better overall engraftment.

And this shows you then the risk of relapse in -- I'm sorry of graft failure in these individuals. We did not see graft

failures in the matched-siblings in the context of younger kids, but only in the adult population. But in this population, as you can see, with the TBI -- alone without ATG it was up to 23 percent in the patients at risk. And as you can see, when we added the ATG in the early post-grafting period we eliminated graft failures in this period between day 12 and day 25 to 50. And what we found in this circumstance is that we had eliminated immune rejection. We no longer saw the redevelopment of host T cells reactive against donor.

In those patients who did have graft failure, what we found was that they remained full lymphoid chimeras of donor type, but that they had lost their hemapoietic grafts.

In contrast, however, when we added thiotepa that basically has eliminated the issue of graft rejection to a very, very low level. And this actually can be updated now

to be even lower than that. So thus what we have seen is by giving this combination of thiotepa coupled with ATG, we have been able to overcome the immune rejection, principally with ATG and with thiotepa then the incidence of late graft failure post transplant.

The end result of that has been very salutary. And this is a slide from a study that was published recently by Essie Papadopoulos and Jim Young in blood and she can detail it, but what we have found is now in this group of adults who were transplanted for AML in first remission within three months of achieving a first remission that the long-term disease- free survival for this group is 78 percent despite the fact that median age for this group is 40.

Now, thus in these particular adult crowd of individuals all of who engrafted and none of whom developed grade two Graft-verus-Host Disease the salutary effects of the T-depleted graft can be seen. And as

you can see, the incidence of relapse remains entirely low. That's another important point because what we have found, and this is looking at the long- term risk of relapse in patients with ALL or AML in first or second remission. But since we started this whole program irrespective of the protocol used, this is a cumulative incidence of relapse in this group of individuals which is 25 percent and is not different from what one would see with a conventional marrow transplant. Thus, in the acute leukemias T depletion has not been associated with an increment in relapse.

In contrast, however, CML that has been a really striking problem. However, there have been these recent studies initiated by coal which have shown that in fact one can administer T cells late in the post-grafting period and can induce remissions. And, in fact, in a dose escalation study we've actually been able to show that for patients recurring with

molecular cytogenetic evidence of disease doses of ten to the seventh or less T cells will be able to induce them into durable molecular emissions without graft versus host reactions.

One of the striking things that at least holds true in the matched siblings but we cannot say in the mismatched circumstance is that there is this striking alteration in terms of the risk of Graft- verus-Host Disease per dose of T cells administered by the time post grafting. And as you can see here, when we have administered T cells as treatment for example for EBV lymphomas between zero and six months does of ten to the fifth -- to five times ten to the sixth have been associated with a significant incidence of GVH. Whereas if you give those better than two years out, as you can see, none of the 12 patients treated have developed GVH at all.

Thus, there is a dose associated

and a time associated risk of Graft-verus-Host Disease which we believe likely reflects the capacity of the host or the residual host antigen presenting cells to present to the donor cells a suitable target for the initiation of a Graft-verus-Host response. And as a result of that, if you now combine the T-depleted graft and then give DLI for evidence of molecular cytogenetic or clinical relapse the long-term disease-free survival for these patients transplanted within the first year of diagnosis is almost 71 percent and for those greater -- is still 47 percent. Thus, these results are very, very similar to what are basically considered to be the best around in the context of a conventional graft, except there's no GVH.

Now, when we tried to do this in mismatched circumstances this is a long and I would have to say sort of like on all-souls day you get down on your knee and you do your

litany of the saints.

And what we tried to do then was to go through this whole thing, and unfortunately it was incredibly difficult. We set up an approach which basically was as follows. We would change one -- make one alteration in the cytoreductive regimen. We would have a strict stopping rule, because we did not want more than two to three rejections per group. When we used the amount of rejection that you would anticipate seeing for a given level of genetic disparity if the graft was unmodified. And based on that type of a ruling, we were able to do in very small groups of patients 25 at most a series of studies that were stepwise. And, in fact, as you'll see in many of these they were even smaller because the limitation in terms of graft failure was really quite significant. And yet, again, when we added antithymocyte globulin again the incidence of graft failure was significantly lower in this

particular realm. And when we got down here into using either ara-C or thiotepa, the incidence of graft failure really would not be much different from what would be observed with an unmodified graft.

Now, this is the last study that is the current one and I'll talk about and that is based on studies that were done by Frank Aversa who worked with us to learn the lectin separated technique and then went one huge jump further. That is, he used the studies of Yier Reisner demonstrating that in fact you could enhance engraftment in histo-incompatible mice by giving a higher dose of cells. And so what they have used is CD34 position E-negative peripheral blood stem cells. And in our series now there are 22 patients that I'll talk about.

The critical point also to be raised though here is with the lectin-separated marrow, among those who achieve durable engraftment as you can see

the incidence of grade three Graft-verus-Host Disease is minimal in all of the series. Unfortunately, when we have used the CD34 positive selection by separate followed by E-negative we have a very appreciable incidence of Graft-verus-Host Disease that we had not anticipated. Our approach though is different from the aversa approach in that the E-step or the Rosetting step is done after the CB-34 selection, whereas he is doing it before. And that may have very significant differences in terms of the T cells there.

Of the 27 patients that we have done -- I'm sorry, this is the 27 patients done by aversa, and as you can see engraftment has been very high; 25 of the 27 patients have achieved it. They've had a very, very low incidence of Graft-verus-Host Disease.

In our group of patients, we again have looked at this in terms of the

engraftment that has been observed and what we observe is that with the TBI thio side regimen using the lectin plus CD34 we have endurably engrafted 20 of 22 patients. We have only two graft rejections.

The patients that we have been doing this in have been consistently very bad cases in terms of they are late in disease and unfortunately that slide is missing here. But there are 22 patients thus far enrolled. We've had two that have had graft failures. As you can see the time to engraftment has been very short, as early as nine days to an ANC greater than 500. But the important point here is that almost half of this group has in fact developed grade two to four Graft-verus-Host Disease. In most instances this has been treatable, but in certain instances it has in fact led to lethal sequela.

Eight of these patients are now long-term survivors but, again, it's very,

very short. And this Kaplan Meyer has put up with great risk because the vast majority of these patients are in this period and these represent the earliest efforts at this. So this is a very unstable curve at the present time.

Still in all what this has shown us is that now we have a mechanism which allows us to achieve consistent engraftment. What I've been a little bit distressed at is that we have mor GVH than we had anticipated.

The other key thing that I wanted to give to the committee because it's important because I think we are now at the point where we have overcome engraftment. We have techniques that potentially can overcome Graft-verus-Host Disease. What are the central issues? And the central issue remain infection, particularly among the adults.

And this is looking at the proportion of patients with opportunistic infections looking at SBA- negative-related

grafts without ATG or with ATG, as you an see, there's a significant increment here. These are unmodified related marrow transplants and as you can see the T-depleted graft is not associated with any increase in the incidence of infection over what we would see with an unmodified transplant. But what you do see is a further increase in the patients who have received unrelated grafts. And this is seen both in adults and in kids. But as you can see, there's a striking difference in terms of the overall incidence of infection in children to adults.

Now, why would that be? Well, there are some elegant studies that have been done by Trudy Small where we have looked at these patients long-term. And the observation is that irrespective of the type of transplant administered, be it an autologous graft an HLA-matched graft from a related donor, or an unrelated graft or now even a mismatched graft the children all seem

to come back relatively rapidly within about three to six months. Whereas the adult recipients tend to be more prolonged.

Now, unfortunately, and you can see this not only in terms of recovery of T cells but also in terms of PHA responses, for example, individuals receiving lectin graft from an unrelated compared to a related they're exactly the same, and here you see the autologous. There are three superimposable grafts.

Now, why would the adult be a little longer? Well, unfortunately this is an old study that we did years ago, but the fact of the matter is, once we get to 21 we're on the down side. We are on the dark side of it because in fact the thymus is really taking a deep swing. And the fact of the matter is that here's our median age of our patients now transplanted for leukemia with T-depleted grafts. And thus the thymic environment may be significantly impaired,

but there has to be something beyond that because this is looking now at the recovery of T cells following these related marrow transplants that are lectin separated in adults, median age 40, versus the unrelated. And there is a really striking difference in terms of the recovery of the number of T cells. Here we're looking at CD3 positive cells. You can look at this particularly among the CD4s and that is that the unrelated group takes a much longer period of time and the level of recovery appears to be significantly impaired. And I would like to say, this is not the case, but this appears to be reiterated now in the haplotype disparate grafts as well.

And you can also see this strikingly in terms of function, looking at related unmodified or lectin separated grafts. They are here, and then you look at the unrelated graft they're much, much slower. And so one of the concerns that we

have and one of the reasons why I'm so interested in what Joanne is talking about is in fact we may have a major problem in terms of the capacity of the marrow progenitor population that is T- depleted now to actually migrate to the thymus or to develop within the thymus of the adult such as to allow for appropriate reconstitution of T-cell populations. And the disturbing feature about this particular slide, if I can get back there -- this one you have to think about because remember if you're doing an unrelated marrow transplant the marrow is all derived from a population of adults.

It's T-depleted and administered. So the graft can be considered to be at least in terms of time biologically the same. Yet, in the young child the immune reconstitution will go up here. And yet in the adult it takes really for a very long period of time.

So what we are concerned about is that the environment of the adult may be

considerably less plastic, less capable of basically allowing for appropriate reconstitution. One of the issues now that we are back to which is exactly where we started in the mouse when we started with T-depleted grafts when VonVormer and Sprint first did this is the same.

That what we now really have to think about are what are the genetic restrictions that may limit the migration of these cells to thymus. What are the kinds of alterations that could in fact limit the recovery of the immune function either in the context of the molecularly disparate unrelated donor recipient paring or potentially the haplotype disparate grafts as we're doing more and more of these for the future.

I'll stop there.

DR. VOSE: Thank you. Any questions or comments?

DR. SALOMON: In this last slide I

just wanted to make sure I understood. There is or there was not a difference in the median age of the related versus the unrelated patients?

DR. O'REILLY: Oh, I'm sorry, I'm sorry.

DR. SALOMON: You got me a little bit because initially you introduced this slide saying the mean age was 40.

DR. O'REILLY: It is.

DR. SALOMON: And then you're saying that the only difference was related versus unrelated.

DR. O'REILLY: No, no.

DR. SALOMON: And then later you kind of segued into a different state.

DR. O'REILLY: What I'm saying is that if you look at the reconstitution -- put that back on.

The fourth from the last.

DR. SALOMON: This one here -- this is adults. These are all adults. This is

looking at reconstitution in a matched adult who received a T- depleted transplant. This is a quote/unquote matched- unrelated adult receiving a transplant. Okay.

And what we observe here -- shown here as well, is that the adult receiving the unrelated graft is very, very slow in comparison to the HLA-matched adult. Now, if you go back here, if you look at the child on the other hand, whether it's unrelated or otherwise, they all come back. And this is particularly shown here. That is that the SBA-negative related is here, SBA-unrelated is here, the autologous transplant is here. So what I'm saying is that adult marrow from unrelated donors administered to a child leads to abrupt immunologic reconstitution and that reconstitution cannot be distinguished from that which you would achieve of an autologous graft. That same adult marrow put into an adult individual on the other hand -- I'm going the wrong way --

-- gives you this. And so it's not just that microenvironment of the adult is less able to reconstitute because this adult HLA- matched sibling also has a relatively atrophied thymus. It goes beyond that. And what I'm concerned about is that molecular disparities between donor and recipient may in fact affect initial traffic to the thymus or the maturation within the thymus.

And this is kind of, you know, from a safe point, you know, someone asked me one time, what are you going to do, and I said, "I'm going to do research." He says, "Ah, yes, it was my generation to search and yours to research."

DR. O'REILLY: The fact was that studies suggesting that in fact there were modulations of the migration of these early progenitor populations that could be in fact H-2 modulated. In other words that there were genetic differences in the mouse that H-2 disparities could alter mobilization and

movement was that back in the 1970s by OCSC -- and we unfortunately are going to have to revisit this.

Alternatively what we have to do is to develop new approaches which would allow us to make a better thymic environment such as the possibility of a thymic graft or the use of certain kinds of cytokines like aisle seven or IGF one which can actually promote thymic cellularity.

DR. VOSE: Okay. Any other questions, comments? Jean?

DR. HENSLEE-DOWNEY: Well, I'd just add the comment that I didn't show this data, but we do have data in the haploidentical transplant where our outcomes, whether they be GVHD or even survival have not really segregated based on the recipient age, but they have segregated based on donor age. And furthermore in MDP they've looked at unrelated -- there are unrelated donors although they are all adults, but there is an

impact on the age, the older age of an unrelated donor and worser outcomes with regard to GVHD and --

DR. O'REILLY: That has to be added because in real terms older donors, when you're talking about donors over the age of 50, the reconstitution of hematopiesis is poor, the incidence of graft failure is poor as well. You know, you're absolutely correct on that. I don't mean in any way to say that it's all in the context of hosts. I just think that there are environmental issues in the host that are --

DR. HENSLEE-DOWNEY: But it's interesting and actually in designing these studies we do have to pay attention to donor age also. I think it's an important parameter. And in our center we are now actually sometimes going to a younger donor because in the haploidentical setting you often have many available donors and we might take a child who is even more mismatched

rather than older donor who is less mismatched.

DR. O'REILLY: We too, I agree.

