DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

60TH MEETING

Volume II

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C O N T E N T S

P R O C E E D I N G S

Opening Remarks

DR. SMALLWOOD: Good morning, and welcome to the 60th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. Yesterday, I read the conflict of interest statement pertaining to this meeting. Those procedures still apply to today's meeting. If there are any declarations that anyone needs to make regarding conflict of interest, would you please do so at this time?

Hearing none, we will proceed with the agenda as printed for today. Please note that we do have a full agenda. We are trying to end at the time that is scheduled, no later than 3:30. We would ask all of those individuals that are presenting, would you please be mindful of the times that have been given to you for presentation? We will try to assist you in remembering. I will announce, at the time of the break, the order of presentations for the open public hearing.

At this time, I will turn the proceedings over to the Chairman of the Committee, Dr. Blaine Hollinger.

DR. HOLLINGER: Thank you, Dr. Smallwood. Well, we have a single topic today, which is a very important one to the blood banking industry and to the patients as well, on leukoreduction of blood components. There are many

issues about the efficacy of this, and that is what we are going to try to deal with today.

So, we are going to begin this morning with some background and summary by Dr. Lee, who is Chief of the Blood and Plasma Branch, Division of Blood Applications. Dr. Lee?

Routine Leukoreduction of Blood Components

Background and Summary

DR. LEE: Thank you, Dr. Hollinger, and good morning.

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Leukoreduction is a topic with which the FDA has been concerned for several years. With increasing awareness of the risk/benefit ratio associated with leukoreduction of transfusion and blood components and the consequent increasing interest in prestorage leukoreduction, which had at one point been a bedside procedure as the practice of medicine, moved into the arena of blood product manufacturing and came under the regulatory jurisdiction of the FDA.

In order to reach public consensus on how the process of blood leukoreduction should be regulated, the FDA brought the issue to a public workshop on March 22, 1995, on the NIH campus. At that workshop, a series of then the state-of-the-art presentations from many distinguished speakers included Drs. Walter Zeik, Mario Cuscol, Susan

Lightman, Naomi Lubin, Mark Popovsky, Sherrill Slichter, Ann Anderson, Ed Snyder and Ms. Nancy Heddel, of whom Drs. Snyder and Popovsky have graciously accepted the agency's invitation to again serve as key speakers today.

On a more specific note, the effectiveness of leukoreduction in the reduction of the transmission of cytomegalovirus through blood transfusion relative to the use of CMV seronegative units was discussed at the 56th meeting of the Blood Products Advisory Committee, at approximately this time last year, in order to achieve public consensus on one of the leading indications for using leukoreduced blood components.

Today, we meet again to discuss the topic of leukoreduction in yet another context, a context that deserves a few words of explanation in order to make sure that all presenters, committee members and members of the audience have a precise understanding of the issues and operate off of the same page.

As the opening speaker this morning, I would like to spend approximately a half hour to provide the regulatory background as well as an overview of this morning's presentations. The question to be presented to the committee will be shown before the presentations so that the committee members have the best opportunity to analyze the data during the presentations with a specific goal in mind.

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First, I will present the specific leukoreduction issue as defined by the agency, along with an explanation as to why the issue became important to discuss publicly at this time.

As has been pointed out several times yesterday, this Blood Products Advisory Committee is only one of several venues available to the agency in developing public consensus about the safety and efficacy of blood and blood products. If the issue and the question for the committee as presented today appear partial and/or incomplete, please be reminded that today's discussion on leukoreduction is only a part of a broader issue, and also limited to scientific aspects.

Second, I will describe the current regulatory status with respect to the indications for leukoreduction, as well as current product availability and use of leukoreduced transfusion and blood components.

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Third, I will present the single question for the committee, the essence of which is summarized in the six words shown here: Should the FDA recommend universal leukoreduction?

Last, I will present a brief overview of the forthcoming presentations. Of course, a detailed scientific

analysis of leukoreduction with respect to its clinical benefits, manufacturing issues and adverse effects, as well as international perspectives on the subject will follow from the respective experts in the field.

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So what is the issue? Simply put, the issue to be debated today, as defined by the agency, is should the FDA recommend universal leukoreduction? That issue assumes the following obvious points, to be made even more obvious by my pointing them out on this slide:

Firstly, the term leukoreduction as used today refers to routine leukoreduction of every blood unit as an integral step in the manufacturing of blood components. The term, however, does not presume prestorage leukoreduction, and poststorage leukoreduction would remain an alternative acceptable to the agency.

Secondly, the term applies only to non-leukocyte blood components, in other words, to red blood cells, platelets and whole blood that are intended for transfusion. As we heard yesterday, peripheral blood stem cells and granulocytes are beginning to emerge as therapeutic blood components for which the indiscriminate reduction of leukocytes is clearly inappropriate. Likewise, there is no reason to leukoreduce blood components that will undergo further manufacturing into finished products.

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Lastly, the term leukoreduction as defined by the agency refers to the product specifications, process controls and validation requirements outlined in the 1996 FDA memorandum on the subject of leukoreduction.

So, why is the FDA addressing this issue today? For different reasons, many national blood authorities have recently moved to or are moving towards universal leukoreduction, and a growing list of such countries includes the United Kingdom, Ireland, France, Portugal and Austria in Europe, and Canada in the North American Continent.

Discussions among the national regulatory authorities suggest that U.K. has adopted the policy as of July 1998, primarily in response to new variant Creutzfeldt-Jakob disease; France, as of April, for HIV and single case of new variant Creutzfeldt-Jakob disease; and Canada, as of February, for platelets only and not for red cell concentrates or whole blood, after considering the overall general benefits and the cost issues. Austria has not adopted a universal leukoreduction policy, except for the voluntary leukoreduction by the Red Cross in Vienna. Ireland and Portugal are currently considering the policy, as is the United States beginning with this meeting today.

With the goal of providing timely and optimal

regulatory guidance, the FDA intends to thoroughly examine all relevant aspects of leukoreduction, and hopes to compare and contrast the situation in the States with that in countries that have already moved towards universal leukoreduction.

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The FDA plans to develop a public consensus with respect to the universal leukoreduction policy by first examining only the general clinical risks and benefits, and only from a scientific standpoint, a task with which we are engaged at this meeting today.

As a first step, the issues of new variant CJD, cost and blood availability are not the focus today, and should not be discussed beyond the extent necessary to place today's discussion into proper perspective. The outcome of this meeting will guide the agency in making concrete preparations for subsequent potential public discussions. The issue of universal leukoreduction in the specific context of new variant CJD is currently under active consideration as a topic for a meeting of the Transmissible Spongiform Encephalopathy Advisory Committee, tentatively planned to be held on December 18, 1998. The issue of blood safety as it relates to universal leukoreduction in the socioeconomic context of product, cost and availability may be brought in the near future as well before the DHHS

committee bearing the same name, the Public Health Service Advisory Committee on Blood Safety and Availability.

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Having shaped the issue, hopefully, I will describe the current status of regulating leukoreduction or, more precisely, regulating leukoreduced blood components. Over the last 50 years, the benefits from transfusing leukoreduced blood components have been increasingly appreciated.

Today, leukoreduced blood components are used most commonly for three indications. One, to eliminate recurrent FNHTR, or febrile non-hemolytic transfusion reaction; two, to reduce the incidence of HLA alloimmunization of the transfusion recipient that may contribute to the patient's potential refractory state against platelet transfusions; and, three, to reduce the incidence of transfusion-transmitted cytomegalovirus infection under relevant clinical situations.

We have the good fortune of having Dr. Ed Snyder to scientifically describe these indications in detail. For now, it is sufficient to state that of these, only the first indication, the elimination of recurrent febrile non-hemolytic transfusion reaction remains as the only FDA-approved indication today.

This limited labeling claim approval status

resulted from the way in which the agency shaped its regulatory approach through public consensus building. When leukoreduction became a product manufacturing step, performed by blood centers and transfusion services, the FDA sought guidance about this regulation by sponsoring a public workshop in March, 1995, as I mentioned earlier. The agency based this May, 1996 memorandum, entitled, "Recommendations and Licensure Requirements for Leukocyte Reduced Blood Products," directed to all registered blood establishments, on the comments generated at the workshop and subsequently received from the transfusion community.

At that workshop the participants strongly supported the FDA's not approving specific indications for using leukoreduced blood components as such an approach was seen as potentially interfering with medical practice. As a result, the leukoreduction memorandum outlined recommendations for product specifications, control procedures and process validation in manufacturing blood components only.

Despite this initial approach of not approving specific indications with the intent of not interfering with medical practice, the blood industry subsequently sought FDA approval for specific indications through the agency's approval of the language contained in the circular of information for the use of human blood and blood components

which carries the legal status of product labeling. Although the FDA is well aware that the reduction in incidence of HLA alloimmunization and CMV transmission are common reasons for using leukoreduced blood components, the proposed specific wording, and the supporting material submitted to the agency to date, have allowed only febrile non-hemolytic transfusion reaction as the approvable labeling claim.

To approve the remaining two indications without an adequate application for licensure and in a manner contrary to the initial consensus achieved at the 1995 workshop, the FDA needs public support to do so. With respect to the indication for CMV, such public support was received at the 56th BPAC meeting in September of last year, at which the committee members voted 8-1 that leukoreduction of red blood cells and platelets to 5 X 10^6 leukocytes per unit or below reduces the incidence of cytomegalovirus transmission; voted 7-1 that leukoreduction to 5 X 10^6 leukocytes per unit or below is not equivalent to the use of CMV seronegative components with respect to the potential to transmit CMV; and voted 9-0 that there is not sufficient evidence to include that all of the methods of leukoreduction are equivalent in their ability to reduce the incidence of transfusion-transmitted cytomegalovirus infection even if the final leukocyte content of 5 X 10^6

leukocytes per unit or below can be assured.

Based on these recommendations of the 56th BPAC with respect to CMV transmission, the FDA may accept the CMV indication as an FDA approvable indication provided that the proposed wording of the labeling claim is consistent with the committee recommendations.

The indication for reducing the incidence of HLA alloimmunization has not been specifically discussed at a public meeting in an analogous fashion, however, reference to this indication in the circular of information has been accepted by the FDA under the following wording: Leukocyte reduced components are indicated for prevention of recurrent febrile non-hemolytic transfusion reactions. These components may be beneficial in preventing HLA alloimmunization and in reducing transfusion-related immunomodulation, but the use for these purposes should be considered experimental.

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The list of controversial indications for leukoreduction with suggestive but without definitive support in the literature appears to be growing and includes the reduction of immunomodulation related to transfusion, cell storage lesion, bacterial overgrowth, viral reactivation, transfusion-related acute lung injury, and transfusion-associated graft-versus-host disease. To this

list we may also add the reduction of reperfusion injury after a cardiopulmonary bypass procedure.

The benefit with respect to these controversial indications may become apparent only after patients routinely receive blood components with residual leukocytes well below that currently achievable, or after data from an impracticably large patient population capable of demonstrating a small clinical benefit are generated. For example, the reduction in the incidence of transfusion-associated graft-versus-host disease may be demonstrable only with residual leukocytes several logs below that currently routinely achievable, or with an unethical and impracticably large clinical study, involving an extraordinarily large number of patients. Since the ill-advised leukoreduction to reduce the incidence of transfusion-associated graft-versus-host disease may mislead healthcare workers from seeking the definitive manufacturing step for this indication, gamma irradiation, leukoreduction, as understood today, is considered to be contraindicated in the prevention of transfusion-associated graft-versus-host disease.

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In terms of product availability, leukoreduced blood components are currently readily available to all patients and physicians knowledgeable about the benefits of

leukoreduction, as are blood components that are not leukoreduced. At present, leukoreduction is not a manufacturing requirement, nor a recommendation of the FDA.

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At this juncture, it may be helpful for the committee members to peek at the question to be presented to the committee at the end of this session on universal leukoreduction. The question is preliminarily presented with the intent of providing guidance to the committee members as they receive and analyze information during the forthcoming presentations and discussion.

It reads: Is the benefit to risk ratio associated with leukoreduction sufficiently great to justify requiring the universal leukoreduction of all non-leukocyte cellular transfusion components irrespective of the theoretical considerations for transfusion-transmitted CJD?

The presentations to follow have been designed to give us the best shot in answering this question. We will first start off with Dr. Snyder, from Yale-New Haven Hospital, to provide us with supportive scientific evidence for the clinical benefits of leukoreduction, starting with the clearly accepted and FDA-approved indication of recurrent febrile non-hemolytic transfusion reaction to the most controversial reasons for leukoreduction, including the contraindication in transfusion-associated graft-versus-host

disease.

In terms of the impact of the universal leukoreduction policy on patient care, an agency recommendation in favor of universal leukoreduction will speed up overnight an already ongoing change in the transfusion practice in favor of leukoreduced blood components, a change that has been in motion for many years. The use of leukoreduced blood components currently stands at about 20 percent in the United States, and is increasing.

It is unclear to the agency how long this "natural" move towards universal leukoreduction will take depending on the risk/benefit ratio and the projected time to universal leukoreduction in the absence of regulatory intervention. A specific agency recommendation in favor of the universal leukoreduction policy will have a variable impact on blood safety and availability. Although we are not here today to discuss the overall picture of blood safety, cost and availability, some preliminary information about the frequency of leukoreduction with respect to the number of affected patients, blood components and transfusion episodes should serve as helpful information to consider.

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Dr. Snyder will be followed by Dr. Ron Gilcher, from Oklahoma Blood Institute, who will discuss the

advantages, disadvantages and equivalence from a clinical standpoint of the may different leukoreduction methods available through the use of several different leukoreduction filters or automated blood cell separators.

Although the 1996 FDA memorandum on leukoreduction is based on the most up to date scientific information available at the time it was written, the rapid advances in clinical practice and product manufacturing technology suggest that the recommendations about product specifications, control procedures and process validation outlined in the memorandum may be already outdated. The equivalence of the different leukoreduction equipment and methods with respect to each indication, the reproducibility of the leukoreduction process and the reliability of the final blood components merit an in-depth discussion.

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So what are the recommendations outlined in this famous 1996 FDA memorandum? Although not explicitly stated, the memorandum defines leukoreduction as a blood component manufacturing step that effects the reduction of residual leukocytes to 5 X 10^6 cells or fewer per unit, with the retention of at least 85 percent of the original therapeutic cells and, secondly, is performed under conditions that assure product safety and efficacy.

And, what are those conditions? For product

testing requirements, the memorandum requires sampling and testing to be performed according to a previously established and validated sampling plan on at least 1 percent or 4 units, whichever is greater, of each specific license of a product per month. All tested products should meet product specifications and the samples should be randomly selected.

For control procedures, the memorandum requires, firstly, the use of an FDA cleared leukoreduction device in a manner consistent with the device manufacturer's instructions; second, adherence to established standard operating procedures; third, the routine and ongoing quality control of all equipment used; fourth, the adherence to all applicable blood GMPs; and, lastly, the ongoing training and retraining of all involved operating personnel.

For process validation, the memorandum simply states that the manufacturing facility should generate data on a continuing basis to assure a stable and consistent production process over time with any variations remaining within acceptable product specifications.

Along with this definition of leukoreduction, the presentation by Dr. Gilcher on production issues, should provide us and the committee members with the insight necessary to make an informed recommendation on the universal leukoreduction policy.

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Dr. Gilcher will be followed by Dr. Lorna Williamson, from the University of Cambridge, U.K., and Dr. John Freedman, from Saint Michael's Hospital in Toronto, Canada, who have both graciously accepted to travel long distances to assist the FDA in shaping U.S. blood policy, with minimal arm-twisting. I recognize Dr. Freedman, whom I just met this morning, and I have not quite met Dr. Williamson. I look forward to hearing from you, Dr. Williamson.

Dr. Williamson's presentation will include a brief summary of U.K.'s policy with respect to new variant CJD and some initial experience since the implementation of the universal leukoreduction policy in the U.K. as of July, 1998. Dr. Freedman's discussion will focus on the rationale for limiting universal leukoreduction to platelets only in Canada.

In addition to describing the situations in the U.K. and Canada, these two presentations may provide us with some initial insights as to the international trend and the positions of other national blood authorities. In July of 1998, Dr. Karl-Friedrich Bopp, of the Council of Europe, announced that the Council's Bureau of the Committee of Experts on Blood Transfusion and Immunohematology plans to discuss the issue of universal leukoreduction and new

variant CJD at the meeting scheduled in approximately one month, on October 21 and 22 of 1998.

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A discussion of leukoreduction would be incomplete without a discussion of its adverse effects. This is a topic that the agency had some difficulty in identifying a speaker as the expert in the field. Fortunately, Dr. Mark Popovsky, from the American Red Cross, New England Region, has agreed to speak on this subject, along with the comment that the list of adverse events is short and his presentation may be brief. Is Dr. Popovsky here? Thank you, Dr. Popovsky. I look forward to hearing from you as well.

From a regulatory standpoint, and for the purposes of today's discussion, the adverse events associated with leukoreduction may be categorized into three groups: One, those reactions that are associated with a specific leukoreduction device, of which the red eye reaction is an excellent example. Two, those reactions associated with leukoreduction devices in general and, three, reactions that are inherent to the leukoreduction of leukocytes, or inherent to the absence of contaminant leukocytes independent of any leukoreduction device used.

The red eye reaction will be described by Dr. Jaroslav Vostal, of the Office of Blood Research and Review,

in conjunction with Dr. Juan Alonso-Echanove, from the Center for Disease Control and Surveillance. As an example of a reaction associated with the use of a specific leukoreduction device, the reaction is eminently controllable even without fully understanding the underlying pathophysiology.

In fact, no red eye reaction has been reported since the voluntary market withdrawal by the device manufacturer of the implicated leukoreduction filter. However, the red eye reaction is an excellent example of a potentially serious reaction relevant to the topic of universal leukoreduction, without an understanding of which the committee members will not be able to make an informed recommendation.

Following a description of the red eye reaction, Dr. Popovsky will discuss all other reactions, which I have categorized as those associated with leukoreduction filters in general and those inherent to leukoreduction. According to some preliminary communication from Dr. Popovsky, these adverse effects appear to be either extremely infrequent, as in the case of hypotension; clinically acceptable, as in the case of therapeutic cell loss; or clinically insignificant, as in hemolysis, keeping in mind the degree of hemolysis.