AUDIENCE: I'm a little mystified by why you don't see B cells in your SCIDS that were not cyto-reduced. If you're getting engraftment of multi-lineage progenitor cells, so you're getting erythroid or myeloid engraftment it would suggest that you're not.

DR. O'REILLY: If you don't cytoreduce the patients they will get engrafted with T cells only.

AUDIENCE: Okay. Okay.

DR. O'REILLY: You don't get the rest of the situation. And even if you cytoreduce with busulfan and cyclophosphamide in not only SCIDs, but in any of the metabolic diseases oftentimes you are left predominantly with host hematopoiesis, donor T cells and then a mix after that.

AUDIENCE: Thanks.

DR. VOSE: Okay. Other questions or comments?

Okay. Why don't we break for -- yes --

DR. SIEGEL: For the record, there was a remark there or two earlier this morning about FDA jurisdiction that I wanted to clarify for the record. It's not really the topic of these discussions, but as people read the transcript and view the video tapes, I wanted to make sure that we haven't increased confusion in a very confusing area. Dr. Litwin in noting the increasing number of IND we received also noted that we received largely INDs that involved growth factor devices or other regulated materials aside from the allogenic cells themselves, and that is correct. However his remarks, and I don't remember his exact words, which should not be misconstrued to indicate that the agency position is that the cells themselves are not a regulated product indeed as Dr. Marti

summarized in your handouts there was a Federal Register notice in January indicating that we consider unrelated allogeneic cells whether of peripheral blood or umbilical cord to be a private group that will come under FDA regulation and we were seeking input as to what standard should be applied or in lieu of that the possibility of implementing alternative regulatory approaches. Those were discussed in a September meeting that was summarized and that's under discussion. But I did want to make sure that we weren't creating more confusion because those remarks do represent in fact the current approach to regulation in that area.

DR. VOSE: Okay. Why don't we break for lunch and we'll come back for discussion at 1:30.

(Whereupon, at 12:30 p.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:35 p.m.)

COMMITTEE DISCUSSION

DR. VOSE: Why don't we just frame a discussion with respect to what the questions were from the FDA. I think they pretty much go over the things that we need to discuss. I think everyone has the questions. It's on the second sheet of the agenda sheet.

Question number one deals with kind of how to frame future studies with respect to looking at this issue and first of all it talks about basically wondering if it is possible or not possible to do a randomized trial with an unmanipulated graft in this situation. And assuming that it's not possible which I think most people would say, to discuss the feasibility, advantages and disadvantages of an active controlled trial such as randomization to another investigational modality or randomization to

arms that differ only by the amount of T-cell depletion or comparison to historical or registry experience.

Rich, do you want to start any discussion on any of those issues with respect to what do you think how could best frame a trial in this circumstance?

DR. O'REILLY: I think that we're, you know, getting close to a situation where at least two or three approaches now are showing very exciting results. I mean, obviously I think clearly Jean has some very, very good stuff. I think Franco has some good stuff.

I think we're in the early stages of the protocol that we've had and we're making some adjustments. But I am still impressed that, you know, we have some three edge and disparate circumstances without much in the way of GHV, and that I knew before. But I think the other issue that we were concerned about was engraftment, and now we

can get engraftment. So I think the possibility of doing it, you know, doing a trial in which you have one or another type of transplant could be done.

One of the problems that I have right now in terms of formulating this though is -- you know, I'm sure it would seem like something of a cottage industry, but it really isn't that much so. But there are some tremendous levels of sort of experience that go into the whole issue of cytoreduction regimen used. And so all I would say is, you know, given the fact that we're kind of early, it may be worthwhile to consider it in the context of a whole package rather than one particular technique versus another. And I don't know if that's going to be easy to really stomach.

But you're asking this specifically in terms of what would be required for licensure of a product.

DR. VOSE: I think that's the FDA's

question, yeah.

DR. O'REILLY: Yeah, I would say, again, you know, some kind of standard approach would be appropriate for at least for certain diseases you could do it that way.

DR. VOSE: So you're saying for comparison of two techniques?

DR. O'REILLY: Two -- yeah, two approaches to the haplotype disparate graft.

DR. VOSE: So comparing two experimental techniques, one versus the other?

DR. O'REILLY: Yeah, I think that that potentially could be done. And I think to say we will -- the only other approach would be to ask a simpler question. That is, you take a technique and you compare it, you know, current therapy and say, at this point we could potentially do a better job if we do these patients earlier in disease. So let's say you take good risk cases quote/unquote

who are in, for example, a second remission of acute leukemia or are relatively late in the chronic phase of CML and you're now going to compare them versus a chemotherapeutic approach which has a very low likelihood, but has some finite likelihood, you know, could you do that. And that might also be at least something that could be reasonable one.

DR. VOSE: So for patients that do not have an HLA identical sibling, to compare that versus some standard chemotherapy which we know is not very beneficial. And that's not a very fair comparison -- I don't know, it's hard to say what's fair.

DR. O'REILLY: Well, I think that that one may be bucked. But, I mean, one of the questions that is coming up now, for example, in a good risk case, if you have an acute leukemia either first or second remission and you have a choice between continuing chemotherapy versus an unrelated marrow transplant, there are several groups

that in the first remission would -- there are several groups that would think, you know, you shouldn't be doing unrelateds in the first year of remission and other groups that you should. My own read of it is that's actually probably a decent and ethical question at the time.

I don't think we're quite there with the haplotype circumstance yet to be able to -- although, you know, I -- well, you certainly are.

DR. HENSLEE-DOWNEY: Yeah, I mean, I think that in an experience center you might get a little bit closer to that, but I think that it is a developing technology and that I don't think that you would open it up under those circumstances because you know you're going to have a learning curve in new centers necessarily. That would be one caveat for that.

DR. VOSE: But I think any of these studies need to be done in experience centers

because there's -- it's not only the transplant it's the after care.

DR. HENSLEE-DOWNEY: Yes, without question.

DR. O'REILLY: But you have to have -- the other arm has to have a very clear, finite possibility. Like, for example, a controlled trial of T-depleted transplants from haplotype disparate donors for severe combined immune deficiency is inappropriate insofar as the disease is uniformly lethal. You go one versus another.

DR. VOSE: Right.

DR. O'REILLY: Or an unrelated transplant versus a T-depleted haplotype disparate graft, I'd like to get that finished with and that's probably reasonable. That's not necessarily something that's going to be marketing kind of a thing.

DR. HENSLEE-DOWNEY: With regards to the patient population, in large part that's controlled by the referring physician,

you know, when you get right down to it.

DR. KURTZBERG: In managed cared.

DR. HENSLEE-DOWNEY: Or managed care, this is true.

DR. VOSE: I think Dr. Miller had a comment.

DR. MILLER: But I think for the purpose of this discussion we are not so much talking about the utilization of transplantation, we're looking at ways of trying to determine the effectiveness of a technique, not the role of transplantation. And I think the question has to go back down to how are you going to compare a method versus something else if you don't have a standard. And I guess one question I have, and I don't know if anybody has this data, if you're talking about potentially looking compared to -- if you say you can't do a randomized trial in haploidentical transplants because nobody quote does non-T-cell-depleted haploidentical

transplants. Is there any comparable database that you could use for historical controls? I don't think there is.

DR. O'REILLY: Is there a comparable database for three antigen disparate?

DR. MILLER: Right.

DR. O'REILLY: Yeah, there are some that have been done in Seattle, and there are certainly several in the literature. And --

DR. MILLER: But they are years old. They're not contemporary. I mean, over the last ten years.

DR. O'REILLY: Yeah, but they're in the cyclosporin era.

DR. MILLER: And we do them regularly all the time. And --

DR. O'REILLY: Not in three antigen --

DR. VOSE: No, no, three antigen non-T- depleted?

DR. MILLER: Oh, not on modified.

What they're looking at from here, my understanding is that you have to figure out -- if a sponsor is going to come and say, I have this T-cell depletion technique, I want to get it approved. In order to get it approved I have to prove equivalency, I think, and decreased Graft-verus-Host Disease against something. And it's either a randomized trial which is the gold standard or in the case of the randomized trial cannot be done, well, controlled prospective trials against a reasonable controlled group. And I guess the first question we have to -- is it possible to have a reasonable control group that's not modified. And I think the answers are no.

And then the second question is, I don't -- how can you -- the question you asked here, I mean, my feeling is that there's no reasonable, unmanipulated that's in the same generation that's going to be robust enough to be able to show a

difference.

The second thing is, are you able, are you allowed to compare to experimental arms when either -- to try and get one approved?

DR. SIEGEL: Well, I think that --

DR. MILLER: I mean, you asked us whether it happens, but --

DR. SIEGEL: My response is, how can we be asking that question. The answer is that we do permit trials which compare to experimental therapies and we'll approve one on the basis of showing superiority to the other if we're comfortable with the presumption that the other is not harmful. I'm speaking now in broad terms, not specifically in engraftment. So in treatment of any disease, if you have two therapies and two compared to experimental therapies and show one to be superior and we know the inferior one not to be harmful or can presume that, we will and can approve the superior

one.

Showing two experimental therapies to be equivalent has no bearing on establishment of efficacy. Such a trial may establish efficacy, but it would only establish efficacy as a historical control trial in which you would -- showing they're equivalent tells you nothing about efficacy. If you're presuming efficacy on the basis of that trial, you're presuming efficacy on the basis of comparing the outcomes on either or both arm to the expected outcome without therapy.

DR. O'REILLY: Okay. But that then -- that answers your question and that comes down to it. And that is, what is the efficacy of a transplant versus current chemotherapy? That is the appropriate approach. It will not be necessarily satisfying but in very real terms either the FDA has to do it as a prospective trial comparing the two or has to look at it

retrospectively and say, is this better than zero? Okay. Because that's what several chemotherapeutic regimens would be.

DR. KURTZBERG: If you got a group of experts together and defined essentially stopping rules and said, you know, if this, this, and this happened related to graft failure and GVH, et cetera, we would stop the trial. You could also do some prediction of statistically seeing a 10 percent improvement or 20 percent improvement over what your historical controls have shown or what your ideal is.

DR. VOSE: But I think the problem is that it's a concern about what the historical control ideal is. There's a wide range of what is seen, and in, you know, particular patient populations there may not be a very good historical control. I think that's the point that Carole was talking about. So it's hard to compare to something that you don't exactly know what the numbers

are. And a lot of times in this particular situation it's difficult for the FDA to use a historical control for those reasons.

DR. KURTZBERG: The pediatric oncology group has been trying for 18 months to get a trial going comparing transplantation to conventional chemotherapy for kids with ALL and second CR. And it keeps going around and around the table and the problems are what kinds of transplants will be allowed and who has the expertise to do which kinds? And haplos go in and haplos go out, and I mean, it's interesting, but they haven't even been able to get consensus to get even, you know, deciding on what kinds of transplants would be considered valuable.

DR. VOSE: Karen?

DR. WEISS: I just wanted to say, in prior discussions with this committee, we've talked before about the topic of whether or not you have to actually show that the -- I mean, ultimately what Dr. Henslee-

Downey said earlier, you really want to improve patient survival. But certainly in the past, and even in our prior approval of things like growth factors for improving neutrophil recovery post, you know, transplantation we haven't really addressed the issue of whether transplantation, per se, is an appropriate therapy for a particular disease. We just looked at within that transplant context is it doing something beneficial to the patient which, I guess, gets to the dilemma of whether in this kind of setting you want to look at a trial to really decide whether or not transplant itself s a better or therapeutic option than more conventional therapy or are we just trying to use some of these purging and other types of techniques to say in this particular context using this technique improves your incidence of acute and chronic GVHD and the relatively speaking shorter-term outcomes. So, I mean, I've heard both things being

discussed --

DR. VOSE: Compared to what though?

DR. WEISS: Well, that's where the --

DR. VOSE: That's the problem.

DR. WEISS: -- that's the fundamental problem which is why we've had such a dilemma with these kinds of studies.

DR. VOSE: Exactly. So it's kind of a circular question. I think that --

DR. O'REILLY: Can I ask a question of the FDA though, or in this regard? In the context of a T- cell depleted marrow transplant, for example, for severe combined immune deficiency, there you have a disease that is uniformly lethal. And back in 1980 when we were talking about this, it was a uniformly lethal disease for which there was no approach except this kind of a circumstance. Does efficacy depend upon a randomized trial? I mean, I don't think that there's anyone around who would not recognize

the efficacy of T-depleted graft for severe combined immune deficiency and no one would consider it to be even remotely ethically appropriate not to administer a transplant to a kid with severe combined immune deficiency.

So, I mean, I honestly -- I think the only appropriate control if we were going to ask a manufacturer to come up with a trial would be can he show us something better than current therapy lacking a transplant. Because otherwise these patients cannot be transplanted now unless you sort of sit around for an unrelated donor. And it would seem to me that, you know, you are a little bit caught. Either you do the randomized trial or at least you have to sort of accept potentially some type of a control statement of what chemotherapy can do.

DR. VOSE: But I guess from a manufacturer standpoint to do a trial just in SCID patients, I mean, would be very difficult to do that.

DR. O'REILLY: No, I used that as an example because I think a haplotype disparate graft in the context of an individual where we don't have an unrelated donor, and, you know, there's a large proportion of patients who don't have them who have an active disease, I think that this is clearly an approach which can potentially be cured. And the real issue is what is the -- well, you've asked it, what is the standard against which you are going to compare that?

DR. VOSE: Right.

DR. O'REILLY: And how do you construct it?

DR. VOSE: That's right.

DR. SIEGEL: Was that a question to the FDA or not?

DR. O'REILLY: Yeah. I think the question is, is the issue of efficacy in this kind of a circumstance always contingent upon an randomized trial. And if it is so, then

the other issue is, what will be the limitations or let us say stopping rules for such a trial?

DR. SIEGEL: And by a "randomized trial" you mean a randomized trial between a two-cell depleted transplant regimen and a non-transplant regimen? Or I'm not sure what you're asking.

DR. O'REILLY: Yeah.

DR. SIEGEL: Okay. Well, let me try to restate some things that probably need to be said. First of all, there is no setting in which a randomized trial is absolutely essential for approval, but there's no setting in which a randomized trial doesn't generate better data than other approaches.

I think that the issue you're getting -- the question you're getting at is the same one that Dr. Weiss was trying to address which is, one could either compare a two-cell depleted transplant to a non-

transplantation approach or to a different transplantation approach. In that regard we have phased one issue which I'll reiterate. We've faced and brought before this committee in '94 -- I always say "this committee" although I recognize none of you were here.

DR. VOSE: I was here.

DR. SIEGEL: You were.

DR. VOSE: I was here.

DR. SIEGEL: The very question because it was being asked as noted regarding the CSFs or whatever studies were showing simply that CSFs promoted engraftment whether it was of marrow or peripheral blood or whatever depending on the year, and the patients were engrafting better, the patients were -- or in the case of high-dose chemotherapy they were tolerating high-dose chemotherapy. It wasn't ---- who were tolerating it better, but the question kept arising that there had yet to be in many of the disease settings in which those were

shown any clear cut evidence that there was an indication for myelolative therapy or high-dose chemotherapy.

The standard that this committee recommended and that we applied was -- and there was a tendency to do those trials for some agents that had relatively marginal effects there was a tendency to study them with -- not in the marrow setting, but in the chemotherapy setting with extremely out in left field, if you will, compared to mainstream medicine protocols because only what those highly oblative protocols could they show that adding their agent made a difference.

This committee recommended that it should not matter -- it should not be the burden on the sponsor of a trial for a therapy that is supportive of a hematopoietic transplantation to demonstrate the benefits of transplantation, per se. That, however, they should not use a regimentation whether

that be transplantation or chemotherapy unless it is one that is -- and I won't have the exact words -- but is that is reasonably, widely accepted within the community as a reasonable approach to the treatment of the disease.

So that's the standard that we apply now. It doesn't have to be that it's accepted as the standard approach, but a reasonable approach to transplantation. If you can then improve transplantation outcomes, you need not show the role of transplantation in the disease.

So what we are facing in these diseases, however, is in some cases, cases where the role or transplantation is not yet established, in other cases where I guess it's more widely established. But what we are anticipating looking at are specific manufacturer's products. I have a monoclonal antibody or the manufacturer does, or a coded bead, or a device machine that's going to get

rid of T cells and they want to claim that that contributes something.

So I think the answer to your question is, you might be able to do a study compared to a non- transplantation regimen if you had ancillary data showing that the device contributed to the success of transplantation which may or may not have to be clinical trial data. But you would certainly have to show that -- you would have to make the case that transplantation with the device did something that transplantation without the device did. Or you could take the route of showing that transplantation with the device or the antibody or whatever, did something compared to some other mode of transplantation.

Although while the cleanest one would be one that did not involve the device since that might involve no T-cell depletion it might be hard to -- that may or may not be doable in some circumstances.

So I don't know if I've just made everything a lot more confusing.

DR. VOSE: Thank you.

DR. SIEGEL: I am more confused than when I started.

DR. VOSE: Dr. Auchincloss?

DR. AUCHINCLOSS: But it's a good introduction for me to make the comment that I wanted to make which will echo what I think I've said before in these kinds of settings. Before we go further with these particular questions that you put to us, my suggestion would be to you that the questions are going to lead us into strange places and not effective ones because I actually believe your entire approach to the regulation of the products that are involved in bone marrow transplantation is wrong.

Why? Because the basic issue in bone marrow transplantation has remained the same since the beginning -- engraftment, avoidance of GVH, and anti- tumor effect.

But what we have heard today and continue to hear is that the ways of getting the right combinations there are going to turn out to be multiple. Indeed, hundreds, depending on all sorts of variables -- what kind of donor, what kind of recipient do you have available? What disease you're treating?

Now, the way you're setting up to regulate these products, a T-cell depletion device suggests that you'll need to figure out in each of these variable cases whether there's some kind of clinical efficacy benefit to the patient in terms of the treatment of the disease.

In my view, that creates an incredible amount of work for you because you have so many variables that you need to keep approving a device for. But secondly, you are in fact holding up the development of the field by not making the devices in fact widely available. That's my personal view.

I think the approach should not be for what are in effect devices to look for a clinical efficacy outcome you should ask the question, does the device do what the device says it does? And as I pointed out before, if you have a device that says it depletes T cells it's totally appropriate for the FDA to ensure the public that this device does in fact deplete T cells and indeed it probably is appropriate for the FDA to insist that there be evidence that it not only depletes T cells but that it leaves in tact some stem cells that are crucial for bone marrow transplantation to succeed. But it doesn't get you into the business of deciding in which cases is T-cell depleted bone marrow transplantation appropriate?

The clinicians in the field will figure that kind of question out. You tell them the device can do it. And I think that can be applied to the monoclonal antibodies as well. Where you can set standards for

their safety, their efficacy in doing what the antibody says it will do and let the field determine the protocols that are appropriate for each patient.

DR. VOSE: Dr. Salomon?

DR. SALOMON: Yeah, I was trying to get my hand up to say something along those lines. I think that the idea of using historical controls in this area is really flawed, and I really hope that that doesn't come forward. Because we've been through it in solid organ transplantation and it's really evident that this field is like where we were about 20 years ago, and that was there were dramatic center effects first of all. And the little agreement on these very, very complex regimens both in preparative regimens, the handling of the donor inoculum, and the post-operative regimens. So that it's just -- I think it's an overwhelming concept to even compare one center to another center at this point. And I think you go

down just really a wrong alley trying to do that. So that's one point I would like to emphasize personally.

The second one is, I'm sitting here, I just think, you know, this area is so incredibly important to the history of medicine the next decade, but it's just very early in the process and I think you're way ahead of yourself demanding prospective randomized trials. I love prospective randomized trials, don't get me wrong, but I don't see where you can do prospective randomized trials. I think what you ought to do is a little -- here is where I come to where Dr. Auchincloss is talking, you have to parse this out. I mean, there are very specific problems that this field faces, chronic GVHD, acute GVHD, recurrence of, disease-free survival, take one of those, you don't have to do, you know, a big trial. Just set an example that this product or this manipulation has an effect on one single,

even a relatively short-term parameter. It reduced acute GVHD. Okay. Fine. Let it go forward.

You know, the details may be on a randomized prospective trial at this point.

DR. AUCHINCLOSS: Just let me be clear that that's the opposite of what I said.

DR. SALOMON: No, I don't think it is necessarily the opposite of what you said, actually, but whatever.

DR. SIEGEL: I'm sorry, reduced a single parameter compared to what? I missed that, not historical and not randomized --

DR. SALOMON: What Dr. Auchincloss -- what he is pointing out to me is that he was saying, don't even set an outcome parameter. He's just saying if a T-cell device is supposed to purify T cells let it purify T cells. And I actually have no problem with that.

I was going one step further. I

was saying, if you feel like you have to have an outcome parameter, so this is where I felt I was segueing from you, is if you feel like you have an outcome parameter, don't take on the whole ball of wax which is what you do with a randomized prospective trial, but pick a definable outcome parameter and insist on effect on at least one outcome parameter even though the -- even though you were going to admit and all the experts will admit that the design of these trials are going to get -- you know, there could be complex effects on other outcome parameters --

DR. SIEGEL: But I'm not understanding --

DR. VOSE: Compared to what?

DR. SIEGEL: -- compared to whom?

DR. VOSE: Compared to what?

DR. SIEGEL: So you're suggesting we would do the trials, but only measure one parameter, not measure the others?

DR. VOSE: But compared to what?

That's the problem.

DR. SALOMON: Well, in that case, you can design trials if there is -- if I say I want to improve just reduce the incidence of acute Graft-verus-Host Disease, there I think it won't be that hard to establish a control group for that because you're only making one parameter change.

Adding product X on day two.

DR. O'REILLY: I would suggest that in answer to Carole's question, I think that it's not an exact view, but in this unique circumstance, it might be a worthwhile fit. And that is if you look at experience with two antigen disparate grafts, there is a pretty sizeable amount of data on two antigen disparate unmodified grafts, and there is a cadre of individuals who have at least survived, you could take those individuals as your comparative group and ask, does the T-cell depletion technique reduce Graft-verus-Host Disease in a two- or

three-antigen disparate below what is currently present for two?

My reasoning would be that if you reduce it below what a two does, you certainly can make the minimal jump to say that you also hold true for three. In other words, I'm perfectly happy to take the technique that we use right now and would be happy to do it against a one-antigen disparate unmodified marrow graft because of the fact that I think from the same point of GVH aspects we would be able to do it.

But then again, the last thing, and there I agree with -- I think actually I agree with both of you in this regard. Is that I do think that, you know, you really can state some standards, but you are going to have to make some differences. I think we are early, we should be doing more phase twos with targeted endpoints at this particular point and then ultimately potentially going one against the other.

The problem is the industries may not be such as to be able to tolerate that. So then, you know, go with --

DR. VOSE: I think Dr. Anderson has been waiting a long time.

DR. ANDERSON: She wants to contribute directly to this.

DR. HENSLEE-DOWNEY: Well, actually I think that it has to be a melding of both of these two concepts that have come forward. Now, I do like the idea that if you're going to look at a device or a drug, particularly a monoclonal antibody that's targeted against a certain cell subset that you are actually able to demonstrate and that that should be a requirement that you do what you say that this product is going to do.

But I think you have to apply it then on a clinical trial to ask more questions than just one simple endpoint. Because the endpoints, you can't really just pick up one endpoint and say that's all you

would have to show.

I think that you have to decide based on the published literature using any technique, and I think that's important too. I don't think that you can say I'm going to use this technique and I'm going to only compare it to something else that looks the same. It has to be with regards to all approaches to doing haploidentical transplant that you would develop -- I guess the term was used "targeted endpoints" and that you would have -- and maybe that's the same as saying -- stopping rules. And that becomes quite reasonable particularly in the context of what is seen using another alternative donor.

I do think eventually that the interesting question may come forward as to whether there are certain diseases that are served best by one particular donor versus another; delay in transplant is going to be a driving force always. But we have to show

equivalency between the different donors for people to sort of get over the reluctance to look at all donor sources perhaps so that the patient then has access to their best chance for effective, curative treatment.

I think already the field defines the patient who we feel really has no opportunity for successful outcome with non-transplant therapy and that those are the patients that go forward into alternative donor transplants. And although there are few exceptions in unrelated donor transplant that it has been really embraced though by the field and often viewed by some to be so similar to matched-sibling donor transplant. And those who have really gone courageously along those lines so that they can treat patients that are in the very best situation with the very best matched donor have produced those kinds of excellent outcomes that would be comparable to a matched-sibling donor. And we're not going to ever be able

to do that in haploidentical transplant, or in cord blood transplant until we can all have established the techniques that give us the confidence to take this technology to those patients.

But, we can still, within those worst patients, if you will, we can still develop targeted endpoints that would be expected that would make it a reasonable approach to study further. And I think that would be the responsibility of the FDA that they would not give approval to a technology even though it was shown to perhaps target what it was supposed to target and maybe reduce GVHD if in the long run it still had all these other problems associated with it. That's why I think you have to do targeted endpoints that cross all of the major problems -- engraftment, acute and chronic GVHD, immune reconstitution, and survival.

DR. VOSE: Dr. Kurtzberg?

DR. KURTZBERG: I think one of the

problems is you can't study these devices in a vacuum. And the people who are -- the four or five techniques that are active with T-cell depletion all are linked to protocols that don't just involve whatever the T-cell depletion method is, but involve, you know, the preparative regimen and the GVH prophylaxis and all that. So if there's a device to be tested, then that company should partner with one of the places that's already doing haploidentical transplants with some method of T-cell depletion and either add or substitute whatever this device is in that method. And so you could identify or they can identify five or six centers that do this and have at least expertise in it and can do what both these guys showed in terms of comparing to their own historical data, or does this work, does this work, does this work.

DR. VOSE: But the problem is what they're already doing is already

experimental. So you add another experimental whatever on another experimental thing.

DR. KURTZBERG: But I mean, transplantation is experimental.

DR. VOSE: I know, but now I'm speaking for them, and not for me ---- we get caught in the middle.

DR. O'REILLY: But, you know, I think the big problem with the experimental usually has to do not so much with whether or not it is experimental or not, but whether or not you're going to be caught by industry. So, you know, from that standpoint we're in a kind of an interesting situation because we in fact can do these trials because, you know, lectins are not patentable and in fact we can do these kinds of studies, and that's exactly the approach that we're trying to do, is to take, for example, one approach and compare it with the lectin approach at the lab level and at the clinical level, and

then, you know, using the same kind of cytoreductive regimen.

I think we can do it. I think, you know, Jean could do it now having gone through all the pain of developing cytoreductive regimens. You know, this is where, you know, the mutual headaches are really horrific. But then you can say, okay, we're going to try OKT3 depletion versus, for example, what we did with T10B9 or otherwise. And you actually can do them, you know, one against the other provided you don't get caught by the vested interest of the industries that are proposing one or the other partners.