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Although I have created a third category for the

purposes of this discussion, there appear to be no adverse events of leukoreduction inherent to the reduction of leukocytes from whole blood, red cell concentrates or platelets. The third category, however, underscores the point that the adverse events of leukoreduction recognized to date are device related and that these may disappear with improving technology. However, a thorough discussion of these reactions is relevant to today's attempt to develop a public consensus about the universal leukoreduction policy as applicable today, using currently available devices and methodology.

As the adverse events are described, the committee members are well advised to bear in mind the nature of the effect, its frequency, severity, reversibility, as well as the ability to intervene in attempting to assess the impact of mandating universal leukoreduction on adverse events that are likely to follow from such a policy.

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Finally, after the open public hearing, and after we have had a chance to digest the information presented, as well as lunch, the single question will be presented to the committee for committee deliberations and recommendations in the usual manner.

For one last time, I shall read through the question to bear in mind as we listen to the forthcoming

presentations: Is the benefit to risk ratio associated with leukoreduction sufficiently great to justify requiring the universal leukoreduction of all non-leukocyte cellular transfusion blood components irrespective of the theoretical considerations for transfusion-transmitted CJD?

DR. HOLLINGER: Thank you, Dr. Lee, for that nice overview. Yes, Dr. Buchholz?

DR. BUCHHOLZ: Just a point of clarification with respect to the question as it is phrased, there are, at least for platelets, at least two different apheresis instruments that routinely collect platelet products that would meet the requirements for leukodepletion or exceed those requirements. I would just like to get some clarification with respect to those devices which may already meet or exceed the requirement as defined by that 5 X 10^6, if that is the requirement we are talking about here, that those would not be included because, it seems to me, it would not make a lot of sense to leukodeplete something that is already leukodepleted. So, FDA may wish to clarify that aspect of the question.

DR. HOLLINGER: It is my understanding, if I understood what you said, that they would look at leukoreduction regardless of process. Dr. Lee, do you want to comment?

DR. LEE: Sure. I guess in that way we have used

the term fairly loosely. Leukoreduction is meant to refer to the final product which meets the product specifications, and does not necessarily indicate a filtering step. If the product comes off the blood separators already meeting the product specifications, that component is considered a leukoreduced blood component.

DR. BUCHHOLZ: I was just trying to clarify the question.

DR. LEE: Thank you.

DR. HOLLINGER: We are going to then start with current practices, and ask Dr. Edward Snyder, from Yale-New Haven Hospital to talk, first of all, about the transfusion medicine issues. Dr. Snyder?

Current Practices

Transfusion Medicine Issues

DR. SNYDER: Mr. Chairman, thank you very much. It is a privilege for me to be here to talk on this topic. I would just like to make a couple of comments before I start. First, I am speaking as a professor of laboratory medicine from Yale University, and not in my capacity as a member of the Board of Directors of the American Association of Blood Banks.

I think this topic is an extremely difficult one to address. You will hear from various experts today a variety of opinions, and for me to come here and say there

is evidence that leukoreduction, universal leukoreduction is appropriate I think would ring as hollow as anyone saying that it is not appropriate.

I needed to find some way of being helpful to the committee, and the way I chose was to discuss it from the concept of consensus -- how would reasonable people view a particular indication? And, I think from what I have given you in my written documents, there is no agreement on any one indication.

That does not mean that the problem is not addressable. I think you can look at it as an aggregate to see whether, taken together, the whole is greater than some of the parts. I think from the perspective, sitting here or standing here, of what does the public want, I think the public wants a safe blood supply. We have a blood supply that is currently as safe or safer than any blood supply in the world due to the donor screening, due to viral testing, due to pathogen inactivation technologies which are coming along, and this is another additive aspect for improving blood safety.

So, those who have other things to do in the next 45 minutes, the quick answer is do I believe that universal leukoreduction, irrespective of any effect on new variant CJD, will improve the safety of the blood supply. My answer is yes, and I speak about the transfusion medicine

community, not for the entire community as there are a lot of very respected individuals in this room who may have different opinions. But I think if I have to come down on one side, I think the public expects us to do whatever we can do at this juncture to increase safety. And, you are not going to get consensus on all issues on every topic. I don't think that is necessary.

[Slide]

So, with that as a preface, let me go into my talk here. One of the things that must be considered by the committee is, if we agree that universal leukoreduction is needed, what components are to be leukoreduced? Looking at the components in general, obviously, it would be counterproductive to leukoreduce granulocytes. So, that component is specifically excluded. When you get down to the derivatives, down here, factor concentrates, albumin -- they would not be as well. But you would have to consider fresh frozen plasma, platelets and the variety of red cells. So, I will address these as we go through the talk.

[Slide]

I will give you a very brief overview of blood filtration. This is a standard blood filter with a nominal 170-260 micron mesh which is designed to take out clots, and a filter is required for use. This certainly is a standard blood filter and works well to remove clots, as I mentioned.

[Slide]

In the 60's during Vietnam and with the onset of open heart surgery cases, it became clear that there were other factors in blood -- white cells and platelets -- which were much smaller than the large blood clots which were considered to cause problems, even given the term microaggregates, and were basically dead platelets and bits of white cells and fibrin strands that went through the 170 micron pores because they were about 20 to 120 micron, and were felt to cause problems.

A whole series of microaggregate filters were developed, only one of which I believe is still existent today, the Pall filter. These worked to remove the debris. There was a whole series of issues: Was it going to prevent shock lung? Was it going to prevent the cardiac symptomatology that was seen in transfusion during open heart surgery? While all of that was raging in the literature, the concept of leukoreduction to prevent febrile reactions, which had been discussed by Dr. Herb Perkins in 1959 and Dr. Tibor Greenwalt, by removing white cells with cotton wool material in the laboratory, became an issue and that actually replaced the discussion about whether microaggregate filters prevented lung shock and the other aspects because it was really more of a concern for peacetime rather than the massive transfusion that occurred

during Vietnam. So, in peacetime with civilian casualties and massive trauma it was, I think, believed that hypotension and appropriate attention to infection were more important than leukoreduction, and we concentrated on its effect on preventing febrile reactions.

[Slide]

This is a slide taken from the literature, supplied from the Pall Corporation, which shows microaggregate debris trapped on one of the filters, and then a second filter in series shows much less. These pictures are very impressive, showing that there was a fair amount of debris but it turned out they were probably not as harmful as was hypotension and potential sepsis.

[Slide]

The field then moved on to removing not just debris but the individual white cells, and that was contemporaneous with our understanding, and a revolution in our understanding and knowledge of the individual leukocytes and what leukocytes could do. For leukocytes, I include lymphocytes as well as granulocytes and monocytes.

We now have leukoreduction filters. In this picture you can see filter media with trapped white cells on it. The reason the filters trap the white cells is for two reasons. One is by interception, and the other is by surface tension properties which are different for red cell

leukoreduction filters and platelet leukoreduction filters. All cells have a surface tension based on a variety of charge considerations on the membrane, and these filters are designed to remove white cells but leave either red cells or leave platelets. We are now facing whether or not removal of individual white cells is of benefit, and that is where the field is moving now.

[Slide]

I have listed here the non-controversial indications --

[Laughter]

-- I do this not to be flippant but to show you that, again, there is no 100 percent consensus, but that does not mean that we may not be able to move forward in this area.

[Slide]

So, first is looking at levels of consensus, what I considered high and, again, these are my formulations. I believe the consensus is high that universal leukoreduction would provide increased safety of the blood supply by decreasing the incidence of febrile transfusion reactions, as Dr. Lee mentioned; decreasing the incidence of primary HLA alloimmunization -- primary as opposed to secondary. Secondary would be someone who would already have been exposed and would have HLA antibody, such as a woman who has

had children or anyone who had been transfused and already has an antibody. If they then come in and get blood, would leukoreduction prevent or remove their HLA antibody, or would it prevent it from coming back in an anamnestic response, sort of a rechallenge, if you will? Decrease in generation of cytokines, which are biologic response modifiers that can cause a myriad of effects in the body during storage, and decreased generation of platelet and granulocyte microparticles, that is, the breakdown of these cells.

These are the areas, as I will go through them very quickly, where I believe we have high consensus that leukoreduction is useful and will improve safety, and I will try to discuss what is safety.

[Slide]

Indications for febrile reactions -- about 10 percent of chronically transfused -- by the way, I used slides that have been provided by some industry companies for benefit of clarity, and not because I am in any way involved with any particular company. But in academics, if you can get a colored slide that explains the data and has a reference, it is used and gratefully accepted from the organizations. Incidence of febrile reactions is about 10 percent in chronically transfused patients, about 1 percent overall in the population.

[Slide]

Looking at febrile reactions, why do you get a fever in the first place? You get a fever because of an antigen antibody reaction that occurs, the antigen being the white cells in some form, either lymphocytes or leukocytes, granulocytes or monocytes, and a white cell antibody. What happens is that you get activation of other cells, other white cells in response to this antigen antibody reaction, and you get the release of cytokines. It used to be called endogenous pyrogen and it now has more sophisticated names, interleukin-1, interleukin-16, IL-8, neutrophil activation factor -- a variety of cytokines, biologic response modifiers that have an effect on what happens in the body. Activation of the generation of these cytokines results from infusion not only of antigens but of microorganisms, bacteria and so forth, antigen antibody complexes complement other cytokines and toxins.

So, I think that one of the benefits is, if leukoreduction can decrease the likelihood of a fever due to a febrile reaction, it will help physicians distinguish a febrile response during the time of transfusion from some other cause, such as sepsis or some other problem, and sort of unmuddy the waters, if you will. So, I think there is a benefit to safety in that regard.

[Slide]

The people who are likely to get these febrile reactions are either multiply transfused patients because of the presence of white cells and buffy coat or multiparous women who are exposed during parturition at the time of birth to the white cells, 50 percent of which of the child's complement come from the biological father.

[Slide]

This is an old slide which actually shows temperature and hospital day. This was a woman who had Crohn's disease, who had a very high titer of leukoagglutinins, a white cell antibody from prior transfusions. This goes back to the late 1970's. She was afebrile, came to the outpatient clinic and got one unit of packed cells and spike the temperature to 104, which came down. Later she got another unit and spiked again. We finally realized what was happening and she got washed cells, which is a cruder way of removing white cells but certainly will remove 1-2 logs of white cells, and she did not have a fever with those transfusions.

So, here is an example of an antigen antibody reaction. The antigen was in the white cells in the transfusion; the antibody was in the patient, and the fever was due to the generation of endogenous pyrogens.

[Slide]

Again, the differential diagnosis can be a

hemolytic transfusion reaction. That is an inflammatory response and that will result in a final common pathway of the production of cytokines, which will result in a fever. Bacteria could be unrelated to transfusion if someone had a malignancy or if someone had an inflammatory process, such as rheumatoid arthritis, or other causes, drug induced and so forth.

Having universal leukoreduction would decrease but not eliminate the likelihood of fever. I don't think there is even a consensus that universal leukoreduction would prevent fever, and there may be some data that someone who was already febrile may be more prone to spike a higher fever with additional transfusion rather than someone who is afebrile developing a fever in the first place because there is synergy among cytokines. If you infuse IL-1 you will get a temperature rise. IL-6 may increase that temperature by causing some synergy with IL-1. So, if you already have IL-1 being produced because you have an infection and then you get a transfusion you may be more likely to go from 100 to 102 than you would from 98.6 to 100. But I don't have a lot of hard data on that aspect of it.

[Slide]

How does the fever actually occur? This is from a paper by Dr. Sapper, in The New England Journal. It revolves around the hypothalamus, where the thermoregulatory

nucleus is. The actual way it gets in is that the cytokines that are produced by the antigen antibody reaction, such as interleukin-1 or TNF-alpha, go into the circumventricular organs where they are involved with attachments to neurons which go into the brain and produce various responses, autonomic responses and so forth. So, it gets through the blood-brain barrier.

[Slide]

The key aspect of this, and I thank Dr. Sonny Zeik for letting me copy this slide, is that in the brain there are receptors for interleukin-1 as there are for others. You get stimulus response coupling across the membrane which leads to the metabolism of phospholipase A2, down a pathway which leads to prostaglandin E2. Prostaglandin E2 will affect the firing rate of thermoregulatory neurons. So, the more prostaglandin E2, the faster the firing rate which results in an elevation in temperature. There is an enzyme involved in this pathway, cyclo-oxygenase, acetyl cell acidic acid, common aspirin, acetylates that enzyme and when it does it activates that enzyme. That is why aspirin or nonsteroidal anti-inflammatory agents will lyse a fever because it blocks the production or prostaglandin E2.

Once you have a fever and you take an anti-inflammatory, it takes a while for that temperature to come down. If you give is as premedication you may be able to

prevent it but it is a dose and rate related phenomenon. So, it is a lot better to prevent a fever than try to treat it once it has occurred. Again, if you have a fever and you don't know what is happening with the patient, especially an outpatient who has a fever in renal failure, for example, may need to be admitted because of the potential for sepsis in someone who has some degree of impairment with renal failure or a malignant condition.

If you can avoid a fever, it will be helpful and increase the safety of the transfusion. Is that enough to go to universal leukoreduction? No, but it is just another brick in this wall that I am building of a variety of indications.

[Slide]

As to what would be helpful, there was a paper by Dr. Chambers, and others -- this is the abstract from Transfusion in 1989. When the PL-100, the Pall filter, came out we looked at it because the concern was that now we have a filter that will remove 3 logs of white cells and will get rid of febrile reactions, and they concluded in the studies that they did that really there were only 3 patients that accounted for the overall difference in whether there was a fever or not, and that the PL-100 was not effective. They found patients still having fevers even though they got blood through a bedside leukoreduction filter, and they

concluded the filter wasn't effective.

Well, they were right and they were wrong. We now can look back and understand why. That is, because during storage white cells generate cytokines in the bag, more in platelet bags than in red cell bags because platelets are stored at room temperature. Why they produce it we do not understand, whether it is sheer stress from the platelets moving back and forth in the bag or whether there is something in the plasticizer -- it is certainly not because of bacterial contamination of these units, but it is now well established that a variety of cytokines are produced in storage bags, platelets or red cells.

[Slide]

This is a study that Dr. Gary Stack and I published, showing that for levels of interleukin-8, which is another cytokine -- these are individual platelet bags and over time of storage, going from 2-5 days, and with an increasing number of white cells, greater than 4000 white cells, the amount of interleukin-8 increased. So, the highest amount of interleukin-8 generated is in those platelet units that had the highest white count and were stored for the longest period of time.

[Slide]

This is shown on another slide which, again, I was able to obtain from Baxter. These are levels of IL-8 and

this shows that non-filtered blood over 5 days of storage had varying levels. Why they varied we don't know either but some produced more than others, and that may again be related to the white cells. But if you prestorage leukoreduce, if you take out the white cells before storage you prevent generation because the white cells have been removed.

So, among the things that the community will need to consider is whether prestorage leukoreduction should be the universal methodology, or whether bedside leukoreduction, or whether in the laboratory. Cytokines will be generated and will not be removed, by and large, by bedside leukoreduction. I have one or two slides on that later on. The most efficient way to prevent cytokine formation is to prevent it by prestorage leukoreduction.

[Slide]

So removing or preventing these response modifiers, how does that improve safety? Well, as an example, TNF-alpha can produce fever, shock, capillary leak syndrome, leukocyte activation, endothelial coagulation cascade. In general terms, what do they mean? You can imagine what might happen if your leukocytes are activated. They stick. They go places they are not supposed to. They degranulate and can cause capillary leak syndrome -- a whole variety of things -- granulocytes destroy joints, and

rheumatoid arthritis, and so forth.

Cytokines that produce these effects in someone who may be critically ill might have a synergistic effect on what is happening in these individuals in their particular clinical scenario. So, there is an improved safety aspect to the prevention of generation of these response modifiers.

[Slide]

This was brought home nicely by Dr. Nancy Heddle in a paper published in The New England Journal. If cytokines are that important, can anyone show what the relationship is of cytokine generation and fevers due to fevers from the transfusion of cells themselves? What Dr. Heddle did was to take 64 patients, and what she did, she took platelet concentrates and she spun the platelets down to take off the supernatant and have the platelet-poor plasma and the cells. Then she infused the supernatant without the platelets and then several hours later infused the cells and looked to see when reactions occurred. And, 30/64 patients infused had no reactions; 20 of the patients reacted only to the plasma, not to the infusion of the platelets when the platelets were given, and they were given in mixed rotation so that one time they got platelets and then they got the platelet-poor plasma the second time, and another group got it reversed so there was not a bias. Six of the patients reacted only to the cells, and 8 patients

reacted to both the cells and the plasma.

The conclusion was that there was more of a febrile reaction, fever and chills response due to the infusion of the plasma without the platelets than there was from the cells, the implication being that the cytokines present in the stored platelets actually were more likely to cause febrile reactions than were the cells themselves which, with antigen antibody reactions, you might expect would cause a problem.

This study actually crystallized the idea that stored platelets may cause problems, and how serious is a febrile reaction? Is it likely to kill someone? Not likely, but there are some very young individuals who may be critically ill, or very old individuals, and individuals who may be very, very debilitated for whom a fever of 104 with Reigers may not be tolerated and could precipitate a very untoward cardiac arrest, respiratory arrest -- obviously a very small percentage, but if the question is will leukoreduction improve the safety of the blood supply, here is another little piece of a brick that, yes, it will improve safety for some of those patients.

And, no one would like to have a fever and chills, and sit in the bed and shake. It is an uncomfortable feeling. Physicians tend to get a little concerned if someone isn't in extremis where you are really not that sick

but when you are sick and you need some comfort, not having Riegers would be reasonable. Is that enough reason to universally leukoreduce? Not in and of itself alone.

[Slide]

That is the febrile part. The second aspect is HLA alloimmunization where there seems to be very good consensus. As a very brief summary, in order to make an HLA antibody, what generally happens is the HLA antigen that is foreign -- or, we will talk about HLA in this particular case -- that is foreign to the recipient is presented by the donor lymphocyte known as an antigen-presenting cell. This is a specialized cell whose job it is to present antigen. Here is the antigen-presenting cell, and this is how it is presenting it. The object of our affection is this little squiggle in here which is the protein or peptide fragment, and this is the T cell that it is looking for. When the T cell sees a peptide in this pocket reactions occur, as shown here by these various abbreviations for protein kinase C in a variety of metabolic pathways which, fortunate for you, I will not go into in any detail.