DR. VOSE: Right.

DR. O'REILLY: And I'm just lucky, because I don't have a vested interest.

DR. SIEGEL: But, Dr. O'Reilly, I wonder if I could ask you a question and this regards some of the data you presented.

DR. O'REILLY: Okay.

DR. SIEGEL: You showed in recent studies, if I understood correctly, a higher -- when you moved from lectin and E-rosetting to CD34 positive selection and E-rosetting a higher incidence of GVHD, I'm not sure I caught whether -- is the numerical T-cell depletion significantly different between those --

DR. O'REILLY: No. Actually what we have done is to recognize that we made targeted dosings in the trial. And we initially had a targeted dose that the dose of T cells to be administered in the combined graft would be not higher than ten to the fifth per kilogram. What we've done is to reduce that now to five times ten to the fourth kilogram. And all I can say is that with the lectin graft historically we would be out to ten to the fifth realm and we saw very little. In this circumstance we are seeing more.

And I'm now in a situation where I

would have to say, it's not just the T depletion, unfortunately, it's going to be some type of T depletion. And the concern, I think that all of us have is we're looking at peripheral blood stem cells is that the peripheral blood pool of T cells may have a different type of population.

What I would also like to know and what we are trying to get squared off would be if we did lectin E on peripheral blood stem cells that's how Aversa did his early studies and he had little or no Graft-verus-Host Disease. He's only recently moved to a separate E or an E separate.

You know, that's one that we're going to actually compare laboratorywise and I want to compare it clinical.

DR. VOSE: I think that is a good point though, peripheral blood is different than bone marrow and you certainly cannot compare the two in any way, shape, or form.

DR. HENSLEE-DOWNEY: Or you should

compare the two in a randomized trial if you want to really answer the answer.

DR. VOSE: I was speaking about historical controls.

DR. HENSLEE-DOWNEY: Right.

DR. VOSE: That you shouldn't compare the two in historical controls.

DR. HENSLEE-DOWNEY: Right. No, absolutely.

DR. MILLER: Can I say something? I have sort of a radical term difference. I agree with what they talked about that a device should do what a device is supposed to do which in this setting is decrease T cells and show equivalent engraftment. And so my question is why are we looking at it in haploidenticals to do -- to get a -- to tell people how to get a device approved? Why not do it in places where you actually can randomize to get those early endpoints in good risk patients -- standard risk patients, not good, but older patients over the age of

40, and then you can get those two endpoints. And then once you got -- just like with --

DR. VOSE: Are you talking about unrelated donors?

DR. MILLER: No, no, related donors. All you want to show is we want to show that you get decreased T cells, you decrease acute Graft-verus-Host Disease and you don't safety, you don't impair engraftment.

DR. VOSE: And infection.

DR. MILLER: And increase infection. And in that setting, I mean, you can look at that. And just like for the cell pro column for -- that we approved for peripheral blood, we did it based on the fact that it showed efficacy, and that it did what it's supposed to do and it showed relative -- we didn't come out and say that the biggest burden was on -- that we worried the most about purging tumor cells out of -- I don't think that was the answer why we purged it.

Why we approved that device is because it did what it says it was going to do.

And I think that if you're going to do it, yes, I agree that T-cell depletion is most important in the haploidentical transplants, but to actually show that the device works you don't need to do it in that. Why not say, give us a small study in patients who you can randomize and get that data and then prospectively controlled studies that will tell the field -- I mean, the field will determine -- the experts of the field will determine how to use it after it gets out there in the patients that you cannot randomize.

DR. SIEGEL: Dr. Miller, just for clarification though, you're using some of the same language Dr. Auchincloss did regarding devices doing what they're supposed to do. But if I understand -- although he was suggesting that if they deplete the T cells that's doing what they're supposed to

do and engraft. You're suggesting also though in such a study you could and also should look for decreasing Graft- verus-Host Disease as well.

DR. MILLER: Yes. Or just a safety. I mean, you want to show safety and efficacy and you could say that the efficacy is decreasing two and a half logs of T cells, no different than decreasing two and a half logs of multiple myeloma cells which is what we had as a standard. But then you have to somehow show safety. And the safety in this is since you're working with a hematopoietic cell process, what we've said the safety issue was is that grafts are enabled to engraft.

DR. SIEGEL: There's an importance difference though between asking for a decrease of two and a half logs of T cells they're asking for a decrease in Graft-verus-Host Disease.

The logic of the committee in the

tumor was in part that it was several years of follow up to see whether tumor cell depletion mattered and that in fact the interactions with chemotherapy regimes are something that made that somewhat not practical. Whereas if you're getting engraftment data and you're getting infection data, there's not that feasibility issue of getting Graft-verus-Host Disease data.

DR. HENSLEE-DOWNEY: And, Carole, I would be concerned that if you test it in a matched-sibling donor setting that doesn't mean that it's going to work in a haploidentical setting. And a lot of people would come to the table and argue you don't need to demonstrate to anyone that you can develop a technology that will do T-cell depletion in the matched-sibling donor setting. Because, you know, then you beg the whole question about whether T-cell depletion should be done in the matched-sibling donor. And that can be argued where it is being

argued. But showing that a device produces the T-cell depletion that can result in successful engraftment with a matched-sibling donor and control Graft-verus-Host Disease means nothing when you come to haploidentical transplant.

I had no idea whether it will work.

DR. MILLER: But we're testing what a device what something does and then what they do -- is phase two studies after --

DR. O'REILLY: Carole, my read of it is that actually, you're correct. I would just sort of two caveats. One to you and one to you. The one to you is that, yes, it should do what it's supposed to do. But the first one to do that was, for example, Dr. Bocci -- in Genoa. And he set back the T-cell depletion world by about three or four years in Europe and in this country because he did T-cell depletion using his particular garden variety monoclonal antibody generated in Genoa. And it turned out that it did

deplete some T cells. The problem was that it did not in any way affect graft versus host disease and 11 out of the first 13 patients that he transplanted relapsed with disease within six months.

Now, he was relatively smart and he recognized that he hadn't picked out all T cells, he had actually probably picked out some sort of regulatory cells. But from that time on that was the basis of the IBMTR saying that the instance of relapse in acute leukemias is higher in T-cell depletion. And that went on for years until enough data were accumulated to say all of a sudden, it is not.

Now, Monmouth was the guy who recorded -- Monmouth is from that center and he just doesn't want to hear that, but that is it. Their GVH was not altered. So I would suggest that one, you have to have a biological parameter, so, so if you do the T-depletion, you have to show that numerically.

But I think you have to correlate it with the absence of GVH where the reduction in GVH because that's why you're doing T-cell depletion in the first place.

The second part, though is yours. Now, I concur now randomized trials has to be done, but Essie can tell you this, one of the things that's most discouraging about this is when we set up that kind of a trial specifically for a grant in 1994. No matter what we do in offering that trial, discussing that trial, et cetera, patients come to Memorial because they wanted T-depleted graft. If they don't want a T- depleted graft, they're going to go somewhere else. But it has been almost unbelievably difficult to accrue patients in that randomized trial because it is in a, you know, for those who believe -- you know, for those who don't believe, no explanation is possible; and for those who believe, no explanation is necessary.

I mean, it really comes down to that. And we have been frustrated by that to the point where, you know, I proposed this in a program project grant and my group is saying, we can't do it. And I say, but if we don't do it, you know, we uniquely must do it, if we don't do it it's a problem. The fact is, accrual-wise we may never be able to pull it off.

DR. MILLER: But a company, if they want to get their device approved they'll have the wherewithal to have enough centers to do that. I mean, it's no different than a drug such as, you know, 4HC, that, you know, always you need to have something to compare it against, how do you -- you know, people who either believe or don't believe, well, you know, the bottom line is, we don't know the answer and so you've to show it. And so that's why I'm saying, if there was a group that it could be done with, even though it's not that easy, why not do it in that group?

DR. O'REILLY: Well, yeah, I --

DR. VOSE: I think you can reasonably --

DR. MILLER: I think you can very easily randomize people who are matched siblings --

DR. VOSE: But I have to agree with Jean, I don't think that doing that trial in a matched sibling donor means anything to using it in a different situation. Maybe a closer situation as unrelated donor that's fully matched would be a possibility. I think that's a possibility, but I don't think the related would be good.

DR. O'REILLY: One of those trial is ongoing.

DR. VOSE: Right. That actually was my other question. What's going on with that it's an NHBL trial right?

DR. O'REILLY: It's accruing. You know, in large numbers. It's supposed to be finished in what, another 18 months?

DR. PAPADOPOULOS: It's behind in accrual.

DR. VOSE: So it's behind in accrual, but there are approximately 300 or so patients accrued out of 560, I think.

DR. PAPADOPOULOS: Right.

DR. VOSE: That's nothing --

DR. KURTZBERG: Well, I know they just cut it back because it was going to take too long to form something.

DR. VOSE: They may have cut back the total --

DR. MILLER: And that has two different types of T-cell depletion right there elutriation and T10B9.

DR. KURTZBERG: But, again, those are packaged deals.

DR. VOSE: Right.

DR. KURTZBERG: The prep regimen for the conventional non-T-depleted arm is completely different than the T10B9 --

DR. VOSE: Right.

DR. KURTZBERG: -- which is completely different than the elutriation. And, in fact, there are two T10B9 prep regimens.

DR. VOSE: That's because none of us can agree on anything. Dr. Anderson?

DR. ANDERSON: Yes, I keep relinquishing my spot because it's fascinating listening to everybody talk. Basically all the points I wanted to make have already been made. So let me just make a brief summary. What I had wanted to point out was basically what Hugh said, but from a slightly different perspective. And the perspective is as a person who deals with bone marrow transplanters, but is not a bone marrow transplanter.

In my experience from ten years ago, Rich, when you and I worked together to the present is every time you sit down with someone in bone marrow transplant and start to go over the real results of somebody's

data, and you say, well, what about such and such, it's because they varied this, they varied -- there are 25 different variables and so it's just -- it's fuzzy. This is very early in a very complex field. And since all the points bearing on this have already been made, let me just emphasize in a slightly different way what you said, and that is what I would hope that the FDA takes as one of its primary criterion dealing with this, clearly the safety of the public, but basically what can the FDA do to help the investigators further the field? That that should be the primary objective. Clearly safety is -- that's a non-issue, we all agree with that.

But there is the potential danger because this field is so complex, because each investigator does things their own way, and Rich has made the point I was going to make which is that how can you accrue a large number of patients in any kind of a randomized trial when people go to people

because they do something and get away. This is a field where you can't really do that. It's not like drugs where you can set up 20 institutions and they all agree, this is the dose they're going to give, and if the age is this and the symptoms are that.

So a plea to the FDA to think in large measure what position can the FDA take which helps the investigators answer the questions.

DR. SIEGEL: I certainly agree that's an important goal, but in some sense, implicit in your preamble is an answer I think different from the one you're implying.

DR. ANDERSON: Okay.

DR. SIEGEL: Because if I might rephrase what you just said to me --

DR. ANDERSON: Sure. Okay.

DR. SIEGEL: -- is -- what I just heard you say at least, is that having talked to bone marrow transplanters over the years, there are so many variables in comparing any

therapy that it's very difficult to make any conclusions regarding how to compare those therapies. But then you're suggesting to advance the field we should, rather than move into a situation where were we have controlled clinical trials with a single variable, rather than suggesting that, you're suggesting that we should continue that way and --

DR. ANDERSON: No, no, I didn't. If that's the impression I gave I shouldn't have cut it so short. No, no, it was simply to try to point out the situation that it is going to be much more difficult in this field than in many fields in order to do the best type of clinical trials and not to be rigid in terms of the approach. That's all I meant to say.

DR. KURTZBERG: I also think it's too early to just say there's going to be one answer. And each one of these methods has their own challenges and none of them are

good enough to give up the other ones, and like Jean said, there may be certain diseases -- you know, CML may need more cells and cord blood may never work, but, you know, some other disease may be fine with fewer cells and may need more T cells and so T- cell depletion won't work. And we're just not there. So each method has its own challenges. And if the devices can fit into addressing what those challenges are, then it makes sense to test some of those methods.

DR. VOSE: I think transplantation we all know is an art and a science. And those little final points are things that we need to work out. But you have to think about it from a manufacturer and from FDA's standpoint they're asking kind of different questions.

DR. KURTZBERG: Yeah, but the transplants have spent 20 years figuring out how to get where they got with a certain method, then it's not unreasonable to -- you

know, you can't just drop a device in and all of a sudden assume that's going to solve everything and then work with everything.

DR. VOSE: No, I don't think anybody thinks that.

DR. O'REILLY: I would just -- you know, I don't feel that the transplanters also have to be particularly defensive because the actual result is a pretty good one to say the least. And I think that certainly for diseases like CML, it's better than around. But I think that what was stated before though is that the devices fit within, in fact, the package. That a T-depleted graft is more sensitive to host resistance than an unmodified graft. That the critical facilitator cell that we can talk about is in fact an alloreactive T cell that's in the graft. That was shown in the 1970s by Bob Lowenberg where he just took early fetal liver cells and shot them in and if you even add a minuscule number of T cells

from the thymus you massively potentiate the engraftment process.

So removing T cells it was not surprising that you would have a problem of graft failure. And the fact of the matter is with modifications in terms of how one does these, in fact, you can overcome that.