[Slide]

However, if you look at it from the T cell's point of view, looking sort of like the "Mir" docking with an American spaceship, what we are seeing is that here is the receptor on the antigen-presenting cell and here is the

peptide in class 1 or class 2, and there are varying difference which I am not going to go into. This is how the antigen is presented to the recipient.

It seems unusual that in an HLA scenario you need to have donor antigen-presenting cells. If I were to give any of you a tetanus shot you would not need to get a blood transfusion to make an antibody to the tetanus, or with hepatitis you wouldn't need a transfusion. Why do you need donor white cells in the HLA system? It is not required. You do not have to have donor antigen-presenting cells. You have your own antigen-presenting cells which could present antigen, but that does not do it as efficiently apparently as the antigen-presenting cells from the donor.

[Slide]

These antigen-presenting cells are monocytes, macrophages and dendritic cells, specialized cells which are susceptible and amenable to removal by leukoreduction filters. So, the rationale for why you want to leukoreduce to prevent an HLA antibody is removing the antigen-presenting cells to decrease the likelihood of transmission of HLA.

[Slide]

Some studies that were done by Dr. Blajchman in New Zealand rabbits is a model that showed that if you did not leukodeplete at all -- what he did, he transfused

rabbits with blood from other rabbits, and if you did not leukodeplete the donor rabbit blood he had a refractory rate, that is, a lack of responsiveness to platelet transfusion, presumably due to rabbit antibody in 95.8 percent. If you leukoreduced the blood after storage the rate went down to 66 percent, and if you leukoreduced before you infused any of these rabbits the rate was the lowest, 33 percent.

This would go along with the concept that if you don't leukoreduce you are going to get a fair amount of alloimmunization. Poststorage was less efficient than prestorage was. The numbers are much higher than we see in humans. Humans are about 50 percent if you don't use leukoreduction, but this is a rabbit model and I think, as far as the trends, gets the point across that prestorage leukoreduction appears to be the best; poststorage is more beneficial than nothing at all for prevention of at least the rabbit antibody.

[Slide]

This is a slide, taken from advertising material for the Pall Corporation, which I used because it provides a list of the studies and the authors. If this is true, that leukoreduction prevents alloimmunization, then the lower the level of white cells in the product transfused, the lower the level of HLA alloimmunization should be, and this is

what was found.

Here, again, 50 percent, as I mentioned, in several studies when there was less than 1 X 10^9. As you go down to the 10^8, to the 10^7 and to the 10^6, the level of alloimmunization drops but it does not go to 0. It looks like it is at 0 but it is not absolutely 0 down here.

So, the concept fits. There is a lot of data that shows that the more you can leukoreduce the less likely you are to have alloimmunization but it doesn't go to 0.

[Slide]

Well, a study was recently published, the TRAP study trial, to reduce alloimmunization to platelets, sponsored by NHLBI. Dr. Sherrill Slichter was the lead investigator. It was a multi-institutional, randomized, blinded study. The purpose was to determine if leukoreduced platelets, and also UVB irradiation, prevented formation of antiplatelet alloantibody and refractoriness to platelet transfusion. Alloimmunization is one type of reason for refractoriness; there can be others but for the purposes of our discussion let's assume that they are synonymous.

[Slide]

The conclusion of this study -- shown here is just one of the slides but it does show the results fairly well. This is for lymphocytotoxic antibody. There are similar slides showing percent refractoriness. The control group

that did not get leukoreduced blood had the highest level of lymphocytotoxic antibody and the highest level of refractoriness, whereas, if you did UVB irradiation and UVB affects that -- when I showed you those two cells coming together, what UVB does is that it interferes with the adhesive molecules, ICAM-1 and others, to prevent those two cells from staying together long enough to give a signal to produce IL-2 and other cytokines to make an antibody. But that is how UVB works and we are not going to get into that. Filtration of platelet concentrates made from whole blood or filtration of apheresis products or UVB all gave the same result, that is, a statistically significantly lower incidence of alloimmunization compared to the control which did not have any leukoreduction. There was no difference among these 3 types. So, again, here is a very controlled clinical trial showing benefit. It doesn't go to 0 again, which we will talk about in a second.

Their conclusion was that leukoreduction by filtration and UVB are equally effective in preventing alloantibody-mediated refractoriness to platelets during chemotherapy for AML, which is the population they studied, and, as a sideline, they mentioned that leukoreduction of single donor platelets versus random donor platelets was of no added benefit.

[Slide]

Now, there is controversy, which will rage long after we have left this room, as to whether process leukoreduction, that is leukoreduction by machine as Dr. Buchholz referred to, versus leukoreduction by filtration are equivalent. There is some data coming out that they are different. Whether it is clinically important is the question.

This is a paper that was published by Dr. Coker, from the Pall Corporation, in Transfusion, I think last month or two months ago, showing that with leukoreduction by filtration versus leukoreduction by process in various cell separators you get different concentrations of subsets of white cells. Whether this has meaning or not, I am not going to address. You should be aware that there is controversy in some people's minds as to whether at the same level of total leukocytes, 10^6 for example, you may have different percentages of lymphocytes, monocytes, macrophages and so forth among the different groups. Most of the studies that have been done have been done with filtration as opposed to leukoreduction done by pheresis machinery. So, I just raise that as another area that is controversial, and there really is no knowledge whether this is so or, "my gosh, look at that!" There is no answer at all on that question from my perspective.

[Slide]

What happens during storage, and why don't you get down to 0 with the transfusions? Well, here is an example. This is from an unrelated paper but it shows a neutrophil fragmenting. I apologize, I don't have the reference on here. I usually put them in but I forgot this time and I am sorry.

These little circles are fragments of white cells. White cells fragment during storage. Platelets fragment; red cells fragment. The longer the period of storage, the more fragmentation there is as the membrane blebs off.

[Slide]

Why is that important? Well, I am glad you asked. It is important because these fragments will go through leukoreduction filters. Here is a paper by Ramos that I borrowed from Baxter showing the amount of fragments over time of storage for platelets. The longer the time of storage, the higher the level of fragmentation. The red is pre-filtration; the yellow is post-filtration, showing that there is no difference pre or post. The little fragments that are there pre-filtration come through.

[Slide]

These fragments contain, although you can't see them, little pieces of HLA antigens. So, if you are trying to prevent the presentation of antigen by removing white cells, if the white cells have started to fragment one of

the reasons you may get antibody production is that you are getting fragments going through because the products have been stored, and those fragments are able to get through and be presented by the smaller number of antigen-presenting cells that also get through the filtration process because there is only a 3 or 4 log reduction as opposed to 100 percent. Nothing is going to remove 9 logs of white cells.

The other factor is that there may be soluble HLA that would also go through, that could be picked up by the recipient's own antigen-presenting cells and presented to the recipient's own white cells, as happens in tetanus or hepatitis or any other vaccination that we get. It is just not as efficient for HLA. So, there is another reason to leukoreduce.

[Slide]

Dr. Blajchman, as he is wont to do, has shown this very nicely in his rabbit model. He took plasma alone and immunized rabbits, gave them plasma injections and then platelets, and found that if rabbits were given fresh plasma and then given platelets, 16 percent of them were refractory. If he used stored plasma, 61 percent were refractory. The implication is that there was something in stored plasma that raised the incidence of alloimmunization, presumably fragments that were present in the plasma that contained cells during storage and you can't spin out the

microparticles because they are too small -- you can, but he didn't because he used regular transfusion techniques.

[Slide]

Carrying this further, Dr. Bordin, again with Dr. Blajchman, showed that if you took leukoreduced red cells you got a 29 percent rate. If you gave white cells to animals and then you gave them platelets, 34 percent were refractory. That is, they didn't get a response to the platelets. But when they used white cells reduced and plasma reduced as well, washed cells, they had 0 percent refractoriness. So, not only did he remove the white cells, but he washed out the fragments as well.

Now, does that mean that we should all get back our cell washers and start doing that? Not necessarily. And, even at the time of beginning of storage there are some fragments that go through. We are going to be quibbling about how many angels can dance on the head of a pin. You can't get down to zero, I think, in anything but you can approximate. You can improve the safety by yet in another way, leukoreducing, and most efficiently leukoreducing prestorage.

[Slide]

Dr. Copplestone, in Blood, looked at whether leukoreduction was harmful, and maybe this slide would have been better shown by Dr. Popovsky, but he did Kaplan-Meier

plots looking at relapse-free survival in patients in complete remission with AML. They separated by whether or not the products were filtered with a leukoreduction filter and found that there was no significant difference. Leukoreduction did not enhance the likelihood that they would have relapse and it didn't give them a much better survival advantage, for those who were alive. So, this is just another example that it is not decreasing the safety of the blood supply and certainly would tend to prevent HLA alloimmunization, fevers and so forth, but did not have any adverse event in this paper by Dr. Copplestone.

[Slide]

What about levels of consensus that are moderate? There are two key ones. CMV transmission, and I put Epstein-Barr in parentheses, and decreasing HIV activation. These are very important issues. I will try to go through these quickly.

[Slide]

The bottom line -- CMV is amenable to removal by leukoreduction because CMV is primarily an intracellular virus. It is primarily in white cells. If you can remove the white cells, you can remove the CMV.

The key study was done by Dr. Raleigh Bowden, published in Blood, in 1995. She took 252 patients -- actually 500 patients given bone marrow transplants, and

half of them got seronegative blood and half of them got filtered blood, bedside leukoreduction filters, and they did an analysis looking at day 0-100.

In the people who got seronegative blood there were 4 infections, 1.4 percent, versus 6 infections in leukoreduced patients, which was not statistically significant. For CMV disease, there were none who got disease in the seronegative group. In the filtered group 6 people got disease. Of the 6 people in the filtered group, 5 got pneumonitis and died, and 1 got gastroenteritis and did not die. This was statistically significant at 0.03.

However, they said, well, several patients got CMV infection within 21 days of entry into the study, which implied that they had been infected prior to entry into the program and they should have been backed out. Under an intention-to-treat protocol you need to evaluate all of them, which was done. So, they presented both sets of data. If they looked at only people who developed antibody after day 21, that is, who could not have been infected prior to entry into the study, or less likely, there were 2 infections versus 3, and there was no disease, and only 3 in the filtered group, which was not statistically significant.

This has led to a major discussion among men and women in the field as to whether leukoreduction is, number one, harmful or, number two, if this was just small numbers

and the luck of the draw. Several patients, after the study ended in the control group, developed CMV disease and I believe also I believe a couple of them died.

The point is that there was evidence that you could certainly decrease the incidence of CMV transmission by using filtered blood, which was CMV not tested so, therefore, presumably had a fair amount of CMV positivity. There has been no other study done looking at this formally. I have talked to a variety of thought leaders and people at major medical centers around the country, and no one has told me of anyone who is using this leukoreduction in lieu of CMV seronegativity who has found an increased incidence of CMV in, certainly, the marrow transplant population or other populations.

So, the general consensus is that I think the field is coming to the appreciation that leukoreduction, done under CGMP and appropriate technology with the appropriate attention to quality control, is equivalent to or better perhaps than CMV seronegativity as your only test. That is something the committee will have to decide. There is not 100 percent agreement but more and more places are moving towards this concept.

[Slide]

The other aspect is HIV activation. This basically relates to a study that was done by Dr. Mike Bush,

who just walked in. What he did in vitro was to take cells that were HIV infected but were not producing p24 antigen. He exposed them, in this first panel, to mitogens, phytohemagglutinin, and showed that in a dose-related way he could get these HIV infected cells to produce p24 antigen in the cell culture.

He then added blood in varying amounts and found that there was a similar dose response. When he individually went and looked at red cells, platelets and plasma and added that to the cells, he did not get any production of p24, any activation. When, however, white cells were used, whether they be granulocytes, monocytes or lymphocytes, he got a response.

The implication is that granulocytes or white cells in general will cause, by a process of immunomodulation, stimulation of cells, in this case HIV infected cells, to produce more HIV virus in non-infected cells. To translate that into the clinical arena, the question is do individuals who are HIV positive and get into an automobile accident, who are otherwise healthy, and get a transfusion, must they get leukoreduced blood products to prevent activation of their potentially quiescent HIV?

That study, the viral activation by transfusion study, has been funded by NHLBI. I believe they have stopped patient accrual but results are not in. But based

on Dr. Bush's work and work of others, there is an implication that white cell transfusion somehow stimulates viral activation. So, that is another concern and certainly if these have positive results, it would be another strong reason to want to leukoreduce more blood.

[Slide]

Low levels of consensus are a variety of things, and some people might get up in anger and say, "how dare you say that it is a low incidence?" There are some very strong words and some very good scientists saying that you really need to leukoreduce for these indications. I will go through them very quickly.

[Slide]

Bacterial contamination -- the best results from the people who are doing work in the field -- Dr. Blajchman, Dr. Yomtovian -- appear to show that 1/1500 to 1/2000 units of platelets are contaminated. To knock on wood, we do not see this in our institution. We transfuse about 30,000 units of platelets and we don't see that degree of infection, probably because the number of bacteria that are in the units of blood are so small that they don't cause clinical problems. But if you took a sample and cultured it, and gave it 7 days of luxuriating at 37 degrees you might get growth. So, it may be that they are contaminated but we don't see that degree of infection. Others might say

we are just not looking hard enough, and the Bacon study that the CDC and others are sponsoring is intended to look at that.

The point is that there may be bacteria in blood and, as I mentioned, it is inevitable when you do venipuncture with bacteria living under the cells in crypts. You cannot clean the arm well enough to get rid of the bacteria. If you could get down and get all the bacteria out your arm would be bleeding because you would have to get off several layers of cells. So, it is almost inevitable that there would be bacteria.

[Slide]

I think this study is clear and needs no explanation. This is an example of a slide that was done with a study we published in conjunction with Dr. Buchholz from Baxter, looking at bacterial spiking of blood and the ability of a leukoreduction filter to remove the bacteria. Just let me point you to this, here is Staph aureus. This is time of storage. It was leukoreduced. This group had the Serratia and Staph. aureus was not leukoreduced. By day 3, 4 and 5 there were too many bacteria to count, although there was no growth in the filtered group.

That is fine. Filters do remove some bacteria, not all types -- gram negatives less than gram positives. The removal is either due to bacteria being phagocytosed in

the white cells and the white cells being removed and taking the bacteria. The bacteria stuck to the white cells and were removed when the white cells were removed, or bacteria stuck to the filter media itself. It is not reliable. You can't put a label indication for it. There are too many strains and serotypes, and too many indications. If, however, universal leukoreduction is adopted this would be another little brick and some units that may be infected may be prevented from having a large amount of bacterial growth because you have removed the bacteria during the filtration process. Again, you are never going to get consensus on this idea but there may be some benefit in some cases.

[Slide]

I have about five more minutes and then I will be finished. I apologize for going over; this is a big topic to discuss.

This is another paper by Dr. Blajchman looking at tumor. There is an enormous literature on whether leukoreduction decreases the incidence of tumor recurrence, or regrowth, or metastases. In this study, with the rabbits that Dr. Blajchman uses, there were 36, 35, and 23 animals that either got blood that was either from an identical twin, syngeneic or litter mate, allogeneic, from a foreign litter, or leukodepleted blood from a foreign litter.

What he found was that the number of pulmonary

metastases was the least in the syngeneic and the leukocyte depleted allogeneic group, and the most in the group that got blood from a foreign litter. The implication is that if you give foreign white cells, they are somehow going to affect tumor so that you get more metastases, more "tumorness" because you are immunosuppressing the recipient and the tumors can grow. So, if you leukoreduce you will prevent growth of tumor. There is no consensus on this, and I am not going to list all of them because there would be no point. The fact is that the answer is maybe, and that is my final answer.

[Slide]

So, if that is the case, what have other individuals said about this? There have been a lot of studies by Dr. Jensen looking in colorectal cancer patients at other aspects. This is a table, which came out in Transfusion, which shows that patients who received no transfusion, the total bed days was 967 days; people who received unfiltered whole blood, 974 days; and people who received filtered blood, 537 bed days.

The implication is if you leukoreduce blood for people who are recovering from colorectal surgery you can decrease their length of stay by 50 percent. That seems a bit much to me. However, there are other studies by Dr. Jensen and others showing that you can decrease the

incidence of infections from 12 percent, postoperative infections, to 0. You can decrease the incidence of pneumonia from 23 percent down to 12 percent -- much lower numbers. These are very dramatic decreases. I don't know whether we see 23 percent infections after colorectal surgery at our institution.

These are some of the questions that are raised. Yet, there is a lot of literature that leukoreduction in general prevents immunomodulation and may be beneficial. The only way we are ever going to find out is basically if everyone starts leukoreducing and retrospectively looks back to see if they have a decreased incidence in their institution.

Lots of studies are showing that there are benefits. Dr. Ness was looking at prostatectomy. Patients didn't find a benefit of leukoreduction. It is controversial. That is why I said there is low consensus, but certainly a lot of concern.

[Slide]

Reperfusion injury -- when you have an ischemic episode in a tissue by, let's say, open heart surgery where you close off the vasculature for a while, or organ transplant, where the organ is ischemic, sitting in a box in a Leer Jet getting to where it needs to go, you tend to activate cells. When you activate cells you get a

proliferation of adhesive molecules on these cells that allow cells to stick. If that happens in an organ or post cardiopulmonary bypass the implication is that white cells can get in and cause damage to the tissue once you reperfuse. It is called ischemia reperfusion injury.

The idea would be if you leukoreduce and prevent white cells from becoming activated because you have removed them from the transfused blood, you can prevent some of this damage that white cells can cause when the blood supply is reattached to these tissues.

[Slide]

The mechanism of damage is superoxide formation. You have cells that are damaged by ischemia. They activate neutrophils, and so forth, and the neutrophils, as shown here by the white lines, release proteases and cause additional damage. The problem is that you don't have a leukoreduction filter in the patient's own body. The patient has white cells, so how do you prevent activation of those white cells? And, the answer is that you really can't.

[Slide]

In addition, a study just came out in Blood about a week ago, or two, by Dr. Massberg, where they looked at the role of platelets in reperfusion leukocyte injury. This was in Volume 92. This was an ischemia model in a rat

mesentery. This was a sham and you don't see any lighting up of platelets in the mesentery. Here, you see Rhodamine fluorescent platelets stuck to the mesentery five minutes after reestablishment of blood flow. The bottom line is that platelets will also contribute to reperfusion injury in addition to white cells.

So, does that mean that white cell filters are of no benefit because you have platelets as well and you have the patient's own white cells? Well, leukoreduction would perhaps have some additional benefit. There are some studies showing benefits in pulmonary function and cardiac function when leukocyte filters are used. So, again, it is another piece; not the end-all and be-all but that is what the data are.

[Slide]

Very briefly, can you remove biologic response modifiers rather than prevent them from being generated? Here is a paper where we showed that interleukin-8 can be removed. This is interleukin-8 in a unit of platelets at the start of storage and then, as the amount of blood that was filtered goes on to about 100 mL, the level drops dramatically and then starts to climb again.

[Slide]

We now know that this is because this particular cytokine -- these colored balls over here are positively

charged amino acids. The filter that we used was a negatively charged filter media and there was an electrostatic interaction.

[Slide]

But that electrostatic interaction, as more blood was filtered, became less and less to the point where the cytokines just came through. So, you really can't remove cytokines, and this doesn't work for IL-1 and TNF-alpha, the inflammatory cytokines. This was just one particular one.

So, we are not at the area where leukoreduction filtration can prevent the infusion of biologic response modifiers. You really do need to consider removing them ahead of time by preventing their generation. This will not have an effect on complement because complement is a plasmatic factor, and it is already there and, although that can be removed by filters, it is not 100 percent removable. So, that was just to touch on that one issue.

[Slide]

The last couple of slides -- there is a high level of consensus that if you leukoreduce and do not irradiate you will increase the incidence of post-transfusion graft-versus-host disease. If the committee in its deliberations decides that universal leukoreduction is appropriate, the caveat is that it must be mentioned that it is contraindicated to not -- I don't want to say this as a

double negative -- you must irradiate blood in order to prevent post-transfusion graft-versus-host disease. Leukoreduction may well be, if you get the levels down low enough, prevented by reducing the number of leukocytes that are transfused, but I would not want to be the first on my block to try that.

Dr. Zeik has some good data showing this may have some merit but for now it is contraindicated, as Dr. Lee said. So, there is a high level of consensus that it would not be safe to use this in lieu of irradiation to prevent post-transfusion graft-versus-host disease.

[Slide]

Here is a slide from Dr. Akahosi's paper in Transfusion, just showing someone who received leukoreduced blood, in Japan, who was haploidentical to the recipient and passed away on day 40 because of post-transfusion graft-versus-host disease.

[Slide]

The safest policy, as mentioned, is to gamma irradiate regardless of washed, frozen or filtered. Certainly, filter but you still need to irradiate for GVH.

[Slide]

The last slide, which is the one that shows what was really pushing all of this, CJD, there is very high consensus that leukoreduction will have no benefit for the

prevention of new variant CJD as far as data are concerned.

[Slide]

This is a slide from Science, a paper that showed that you can transmit scrapie in an animal model to animals that have a T cell deficiency, but for B-cell deficiency you could not transmit it, and that led to the concerns that if there is any likelihood that new variant CJD is transmissible, it is through B cells. I think we are at the point of saying what is the best we can do if this is really here, and the answer is, well, I am not sure. Leukoreduction will take out B cells and T cells but I am not sure it is going to prevent any transmission. Many companies and other academics are looking at prion identification assays, and so forth, but we don't have any removal.

[Slide]

One last thing, this is a paper that just came out by Dr. Willis, showing that in fresh-frozen plasma, depending on the methods you use -- this has just been published in Transfusion, some methods will give you levels of white cells above 5 X 10^6 more reliably than others. This is the method that is used in the United States. This is the buffy coat preparative method, and this is another method that they talked about.

So, if you really want to cover the bases you

would have to leukoreduce fresh-frozen plasma as well, which adds another -- I am not going to mention the "C" word, but more financial considerations in that regard. But, apparently if you really want to leukoreduce you have to go the whole nine yards.

[Slide]

You also have to use a regular filter. That is part of the CFR 606.122 Part (b). You have to use a filter in the administration equipment.

[Slide]

So in conclusion, if I have to stand on my perch and look to the future, I think the time has come, for me as a physician with a lot of things that have to be considered, that we do have to consider universal leukoreduction for all of the maybe and yes reasons.

I hope my comments have been helpful to the committee and I wish you all the luck in your deliberations. Thank you very much.

DR. HOLLINGER: Thank you. The next speaker, Dr. Ron Gilcher from the Oklahoma Blood Center, is going to talk to us about the production issues.

Production Issues

DR. GILCHER: Dr. Hollinger, members of the committee and others, thank you for inviting me to be here today and talk to this group on the production issues.

There are four things that I want to attempt to address in my presentation.

The first is the process of leukoreduction itself. I think we tend to use the term leukoreduction rather loosely, and I think the time has come, as Dr. Snyder said, to, in fact, redefine the standard.

The second point that I want to focus on is the quality control of the product. I think this is a very critical issue, and it is very difficult to do.

The third point that I think is one that is also very important, and that is to be able to predict what we call product failures. We use that term instead of talking about a filter failure or a machine failure where the patented technology in the machine is used. It is really a failure of the product to meet our internal specifications, and can we predict that? The answer is in certain instances yes, and we have some data and I am going to present briefly on that.

Then, as I said just a moment ago, I think the time has come to redefine the definition and the standards for leukoreduction.

[Slide]

To put this into perspective, what I have put on this first slide is the current collection procedures that are performed at the Oklahoma Blood Institute. If you add

these up, the total procedures would come to about 162,000 procedures. I have broken them down by the type of procedure.

For example, you see whole blood allogeneic, about 126,000, and we are currently leukoreducing at the 20 percent rate. In fact, that number is continuing to go up, and I will talk more about that.

If you look at apheresis fresh-frozen plasma, the only kind of plasma used in our system, we do not leukoreduce that, and that is another issue, which Dr. Snyder has addressed, that will become important. But if you look at platelets in our system, 100 percent of our platelets are leukocyte reduced, and here I have quite a bit of interesting data to share with you. We do double platelet collection as well and, again, everything is leukoreduced.

[Slide]

The current definition that we have heard this morning for the United States, as defined by the FDA and supported by the AABB, is less than 5 X 10^6 white cells per transfusable product or within the container, really aimed at being an adult transfusable dose. I think that, as I said, needs some change. The Council of Europe, on the other hand, has defined as the standard in many European countries less than 1 X 10^6 residual white cells per

transfusable product per adult dose. In fact, the technologies with which we deal, that is, the filtration and patented machine technologies, are all capable of, in fact, really getting significantly below 1 X 10^6 residual white cells per product. Again, I am defining product as an adult transfusable dose.

[Slide]

At the Blood Institute, as I remarked, all of our platelets are single donor. All are leukocyte reduced to less than 1 X 10^6 residual white cells per product since April of 1996. We have been using both the filtration technology as well as the machine technology. The results are incredibly good with both technologies. If you look at the average residual white cell content -- and remember that the quality control or the counting techniques, that is, the ability or methods to do low cell concentration counting are very difficult -- our products are between 3-5 X 10^4 residual leukocytes per product. So, all of these technologies are, in fact, very good.

For our red cells we do not do 100 percent quality control. That would be an absolutely overwhelming process. It already is with the platelets. But there, again, the red cells in our system that are leukoreduced -- this is currently only by filtration technology -- our goal is to, in fact, do 100 percent within the next 2 years, and perhaps

this committee can help.

[Slide]

As Dr. Snyder remarked, the leukoreduction of blood products currently is for red cells and platelets. But the issue of whether the plasma products should be leukoreduced I think is one that is up for question at this point in time. In fact, there are significant numbers of white cells in plasma products or plasma-derived products, and the question as to whether the white cells should be removed is one that, again, remains to be answered but, again, I agree with you, Dr. Snyder, that this may be an important issue as well.

[Slide]

Looking at the methods of leukoreduction, basically they fall into two types, the filtration technology and what I call the patented machine technology. The filtration technology is used at this point exclusively for red cells. It is used for platelets that are whole blood derived, and there I have no data to share with you because our system is a total single donor system, and then platelets that are derived by apheresis technology, and I will show one of those systems.

There are two patented machine technology systems, the Amicus and the Spectra LRS of Baxter and COBE respectively, and we currenlty use all of these

technologies, the filtration and the patented machine technology at the Blood Institute.

[Slide]

Just quickly, again I am not trying to support any particular company. I will show you quickly a picture of all of the filters and machine technologies. This is a red cell filter which is currently used by the Blood Institute for red cell leukoreduction.

[Slide]

This is a filter that is used on our platelet preparations, or at least some of them, made by the Pall Corporation.

[Slide]

Here is a Haemonetics device which uses filtration as its method of leukoreduction.

[Slide]

Then, here are the other two devices. Again, we use all of these at the Blood Institute, the COBE Spectra which has the LRS leukoreduction system.

[Slide]

Then the newest machine, the Baxter Amicus.

[Slide]

Again, all of these machines and filters do the job extremely well.

[Slide]

Let's focus for a moment on red cells and then we will focus on platelets. With red cell systems one can use an inline filter or one can use a sterile connection. The advantages and disadvantages are listed on the slide for you.

With the inline filter, we have one disposable with the filter inline. An advantage here is that we have no sterile connecting to do. It is clearly easier to use. But a disadvantage from the standpoint of the blood center, and I know the "C" word is something we don't want to address but it is more costly in general to use the inline filters, in part because, and I think this is important to present, there is the loss of an expensive disposable if there is an incomplete collection or if, in fact, the test results on that unit are positive. So, you have lost the filter as well as the collection container.

Using the sterile connection process, you have two disposables. You have the blood pack and, of course, the filter. The advantage here is that it is generally cheaper. You only have to filter what I will call the usable units. That is, one can do the processing, the laboratory testing, and if your laboratory is set up so that you can do this quickly enough, you can achieve what I define as prestorage leukocyte reduction, meaning that the product is reduced of white cell content within 20 hours of collection. When you

get beyond 20-24 hours of collection you are going to have granulocyte breakdown, release of cell fragments, cytokines into the milieu of the product.

The disadvantage of the sterile connected systems is that they are a little more complex to use, and it does require the sterile connection. But the reality is that the end result, the product that is leukocyte reduced is identical whichever technique is used.

[Slide]

To show you some data on leukocyte reduction, in July our institution leukocyte reduced 1960 red cells, in August, 1806. Although that is a slight decrease, actually our numbers are continuing to go up. These were all prepared by prestorage leukocyte reduction using the filtration system with the Asahi SepaCell filter. This, as I said before, represents about 20 percent of the usable red cells, all done by sterile docking.

[Slide]

With respect to platelets, in June, July and August we did a total of 4242 single donor platelets, of which 3898, about 92 percent, were leukocyte reduced by filtration technology and 344, a little more than 8 percent, were leukocyte reduced by the machine technology. I want you to sort of remember those numbers for a moment.

[Slide]

The current quality control is to sample 1 percent, or if less than 400 procedures per month of a product then test 4 per month of each leukocyte reduced product. The sampling, as we understand it, is per site that is performing the leukoreduction. With red cells, there is a requirement currently for 85 percent post-filtration retention. For platelet pheresis, there is a requirement for 85 percent post-filtration retention, or less than 5 X 10^6 white cells per product if no secondary processing occurs. That is, if one uses machine technology. Again, one of the questions I was asked to address is should we redefine this standard, and I have said yes and I will address that more in a moment.

[Slide]

In looking at quality control, and this is specifically on the red cells, and I will show you in a moment the platelets -- we have literally mountains of data -- with respect to red cells, we quality controlled 41 products in July and August.

This is what the data looks like. For products that are less than 5 X 10^6 but greater than 1 X 10^6 there were 2/41, or 4.9 percent. Remember, in the U.S. the current standard is less than 5 X 10^6; in Europe it is less than 1 X 10^6. We, at OBI have, in fact, adopted the European standard so internally our standard is to achieve

both red cell and white cell products that are less than 1 X 10^6.

If you look at the current U.S. standard, all 41 products were less than 5 X 10^6, but if we use 1 X 10^6 then about 5 percent of the products failed with the red cell filtration. The average red cell recovery was 89.1 percent, and this should say 85 percent, not 80. All red cell units were greater than 85 percent recovery. So, that was not an issue.

[Slide]

This slide, unfortunately, is somewhat busy and I will explain it to you because it is an important slide. It represents what, again, I refer to as product failures. I think this is an important way to talk about failures. Instead of using the term filter failure or machine failure, it is really a failure of the product to meet the specifications which we have set internally. I want to go over this with you, looking at the summary data.

Again, there were 4242 procedures that were performed, and then the breakdown as to whether they were filtered or whether they were machine technology. If you look at the number of failures of the products, there was a total, out of this 4242 for the 3 months, June, July and August, of 92 products that failed that were between greater than 1 X 10^6 but less than 5 X 10^6. That represented 2.17

percent or the products. On the other hand, for the number of products that were greater than 5 X 10^6 there was a total of 45 products, and that represented 1.06 percent.

Again, I am presenting this data to you to show you the product failures that will occur with the current technology, depending on the standard that one would use, with the current U.S. standard being less than 5 X 10^6, and the European standard and the OBI standard of less than 1 X 10^6.

Now, if we look at these product failures by the particular type of technique or process used, with the filtration there were 39/3898, which comes out to be exactly, so to speak, 1 percent, greater than 5 X 10^6 residual white cells. But if we look at the filtration processes where we have product failures using the standard of less than 1 X 10^6, so between greater than 1 and less than 5, there were 88 failures, or 2.26 percent, with the total aggregate then of about 3.26 percent.

If you look at machine production and the failures that occurred in the products here, you will notice that, although the numbers are not very great, essentially we get the same sort of data except that it is the reverse. There is a higher number of products that failed in terms of being greater than 5 X 10^6, that is 6 products out of 344, versus 4 products that failed between greater than 1 and less than

5 X 10^6.

But the point is that both technologies are very good. However, as one defines a tighter standard, in this case less than 1 X 10^6 residual white cells, it is going to be more difficult to predict which products, in fact, will fail. That is one of the things that we have looked at.

We have looked at predictors of product failure specifically with respect to platelets by apheresis. The reason we have been able to do that is that for the last 3 years we have counted 100 percent of the platelets by low cell concentration counting techniques, which I am going to go over with you briefly in a moment.

[Slide]

Here are what we have found to be predictors of product failure. Again, I think this is important as we redefine the standards. Any time there was an operator intervention of an automated procedure there was likely to be a failure of the product to achieve the desired result. Clearly, whenever there was a visible bloody product, regardless of the cause -- and I have listed for you some of the causes of why a product, and I am talking specifically again about platelet products, could be bloody. That is lipemia. There can be machine malfunction or operator intervention. So, this is a signal.

Very clearly, low predonation counts. You might

have thought that I would have said high predonation white cell counts. Not so. That was nearly as much a predictor as a low predonation platelet count. That relates to number 4, where you do high volume of blood processed. This stands out on its own because many of the blood centers today want to collect what are called double products. If you have a donor with an average predonation platelet count and you are attempting to collect a double product and do high volume blood processing, you are more likely to see a failure in the desired level of white cells in the product.

Then, clearly, the donor who is lipemic. Then machine malfunction. So, in our system if any of these occur, then those are products, even though currently we are counting everything, that would clearly require counting.

[Slide]

Dr. Snyder addressed this issue so I won't belabor it at all. That is, is there a difference between filtration versus machine technology? There are no measurable granulocytes or monocytes using the filtration technology, as you saw from the paper that was presented that was recently published in Transfusion. Filtration essentially is removing virtually all of the granulocytes and monocytes, whereas, the machine technology may leave a few granulocytes and monocytes, and both leave a few of the B and T lymphocytes. The question is, is there really a

difference in the product? I don't think that any data exist to support one or the other being better.

[Slide]

An issue that I think is very important is the issue of prestorage versus bedside. You can see clearly how I feel from this slide. With prestorage where we prepare the leukocyte reduced at the time of collection or within 20 hours of collection, it really allows for all the white cells that are within the product to be removed. That is, they have the chance to be removed. Clearly, the procedure can be validated, and I think that is extremely important. One can adhere then to strict process control once the procedure has been validated, and there is the ability to quality control the product.

With respect to bedside filtration, none of this really exists. Leukoreduction obviously occurs during the administration of the red cell or platelet product if it is being done at the bedside by virtue of the fact that the unit of blood has had to be processed in the laboratory, virtually always that product is beyond 24 hours of age and, therefore, granulocyte lysis will have occurred, releasing cytokines and cell fragments. This is a procedure that is difficult to validate -- in my opinion, impossible. It is impossible to control the process really, and there really is no adequate quality control of the product that is being

administered to the patient.

So, I think what is important is that if we are going to talk about leukocyte reduction, the bedside leukocyte reduction really is not, in my opinion, an adequate form of leukocyte reduction. We really should be focusing on prestorage where, in fact, we can achieve products that will have very low levels.

[Slide]

I only put this slide in to emphasize how good the filters are today. We are in a third generation of filters. We are achieving log reductions that exceed 3-4 log reductions. The machine technology clearly is in the same range, 3-4, and, in fact, sometimes both with filters and machine technology we are achieving almost close to 4.5 log reductions of white cell content from the original product or the material presented to the machine.

[Slide]

What about the issue of quality control? This is, I think, a very important and very serious issue because it is very difficult to do low cell concentration counting. The standard, so to speak, in the industry is the Nageotte full chamber count. That is currently what we use at the Blood Institute. Aalthough we have done parallel studies using flow cytometry and a newer technology called spatial laser imaging, in fact, our data shows that both the flow

cytometry and spatial laser imaging, for practical purposes, are equivalent.

I want to take a second and just say something about the spatial laser imaging technique because it is not nearly as operator dependent as, for example, flow cytometry. That is, it is an easier technology to train someone to do and the results are more consistent. The flow cytometry is, I think, more of a research-based technology and it is more difficult to do. Again, the two clearly parallel very equally comparing it to the Nageotte full chamber counting, which is a manual technology. Remember that we are going to be counting at levels that are equivalent to 1 white cell or even as low as 0.1 white cells per microliter.