So, therefore, I think it is going to be a package, it's going to be a package of cytoreduction plus a T-depletion technique, but then at that point, you know, the way -- for example, the NHLBI trial was set up, that was set up with a reasonable mode. Because what you're really asking is fundamentally, can a T-cell depletion technique achieve engraftment, reduce Graft-verus-Host Disease and potentially as a result of that lead to a reduction in non-leukemic mortality and potentially in improved long-term survival. That's what they're asking.

Now, the second thing I would say

from the FDA point which could be helped -- could help us enormously in the field and also could help the real aspect of what happens with the industrial folks is that we as investigators look at a particular procedure, or a particular device and we say, all right, let's say I take it in the lab and I look at it, and I say, God, this device does a really good job. It allows me to concentrate progenitor cells and removes T cells and as far as I can see it removes alloreactive T cells. I want to go at it.

And the manufacturer says, well, we'd love to give you these devices, but the problem is we're going to go out of business because our burn rate is so high. Okay. And we as institutions say, well, we would love to just go ahead with this and not worry about that, but we have no mechanism to pay.

Now, one of the things the FDA has done for several devices, and I think if they could make that almost as a sort of a general

approach is that if you have preclinical evidences that in fact these things do what they say they do on a reproducible level and they want to now go into clinical trials. At least the clinical trials can be done in a cost-recovery mode. If that could be done initially rather than sort of somewhere down the line, that's going to be a huge boost to these kinds of trials.

The second aspect of it is if you don't have the package recognizing the biology of these different types of transplants, okay, you can probably get, you know, quite literally, randomized trials done. But they would have to be in a context of a package of a cytoreductive regimen plus.

DR. HENSLEE-DOWNEY: Although I think it's hard to talk about cost recovery in an era of capitation because you may be shifting costs and therefore you might still be able to say you can recover the costs, but you can't directly recover --

DR. VOSE: You can't bill the patient for that current thing that's in the package, and so basically you're still --

DR. HENSLEE-DOWNEY: No --

DR. O'REILLY: No, no, but they can. If they allow you to bill the patient for cost --

DR. VOSE: But --

DR. O'REILLY: -- recovery --

DR. VOSE: -- most of them you can't bill the patient.

DR. KURTZBERG: But even if you do bill the patient, if you're getting $100,000 and it's --

DR. VOSE: Right.

DR. KURTZBERG: -- and it only can go so many places whether you bill or not.

DR. VOSE: Right. If it's just a package deal, a package transplant --

DR. SIEGEL: I should point out cost recovery is covered by our laws and our regulations and is as with many of the things

we do somewhat subject to what our policy and scientific judgment is and somewhat dictated by what the laws of the country are which we must uphold. But it applies different -- your comment mentioned devices and it does apply differently for devices. There's much more leeway to the Agency in allowing cost recovery for a device early in its development in an experimental stage than would be for if we're talking about, say, a growth factor or an antibody that is not part of a device, but is being sold as a drug for example.

Although in those cases cost recovery is possible. It requires additional showings as you implied in terms of clinical utility in addition to financial hardship issues.

DR. KURTZBERG: But that's going to be a Catch 22 because if you've got a capitated rate and your hospital is already unhappy with what you're doing and you put in

something that's more money, it's going to take out of their -- it's coming out of the same pot, it's not going to be popular.

DR. VOSE: No, it's not going to work.

DR. SIEGEL: Right. Well, in that regard, you know, one could argue, although this isn't where we're going, but a lower FDA requirement for approval may not further the field by --

DR. SALOMON: The thing you have to remember in this capitation argument is that you have to look at then long-term outcomes. In other words, if I have a patient with leukemia and I cure the leukemia and then I get a relapse or I get a bad GVHD it costs me more per patient to manage that than if I've reduced the costs. So, yeah, it might cost me $10,000 more because of my device or drug, but if I reduce the complications in one in other vocal points, I significantly reduce the overall cost. So that's the thing you've

got to keep in mind.

DR. KURTZBERG: But if you're a transplant referral center and all your hospital is looking at is their piece of the pie, they don't care what happens to that patient a year later, because it's not going to be coming out of their pocket --

DR. SALOMON: But a lot of the money is --

DR. KURTZBERG: I'm not saying that's right, but that's what is happening.

DR. SALOMON: I understand, but a lot of the money now is coming from managed care organizations who have a stake in the patient from the beginning to the end. Your hospital may be in the middle of it, but --

DR. VOSE: Most of the large transplant centers that's not how it happens anymore. The patients come there and they get $100,000 to do a transplant and after the patient goes away, that's it.

DR. AUCHINCLOSS: Jay, I think that

was clever. The notion that the FDA is involved in it has actually hastened the field by insisting on companies performing trials as cover, but I don't believe it.

DR. SIEGEL: Pardon?

DR. AUCHINCLOSS: But I don't believe it.

DR. SIEGEL: What did you say?

DR. AUCHINCLOSS: The notion that you're involvement was actually going to hasten the performance of trials and introduction of all of these by somehow forcing the companies to perform them and provide the equipment for free et cetera is cute, I like it, but I don't actually believe it.

I mean, but that wasn't going to be main --

DR. SIEGEL: Well, I don't know if it's true here or not, but a good number of important clinical trial are funded by pharmaceutical companies.

DR. AUCHINCLOSS: There's no question about it.

DR. SIEGEL: A significant number of them are funded because they're necessary to meet regulatory requirements --

DR. AUCHINCLOSS: And that's true too.

DR. SIEGEL: -- and one can -- one needs to look carefully when one suggests lowering regulatory requirements at the possibility that if trials -- if the pharmaceutical companies or the device manufacturers are not required to do the trial in order to market and promote a device the trial may be less likely to get done rather than more likely to get done, and, you know, I don't know that we should argue that issue here, but I wouldn't dismiss it out of hand.

DR. AUCHINCLOSS: I certainly agree with you and we've had that discussion previously about some of the other products,

as you know. Which things should we use your leverage for, et cetera? I mean, the point is potentially valid.

But let me get back -- I did want to make one clarification that I think I've been sort of -- my comments have been used to sort of suggest that I don't believe in clinical trials. I mean, that is not the point that I'm making.

I want you to do lots of trials, thousands of trials, you've got lots of things to figure out. The issue is not, should we have clinical trials, the issue is, what trials are appreciate to get product approval? And that's quite different.

And I actually think that the T-cell depletion device example is perfect at demonstrating how you can misuse product approval and get the wrong clinical trial for exactly the reason that Jean suggested. If I wanted to design a trial that showed T-cell depletion caused less GVH, I know I could do

it. It would probably be one antigen match and it would be a non-cancer situation. I'd work out the variables where I know I could show a reduction in Graft-verus- Host Disease. And once I had the product approved, I'd have the product approved. But the results of that study would be completely meaningless for where you really need T-cell depletion which, of course, is in the haplo transplant.

DR. SALOMON: Yeah, but that was your point. Your point was that if it worked, and it did it, and you proved it in your trial, which is my point, pick a parsed outcome and then establish it, then let the field -- the experts in the field segue it into other trials and be responsible for the results.

DR. AUCHINCLOSS: The second part of what you said is my point. Let the experts in the field figure it out. But let me just keep my point -- my point is my

point. My point is the device should be licensed on the basis of it doing what the says the does.

DR. VOSE: But it needs to do it in a situation where it makes some relevance or --

DR. SALOMON: I disagree with you -- I'm sorry. I can take -- I can go into the lab and separate T cells in 200 bone marrow preparations and show that the device does what it does. And that's all you're expecting for approval, then I don't buy it.

DR. VOSE: No, I think that's wrong. And you need to show some benefit for what you're doing or it's meaningless. I'm sorry. It has to have some benefit.

DR. MILLER: You need to show some benefit, but not the maximal benefit.

DR. VOSE: Well, no, I'm not --

DR. MILLER: I mean, you can show in a group of patients you can show that there's a benefit that can be measured

compared to control, but it's not in the same league as the number and the benefit that you expect in the patients that are at the highest risk.

But you're going to be in HLA identical, or one anti mismatch or some good group, you're going to be able to show that there was a basis for really taking it in to what patient population you are really concerned about with this device as compared to OKT3 which is what you're using now. Just similar things in the good risk patients and now you can take it and then do to phase II study or, you know, the study that you want to do in your patients, with the only stopping rules and the very, very high risk patients, but at least you know are very good data on what it does to T cells, CFUGM, CD34 cells and early evidence of, you know, other immune functions even in those patient populations.

Yes, it's going to be different

than your patients, but it still is going to be able to help you build on it, and you're going to be able to compare it to something else. These patients are very complicated. The preparative regimens are very complicated. So in the absence of doing something where you're comparing one to another we'll never every know what these devices do.

DR. HENSLEE-DOWNEY: I guess my concern is that it's a huge issue that might be handled as a silent nuance. And so that the unsuspected or unexpected population are told, yes, look how beautifully this worked. I mean, I've seen this too many times and no one is telling them the caveats underneath that. And so patients sort of blindly go into a trial believing that this is what they're going to get. And yet you change the stem cell source. It's a huge difference.

DR. MILLER: Right now you're doing it with OKT3 where you don't even have any of

that data on what it does compared to a randomized control group, so you're making that leap of faith one step better to the patient saying, okay, I have no data what this does in vitro, but you're a very high-risk patient, I'm going to use it. And so why not do something you actually have the data on before you do the high-risk patients.

DR. VOSE: Well, you have to do it in a patient population that has at least some of the same problems that we're talking about.

DR. MILLER: Well, GVHD -- you know, you can get stage four with GVHD in a sibling --

DR. O'REILLY: But, Carole --

DR. VOSE: But it's different. I mean, the percentage is much different, and the engraftment is much different.

DR. HENSLEE-DOWNEY: And the management.

DR. VOSE: Management is much

different. Yeah.

DR. O'REILLY: But I would also note, it is not so much of an art to, you know, the devices we're talking about, for example, anything that's entered into clinical trials at our shop. The in vitro data has been, you know, really put through a lot before we even introduce it. My readout when we did those comparative trials was that I -- you know, did I think that lectin agglutination and E-rosette depletion in 1980 was going to last very long in that time? No, I didn't because the thought, you know, there's going to be much more sophisticated programs. At that time we didn't even have monochromals against T cells. But the problem -- the issue was that it was very effective in terms of T-cell depletion and we could show it. All we basically said was, we'll take anything that can give us comparable levels of T-cell depletion and we could consider testing it because that

technique has been tested in animals, in primates. We did all of that before we ever did the first SCID kid. And I think that we do have, you know, in this sort of a stepwise approach where you have several standard approaches based on in vitro in pre-clinical studies that we developed that other groups have developed in concert with industry before they're introduced. So it's not that OKT3 doesn't, but it does. You know, T10B9 does. There's a lot of studies that will show that these kinds of agents will in fact deplete T cells and we do ongoing studies of those even before we introduce them.

I think the issue though -- I'm switching on this score though -- is that some aspect of a biological parameter I think both you guys are saying the same thing, and there I do disagree with you. I think that you want something that will deplete, yes, but you want to have something where the depletion is correlated with a true reduction

in GVH.

My real problem is that I've seen people who deplete quote/unquote T cells. But, in fact, do not in any way deplete Graft-verus-Host Disease. And I don't think that's T-cell depletion, or I don't think it's allo T-cell depletion as opposed -- and I do think that that's a reasonable thing we have to --

DR. VOSE: I don't think it's necessary to show an improvement in overall survival, for example, but I do think you need to show an improvement in Graft-verus-Host Disease that that will --

DR. O'REILLY: But you would not --

DR. VOSE: -- at least be a better quality of life for the patient, you know, something like that.

DR. O'REILLY: But all I would really say is that I think one of the areas that we can use as a marker that I think is really useful would be a reduction in

transplant-associated mortality.

DR. VOSE: Sure.

DR. O'REILLY: So, namely GVH that's your target. But if at the same time as when we started, you know, you come up with a high level of graft failure that's not helpful. So you want, you know, an acceptable level of graft failure or graft failure no greater than unmodified grafts coupled with a reduction in GVH and your expectation would be that that would be associated with a reduction in transplant-related mortality. It would not be something for disease, but I would suggest that for several of these diseases adding in the issue of relapse gets pretty dicey.

DR. VOSE: Right. That's what I'm saying. I don't think you need to size or power a study to say that they have to have an improvement in overall survival. An equivalency of that would be adequate, I think. Jean.

DR. HENSLEE-DOWNEY: I think another way to look at it is if you are a company trying to produce a monoclonal antibody or some molecule that's going to help transplanters deal with histoincompatibility or whether you're using some cell sorter device to do T- cell depletion or whatever. The driving force is haploidentical transplant. Because if a company is going to invest a large amount of money into trying to produce something that they can put on the market, it's because it's going to be used a lot, and that's the only reason. So if you do this for a matched sibling donor, you'll never even recoup your R&D costs. You have to do it because now you're going to really create new opportunities to do transplants. And with haploidentical transplants, that's the beauty that really everybody has a donor and they immediately have a donor. So now you've created complete universal access to

allogeneic transplant.

Now, that would drive you to expend money to develop that technology.

DR. VOSE: But I think the question is, can you do a study that's not necessarily in haplos and then perhaps in --

DR. HENSLEE-DOWNEY: No, because if it doesn't have any meaning --

DR. VOSE: No, I'm saying --

DR. HENSLEE-DOWNEY: -- I mean, that's what you would -- you have to develop --

DR. VOSE: -- for us to use that device for that antibody than to further modify it and to do it in appropriate trials once it's been looked at in perhaps a less high-risk population. I'm not saying for it to be generalized approved.