[Slide]

This is what the spatial laser imaging device looks like.

[Slide]

It uses a special cuvette which is easily loaded and, therefore, it is a simpler technology. Again, I am not supporting any particular technology, it is just that the Nageotte full chamber counting, a manual technology, is difficult and really can drive the technologist crazy when you are doing literally thousands of these, and you can see the numbers that we did -- if you remember, 4200 in a period

of 3 months. So, you can multiply that to see the number that we are doing per year.

[Slide]

In the letter that was sent to me from the FDA there were some questions that I was, at least in part, asked to address. One of the questions was should the current definition of leukoreduction or leukocyte reduction remain the same, that is, less than 5 X 10^6 residual leukocytes per container?

[Slide]

Well, I think I have already made the point that I believe that it should not be. I believe that we should adopt a tighter standard. The Europeans have done so. I think the end result outcomes would be improved if we did that. Leukoreduction, I think, should be less than 1 X 10^6 residual leukocytes per transfused dose for an adult person, and we can define that as per container.

But I think that part does need some work because one of the things that I, again, feel is important is to define is dose of the product. Again, Europeans use different doses in different countries. The standard in the United States has been, for example with platelets, greater than or equal to 3 X 10^{11} platelets. But should that be greater than or equal to 3 X 10^{11} leukocyte reduced platelets? Clearly, these filtration technologies will

reduce the number of platelets in the product that is being presented to the filter, whereas with the patented machine technology we are, in fact, getting a product that is in effect leukocyte reduced as it is being produced.

I think the definition of the product should be that we are talking about greater than or equal to 3 X 10^{11} platelets per leukocyte reduced product. We can do the same with red cells, depending on whether we were drawing in a 450 or 500 mL aliquot, and I won't get into that because of time.

[Slide]

A second question that I was asked to address is, are current methods of leukoreduction sufficiently reliable and reproducible for all recognized indications for using leukocyte reduced blood components? Well, we have heard what Dr. Snyder has had to say for what are current indications. But, in fact, depending on the patient, their disease, etc., the recognized indications can vary all over the place.

[Slide]

Our response to this is that bedside filtration should clearly be discouraged and only used as a last alternative. Again, that is because the product cannot be quality controlled and leukoreduction at the bedside cannot be process controlled very well. Prestorage leukoreduction

with a validated procedure, using strict process control and adequate control of the final product should be our major option or method to achieve the desired result.

[Slide]

My last slide, what are the desired results? Dr. Snyder, I think, has very beautifully discussed this and illustrated these: Clearly, prevention of febrile non-hemolytic transfusion reactions, prevention of alloimmunization, prevention of CMV transmission, and you note that I have put here possibly HTLV.

We already know that both CMV and HTLV are not transmitted by frozen blood products, presumably because of the destruction in some way of the white cell and of the virus associated with that white cell. There is some data currently to suggest that HTLV itself might also be reduced.

The reduction of bacterial contamination of blood products -- I think this is a desired end result.

Reduction of immunosuppressive effects, which you so nicely elucidated, Dr. Snyder, and I will not discuss.

Then, the reduction potentially of what are called reactivation diseases from endogenous viruses.

Then, the last point here, and here I perhaps slightly differ from the two prior presenters in that I do see an advantage to leukocyte reduction in preventing transfusion-associated graft-versus-host disease, not to

replace irradiation but to, in fact, serve as an adjunct to irradiation. In our system all products which are irradiated are now also leukocyte reduced to further enhance the effectiveness, so to speak, of the irradiation because there have been occasional irradiation failures that have been reported, and we believe that leukoreduction, if it achieves the desired levels, may in fact also act as an adjunct to irradiation.

So in summary, to go back to the first points that I made at the beginning of my talk, I will readdress those for you. The process of leukocyte reduction, I think, really requires very strict process control, and I don't think that that can be achieved by using bedside filtration. I think that this really has to be a prestorage phenomenon if we are really going to achieve the desired results.

The quality control of the product is a critical issue. It is very difficult to do Nageotte counting. I think the time has come to have other methods of counting with validated processes, specifically flow cytometry and spatial laser imaging.

Prediction of product failures -- I think this should be included in future recommendations so that those of us who are generating these blood products can predict which products will fail to achieve the desired end result and, therefore, those products would specifically be quality

controlled before they would be released as a leukocyte reduced product.

The last point, again, is redefining the definition and standards for leukoreduction. I think the time has come to drop that standard from less than 5 to now less than 1 X 10^6 residual white cells.

Thank you.

DR. HOLLINGER: Thank you, Ron. We are now going to move toward the topic of the international experience and two sites that are using leukoreduction for various reasons and under various terms. So, the first one will be Dr. Lorna Williamson, from the University of Cambridge, the United Kingdom.

International Experience

United Kingdom

DR. WILLIAMSON: Good morning. Thank you very much for inviting me to come and share with you some of the thoughts we have had in the U.K. regarding the subject of universal leukocyte depletion. Dr. Smallwood tells me I have 15 minutes. This may mean your coffee break is sacrificed but I will try and get through what I have to say in the time. There is a lot to cover, as you might imagine.

[Slide]

So, what I want to do is three things: firstly, tell you where we were in the U.K. with leukocyte depletion

prior to the events of the last 12 months surrounding new variant CJD. The second thing is to tell you the process by which the decision to undertake universal leukocyte depletion was reached. Thirdly, and this is work in progress, share with you where we have got to in considering our implementation plan, and the operational, scientific and medical aspects of that.

[Slide]

The heading more accurately should say U.K., but the data on the first slide relate to England. Prior to recent events, leukocyte depletion in the U.K. took place only on a minority of products. Around 5 percent of red cells and somewhere in the region of 50 percent of platelets were subject to some process of leukoreduction, not necessarily one which I would classify as leukocyte depletion, as I will discuss. Some of this was undertaken in blood centers and some of it at the bedside. So, totally reliable figures for how much was going on were difficult to come by.

We first considered the question of leukocyte depletion in the U.K. back in 1993 when a consensus conference was held, in Edinborough. After some considerable time, mainly because we were awaiting the results of the TRAP study, the British Committee for Standards and Hematology Transfusion Task Force came up with

some guidelines, which I have provided to Dr. Smallwood for distribution, in March of this year.

I should say that the BCSH is an offshoot of the British Society for Hematology. It is a professional body composed of hospital hematologists and transfusionists. It is not a regulatory body as such, but has produced over the years a number of clinical guidelines relating to transfusion practice.

I am going to give you the salient points of those guidelines. The first point was that we clearly wanted to differentiate between bedside filtration as a process and leukocyte depletion as a process. We concurred totally with the previous speaker's views that the two activities, if you like, could not be considered equivalent, mainly for three reasons:

Number one, the start product is completely different in the case of bedside filtration where there is no control over the age of the component. It is full of cytokines, as you eloquently heard this morning. There are cell fragments there. It is not the same product that you have in the prestorage situation on day 0 or day 1.

Secondly, we couldn't see how you could discuss leukocyte depletion without coming up with a recommended figure for residual white count. That then implied that you could count residual white count and, clearly, bedside

filtration is not amenable to quality control. You cannot count residual white cells because they are in the patient.

The third point, which is perhaps slightly less critical but, nevertheless, important is that we are beginning to understand the optimal conditions for filtration, and with many filters bedside filtration is the worst possible scenario. It is slow, and the blood has had a chance to warm up. Both factors, we know, have an adverse impact on the process. So they are not the same, and we mix them up at our peril I think.

Did the committee conclude, therefore, that bedside filtration had no purpose at all? Well, more or less, actually, but not quite because the evidence does suggest that if you are trying to prevent febrile reactions to red cells -- not to platelets but to red cells, then bedside filtration does appear to be efficacious. However, in the U.K. we have the advantage of production of intermediate products. We have red cells where the buffy coat has been removed, giving around 80-90 percent leukocyte removal. We have platelets produced by the buffy coat pool method. Both these products, in and of themselves, without filtration are associated with a low rate of febrile reactions. So, there is not the same requirement in the U.K. to undertake wholesale filtration solely to prevent febrile reactions.

So, we moved on then to consider that leukocyte depletion should be done in blood centers for limited indications. I am going to come back to the question of residual white count in a minute.

[Slide]

These indications really were very limited. We recommend leukocyte depletion of blood which is going to be used for transfusion, be that red cell or platelet transfusion; transfusion of neonates, and at the request of the Department of Health extended this to infants up to one year of age. We can discuss, if you like, later why that was included. We thought that patients who had febrile reactions despite the use of intermediate leukoreduced, buffy coat reduced red cells or standard platelets should have components which have been leukocyte depleted prestorage.

Prevention of HLA alloimmunization is an interesting subject, and what we felt was that clinical benefit in terms of death, bleeding, and need for increased transfusions had not really been demonstrated in clinical scenarios, other than severe aplastic anemia in which prior exposure to donor leukocyte HLA antigens has been associated with reduced engraftment of allogeneic marrow in patients who go on to this procedure. So, now in the U.K., young potentially transplantable patients with severe aplastic

anemia are given leukocyte depleted blood and platelets from the outset.

This document also considered -- and, remember, it is a clinical guideline, not a regulatory document -- that there was sufficient evidence to regard leukodepleted components as equivalent to CMV seronegative ones based on a number of studies where leukocyte reduction was performed prior to storage and the cumulated total of transmissions in these studies was actually zero, despite the fact that many of the studies are now quite old, and the level of leukocyte reduction obtained was pretty feeble by today's standards.

The study which Dr. Snyder discussed in some detail, the Bowden study, where there did appear to be breakthrough transmission from leukocyte depleted components -- I should perhaps emphasize that that was a study of bedside filtration and, therefore, cannot quite, I believe, be considered analogous to all the previous studies. However, the U.K. transfusion services at this point still test for CMV, although a number of clinicians are beginning to feel comfortable to use leukocyte depleted components instead.

We estimated that to meet these requirements would probably require leukocyte depletion of no more than 10 percent of red cells and 50 percent platelets. Then the world turned on its head.

[Slide]

So, a lot has happened in 12 months. Last October, two papers appeared in Nature, which for the first time provided some evidence -- pathological in this paper and biochemical in this paper -- that the new variant form of CJD restricted to the U.K., apart from one case in France, could be related to BSE. Subsequent to that, there has been some evidence, and it is not hard scientific -- it is not from data by any means, firstly, of infectivity of buffy coat by Paul Brown's group at NIH, I think published this month in Transfusion, and the paper in Nature from Prof. Aguzzi's group in Zurich, showing that in an experimental model TSE B lymphocytes were necessary for transfer of agent from the periphery to the brain.

Now, it requires a great leap of faith to go from these small pieces of evidence to a scientifically based decision to leukocyte deplete the entire blood supply. However, there is in the U.K. in government circles something called the precautionary principle, and it is worth reading out because in the context of new variant CJD this probably applies, and it says that we must act on facts, and on the most accurate interpretation of them, using the best scientific information. This does not mean we must sit back until we have 100 percent evidence about everything.

Where the state of health of the people is at stake, the risks can be so high, and the costs of corrective actions so great that prevention is better than cure. We must analyze the possible benefits and costs of action and inaction, in other words, waiting for good data. Where there are significant risks of damage to the public health, and I guess a new variant CJD epidemic would come into that category, we should be prepared to take action to diminish those risks even when the scientific evidence is not conclusive if the balance of likely costs and benefits justifies it. So, that is the precautionary principle which I think could be applied to this case.

Just another bit of data -- a couple of papers and some unpublished work showing that the normal prion protein is expressed very well on platelets. Most leukocyte reduction filters do also remove platelets except, of course, where platelets are the component you wish to transfuse. That is just a little observation.

[Slide]

I want to just clarify something Dr. Lee said because I wouldn't want the committee to have the impression that the decision was actually taken by the U.K. transfusion authorities. The decision was taken by the Department of Health by the following process. The Spongiform Encephalopathy Advisory Committee, which advises government

on BSE and now also on new variant CJD, obviously considers all evidence relating to this issue.

As a response to the two papers published in October, last year, the Secretary of State for Health commissioned two things: an independent risk assessment of new variant CJD and transfusion, and this has been carried out by an independent risk assessment company by the name of Det Norske Veritas (DNV) who have worked with the government on issues relating to BSE. This report has been in the hands of ministers in several drafts over the last six months. It isn't yet published. We understand that it will eventually be published and, clearly, would be of interest to you, I am sure.

At the same time, last November, the U.K. transfusion services were asked to submit a feasibility report on universal leukoreduction.

[Slide]

The time line for submission of this report was February of this year. So, we have three months including Christmas to work on this. So, what was submitted and eventually accepted by government was a very preliminary document, and I have provided it, again, to the committee.

I will tell you the salient points of this in a minute. Following submission of this report we all felt we would like to go on holiday but we couldn't really because

we thought we should get on and establish a project implementation board, assuming that at some point the decision to leukocyte deplete the entire blood supply would come and we wanted to gain some planning time and, sure enough, in July the Secretary of State for Health announced that universal leukoreduction would be introduced, and I have put in italics the very important words, "without jeopardizing the blood supply."

I think that has two implications. One, let's do it in a sensible time scale and, two, let's do it in a way that doesn't prejudice the availability of product. When we come to talk about quality control, that is a very important point.

The Secretary of State did not at that point specify an implementation date, but further work and further discussion has resulted in a decision that by the November 1, 1999, which happens to be my birthday, we will have 100 percent leukocyte depletion of the blood supply.

[Slide]

So, the salient points of the feasibility report are the following: With regard to new variant CJD, we have no idea what target we are trying to hit in terms of residual numbers. We have no great confidence at this point that we can reliably count leukocyte types -- monocytes, granulocytes, leukocytes -- far less than we can tell you

how many T cells and B cells we have. So, we took the view that we would go for this target, which is less than 5 million per unit of red cells or per adult therapeutic dose of platelets.

I think I should clarify some remarks from the previous speaker around the apparent difference between the U.S. and European specifications because they are more apparent than real actually. The Council of Europe document does specify a residual count of 1 X 10^6 cells per unit, but the next bit of a sentence says, in 90 percent of units processed. Statistically, we felt that we would rather have a specification that applied to a higher percentage of units even if that specification were slightly higher. So, we have gone for a specification of less than 5 million but we have to achieve it nominally, and it has to be nominal 100 percent of the time. If you look at the distribution, actually, 1 million 90 percent of the time and 5 million 99 percent of the time are not so different actually. So, that is where we are with specification.

We thought it would take 12-18 months, and we wanted to use existing technology to begin with simply because of the very tight time line. This is extremely challenging. And, we are not going to talk about cost, which is nice, but one very important point is that in contrast to previous introductions of mandatory microbiology

screening tests where we have had a D-day -- on that day all blood on the shelf will have been tested for HIV -- we cannot do that for universal leukoreduction. We cannot go from 5 percent to 100 percent over a weekend. So, there is going to be a gradual, and in some cases quite protracted ramp-up from the current position to 100 percent, and that has possibly some medical-legal considerations around the fact that we will have a mixed economy for some time.

[Slide]

The way we want to get there operationally, and clearly many suppliers beat a record path to our door following this announcement, but we felt we should, at least to begin with until we had some confidence in what we were doing, use suppliers whom we know and love and also, where possible, team up blood banks and filters.

I should say a little about approval in the U.K. All bags and filters are approved by the Medical Devices Agency, but because this approval can be Europe-wide, systems can be approved and marketed in the U.K. without us ever having looked at them. So, what we are trying to do is, we have developed quite a formal process of blood service in England for putting blood bags onto our approved list, and we want to do the same with filters.

Because we want to eventually move towards integral filtration, despite some of the drawbacks you have

heard, our initial evaluations are around blood bags from companies where we already use their filters, or filters from companies where we already use their bags. We have drawn up a national evaluation protocol which for filters consists of a small phase trial, if you like, on a small number of components, tested for many parameters including relevant biological response modifiers, the most important at the moment being bradykinin, and looking at storage data, coagulation activation, complement activation, and so on, and then going to large-scale field trials where we can learn something about blockages, breakages and product failures.

We will maximize apheresis capacity using our current donor base, using obviously systems which have the capability to provide a leukocyte depleted component -- one already in widespread use, a second under evaluation. Filters now exist from two or three manufacturers to filter whole blood. You may be aware that another decision which fell out of the new variant CJD problem is that U.K. plasma is no longer fractionated; it is disposed of, other than clinical FFP. So, we will filter whole blood as far as possible, but with one possible exception. All whole blood filters also remove platelets. So, clearly, for units of blood from which we wish to manufacture platelets we will have to undertake separate filtration of red cells,

platelets, and we will do FFP because less than 5 X 10^6 is not always achieved. We will have to use the dock-on-filters we know and love at the moment, but with moves towards integral systems.

[Slide]

So, we have drawn up a user specification, which we can go through fairly quickly I think. It will all be done in the blood centers. None of it will be bedside. This is the residual, 5 million, and we have said in 100 percent of the units with greater than 99 percent confidence, and I have an overhead on quality assurance in a minute.

We have decided that the balance between early filtration and a specification we can live with over 4-day bank holiday weekends, and so on, is that everything will be done by the end of day 2 after collection. That will be computer controlled through our mainframe production computer.

We considered whether we needed a hold time of a few hours following collection to allow cell sterilization, but felt that this would be inconsistent with our current practice of issuing platelets which had been leukocyte depleted on apheresis machines. So, we haven't built in a consistent hold time for red cells. They can be filtered either warm on the day of collection, or cold the next day

because if you can cool red cells filtration is more efficacious.

We would like to keep at least two manufacturers of each filter type in the frame so that we have some flexibility of contracting.

DR. HOLLINGER: Dr. Williamson, could you bring your talk to a close?

DR. WILLIAMSON: Sure.

[Slide]

Some desirables -- clearly, we would like to have filters which spare platelets. We would like to have good methods of measuring leukocyte subtypes. We need to understand more about fragmentation and activation, and the Department of Health has just agreed to fund a study on this.

[Slide]

I need to spend one minute on quality monitoring because it is so important. We will not count every unit. This would clearly have some impact on product availability we think. We have been greatly helped by publication of the BEST guidelines because we didn't feel 1 percent quality monitoring for something this important was quite enough, and we are looking at different ways of using statistical process control after process validation to national protocols.

I agree with the previous speaker. We have to move to flow cytometry, which is currently used in many centers, and the imaging system which he described. We also need a quality assurance scheme for white cell counting so that we know that different centers are counting in the same way.

[Slide]

The last couple of slides -- can we eventually stop CMV testing? Probably not yet. We don't test for HTLV in the U.K., but leukocyte reduction would be expected to reduce that risk. Febrile reactions and alloimmunization will become less. Bacterial contamination may be better recognized as other causes of febrile reactions are removed from the system. We are taking advantage of this to try to conduct a cohort study on length of stay in postoperative infection now compared to 12, 18 months time to see if we can get a better handle on the immunomodulation question.

[Slide]

The last slide -- will there be problems? I think there will be some problems. The rest of the slide is all the ones we don't know about yet. But we won't perhaps have an increased wastage of units. Obviously, you lose cells in the filter.

Will there be an increased bacterial risk? There is no evidence but we will see some side effects. We know

about red eye and hypotension. There must be some out there that have yet to happen and which may show up only when large populations are exposed to filtered products. And, we do have a system in the U.K. called SHOT, which is designed to receive and collate reports of transfusion hazards.

Thank you for your patience.

DR. HOLLINGER: Thank you, Dr. Williamson. The last speaker before the break is Dr. John Freedman, from Saint Michael's Hospital in Toronto. Dr. Freedman?

Canada

DR. FREEDMAN: Mr. Chairman, members of the committee, thank you for inviting me as a member of the Scientific Advisory Committee of the Canadian Blood Agency to talk to you, I am afraid also for 15 minutes, about how we arrived at the current leukoreduction policy in Canada.

[Slide]

I am not going to talk about the science. In fact, with regard to that, I would echo the excellent comments of the speakers before, but I am going to talk to you more about the steps that were taken to achieve a decision in Canada.

[Slide]

The Scientific Advisory Committee was set up in 1992, and right from its inception began to talk about issues related to leukoreduction in terms of blood product

safety, and at its meetings probably two to three times a year the issue was raised with updates.

In May, 1993, the Canadian Blood Agency sponsored a symposium by the Canadian Red Cross Society to review the issues, and it had a panel of seven or eight speakers who addressed various clinical issues and also logistic issues related to leukoreduction.

It is of some interest that the 200 transfusionists in attendance were polled after the conference and the vast majority felt that the indications, as outlined by Dr. Snyder, were, indeed, valid clinical indications. About 60 percent of the attendees felt that the process would be, in fact, cost effective. Only about 30 percent wanted it to be universal leukoreduction. That 30 percent, however, did represent a doubling of the number in a poll taken prior to the conference.

In June of 1994, at a meeting between the Scientific Advisory Committee with representatives from the Canadian Red Cross, we were informed that the Red Cross would be providing a proposal to the Canadian Blood Agency for funding for prestorage leukodepletion once guidelines were developed by the Canadian Hematology Society. To the best of my knowledge, such guidelines have not as yet been developed.

But in July, 1996 the Red Cross did submit a

proposal for filtering platelets, 50 percent of the inventory, and in the fall of that year the advisory committee was asked formally to assess the situation.

[Slide]

Just as a small bit of background, the Canadian Red Cross annually provides almost half a million units of random donor platelets, and in its proposal it estimated the incidence of significant febrile non-hemolytic transfusion reactions to be around 20 percent.

It acknowledged the FDA workshop on leukoreduced products, that third generation leuko-filters were the current standard of practice in preventing febrile reactions, and requested 9 million dollars for the use of 100,000 bedside filters, and felt that part of this cost would be recovered -- I am sorry, for prestorage leukodepletion, and felt that part of this cost would be recovered by not using bedside filters, and there would also be a significant cost saving from reducing the clinical adverse events of unfiltered products.

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In its review, the Scientific Advisory Committee had some concerns with the Red Cross proposal. It was concerned that it was essentially exclusively focused on febrile reactions. It did not address guidelines for use. There are febrile reactions, and there are febrile reactions

and they are not all equivalent in severity or significance. There was some cost-benefit analysis but no specifics on the costing were provided. There was no background information provided regarding the assumptions made or the forecasts for demand. And, we knew from limited studies that where its use was made available for febrile reactions, it didn't take very long before it was being asked for, for every transfusion.

There was a minor concern that two inventories of platelets might cause operational problems for hospitals, but that was minor.

Of more concern was that there was no plan provided, as is required by the CBA's strategy on utilization, for monitoring utilization. Filtration of other blood components was not addressed in the proposal. Alternative approaches, such as plasma-reduced platelets, were not assessed. At the time, we were still awaiting anticipated industry submission about technology feasibility. We also felt we had to wait for the results of the TRAP study.

Nonetheless, the advisory committee members did agree that the Red Cross proposal fitted in with the general direction of improved safety and recommended that more information be obtained.

[Slide]

In fact, the minutes stated it was agreed that evidence as to benefits of leukoreduction continue to accumulate and that these benefits relate to alloimmunization, immunomodulation, febrile transfusion reactions, and reduction of transmissible infection. I am here specifically referring to CMV, with some allusion to HTLV-I/II.

In addition, the evidence indicates that prestorage filtration is superior to poststorage. So, the specific recommendation was made that red cells and platelets be leukoreduced universally; that prestorage is preferable and leukoreduction should result in a threshold white cell count of equal or less than 1 X 10^6 for transfusion or lower as the scientific evidence in the future may indicate; and that a utilization management plan and outcome evaluation must be developed along with the implementation.

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This report and recommendation was submitted to the Canadian Blood Agency in February, 1997 and shortly thereafter Health Canada Commission received an extensive assessment of the technologies available from Dr. Zeik. The following month a meeting was convened in Winnipeg to discuss leukodepletion.

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This meeting was attended by a group comprised of members of the advisory committee, officers of the Canadian Blood Agency and, importantly, a number of members of the Board of Directors of the Canadian Blood Agency. There were guest speakers in addition to those on the advisory committee, Dr. Slichter, Dr. Blajchman and Dr. Blanchette, who spoke about various clinical aspects, and half the day was taken discussing the scientific evidence for leukodepletion. The other half of the day was spent talking about the logistics of implementation, were this to be done. At this meeting were also two invited people from an organization called CCOHTA. This stands for Canadian Coordinated Office for Health Technology Assessment.

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The issues specifically discussed were a review of the Red Cross proposal, a review of a submission from a supplier. The alloimmunization data was reviewed, the febrile reactions, the logistical issues to consider when evaluating leukodepletion. The results of the TRAP study were discussed, as was immunomodulation and logistical issues.

The consensus of pretty well all the people there at the end of that day was that although outside of febrile reactions definitive evidence of benefits of leukodepletion were not absolute, the cumulative or aggregate evidence was,

indeed, compelling and that one should proceed.

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Concomitant with this, over the same time period, there was in Canada a quite audible increase in popular vocal desire for leukodepletion by transfusionists. It was also evidenced that through this time period the use of leukofilters and bedside filters in hospitals increased quite significantly, and a number of major university hospitals were providing bedside filtration for all blood products. Other hospitals were providing little leukofiltered products. There was certainly a variable practice throughout the country.

It was also becoming evident that there was an increasing use of single donor apheresis platelets, primarily to manage patients with febrile non-hemolytic transfusion reactions.

In the summer of 1997, the CBA asked this private company, CCHOTA, the Canadian Coordinating Office for Technology Assessment, to perform a cost effectiveness study on the issue of leukofiltration.

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This full report, all 80-odd pages of it, has been supplied I believe to the members of the committee and I don't intend to discuss it as such, but just to indicate for the other members of the audience the things that were

covered were an extensive literature review of the topic, with evidence-based guidelines included. The current situation in Canada was reviewed, clinical issues and the sequelae of adverse reactions to non-filtered products. Filtration techniques, the different types of techniques and their pros and cons and costs were evaluated, and there was an extensive cost comparison of the potential approaches.

[Slide]

I put in only this slide to show you the nine different approaches that were considered in this extensive analysis. Really, we are looking at apheresis platelets, pooled platelets and red cells, and in each case either prestorage filtration, blood bank filtration or bedside filtration of the products. So, this leads to nine options.

[Slide]

As I say, you have the report. It is fairly clear, and it was submitted to the Canadian Blood Agency and the Canadian Blood Agency gave final approval in September, 1997 but only for leukodepletion of platelet products for implementation in 1998, and, in fact, implementation occurred in February-March of this year.

I just want to indicate to you some of the issues that have come about as a result of the implementation. Initially, blood centers found it quite difficult but really within a month they were quite familiar with the whole

process, and there haven't been major difficulties.

For the Toronto Center, which I think is the largest center in Canada, preparing around 90,000 units a year, they had to add an additional 1.5 technologists for this approach. The filtering time, they found, took about 10-15 minutes. This was mostly composed of little things like having to put the bags in centrifuges, adjusting Velcro tabs, and so on. With batching of the products they needed more expressors in a row. So, it needed minor physical changes in the laboratories just to have more bench space but this was relatively minor.

Initially, a large number of the platelets from the prestorage filtration process had visible aggregates, and when they were sent to the hospitals the hospitals sent them back, and rejected them. This happened with quite a number of units. However, the aggregates dispersed with time and agitation. Dr. Ballem, in Vancouver, did studies of platelet function and survival with these units and found that they were essentially normal. It must have been a technical thing because I think these aggregates are much less common now, and there is general acceptance by the hospitals of units with small amounts of aggregates.

There has been a 10-15 percent loss in platelet count per unit but virtually all of them remain within the quality assurance limits for platelet content.

There is also a white cell quality control program of 1 percent of units per month, or 32 units per month, and these counts are done centrally by flow cytometry. I reviewed the last three-month data for the Toronto Center, and the mean leukocyte content was 0.04 X 10^6 per unit. So, that is pretty low and, indeed, no units were rejecting for not meeting quality assurance standards.

To this date, and that is almost six months, there have been no adverse reactions reported to the blood center from the institutions related to leukofiltered products.

Has it reduced febrile non-hemolytic transfusion reactions? We have some small data on that. In Toronto we did a multi-institutional study of 2500 platelet transfusions to hematology patients prior to leukodepletion and then 1500 transfusions after leukodepletion was implemented. The febrile reaction rate fell from 28 percent to 17 percent. So, there clearly was a reduction but it didn't disappear.

There is an impression that there has been a reduction in the requests for single donor apheresis platelets, but this documentation is not yet complete.

Thank you very much.

DR. HOLLINGER: This completes the current practice. We are going to take a break and then return to discuss the adverse reactions to leukoreduction. By my

watch, it is now about 10:52. So, we are going to reconvene at about 11:10.

[Brief recess]

DR. HOLLINGER: We are now going to look at the adverse reactions to leukoreduction, and first the red eye reaction, and Dr. Vostal, the Senior Staff Fellow, Division of Hematology, will begin.

DR. SMALLWOOD: CDC is going to be first.

DR. HOLLINGER: I am sorry, the first one is going to be from Dr. Alonso-Echanove, from the Hospital Infections Program, CDC.

Adverse Reactions to Leukoreduction

Red Eye Reaction

DR. ALONSO-ECHANOVE: Mr. Chairman and members of the committee, thank you very much for inviting me as a member of the Center for Disease Control. I hope that our experience with the epidemiologic investigation on adverse reactions with these filters is of some help for your work.

[Slide]

We investigated, in the beginning of this year, a nationwide outbreak of adverse ocular reactions that were associated with the use of red blood cells that had been filtered and used for transfusion.

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On December 23 of 1997, the Washington State

Health Department received a report from the American Red Cross on six patients at one hospital that had developed severe ocular reactions.

All the patients had in common the fact that they were oncohematologic patients who had been multiply transfused. All the patients received leukocyte reduced red blood cells, and all of them developed severe bilateral eye redness of simultaneous onset.

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They complained of other symptoms, mostly periorbital edema, conjunctival edema, and some of them myalgias, headaches, nausea and vomiting.

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By December 31, there were 16 reactions in 3 different states reported to the American Red Cross. All the patients received LeukoNet filtered red blood cells, and 7 lot numbers were specifically associated with those reactions. By that time, the American Red Cross issued a voluntary quarantine of the red blood cell products filtered with these implicated filters.

By January 7, however, 40 reactions in 5 different states were reported, and the number of lots implicated increased to 15. So, by that time the American Red Cross increased the voluntary quarantine to all the red blood cells filtered products.

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Altogether, from November 1, 1997 through January 8, 1998, the American Red Cross reported 159 reactions in 117 patients in 16 different states. The Hospital Infection Program by that time coordinated on-site investigations in 3 different states, in Washington, Oregon and Michigan, and the results I am going to present today are the results of the investigations we conducted in one hospital in Michigan.

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For our investigation, we defined a case session as any red blood cell transfusion at hospital A during the study period, after which simultaneous onset of bilateral eye redness occurred within 24 hours. A control case session was any red blood cell transfusion within the same epidemic period after which eye redness did not occur. We found and assessed cases by phone interview and reviewing the medical chart records.

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We identified 19 reactions in 17 patients. All patients developed, as part of the case definition, bilateral simultaneous eye redness. Other common ocular symptoms were photophobia in about 50 percent of the cases; eye pain in about 40 percent; and decreased visual acuity in about 30 percent. All these ocular symptoms were significantly associated with the reactions.

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Eye redness occurred after somewhere between 4 hours to 24 hours of the start of the transfusion, and with a median of 22 hours. The duration of the symptoms lasted somewhere between 1 day to 19 days for most of the symptoms, and a median of 3-4 days for all the ocular symptoms.

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Only 4 patients sought an ophthalmologic consultation, and the diagnoses were different -- conjunctivitis, conjunctival hyperemia, iritis and periorbital hemorrhage. However, all these diagnoses are consistent with the broad syndrome of uveitis.

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As I said, the ocular symptoms were significantly more frequent in case sessions than the control sessions, but there were other symptoms and these are listed here but these are not significantly more frequent among case sessions -- headache, nausea and vomiting, fever, dyspnea, arthralgia, rash, vertigo, and the frequency was in about 5-10 percent of the cases. This could be interpreted as a background rate of reactions among LeukoNet filter transfused patients.

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The patients had a median age of 49 years. The majority were female, and had an underlying malignancy and

had received a prior transfusion. Actually, these were pretty much multi-transfused patients and received a median of 10 units of blood in the preceding 12 months before the reaction.

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We conducted three epidemiologic studies. With the first control case study we assessed risk factors for ocular reactions on all transfused patients in the epidemic period. In the second case control study we assessed risk factors for reactions, and on those transfusions where at least one leukoreduction product -- LeukoNet filter, red blood cells had been transfused. In the cohort study we assessed the distribution of the attack rate by the number of units of LeukoNet filter red blood cells received by the patients.

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To assess the transfusion-associated reactions among all transfusions, among all red blood cell transfusions, we compared 19 case sessions with 42 control sessions. As you see, 19 or 100 percent of the case sessions versus 14 or 33 percent of the control sessions received at least 1 unit of filtered red blood cells, and this difference was statistically significant. Moreover, 18, or 19 percent, of the case sessions versus 7, or 16 percent, had received at least 1 unit of a specific filter,

the LeukoNet filter. This means that case sessions were 90 times more likely to develop a reaction than the control sessions and, again it was highly statistically significant.

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Then we assessed the risk factors among the LeukoNet filter sessions. We found that the 19 case sessions had a median number of units of 2 versus 1 among the 40 control sessions. This was statistically significant again. But we also found, interestingly, that giving Benadryl before the transfusion was associated with a protective effect.

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Last, we assessed the distribution of the attack rates. Among the cohort of 321 transfusion sessions with the LeukoNet filtered blood the overall attack rate was about 6 percent. We saw a beautiful, nice dose-response relationship here, and among those who received 1 unit of LeukoNet filtered product the attack rate was 0.7 percent and among those who received 2 units it was 7.4 percent, which means almost 10 times higher than those who received 1 unit. Among those who received 3-4 units the attack rate was 25 percent, or 33.5 times higher. And, all these associations were highly statistically significant.

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So in conclusion, we investigated this nationwide

outbreak of red cell transfusions associated with adverse ocular reactions, and we implicated the LeukoNet filter red blood cells as the most likely cause of the reactions. However, we are still planning some ongoing studies in the laboratory phase to identify what the possible mechanisms are for this reaction were.

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As a result, you already know that the product was voluntarily quarantined by the Red Cross, and to identify other cases that could happen in facilities other than the Red Cross, we sent alerts to all the non-American Red Cross facilities and to professional associations and to the state epidemiologists, plus we published this in MMWR.

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As a result, although with this surveillance we received about 70 calls from potential cases, none of them were confirmed cases and so far no case has been reported from a non-American Red Cross facility nor from the American Red Cross since the product was recalled.

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I want to acknowledge all the collaborators from this investigation.

[Slide]

This is just a picture of a patient 9 days after the reaction.

Thank you very much for your attention.

DR. HOLLINGER: Thank you. The next talk I believe is going to be by Dr. Vostal, Senior Staff Fellow, Division of Hematology.

DR. VOSTAL: Thank you for this opportunity to present a brief overview of the FDA investigation, and the rationale behind this investigation, into the causes of the red eye reactions.

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When it became clear that the process of leukoreduction was associated with these red eye reactions we considered these potential factors as being the causes of these reactions. We considered that there would be an active bacterial or viral infection that was transmitted during leukoreduction. We have also considered that there were some leftover bacterial products, or fungal products, or bacterial endotoxin that could have been extracted by the red cells and then transfused to the patients. Another possibility was that there would be an allergic response to an allergen in the filtration collection system and, finally, a possibility that a toxic reaction to a chemical used to manufacture the filtration system was the cause of these reactions.

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A search of the literature helped in focusing our

direction to certain factors that could be causative. There was a publication by Dr. Oba, in 1984, on an outbreak in Japan. The title of his report was, "Migration of Acetylated Hemicellulose from Capillary Hemodialyzers to Blood Causing Scleritis and/or Iritis."