DR. O'REILLY: Yeah, I would honestly say from the standpoint of the issue of GVH. You know, certainly we've done it without prophylaxis, so I can say that. I

mean, we saw a dramatic reduction in GVH in the haplotype disparates, that's actually how we started. But the fact of the matter is, in the leukemic circumstance we went back to the drawing boards for matches. There was no doubt it reduced GVH, and then we got over the issue of rejection. Once we go over that, the principles learned there could be then applied to the broader realm.

I don't know that we couldn't do a stepwise one to two antigen disparate graft, for example, that's where you're at as well; right? One two antigen disparate, you know, you prefer not to do a three even in the absence of the historical. I don't think it's completely apples and oranges. I think you can make it stepwise.

DR. MILLER: But we still have real problems in allogeneic sibling donor transplants, especially if people want to go to peripheral blood stem cells. I mean, you're looking at a much greater incidence of

acute -- I mean, of chronic Graft-verus-Host Disease and no decrease. So, I mean, there's a patient population where you -- you know, where the standard has a pretty high incidence of chronic Graft-verus-Host Disease and a reasonable incidence of acute Graft-verus-Host Disease that we don't think -- you know, that a lot of people are uncomfortable -- may be uncomfortable starting to use peripheral blood progenitors because we don't know if it's going to increase the up front mortality. That's a place where why not do the study in that patient population. There's a question to be asked as we don't think we have all the answers.

The second thing that makes me think of why we can't look at this T-cell depletion in those patients is the data that you showed, Rick, looking at your data as the 78 or 80 percent in the first remission -- that's T-cell depletion showing very, very good data, I mean, in a single institution.

But it would be nice even in the good risks to get that type of data. And the only way you're ever going to prove and have these devices available is by showing that it works. And I think if you really want to answer the question, do these questions work in a randomized trial, you get the transplant and say, okay, we'll do the trial, maybe we don't -- you know, I believe in T- cell depletion, or I don't believe in T-cell depletion, but the only way you're ever actually going to get the device out there so that you could -- if you wanted to keep using T10B9, well, you can't now, because you can't get it. You'd really probably like to be back to doing it.

If you're told the only way you can get T10B9 with which you've got great data is to do this trial, you would probably do the trial. Right?

DR. HENSLEE-DOWNEY: I'm just saying that the real home run though would be

to do the trial in haploidentical transplant.

DR. MILLER: There's no control. But how? How can we do that? There's no control.

DR. HENSLEE-DOWNEY: But then you don't have to have --

DR. VOSE: But folks, I think we're missing the --

DR. HENSLEE-DOWNEY: -- the randomized.

DR. VOSE: But there's no adequate historical control.

DR. PAPADOPOULOS: But, Julie, I mean, we're talking about haplos as though they can be done and they're done easily and we just --

DR. VOSE: No. No.

DR. PAPADOPOULOS: -- compare two approaches and see if one is better than the other. The fact that they're being done at all, mind you, by a relatively small number of centers compared to regular allo bone

marrow, or peripheral blood stem cells from a matched sibs or unrelated, it's short of a miracle, basically, the fact that you can do this against such HLA barriers. And we're still way down low on the learning curve. There's a lot of room for improvement in these kinds of transplants. See, I agree with Jean, I think the place where a sponsor could market this type of a device, and agent to reduce Graft-verus-Host Disease would be in the haploidentical transplants.

I think randomized trials comparing conventional to T-cell depleted is much more of a scientific question for the scientific community and I'm not sure sponsors are really going to want to get into that because there is such a bias in the transplant community for one versus the other.

DR. O'REILLY: In the matched.

DR. PAPADOPOULOS: In the matched setting that it would be a very difficult trial to perform.

DR. SALOMON: I think the thing to remember is this is -- in agreeing with Essie, it's just like where we were at in heart transplantation in 1980, right at the time of the introduction of cyclosporin, one-year graft survivals were in the 20 to 35 percent range. Most of the centers had decided they wouldn't do them, and all of a sudden you introduce this drug and it went to 70, 80 percent within about three years.

You couldn't do a randomized prospective trial of that and certainly no one in his right mind would suggest that the FDA impeded it or in the future should not learn from how they handled it and impede something like this. So I think that's the point, you know, picking a parameter. That was what I was trying to say earlier. The parameter there was, let the patients survive.

DR. MILLER: You're just proving my point. You got the data on the heart

transplant by looking at cyclosporin in kidney transplants, an easier thing where you got to do randomized trials and then the scientists or clinicians in heart transplants took it the next step and said, okay, this is a really awful disease, let's go ahead and use cyclosporin here. But the data to say that it's safe and effective was done for the easier transplants. So --

DR. SALOMON: I think you have to recognize there's a transition here and there's a time when you demand these really rigid wonderful randomize prospective trials and no one is going to sit here at the table and not tell you how great they are. But there's also a time when you've got to relax and you've got to just allow an outcome parameter like the patient survived, or the patient didn't get GVH, or the patient didn't relapse. The patient engrafted better.

DR. SIEGEL: I understand that. Obviously different standards apply for

different types. What I don't understand is this notion of one parameter. We've seen --

DR. VOSE: There is no one parameter.

DR. SIEGEL: We've seen really extensive excellent T cells depleting in the IND phase programs where you see no Graft-verus-Host Disease but a tremendous problem with engraftment rate.

DR. O'REILLY: But that's gone. I mean, that's really old. I think that's really become old. I mean, when Jean's talking about these haplotype disparate grafts, or when I'm talking about the haplotype disparate grafts. If you gave an unmodified marrow transplant from a two antigen disparate individual, your risk if graft rejection right now is in excess of 15 -- 12 to 15 percent. That's the Seattle series, and there have been several series to show it.

So if we're talking about something

in the 10 percent or 10 to 15 percent, we are not talking about an increased incidence of rejection. What I would say is, we're now with that TBI thyoteposide with ATG or ara-C or ATG, the fact of the matter is we are now at a point where the issue of graft failure following T- depleted transplants should be moot because it's really largely over.

The GVH issue remains because not all T-cell depletions are equivalent either in removing Graft- verus-Host Disease or how they deal with, for example, whatever contributes to leukemia resistance. And I still think that there are big issues in the haplotype disparate grafts that we -- you know, there are other fine tunings that are going to make for long-term survival, not the least of which is, you know, how do you choose or what kind of disparity do you have to get around some of these infectious problems.

DR. SIEGEL: But what you are

suggesting, if I understand it, is that the issue of graft failure. We can establish the safety vis-a-vis graft failure --

DR. O'REILLY: We can establish --

DR. SIEGEL: -- on the basis of a historical expectation we know what range of graft success we can now expect. And if a new product falls in that range, we can be relatively comfortable.

DR. O'REILLY: Yeah. We're getting not completely -- and I recognize you're hearing this from a guy who has really been a stomper, you know, in terms of aggressively trying to avoid some of the issues of the definition of the stem cells because I fundamentally agree with certain people such as Fred Rosen, Harvard, who says, "I've never seen one."

I don't know what a stem cell is. But what --

DR. SIEGEL: There must be some in that bag there.

DR. VOSE: They're in there somewhere.

DR. O'REILLY: But I do think that you take the cord blood, the T-depleted transplants, all these ones, you're getting some fairly reasonable sort of universes in terms of inadequate dose on the one hand and then for after the adequate dose you're talking about what is the kind of cytoreduction that's required to get one of these grafts in. You can take those kinds of things and put those together. And from there you can move and test the device or a technique. I really think we're getting there. And we're close. There may be some mild modifications, but I think we're pretty close there.

DR. VOSE: How about this as a possible suggestion. If we want to test it in a randomized fashion to consider testing it in the matched unrelated setting and then to do it with a package deal of phase II

trials in the haplo setting so that you show efficacy in both types of settings, but you only have the randomized trial in one type of setting. What do people think of that?

DR. HENSLEE-DOWNEY: Can you say that again?

DR. VOSE: Well, if you're going to test a device or an antibody or whatever you're going to test to test that in a randomized fashion in a matched unrelated setting. But in order to broaden the possible applications to test it in a phase II setting in the haplo setting to compare it to the historical controls that you're talking about.

DR. HENSLEE-DOWNEY: Right.

DR. VOSE: So that they would bring it as a package to the FDA as sort of a type of a thing.

DR. SALOMON: The only minor problem with that though is, if you have a --

DR. HENSLEE-DOWNEY: With targeted

endpoints.

DR. SALOMON: -- if you have a 15 percent incidence of GVH in the matched, right, sibling matched transplants.

DR. VOSE: No, I'm talking about matched unrelated donors.

DR. SALOMON: Or take matched unrelated, it's still 15 percent.

DR. VOSE: Much higher.

DR. HENSLEE-DOWNEY: No, no, no, much higher.

DR. O'REILLY: 75 percent.

DR. VOSE: Much higher, 75 percent.

DR. SALOMON: That will be fine. If you start with 15 percent you reduce it to 10 percent --

DR. VOSE: No, no, no, no, no. We're talking 75 percent.

DR. KURTZBERG: But I mean, the T-depletion trial ought to be an example of how hard it is to do a randomized trial. I mean, they keep adding centers just to be

able to get to some marginal --

DR. HENSLEE-DOWNEY: But on the other hand, you should still be able to achieve with whatever technology you use, outcomes similar to published outcomes. I mean, that's a part of creating those endpoints.

DR. MILLER: But also the T-cell depleted trial is power to look at overall --

DR. VOSE: Overall survival.

DR. MILLER: -- and what we are saying is whatever trial they do, power to look at more short- term outcomes than to look at the safety efficacy of the device. I'm a little concerned about doing -- transfers because, you know, then you're changing two things. Because in that setting, if you don't T cell deplete, you're going to have to give additional immuno suppressants. So it's not going to be -- the best trial would be cyclosporin or FK506 alone versus cyclosporin FK506 with T-cell

depletion.

Well, if you don't T cell deplete, you've got to do something else in the unrelated transplant.

DR. HENSLEE-DOWNEY: Actually the unrelated trial --

DR. VOSE: Not everybody does that.

DR. HENSLEE-DOWNEY: -- immunosuppression with the T cells --

DR. MILLER: Again, with that unrelated trial you're not testing the device, you're testing methodology. You're testing, quote, "T-cell depletion versus non-T-cell" look at the whole outcome. What a sponsor needs to do is test the device, so you really should change just one parameter and that's going to be difficult to do in the unrelated setting. Like this, you know, getting back to the cell pro trial which was easy to do for myeloma, they changed one thing. It was peripheral blood progenitor cells, you looked at the -- you know, one bag

versus the other bag at the end whether or not how many -- you know, how many myeloma cells were there. You didn't have to change anything else whereas with the unrelateds you'd have to change two things. You would have to add the immunosuppression to one, and T-cell deplete the other which makes it --

DR. KURTZBERG: No, I mean, you would just -- I don't think so. I think you --

DR. VOSE: No, I think you could just do it with having the same depletion, just adding the depletion. I think you could design something to do that.

DR. O'REILLY: But you would have differences in cytoreduction regimens.

DR. MILLER: Right. You would have to have some of the other differences.

DR. KURTZBERG: That's why I'm saying, test it in the context of an already-established -- whether it's Jean or Rich, or Milwaukee or -- I mean, there are

places in this country that do this, and there aren't that many. And that's where you ought to test.

DR. VOSE: I'm not saying not to do that.

DR. KURTZBERG: What?

DR. VOSE: I'm not saying not to do that.

DR. KURTZBERG: I mean, because otherwise you're going to get people who don't do it --

DR. VOSE: No, you should not --

DR. KURTZBERG: -- starting out with new technical --

DR. VOSE: -- you shouldn't do it in places that don't do it, no.

DR. SIEGEL: If I could clarify, you made a comment about short-term versus long-term outcomes. Which are you referring to as the -- I know the long- term are the longer ones, but --

DR. MILLER: I mean, I think T-cell

depletion will affect the short -- the incidence of acute Graft- verus-Host Disease in the 100 day mortality and look at engraftment. And I think, again, that's what we're looking at. We're trying to show that it reduces acute Graft-verus-Host Disease and allows engraftment.

DR. SIEGEL: But I guess I would wonder, and this is what I was wondering is short or long term, in the past the advice we have received is even in therapy is that which did not raise as much concern about immunologic defects such as CSFs, we've been advised that the trial should carry out data at least to the 9 to 12 month range to look at infection rates and immunological reconstitution. I wasn't sure if you were thinking of that in the short term or the long term or --

DR. MILLER: Well, I think that the primary endpoint should be you should probably follow the patients out one year. I

don't think that in this, you know, that relapse is, per se, for these trials the number one endpoint or disease free survival. Because now there's post-transplant -- post-relapse or immunotherapy or different things you can do. And so what you are actually looking for this device is to see whether or not you could decrease acute Graft-verus- Host Disease that will allow engraftment. So I think those are what you should test and then do secondary endpoints for infections or secondary EBB but a short term, and not test the long-term outcome. Because those are the types of questions you're going to ask out of -- you know, more center-directed protocols that are designed to look at that. Not at the device specifically.

DR. VOSE: I think it is important to follow the patients for maybe a year for EBB, you know, for lymphoproliferative disorders and infections, but I think what

we're saying is you don't have to say five-year disease-free survival. Yeah, something like that.

DR. O'REILLY: I also think in this regard I think as far as I understood it, the role of the FDA is to protect the public. That's what they're supposed to be doing.