This report concerns an outbreak of eye reactions in Japan between November 1981 to March 1982 in hemodialyses patients treated with Nipro brand NAC series cellulose capillary dialyzers. Reports of these eye reactions stopped after this particular dialyzer was withdrawn from the market.

The symptoms experienced by the patients in this outbreak were very similar to what we have just heard about the red eye reactions. Their reactions started during dialysis, and after 10 hours post and continued for 2-3 weeks. They experienced redness, hyperemia and pain of the eye. The ophthalmologic diagnoses included sclerosis, iritis and uveitis, excessive epiphora or lachrymation, and in some cases there was tinnitus and/or earache. This, actually, is different from what we observed in the leukoreduction red eye reactions.

The mechanism behind these reactions was found to be a material that was used to manufacture the dialysis tubing, and this material was cellulose acetate derived from wood. This report went on to show that extraction of

cellulose acetate derivatives from the dialyzers and injecting this extract into animals induced similar eye symptoms in a dose-dependent manner in rabbits, and scleritis-like changes in dogs.

Of interest was a potential association or causative effect in a manufacture change by the company. In December, 1981 the company went from a pilot production to full-scale production. The sterilizing method was changed from washing of the tubing with benzalkonium chloride to UVB light irradiation. Now, it is now known that UV irradiation causes a decrease in the degree of polymerization of cellulose acetate and its oxidation, and the less polymerized cellulose acetate was more easily migrated out of the dialyzer into the blood stream, thus causing the reactions found in these patients.

So, the take-home message from this study is that there are materials being used to produce blood filters that are capable of producing a reaction similar to what we have seen in the leukoreduction cases, and that there may be manufacturing changes that go on that may produce unexpected results leading to similar type of reactions.

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Another report that was published by Dr. Leitman, from NIH blood bank, in 1986 was called "Allergic Reactions in Healthy Platelet Apheresis Donors Caused by Sensitization

to Ethylene Oxide Gas." Dr. Leitman looked at 600 donors, and 6 of these had reactions while being pheresed. And, 5 out of these 6 donors which had the reactions donated frequently and the mean number of donations was 196. There was no difference in sex, race or age from the rest of the donors.

Their symptoms were predominantly ocular, with periorbital edema, chemosis and tearing. However, they did not experience the red eye redness that we see in the leukoreduction red eye syndrome. They also had generalized symptoms like pruritus, urticaria, rhinorrhea, abdominal cramping and diarrhea.

The laboratory investigations demonstrated that 4 out of these 6 had hypersensitivity in a skin-prick test with ethylene oxide albumin as compared to 0 out of 40 controls. And, 4 out of these 6 donors had increased IgE antibodies against ethylene oxide albumin as opposed to 1/95 controls, and 6/6 of these donors had basophil histamine release with ethylene oxide albumin as opposed to 0 out of 4 controls.

The conclusion from the study said that residual ethylene oxide in the plastic harness that was sterilized with ethylene oxide gas reacted with plasma proteins. When these were returned to the donor they were recognized as foreign and an antibody was generated against the ethylene

oxide protein moiety. Subsequent donations elicited an immediate type hypersensitivity reaction.

This report suggests that there could be an effect from multiple exposures to products that are used to collect and store blood, and may be, in a way, similar to what we have seen with leukoreduction eye reactions where the patients who react have had a number of transfusions.

[Slide]

The FDA investigation into the red eye reaction was undertaken at the beginning of the announcement of the leukoreduction red eye reactions, in December, and what the FDA did was request and obtain unused filters from implicated lots, the lots that produced the reactions in patients, and from non-implicated lots. We have also been able to obtain units of red cells filtered with the implicated lots and for controls units of red cells filtered with lots that have not given the red eye reactions. We have also been able to obtain samples of raw materials used to manufacture the filters from the manufacturer.

Tests at FDA are ongoing at CBER and CDRH to determine whether there are extractable materials in the filters and the raw materials that could cause these symptoms. Additional tests have been done on the filtered red cells to detect the presence of endotoxin. No conclusions on the causative agents have been made so far.

Thank you.

DR. HOLLINGER: Thank you. The next talk is on other reactions by Mark Popovsky, from the American Red Cross.

Other Reactions

DR. POPOVSKY: Good morning. Mr. Chairman and committee members, thank you for inviting me to address you today. I am here today as a transfusion medicine practitioner and Associate Professor of Pathology at Harvard Medical School. My views should not be construed as official policy of any organization. I also realize that my talk stands between you and lunch, and so I will take my time very seriously.

[Slide]

Almost all of the literature of leukodepletion attests to its advantages, and for good reason. The removal of white blood cells is beneficial for the transfusion recipient from many scientific perspectives, as you have already heard this morning. While honest debate persists over the cost-effectiveness of some of the purported advantages of leukodepletion, there has been little debate about whether leukodepletion results in harm to a transfusion recipient. In fact, there are only two complications that have been linked in any way to the removal of white blood cells.

[Slide]

These are hypotensive reactions and the red eye syndrome which was just described.

[Slide]

As a way of background, hypotensive reactions are a very infrequent complication of transfusion. They are associated with the following: hemolytic transfusion reactions; bacterial contamination; severe allergic reactions and anaphylactic transfusion reactions; transfusion-related acute lung injury, which is the adult respiratory distress syndrome due to transfusion; and the presence of angiotensin converting enzyme, or ACE, inhibitors in transfusion recipients as described in patients undergoing a plasma exchange.

[Slide]

In 1993, the American Association of Blood Banks received reports of apparently unexplained severe hypotensive episodes associated with platelet transfusions. The Board of the AABB charged the Transfusion Practices Committee, which is a voluntary committee of the Association made up of transfusion practice experts, to dig into the matter and try to determine whether or not this was a real reaction, and whether it represented something new on the transfusion horizon.

[Slide]

That committee surveyed the membership at the institutions of the American Association of Blood Banks, and was able to elicit from the membership reports of 24 episodes, which were then gone into in considerable detail by the committee with follow-up questions.

The result of that was a paper published in 1996 by Dr. Hume and myself, as well as others on the committee, which discerned the following, that of these 24 episodes, 4 were considered to be not related to a transfusion at all; 3 were determined to be transfusion-related acute lung injury. That left 17 reactions that were unexplained and that the committee questioned whether or not this represented a new complication of transfusion therapy related to leukodepletion.

[Slide]

A quick high-level clinical overview of the findings in that study were as follows: That these reactions, those represented by the 17 that I just referred to, were of relatively rapid onset. They occurred within 1 hour of transfusion, and were associated in 4/5 of cases with respiratory distress, often very severe in nature. In 4/5 of cases, again, there was rapid resolution of the symptoms. With discontinuation of transfusion the symptoms disappeared or regressed within 6 hours of the discontinuation of the transfusion therapy.

[Slide]

This table from our paper summarizes some of the factors that we were looking for to see if they might be co-factors or be contributing factors to this type of reaction. From the table, one can see that the platelets that were transfused and were involved in those episodes ran the gamut from pooled random-donor platelet concentrates to either non-HLA matched or HLA-matched apheresis platelets.

ABO-identical transfusion was the situation in the vast majority but not all cases. And, looking for some type of factor between storage time and the appearance of the symptoms didn't bear much fruit, with transfusions occurring with relatively fresh platelets, less than 3 days, to those that were 5 days old.

Again, looking for some type of factor with gamma radiation, they basically were split between gamma radiated and non-gamma radiated states.

With regard to white cell reduction filtration, there were, in fact, 2 cases that were seen where filtration occurred prior to storage. Most occurred at bedside, and in 1 case we were unable to discern from the data we had what the timing and site exactly was. In 2, apparently no leukoreduction was involved.

[Slide]

If one looks at the clinical literature of the

last several years for those cases that have now been described and associated with this phenomenon, they can be summarized as follows: First, severe hypotension that is relatively rapid in onset, usually within minutes of the onset of transfusion therapy, associated with respiratory distress, and often skin flushing, and in some cases loss of consciousness.

A common theme is the presence of bedside filtration. And, another theme, and I will talk more about that in a moment, is the presence in the transfusion recipient of ACE inhibitors, angiotensin converting enzyme inhibitors.

[Slide]

This is a rather busy slide, for which I apologize but please remember Dr. Snyder's slide from earlier this morning --

[Laughter]

-- summarizes the clinical literature in the English language. There are 42 reactions described, and I will walk you through the table. First we have the investigator, the number of patients, the number of reactions reported, the blood component transfused, the type of filter and whether or not it was a negative or positive charge, the presence or absence of ACE inhibitors in the recipient, and whether or not bedside or prestorage

filtration was used.

Again, there are 42 reactions described. Several themes emerge. The first, in this column, is that there is reproducibility of some of these reactions. So, in the case of Sano and colleagues, this is a pediatric patient that had 2 reactions and no reactions were seen when the patient was transfused with positively charged filters.

We go to the case of Fried and colleagues, this was 1 patient with 2 reactions, and the reactions were stopped when those types of filters were no longer used.

In the case of Mair, Mair involved cardiac surgery patients, 14 patients and 6 reactions. These reactions again were reproducible.

In the case of Abe, 1 patient, 2 reactions. When this type of filter was replaced or no filter was used there were no more reactions.

The blood components represent, again, apheresis derived platelets, whole blood derived platelets, fresh-frozen plasma, red cells and even autologous whole blood. So, it is an interesting gamut of products. The filters represented here are predominantly, as you see, negatively charged, however, there are instances here and here of patients who developed these reactions with positively charged filters.

Again another theme, but not an overriding one is

the presence in many of these instances of ACE inhibitors that the patients had been on. One other constant is the presence of bedside filtration.

[Slide]

So, what is the cause of these reactions? Well, first I need to go back a minute and talk about what investigators had been focusing on, and that is bradykinin. The reason for that is that it is documented that negatively charged surfaces activate the contact coagulation factors, including Factor XII, a high molecular weight kininogen, and that results in the generation of the potent vasodilator bradykinin. So, bradykinin has been the substance that much of the research has been devoted to in the last few years since this problem has become revealed to us.

In the case of Takahasi and colleagues, published a few years ago, they looked at bradykinin levels measured by RIA in apheresis platelets. This is an <u>in vitro</u> study in which platelets were filtered over a negatively charged filter and were shown to generate during filtration -- that really should be pre-filtration and post-filtration, and these were not transfused to patients -- very significant amounts of bradykinin, such that at the beginning of the filtration procedure there was almost 6800 pg/mL from baseline of 37 but by the end of the transfusion, and this is a theme that I will come back to, there were 2500 pg

measured.

Interestingly, and perhaps significantly, when this was repeated with positively charged filters no such significant generation of bradykinin was noted.

When the investigators added the ACE inhibitor captopril at a concentration of 50 ng/mL to platelets to generate a final concentration of 0.2 mg/mL, then very significant levels of bradykinin, 36,000 pg/mL, were generated during that filtration.

[Slide]

Pursuing this line of reasoning, Shiba and colleagues looked at 4 patients who had been transfused with apharesis platelets for hematologic disorders, and they took venous blood samples pre-transfusion and during various intervals post-transfusion and evaluated the level of bradykinin that was or was not generated. What they found was that when filtered over negatively charged filters there was a 10-fold increase in bradykinin during the transfusion period.

[Slide]

As shown here, the solid circles represent bradykinin levels over intervals in minutes before and up to 60 minutes after the transfusion. You notice a significant increase. This is negatively charged filters. The open circles represent positively charged filters.

[Slide]

Interestingly, again in an in vitro experiment when captopril, an ACE inhibitor, is added, there is significant generation of bradykinin levels and, interestingly enough, 2 of their patients who had abnormally low levels of ACE activity, these 2, had the highest levels of bradykinin generation.

[Slide]

In a very recently published paper by Hild and colleagues, they looked at 3 filters, a negative charge, a positive charge and a neutrally charged filter, and they looked at bradykinin measurements up to 90 minutes post-filtration -- an in vitro study in platelet concentrates, and they found only significant generation associated with the negatively charged filter.

[Slide]

Interestingly enough, and not explained by the data or the authors, there is high variation between individual donors and within the same concentrate that is divided into aliquots, as was used in this study. Importantly, they found that bradykinin is rapidly -- rapidly -- degraded, within 60 minutes.

[Slide]

Not all the data has been consistent in this direction. In fact, Coleman and colleagues, looking at high

molecular weight kininogen as an index of bradykinin generation found no evidence of significant cleavage of high molecular weight kininogen during the filtration of platelets.

[Slide]

So, what are the factors then which may be influencing the occurrence of these hypotensive episodes? I think there are four factors. I was remiss in not acknowledging the contribution of Dr. Zeik in providing me the table that I showed before from an article that will be coming out as a chapter in an upcoming book. So, I want to give credit where credit is due.

So, what are the four factors in my view? One is the nature of the transfused product. Bradykinin may be generated in greater amounts during filtration of platelets compared to red cells, as appears to be the case from the case reports, because of the larger plasma volume in a dose of platelets, in a pooled dose, compared to what is found in a typical red cell.

Secondly, the kind of filter. It does appear that negatively charged filters are associated with a great preponderance of these reactions, and that is probably due to the fact that negative charges activate the contact system. But, on the other hand, as I pointed out, there are cases that have been linked to positively charged filters.

The third is the presence of ACE inhibitors in recipients. Kininase II is known to prevent the degradation of bradykinin. So its presence, by preventing the normal physiologic occurrence of degradation of bradykinin may allow for very large amounts to accumulate and then ultimately be infused into the patient.

That leads to the last point of bedside filtration. If bradykinin is being generated during filtration at the bedside, then because most transfusions take place inside of an hour with platelets, the vast majority of that material is going to be transfused into the patient. On the other hand, with prestorage filtration, with time on the side of the blood product, the bradykinin will have time to degrade and that may be the reason why we are not seeing these in many instances with prestorage leukodepletion.

[Slide]

One last point, and that has to do with loss of product. Filtration is associated with loss of platelets and red cells because they are retained during the filtration process. This fact is filter dependent. Published literature suggests that it is in the range of 5-15 percent whether they be platelets or red cells.

Not much, if anything, has been written about the clinical implications of that fact. It could theoretically

reduce the therapeutic benefit of a transfused component whether it be a platelet for a prophylactic or therapeutic reason, or a red cell being used to treat anemia. But, again, this has not been studied closely and, to date, the assumption has been that most patients are not compromised by this level of product loss.

[Slide]

So in summary, reports of adverse reactions associated with leukodepletion are, indeed, very rare.

Bradykinin is likely to be involved with these reactions as a result of the generation of the contact system through coagulation factors. But bradykinin may not be the entire story.

Importantly, we do not know the true incidence. In the study that I reported through the Transfusion Practice Committee of AABB, what was missing, of course, was the denominator of how many transfusions had occurred over that period of time in 1993. As a result, we really do not know what the incidence is. Based on the very small number of cases and the very vast numbers of leukodepletion units that are being transfused today, the assumption is that it is a very rare event. Therefore, in my view, the advantages of leukodepletion far outweigh the disadvantages.

Thank you very much.

DR. HOLLINGER: Thank you. That concludes the

formal presentations for today, and we are going to go into the open public hearing now. The first person to comment will be Dr. Steve Kleinman, for the American Association of Blood Banks. Steve?

Open Public Hearing

DR. KLEINMAN: Good morning. Good morning to the committee and to all the audience. I am presenting this on behalf of the American Association of Blood Banks.

The AABB is a professional association for approximately 2200 institutions engaged in the collection and transfusion of blood and blood products, including all American Red Cross blood services regions, independent community blood centers, hospital-based blood banks and transfusion services, and more than 8500 individuals engaged in all aspects of blood collection, processing and transfusion.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. The AABB's highest priority is to maintain and enhance the safety of our nation's blood supply. The AABB submits these comments in response to the Blood Products Advisory Committee's request for information on the effects of leukoreduction on the blood supply.

The AABB, through its ad hoc leukoreduction committee, is currently exploring issues regarding

generalized leukocyte reduction of the nation's blood supply. A report is expected for consideration by the AABB Board of Directors at its meeting in November, 1998.

Information currently available, however, documents that for certain specific patient populations leukoreduction offers distinct medical benefits and improves the safety of blood transfusion. For example, basic scientific and clinical research has substantiated that leukoreduced blood prevents primary immunization to leukocyte antigens and histocompatibility antigens for patients undergoing chronic transfusion protocols. These include patients with sickle cell anemia, thalassemia, aplastic anemia and hematologic malignancies.

Leukocyte reduction is also an effective means to prevent transmission of cytomegalovirus to at risk transfusion recipients, including neonates, recipients of bone marrow, recipients of stem cell or solid organ transplants.

Leukocyte reduction has also been demonstrated to be an effective means to prevent cytokine-mediated, leukocyte-mediated febrile transfusion reactions.

Other benefits, not yet fully substantiated scientifically, may apply to the general patient population. These include, among others, the potential to reduce the risk of transmission of those less pathogenic leukotropic

infectious agents for which blood donors are not currently tested, and the potential to prevent a possible immunosuppressive effect of blood transfusion.

As with any change affecting the processing of the nation's blood supply, the AABB strongly urges that recommendations for leukoreduction be made in the context of quality management and good manufacturing practice approaches, consistent with FDA regulations and AABB standards.

Finally, although it is not within the purview of BPAC, the AABB ad hoc committee has been charged to consider operational concerns for blood centers and transfusion services, cost effectiveness of the procedure, and international issues. Conclusions of the working group will be provided in its report to the Board of Directors later this fall. AABB will be please to share the results of this initiative following the completion of the committee's work.

Thank you for the opportunity to present these comments.

DR. HOLLINGER: Thank you, Steve. The next comments will be by Dr. Louis Katz, from America's Blood Centers.

DR. KATZ: Thank you for the opportunity to present the views of the nation's independent community blood centers, represented by ABC, on the issue of universal

leukoreduction or cellular blood products.

With all due respect to Dr. Snyder, non-controversial indications for the use of these products are reasonably well understood, and transfusion recipients can be recognized who clearly require leukocyte depleted components. These include those with recurrent febrile non-hemolytic transfusion reactions, patients for whom transfusion-associated CMV infection is a serious clinical problem, and some patients at risk for alloimmunization.

Theoretical arguments have been advanced that the risk of other white blood cell associated viral agents and transmissible spongiform encephalopathies may justify routine leukocyte removal.