And, in real terms, for example, in cytokines, you know, if you're looking at this as the retrospective scope, you could look at it in two ways. One would be, you know, do the cytokines do what they're supposed to do in terms of simulating a cell? You take GCSF or GMCSF, do they simulate the cell? The fact is they do. Can they, as a result of that, potentially reduce infections? The answer there was yes.

Now, based on that, fortunately those guys got licensed. But if it were the issue, does it alter the disease, the fact of the matter is, these cytokines are supportive care. They don't necessarily alter the

outcome of the disease. Would it be appropriate for -- there were several in the FDA who actually raised this that that's what they should do. In other words, you should give GCSF and the only basis for its being approved would be that it improved long-term survival. And I think somebody argued successfully, hey, that's not -- test it.

My own read of it is, if it's not really useful in the long run, the marketplace will tell it pretty quickly, and it just will be abandoned. However, in the process you now have agents that in several circumstances are of extreme use.

DR. SIEGEL: No, I think that's a -- actually the one part I don't know is correct is what positions may have been taken many years ago in the agency, but with the support of this committee, our position with the CSFs and consistently has been that those therapies which are adjunctive to hematopoietic transplantation need -- which

includes some of the ones we're talking about here, including a few cell depletion -- need to assess their impact on hematopoietic transplantation. And the issue of their impact on the underlying disease, actually the advice of this committee in the past has been -- and the one that we continue to promulgate is that if in studying the impact on transplantation one powers a study out of it to do that, say 100 to 150 patients, one must capture -- one should capture the outcome of disease of recurrence relapse rates on those patients as well. But one need not power the study to exclude a given size of adverse effect except potentially in exceptional cases where specific concerns might rise like this committee originally mentioned concerns about the abilities of GCSF to stimulate myeloid leukemias and that approval didn't occur until there was specific evidence excluding the possibility of a large effect in that regard -- or a

substantial effect.

But I think that does capture where we're going and I think that is, unless we hear otherwise, and I haven't heard otherwise what we're looking for here. The realm of things including immunological reconstitution engraftment, you know, infections, and Graft-verus-Host Disease, but not tumor outcomes. There have, in the past, however, been concerns expressed from this committee about the impact on Graft-verus-Host Disease leukemia effect in particular, I guess, in the allogeneic setting.

And is what we're hearing that -- what are we hearing -- let me not guess, but let me ask about that. What would it take theoretically to make sure that you weren't adversely impacting that and what is it reasonable that -- because, you know --

DR. HENSLEE-DOWNEY: The most important thing --

DR. SIEGEL: -- what sort of data

are you going to want see when you see these products to make sure that you're not --

DR. HENSLEE-DOWNEY: The most important thing would be a consistent patient population. Because the disease and the status of the disease is going to be more powerful, particularly probably in the use of alternative donors than perhaps T-cell depletion will be.

So you'll have to study the exact same patients if you wanted to ask it in a randomized trial.

DR. KURTZBERG: And when you're first testing your device, you're not going to look at your easiest patients to study that, you're going to look at your poorest patients. And essentially get a negative answer with that group.

DR. HENSLEE-DOWNEY: So I think that's probably an unrealistic goal to expect to answer those questions in these trials that would be really looking at developing

technology that could facilitate transplantation.

DR. SIEGEL: It would follow then that if the trial were done in a less homogeneous population where you couldn't assess that, although those questions would be outstanding, you're saying that if that trial demonstrated a reasonable impact on engraftment parameters that that ought to suffice if nothing jumped out in terms of an adverse problem.

DR. VOSE: But that's sort of if you did have a lot of different patient populations in a trial like that, they need to be balanced for those, I think is what Jean is saying, so that you're not, you know, putting all the bad patients in the T-cell depleted arm, for example, that wouldn't be appropriate.

And the other issue --

DR. HENSLEE-DOWNEY: Well, you even have patients you can just ask the question.

DR. VOSE: Right.

DR. HENSLEE-DOWNEY: And one of the ways you can do that is you can look at even the data in matched sibling donors. If you're relapse rate is not outside of the sort of range that you would expect relapse to occur in the matched sibling donor setting, then you don't need to really raise your eyebrows because that's a feature of the underlying disease.

DR. VOSE: One other issue I just wanted to bring up too that we didn't really discuss was that I think any trial like this needs to have a quality of life component as one of the important endpoints, too.

You're smiling, Jay.

DR. SIEGEL: Oh, we've been in the midst of -- in totally unrelated situations and diseases there's a great deal of controversy at the present time as exactly what quality of life means and how you establish a --

DR. VOSE: Speaking from my own from my own viewpoint and from these guys, I'm sure they'll tell you that the quality of life of some of these patients that have bad Graft- verus-Host Disease is awful. And so I think, you know, that is an important endpoint in this kind of patient population.

DR. KURTZBERG: But you're looking at a much later endpoint. I mean, I think --

DR. VOSE: That's chronic.

DR. KURTZBERG: -- if you want to get devices into the marketplace so they can really be worked out and tested, then you want to look at short-term endpoints, acute GVH engraftment and 100-day infection rate.

DR. VOSE: Right. But even acute GVH, I mean, there's quality of life issues with that as well.

DR. KURTZBERG: Yeah, but I don't know that you have to do special measurements because you can measure bilirubin and stool volume and rash for a lot less money and get

the same information.

DR. VOSE: I think it's important personally.

DR. KURTZBERG: I think later when you do, you know, the phase II kind of trials and phase III trials you measure that. But that's not where this would be.

DR. VOSE: Well, we're talking about a phase III trial. We're talking about a randomized trial. So that would be.

DR. O'REILLY: Well, you know, I think one of the issues that's going to come up would be if you -- if you assume that there was equivalency, and I don't think that that's going to be the case --

DR. VOSE: Equivalency of?

DR. O'REILLY: Let's say T-depleted versus unmodified would be -- in the haplos they're not going to be equivalent, I mean, that's not an issue. But, I mean, even in the matched sibling, if they were equivalent, then the quality of life circumstance you

would really need to develop the kinds of useful parameters of quality of life that everybody can agree to. That has been the real bugaboo and I think that that's what you're saying. They're very loose, unfortunately, that's the problem. They've been cited in several papers, but they become very loose.

My own read of it is though that in terms of issues like acute GVH and other things, if T-depleted grafts are going to be good in the long term, and I think they are, and certainly in certain diseases they are sort of almost like a treatment of choice, then, you know, I think that in very real terms they should be able to do it and not just on that.

DR. SIEGEL: I guess in part this question is -- we've been having a very useful discussion that moved all around the actual formal questions we wrote which is fine. In part we're getting to some of the

issues in number three which is less whether you have an integrated measure of quality of life, but how you do integrate different outcomes. If it's anticipated in a certain setting that the patients on the treatment arm may have less Graft-verus-Host Disease and say more infections, or a worsened outcome in terms of engraftment rates where we faced this situation before and it's often very difficult to figure out how to integrate that. I'm not sure there's a way to answer those questions prospectively. Sometimes you almost have to, you know, look at it and then we come back to you and you say, well, why did they design the trial that way -- or done a different trial.

But I wonder what -- are there specific comments on how to look at all of these parameters? It's easy if one thing is better like Graft-verus-Host and everything is the same or better or equivalent within height statistical bounds. But any

particular thoughts about the tradeoffs that are appropriate or reasonable in these settings?

DR. AUCHINCLOSS: Well, I think in that context I guess I'd sort of like to go back to this graft versus leukemia effect which I got the sense everybody was sort of pooh-poohing. To me it was --

DR. O'REILLY: No, no, I mean, certainly from my standpoint, no. The allo effect is very real. If you look at the instance of relapse following a congeneic twin graft in AML and first remission, at 60 percent, that's what it is.

DR. AUCHINCLOSS: I mean, that to me would be the critical issue in a T-cell depleted graft is what is going to happen --

DR. O'REILLY: And all that has come out of where we're at is -- and all we're saying is that it goes beyond the allo effect of GVH because the incidence of relapse remains extremely low in the acute

leukemias. In CML, on the other hand --

DR. AUCHINCLOSS: That you can separate the two?

DR. O'REILLY: Yes. I understand that and I believe that's true. But it's something that you need to actually -- I think it's the most important variable in this mix of what you're trying to determine out of --

DR. AUCHINCLOSS: I agree with that.

DR. KURTZBERG: I'm concerned that the infrastructure isn't in place to answer all these questions. I don't think they're bad questions, but this is years ahead of where the field is.

DR. O'REILLY: I understand that.

DR. KURTZBERG: And if this is what the requirements are going to be and they're noble, then how are they going to be funded?

DR. HENSLEE-DOWNEY: How do you get the right patients?

DR. O'REILLY: See, one of the things I'm also -- part two of the questions to be asked was, you know, the issues of covariates. I'm also really interested in what the feeling of the group would be now vis-a-vis the kinds of patients that we do. Because one of the biggest covariates that we have is the stage of disease. And right up to now the haplotype disparate grafts are in a position where at least you're saying you got a lot less GVH than you would expect in the unmodified grafts. The incidence of engraftment is certainly within the realm of what you would get with in a modified graft, but the results in different groups basically reflect the risk categories that we're talking about. And the fact of the matter is if we gave an unmodified graft now to the high-risk cases that Jean does or I do, long-term disease-free survival is 10 to 12 percent if it's that. So is that our equivalence rate, or do we basically say

perhaps what we really should be doing is really looking at this in, you know, earlier disease. When in real terms we can -- and that was one of the questions that was raised before. And I think that that's a really important one.

There are downsides to it, but there are also some big upsides in terms of being able to see a meaningful result. That it's not quite so tarnished by the vagaries of the patient's disease or the prior therapy which so oftentimes mixes things up.

DR. VOSE: That's why I think you should do the little bit better population in the matched unrelated setting and then for the phase II trial that you guys, you know, are talking about in doing to do that with the poor-risk population and then if they come with both of those types of populations into a separate type of trials, then that looks a little bit at both of those issues. It's a difficult question, I don't know.

Sure. Please identify yourself.

AUDIENCE: Mike -- Nexell. One of the things that we're seeing with the technology as it improves is the ability to deplete T cells to the point where folks are adding back to the graft -- graft engineering. And I didn't want to leave today without throwing that out for discussion since what people add back to the graft is going to be independent of my ability to deplete T cells. And I think it gets back to the system depletes T cells then people are going to engineer graft for the graft failure issues or the GVL. And I think that's got to -- we're going to be faced with that in trying to run a trial in unrelated donor setting where they're going to be concerned about that.

DR. SIEGEL: Actually that opens up sort of an aspect of -- I think it was in one of our questions, the first question regarding differing in the amount of T cell

depletion. One design that's been discussed, I wonder how the committee would react to this, would be using the same device, either using it more or less intensively or with various add back to do a controlled trial where you gave a graft with different amounts of T-cell depletion both being within the realm of what's considered acceptable, potentially acceptable for whatever disease and a degree of matching your treating, but then through that comparison being able to show that substantial difference in the amount of T- cell depletion had significant impacts on Graft-verus- Host Disease and/or other parameters in such a way that one might be able to conclude in combination with comparison to historical expectations that one or both regimens was a particularly useful regimen.

DR. AUCHINCLOSS: I read that portion and I found it very interesting because it seemed to me the logic of it was

to start with the assumption that the device works and then see if you can find some number at which the device doesn't work. And I wasn't sure that that's an appropriate way to run a trial.

DR. HENSLEE-DOWNEY: I have a concern too. And that is reading what you've provided to us is that there's sort of an assumption that already we know that we should go to the peripheral blood compartment to obtain haploidentical cells. And I don't think in any way we're there. And perhaps before you can ask any of those questions, that might be a very good question to ask. To what extent is the marrow and the peripheral blood different and how does it demonstrate that in a haploidentical recipient? We don't have those answers at all.

DR. MILLER: But that's the responsibility of the transplant community not the FDA or the sponsors to show whether

peripheral blood or bone marrow is better.

And I agree, I have a hard time with the -- you know, with the assumption of trying to find a different level of T cells. Because the only way that it will work is that if the one -- to show that you can get the drug approved if the one is better than the other. And you're never going to get anybody -- I mean, if the one is clearly better than the other, can you then extrapolate to zero? I think that's really pretty dicey.

DR. WEISS: There are a lot of study designs though were you an just do dose response. And we had it all the time in conventional drugs where you have maybe slightly better efficacy results at the expense of a little more toxicity and dose rate designs -- I mean, Dr. O'Fallen has been very quiet. And, you know, there are -- the comparisons are maybe not as great sometimes between those and actually more conventionals

do have a, you know, control arm, a high dose and a low dose for instance is much more conventional -- to see. But you can do things with several -- you know, at least one or more different doses and doing some comparisons on looking at dose responses. And it isn't always one works and one doesn't, and it always, you know, deluding ourselves that we're giving something when really we're actually giving somebody basically nothing. It's really the idea that you're having a range of responses.

DR. MILLER: I think the more interesting thing would potentially be something like they're doing potentially had donor in their sequential studies at Sloan Kettering, just do the first step and then compare the first step with one plus two. And then if you feel you had reasonable data with the one step, adding the second step to see if it's better than add T-cell depletion with equivalent engraftment. And that may be

like --

DR. O'REILLY: Yeah, that may --

DR. MILLER: Could you do that, do you think?

DR. O'REILLY: -- that's potentially possible. I mean, one of the issues that has come up with us with regard to the doses is that in terms of the assay systems we have now for looking at, for example, doses of T cells in the matches we got a fairly clean circumstance, but what I'm disturbed by is that in the haplotype disparate or unrelated it's not. They're all, you know, those who do and don't get GVH are in the same universe. And until we really have a much cleaner view of what is the actual alloreactive cell, we're a little caught, you know, several groups have also looked at, for example, HTLPs and CTLs precursors, and assays in an attempt to quantitate these and to then correlate that with Graft-verus-Host Disease. And thus far

they've gotten again kind of mixed grill results unfortunately.

In the unrelated circumstance Carolyn Keeber has been with us and is the co-author of the LDA studies looking at the mixed T cells when she tried to look at this for host-specific CTLs or host-specific HTLPs thus far the clear correlations have not been there. So I think a dose response approach can be used. We're using it late after the transplant and I think that that really has offered us some real options because late after transplant the potential to induce GVH is considerably different from the time up transplant. And that has opened up some real possibilities. Whether that's going to be possible in the mismatched graft, my own bet is it will not because it just takes a few alloreactive T cells to do the job.

I would like though, you know, this issue that was raised before with regard to the issue of a T- depleted transplant, and

what do you do to it is going to be sort of thought about. And I think it is a real problem because in the one -- what we're caught by is you've got a huge number of industrial groups now that have different techniques that potentially can produce good T-cell depletion that want to get into clinical trials and people want to actually get to do the trials. But the next step is not just the T-cell depletion, the step is going to be T-cell depletion for example plus genetically modified effector cells that are in fact overt alloreactive T cells that could be used to actually induce a control GVH response where you can eliminate those cells but those cells could allow you to get grafts in.

And that's going to -- I think that the options now are extraordinary and the query that we have to get to is exactly what Hugh said and Carole is saying is we have to get some sort of a system that allows us at

least to have a biological readout which will at least give some kind of a -- you know, even something like a tentative approval. I don't know, at least to the point where, you know, someone can sell them and someone can actually pay for them. I mean, like a center doing trial could actually because I can't do this on philanthropy.

DR. VOSE: It is a problem because we're always trying to be one step ahead and the approval is always kind of ten steps behind. So, I mean, it's a problem. I agree.

MR. VANEPPS: Dennis VanEpps from Nexell as well. I just wanted to reiterate some things that Mike had mentioned here from the company side. I think we're in the position now where we -- in much of the recent data that we have that we have a device that will virtually eliminate the majority if not all -- close to all the T cells. The problem is that what I heard here

is that we're trying to get to the point where we can manipulate the T cells population.

Now, it's much more difficult to try to make a device manipulate the exact number of T cells that you want to have harvested in the final product. And ultimately what happens is, just as you had mentioned here, Rick, that you're going to be adding bad T cells at some point. And you can control the number of T cells that go back in. That really becomes a T cells therapy, I think, outside of the device.

And I get back to the issue of the device is designed to remove the T cells that allows you now to do the T cells therapy. And so, if that's the purpose of the device and the cells will you allow then to do an efficient transplant and get reasonable engraftment comparable to what's done now, then I think the rest of everything that goes beyond that, then the T cell therapy is

really a totally separate issue and really is the future of all the studies that will go on beyond having the device approved. Obviously a biased opinion on my part, but that's --

DR. MILLER: How are the cell therapeutic machines regulated? I mean, why is T-cell depletion devices, if they're actually used, just to separate out these cells different from like the code spectra or something like that and who -- which we also take the cells out and sort of manipulate them back. Is this considered different because we're -- it's sort of part of a process as compared to just getting us a population of cells?

DR. SIEGEL: I can't tell you specifically about the device to which you're referring other than I would be very surprised if it's not an FDA-regulated device. It could be regulated -- yeah, some devices are regulated in the Office of Blood some in the office you're with which is the

Office of Therapeutics because of their -- of where they're used and how they're used and some in the center for devices. They're all regulated, however, under the same laws pertinent to the regulation of devices.

DR. MILLER: So I think we're a committee that's used to looking at -- or physicians or groups that are very much more used to looking at drugs which is much easier and that's why I was sort of wondering whether that committee -- how they deal with that like the sponsor is saying, you know, this device we give you a product, what you do with the product is then your decision. Tell me how good --

DR. SIEGEL: Yeah.

DR. MILLER: And that's, I guess, what the hematologic products do, they say, okay, how well can you collect out the platelets. What you do with the platelets after that is up to you.

DR. SIEGEL: That's actually not

correct. Platelets are also an FDA-approved product. They have to meet performance standards and --

DR. MILLER: But for qualitative. You don't go in and see -- you don't have to give them back a -- so the patient doesn't bleed. You don't have to show that you have a product that has the --

DR. SIEGEL: If you were to make a new preservative solution for platelets a new way to store platelets, a new way to freeze them or whatever, the requirements on those platelets would involve parameters to establish that you still had an effective and safe product whether that efficacy would be determined by in vitro or by in vivo studies, by bleeding rates or petechia or aggregation rates, I can't tell you and it probably varies depending on the issue. But they are a valuation for efficacy as well as for safety.

And devices in general are --

although there is some difference in classifications of devices there are certain types of what are considered low-risk devices setting intravenous tubing which may not require the same sorts of clinical trials as certain types of -- like I say, cardiac bypass pump might.

I think your point is well taken that this committee, as compared to other committees, just as these regulators at this table as compared to some other regulators have less familiarity with the regulation of devices than with the regulation of drugs and biologics and that does raise complex area issues.

I can assure you that we are in constant and regular contact with our colleagues who regulate devices on a regular basis. I personally meet on a monthly basis with my counterpart office director in the Center for Devices so that you hear interpreted through me, you know, when I'm

talking with you about what are the standards -- what a device does or doesn't have to show. We hope that we are applying those standards and those laws in a level and equal way. It's a constant issue and requires attention. And I think we recognize that it's difficult for this committee to, you know, even for issues that don't come up as often, say, as accelerated approval if we deal with the drugs committee to understand the legal ramifications for that and how to apply it can be difficult. It gets more difficult with devices, on the other hand, most of the device panels don't have anything like the expertise in transplantation that one finds in this committee. So we get our advice where we can.

DR. VOSE: Are there other questions that we haven't talked about that you would like to discuss? I mean, in the other two questions we kind of discussed in --

DR. HENSLEE-DOWNEY: One of the questions that you did write down, number two, had to do with whether you did try to conduct a trial or oversee a trial that used the IBMTR experience as a historical control. And you asked about what kind of covariate would be important. And I did write down a list of -- that I would be glad to share with you if you would like me to.

DR. VOSE: Well, do you think it's appropriate to do IBMTR as a control for -- for what?

DR. HENSLEE-DOWNEY: That's another question.

DR. VOSE: Well, no, why worry about the covariate --

DR. HENSLEE-DOWNEY: Ask this question and I responded to the --

DR. VOSE: There's no sense worrying about the covariates if you don't think that's adequate control.

DR. HENSLEE-DOWNEY: That's true

too. And I think that the list of covariates is long enough that it is going to be very hard to go in and find those matching in the IBMTR historical bank so that it's probably unrealistic, I think I could answer it that way.

DR. SIEGEL: Are you suggesting then that it would be preferable to do randomized-control trials in all of these indications and settings?

DR. HENSLEE-DOWNEY: No. Actually I thought it would be preferable --

DR. SIEGEL: Well, don't bother, because there's no way we'll ever know. I'm sorry. I don't want to put words in your mouth, but if we're not going to have an internal randomized control group -- external control group. And you're saying that the IMBTR is not a suitable one.

DR. HENSLEE-DOWNEY: It's going to be a very difficult one, very difficult one to get the right -- to be able to match the

right covariate so that it's a meaningful historical control group.

DR. SIEGEL: Yeah.

DR. HENSLEE-DOWNEY: I mean, you could make an effort at it, but it's going to be hard.

DR. MILLER: I mean, that's why I asked the question at the very beginning. Do we have a control group that -- you know, does anybody have a comparable control group because if we -- I think I feel very comfortable with the fact that we have a control group that you have confidence in that you compare then you don't need a randomized trial. But you have to have something. And I asked a question that came around from the very beginning is that there wasn't that --

DR. SIEGEL: Well, it sound to me, from what I've heard from many of you, including the presentations, is that we saw this in some when we -- I think coming from

your institute Dr. -- talked about mobilization that what has commonly been done as a control group is the most recent prior series in the same institution which maybe has the same conditioning, variable --

DR. HENSLEE-DOWNEY: Right. Exactly.

DR. SIEGEL: -- but you change one factor at a time.

DR. HENSLEE-DOWNEY: And I think that potentially could be done.

DR. VOSE: You know, I think that the problem --

DR. HENSLEE-DOWNEY: Because there's less changes. I mean, even though there might be a new great infectious disease drug that might come along and save a few more patients in the new series. But still the changes happen very slowly in reality.

DR. VOSE: The problem with --

DR. SIEGEL: -- are better controlled than in external --

DR. VOSE: Yeah, the problem with the IBMTR is that most of the data is old data and it is from multiple different institutions and the data is not as well collected as a single or two centers for example. So I think that suggestion of doing the immediately prior, you know, historical control at an institution --

DR. O'REILLY: You know, you could however do a little bit a preempting here because I do think at some time down the line in the not too distant future the trial will be, for example, the haplotype two or three antigen disparate graft versus the unrelated graft. Okay.

DR. HENSLEE-DOWNEY: That's what I --

DR. O'REILLY: And my own read of it is that the NMDP database is a pretty tight database at the present time. Certainly the National Heart Lung and Blood trial is a very, very --

DR. VOSE: That trial is good. I'm not sure that the NMDP is quite as good.

DR. O'REILLY: Okay. But I agree with that. But even in that group that might at least give you some kind of background data these are the effects of age, disease, stage of disease in terms of long-term results.

DR. MILLER: Actually, that is a potential control group. You could potentially use the -- I didn't think about that. You couldn't potentially use the methyltracsate cyclosporin on that randomized trial as the largest group of patients with -- or unrelated transplants collected in a similar way to use if you want to compare unrelateds with a T-cell depletion one T-cell depletion method, I guess.

DR. O'REILLY: Yeah, it's not going to give you the absolute clean thing, but it would certainly give the FDA at least some sense of security that in fact insofar as

historically, for example, the incidence of grade II to IV GVH in a matched unrelated donor recipient pairing is roughly equivalent to what you have with a two antigen disparate within the family. Now, that may shift as we get into better attuned typing. But still in all, if you had something close to equivalents or somewhere in that, or you were looking favorable in comparison to that circumstance, you would probably be able to feel relatively secure that certainly the public was being well served.

And that's a reasonable one.

DR. O'FALLEN: I'm finally going to weigh in then. I thought we had someone made a position statement earlier that the historical controls were really out of the question because we were faced with an environment here in which things are changing so rapidly and I was awed by the three presentations to exactly that same position. So if we're going to start saying positive

things about historical controls, I have to wake up here and weigh in.

I think they are just fraught with all sorts of problems. The idea of doing these little stage-wise studies, that's just wonderful. And you're doing the best job you can do of having not quite concurrent controls by doing that. But if you're going to mount a moderately large study with the kind of framework of a clinical trial, but trying to use historical controls, I don't think that that's got a chance.

DR. O'REILLY: My only point on that though is, I think it does give you a framework and it would provide you with a reasonable approach to the construction of stopping rules within trials.

DR. O'FALLEN: Oh, that's a completely different thing. I agree with it completely. Of course we should use every piece of information we possibly can and even to going to the point of having the -- I

think someone suggested earlier, a panel of experts get together and decide what targets we ought to be having for what could be equivalently a phase II kind of study to see if we can even approach those targets. It's not a complete replacement for a randomized clinical trial, but at least it's a real organized systematic way of taking advantage of all the data that you can to come up with some targets. But it isn't letting someone choose their favorite historical control group or their favorite registry group to decide what their own favorite target is. It's quite a different picture.

DR. VOSE: Chris, the NMDP database is the same as the IBMTR database for those particular patients. They share information so -- it's the same thing.

Other issues or questions that we didn't talk about, anybody wants to talk about?

DR. SIEGEL: There's one -- I do

think you raised -- in fact, I understand Pat has come up in some discussions with sponsors which would be a developmental program in which perhaps in some settings in which T-cell depletion is considered more optional, for example, I guess matched or nearly matched unrelated, there be control trials with the possibility of extending observations with -- through externally controlled trials in some settings in which it would be difficult there or impossible to do a non-T-cell depletion. Is there a general feeling in which case although if in fact in the second -- the latter case it was impossible to get data other than historically controlled you would have in support of that the control in the other setting which would lend some, I guess, intellectual credence to any conclusions you might make about impact of Graft-verus-Host Disease; is that a correct understanding of what was proposed? And is that a type of

package that people might -- that this committee -- after all, what we're talking about ultimately, you're going to see the results of these trials and we recognize that perfect trials undoable and there's always parts of the data that come in that we're going to be unhappy with. Is that a type of package there's thought would be a --

DR. VOSE: I think that's about the best you're going to be able to do under these circumstances.

DR. SIEGEL: I'm not suggesting that there's only one way to do that or that we would make that a requirement.

DR. VOSE: And then you could use, you know, the most recent cohort from other institutions to compare to -- in a loose way to the phase II haplo portion of that.

No more questions? Comments? Okay. Thanks to everybody for coming.

(Whereupon, at 3:30 p.m., the PROCEEDINGS were adjourned.)

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