Finally, it is argued that since white blood cells in cellular components are not therapeutically necessary they should be removed. We understand these theoretical considerations. We are also aware of the lack of supportive clinical trial data that would justify a policy of universal leukoreduction at this time.

Transfusion-associated immunomodulation due to the white blood cell content of cellular components, particularly its association with surgical wound infection, surgical mortality, and cancer recurrence is perhaps the most compelling argument advanced for universal white blood cell removal. This is because it will theoretically affect

a far larger proportion of transfusion recipients than the traditional indications referred to above, and those at risk cannot currently be recognized before the transfusion. Despite very strong animal data suggesting this effect is real, epidemiological and clinical studies are in conflict and cannot, at this time, provide justification for universal leukoreduction.

America's Blood Centers suggest that FDA and the Blood Products Advisory Committee recognize the equivocal medical and scientific arguments for universal leukoreduction, and recommend areas for further research. FDA should encourage further public policy discussion by the Health and Human Services Committee on Blood Safety and Availability. If a decision is reached to recommend universal leukoreduction of cellular blood components, the rationale needs to be explicitly stated with recognition of additional healthcare costs in excess of 250 million dollars a year.

DR. HOLLINGER: Thank you. The next person to comment is going to be Jan Hamilton, Executive Director for the Hemophilia Foundation of America.

MS. HAMILTON: Thank you, Mr. Chairman. It is a pleasure for us to be able to make a few comments today. Just so that you will know who we are, we are the Hemophilia Federation of America and are advocates for persons with

clotting disorders and their families, and blood safety has been a cornerstone of our existence.

Last month, at the meeting of the Advisory Committee on Blood Safety and Availability, I asked when the United States would join other countries in pre-filtration for leukocyte reduction. It has been said that leukocyte reduction reduces transfusion-associated immune suppression, and helps to protect patients from post-surgical infections which reduces morbidity and mortality rates, and also helps to reduce the length of stay in hospital, thereby causing a reduction in hospital costs.

We have always asked for more purity, more safety and more efficacy in our blood supply, keeping in mind good manufacturing practices. We were delighted to hear Dr. Williamson say that they didn't sit back and wait for 100 percent evidence. It seems to be in direct opposition to the United States' perspective of waiting to see how many people die and then do something to slow the body count.

The Hemophilia Federation of America urges the FDA to act on cost savings and prevention rather than the double cost of lives and dollars which follow inaction. It seems we always wait for the other countries to lead the way while our population suffers the effects of inaction. Please consider any procedure which will save lives and continue the progress toward a safer blood supply.

Thank you.

DR. HOLLINGER: Thank you. Now we have comments by industry. The first is going to be Dr. Barry Wenz, from Pall Medical. You do not look like Barry Wenz.

DR. ANGELBECK: No, I am not Barry Wenz! I am Dr. Judy Angelbeck. I am Senior Vice President for the Pall Medical Company, and I am here just to make a very brief statement.

First and foremost, I would say that we have brought with us today a selected bibliography. This is not intended to be exhaustive. It represents some of the significant references that are available. I understand that the copies that we brought with us have all been taken up. If anyone wants additional copies, please let me know and we will be happy to provide them.

Essentially, all I have to say is that we are here to listen, as everyone else is, and if there is anything we can do to facilitate further information being available, or contacts between transfusion medicine experts and the committee, we would be happy to do so.

Thank you.

DR. HOLLINGER: Next is James O'Connor, from HemaSure, Inc.

MR. O'CONNOR: Good afternoon. It is afternoon now. I am pleased to address this very important meeting.

[Slide]

This slide sort of sums what this meeting is all about as I look at it now. I think it goes without saying that we are all here with the shared responsibility to improve healthcare.

I would like to focus though on what we, as a manufacturer, would do in order to get to 100 percent leukoreduction, or even to expand leukoreduction.

[Slide]

These are the key requirements for manufacturers to follow: Continuous advances in technology bringing solutions to transfusion medicine. Technology results in innovative products and consistent performance. Filtration technology has advanced rapidly. The removal of leukocytes is now routine and readily available. Quality products, safe, easy to use, and reliably designed to meet user needs are expected from manufacturers. Customer training and support are part of the product, and ensure its safe use and in an effective manner.

A key challenge for us now as manufacturers is also to identify and control the costs associated with producing leukoreduced products. Manufacturers have a shared responsibility in effective cost management of the leukoreduced blood supply.

[Slide]

These are some of the product requirements of a prestorage leukoreduction filter for red blood cells. I use these next three slides as an example of how manufacturers can benefit this industry.

Products produced by manufacturers need a broad range of requirements. Key are the guidelines for filtration that have been spelled out in the FDA's memorandum. To these guidelines manufacturers add in many other requirements. Most of them are aimed at helping the users, and also adapting to the users' varying process conditions.

[Slide]

This is a product, as an example, that right now is currently under review by the FDA and is not yet available on the U.S. market. This product is new. It doesn't contain the cellulose acetate that was potentially implicated earlier as causing the red eye syndrome. This product is designed to meet and exceed the requirements set forth by the users and regulators. The product has features in it such as the dockable characteristics and its advantages, mentioned earlier; venting schemes to allow easy priming and draining, as well as additional segments of tubing and bags to allow easy QC in the laboratories, such that the QC process described earlier can take place.

[Slide]

Requirements like these, combined with the ability of devices to adapt to the variations in blood processing conditions, are examples of ways manufacturers leverage technology.

[Slide]

To meet the performance guidelines, studies like this are conducted prior to market. This is an example of one small study that was used to address leukocyte reduction. Here, the filter was used to filter red blood cells that are less than 24 hours old, in this case overnight storage and in this case within hours of preparation.

What I am pointing out here even within the U.S. guidelines as well as the Council of Europe guidelines, as pointed out, leukoreduction filtration has the capability of exceeding the guidelines.

[Slide]

This is the same data plotted in a different way. I won't go into too many details of this complicated slide. The point I want to make is that the manufacturers are capable of characterizing the filter and really qualifying it and creating statistically databases that users can reference when they do the process validation.

Here are the white cell residuals, 10^6. This would be the one million guideline and this would be the

five million guideline. White cell residuals are plotted against the probability of occurrence that the actual unit will meet these white cell residuals.

Here you can see the room temperature filtration. It creates a separate population than the 4C filtration. These are important characteristics that users must take into account when they are doing their actual filtration. This filter, here, as you can see, is also quite capable in this study of creating a very high probability that very high percentages of the product will actually be leukoreduced to meet the guidelines.

[Slide]

So in closing, I have pointed out the shared responsibility among the thought leaders, professional organizations, manufacturers, regulators, blood centers, hospitals, care providers, to improve patient care with universal leukoreduction in a cost effective manner. The manufacturer's role is to provide products to meet the sector of healthcare's needs.

HemaSure, as part of this important industry, is conscious of our responsibilities and is ready to support the challenges of 100 percent reduction.

DR. HOLLINGER: Thank you. The next speaker is Larry Dumont from COBE.

MR. DUMONT: Mr. Chairman, members of the

committee, thank you very much for the invitation to present to you today.

[Slide]

I am a therapy scientist with COBE BCT. We manufacture apheresis devices that make platelet products, plasma and red cells. Instead of talking a lot about the devices, what I want to present to you today is some data on cytokine accumulation in platelet products; some clinical data from Canada that I have been allowed to share; and then a little bit on device performance for white cell reduction, and some comments about subtyping of white cell residuals.

[Slide]

In a paper to appear next month in Vox, we worked with the Canadian Red Cross, in Ottawa, to follow cytokine levels over storage from platelets produced in the COBE Spectra apheresis system.

[Slide]

We essentially looked at 3 types of products. One is apheresis platelets collected on the COBE Spectra version 4. This is actually 2 levels down from where we are now with our device. Control platelets were made from whole blood by the PRP method. Then, there were also platelets produced from whole blood and then filtered prestorage. Then, we stored those products for 7 days, measured lots of things over that period, and among them were the cytokines

IL-1-beta, IL-6, IL-8, TNF-alpha, and we looked at that in relationship to residual white cells in the products.

[Slide]

The summary of this is similar to what we have seen earlier today. On these 4 graphs we have the white cell content. This is 10^9/L measured at day 0 for all 4 graphs. Then, these are the cytokines. You can very quickly see that baseline levels are maintained until you exceed somewhere to the 10^7, 10^8 range for the residuals in all these products when, at day 5, you start to see substantial increases in the cytokine levels.

The products over here are all the controls. The open circles here are the filtered randoms, and the dark indicators there are the COBE apheresis products.

[Slide]

Our conclusion is that leukocyte levels PC's filtered or collected on COBE Spectra are sufficiently low to prevent cytokine production during 7 days of storage, and that white cell levels below approximately 10^7 or 10^8 will avoid any significant cytokine production over the storage of platelet concentrates.

[Slide]

Of course, we keep this in mind because of the hypothesis that cytokines are biological response modifiers that initiate some of the reactions of patients, and we saw

earlier a summary of a paper that Nancy Heddle, in the New England Journal, where she drew that conclusion. Since then, her group and Dr. Blajchman and others in Canada have been investigating this in a clinical setting in two phases. I want to review those quickly.

[Slide]

In a preliminary study, looking at acute reactions to platelets, the platelet transfusions were randomized to patients and, in this study, these were poststorage treatments. The first was poststorage removal of plasma. In this case the plasma was replaced with an FFP. The second arm was poststorage leukocyte reduction by a filter of random platelets.

This study is unique in that there is a very active surveillance system that they have established, where they apply a questionnaire to the patient and they also have clinical monitors there taking objective measurements.

[Slide]

The summary of this result was that the poststorage leukoreduction by filtration out of 186 transfusion episodes resulted in about a 24 percent febrile reaction and about 3 percent allergic reactions in this group. With plasma removal, replaced by FFP, with 194 transfusion episodes we saw a significant reduction in the febrile reaction rate, to about 16 percent. The allergic

reaction rate was about the same.

[Slide]

This was followed up to look at the effects of prestorage. Here we have a design where the transfusions were randomized to patients and we have 3 arms. The first was, again, the poststorage plasma removal and replacement with Plasmalyte. The second arm was prestorage leukoreduction by filtration of random platelets from whole blood. The third arm is prestorage leukoreduction by the COBE Spectra LRS.

I am going to show you some preliminary results because this study won't be wrapped up until probably next month. But a preliminary analysis was done because, as Dr. Freedman showed earlier, since Canada has gone to prestorage leukoreduction there was no more material left to this arm and so that was wrapped up. So, I am going to show you data that has these 2 arms pooled together.

[Slide]

The plasma removal at the end of storage, in this case replaced with Plasmalyte, had 149 transfusion episodes. There was an 18 percent febrile reaction rate, which is very similar to the 16 percent we saw before. In this case there were no allergic reactions.

Prestorage leukoreduction by the LRS and the filtered randoms -- again, this data is pooled; we don't

know which one is which yet -- 417 transfusion episodes. We saw a very significant reduction in the febrile transfusion reactions, to about 5 percent. Allergic reactions were still maintained at about 2 percent.

[Slide]

So, if you put these altogether, it appears that plasma removal has some effect in reduction of febrile reaction rates, and prestorage filtration has an even bigger hit. There are several questions still to be answered about what is going on with the allergic reactions. These differences really aren't statistically significant at this scale.

[Slide]

Very quickly, I want to show you some device performance that COBE didn't do but actually our customers did on red cell filtration, platelet filtration, and some platelet apheresis, and then make a comment about subtyping of white cell residuals.

[Slide]

We saw a plot like this just a minute ago. Down here we have total leukocyte content on a log scale per product. This is a fancy mathematical transformation of percent occurrence. The beauty of this plot is if you have a normal distribution it is a straight line, and we all like straight lines.

This is from blood centers of the Pacific and San Francisco SepaCell red cell filtration. The median number of white cells in these products was about 3 X or 4 X 10^4, and at the 5 million, which is right there, greater than 99 percent of those products would be expected to be less than 5 million. At the one million mark, we expect greater than 99 percent again.

As Dr. Williamson pointed out, this is not the European standard. The European standard says that you need to be greater than 90 percent. So, anything from here up at that line would meet the European standard.

[Slide]

This shows filtration of platelets with the Pall LeukoTrap. This is out of Canada. These are not transfusion doses; these are individual units. So, you have to pool 6 of these for a transfusion dose. But, here again, you can see that the process is pretty adequate to leukoreduce the products. This little rat tail you see here is, in fact, because we lose sensitivity in the measurement method, but we can extrapolate to here. This point, right here, is actually the FDA guidelines for individual units of platelets. So, that is a very adequate process.

[Slide]

Finally, I want to show some apheresis from an unknown, unnamed blood bank in the United States, with the

COBE LRS and the Baxter Amicus. The blue is LRS, as you might have guessed, and the red is Amicus.

My point is that they both seem to be quite adequate in this center for meeting the standards, and can be modelled pretty well with this model.

[Slide]

Subtyping of white cell residuals -- you have already heard comments about Dr. Coker's paper in Transfusion earlier this year, which was an attempt to try to elucidate the subtypes of the residual white cells, and they bring up some interesting questions about what the effects may or may not be of these different subpopulations.

I want to point out that there have been several unsuccessful attempts to replicate those results. In Canada, actually in Dr. Freedman's group; in Pittsburgh, Dr. Triulzi; and in Scotland and in England they have not been able to replicate those results. So, I think the answer is we don't know the answer really about what the subtypes are.

The other thing I want to point out is that once we know the answer, we still don't know what the clinical significance is of that. We don't know the infective dose, for example, of CMV or whatever we might be talking about. So, that is a big unknown, in my mind.

[Slide]

So in conclusion, white cell levels below about

10^7 to 10^8 will avoid significant cytokine production over storage of platelet concentrates. Prestorage leukoreduction reduces the febrile reaction rate. It may be that plasma replacement reduces the allergic reaction rate. And, leukocyte-reduced products may be produced by a variety of methods, including several types of filters and by different types of apheresis devices that do not use filtration. The WBC subset distribution and its clinical significance are indeterminate.

Thank you very much.

DR. HOLLINGER: The next speaker is Dr. Joy Anderson, from Fenwal Division, Baxter.

DR. ANDERSON: Good morning.

[Slide]

I would like to present information today that addresses two questions. First, when should leukoreduction be performed and, secondly, where should leukoreduction be done? Today, transfusion products of varying ages are often filtered at the patient's bedside. Platelet products can be as much as 5 days old, and red cell products can be as old as 42 days. However, there is increasing evidence that white cells should be removed early in the storage period. The early removal of white cells is generally referred to as prestorage leukoreduction.

Prestorage leukoreduction can be accomplished in

two ways: using filters, or by a method known as process leukoreduction in which leukoreduced products are collected directly from apheresis instruments.

[Slide]

During blood component storage white cells degenerate and release cellular fragments. This graph shows data on the breakdown of white cells during red cell storage. After the first week approximately 25 percent of the white cells have disintegrated. By day 42, which is the end of the storage period, almost 75 percent of all leukocytes have disintegrated. As the white cells degenerate, the stored blood component accumulates the intracellular contents, as well as the cellular fragments from these cells.

[Slide]

These cellular fragments may not be removed by leukoreduction filters. This figure shows white cell fragmentation in platelet products as measured using flow cytometry with fluorescently labeled antibodies. The increase in the height of the bars over time indicates that fragmentation is occurring during platelet storage, which is similar to the red cell data.

Looking in more detail at the 48-hour time period, the number of white cell fragments measured pre-filtration, shown on the left in red, is virtually the same as the

number of white cell fragments post-filtration, shown on the right in yellow. Similar data is seen at the other time points. This indicates that when white cells disintegrate the cellular fragments may not be removed by leukoreduction filters.

[Slide]

Prestorage leukoreduction removes white cells while they are intact and before fragmentation. This has several potential benefits for patients. First, any intracellular viruses that may be present in white cells are also removed. Second, there may be a reduced risk of bacterial contamination if the white cells have time to ingest any bacteria introduced during the phlebotomy, and are then filtered out. Third, studies in an animal model have shown that the rate of alloimmunization was less in animals that received prestorage leukoreduced blood as compared to animals which received blood leukoreduced after storage.

[Slide]

Prestorage leukoreduction also reduces the incidence of transfusion reactions in patients. During blood component storage white cells release soluble molecules called cytokines, which have been associated with transfusion reactions in patients. In a study of over 5000 red cell transfusions the incidence of febrile non-hemolytic

transfusion reactions was significantly reduced when products were prestorage leukoreduced as compared to products that were leukoreduced after storage.

[Slide]

Studies by Blajchman in an animal model indicate that prestorage leukoreduction significantly reduced the number of tumor metastases. Three types of transfusion products were evaluated: Transfusion of blood containing white cells enhanced tumor metastases. Blood leukoreduced poststorage was not effective in reducing the number of tumor metastases. However, animals which received prestorage leukoreduced blood had significantly fewer tumor metastases.

While this work suggest an immunomodulatory effect of white cells present in transfusion products, at the present time it is not known if these findings are applicable to humans.

[Slide]

The potential patient benefits from prestorage leukoreduction are summarized in this slide: Decreased transfusion reactions; decreased alloimmunization; removal of intracellular viruses; and reduced risk of bacterial contamination.

[Slide]

Lastly, I would like to discuss where

leukodepletion should be performed, at the patient's bedside or in the blood center. Quality systems already established in the blood center ensure consistency in leukoreduced products that can't be obtained with bedside filtration. These quality systems include formal training of employees, written procedures, validation of manufacturer's product performance, ongoing monitoring of product quality, and assistance for initiating corrective action when necessary.

[Slide]

In summary, prestorage leukoreduction of blood components provides higher quality transfusion products for patients, and utilized quality systems already well established in blood centers to ensure consistency in leukoreduced products.

Thank you.

DR. HOLLINGER: Thank you. The next speaker is Dr. Frederick Axelrod, from Haemonetics Corporation.

DR. AXELROD: My name is Frederick Axelrod, and I am the Medical Director of the Blood Bank Division of Haemonetics Corp. Haemonetics Corp. is a global company engaged in the design, manufacturer and worldwide marketing of automated blood processing systems.

The purpose of my comments today is to reflect Haemonetics' position on the matter of leukoreduction blood cell products being discussed as part of today's agenda.

The literature contains many manuscripts of scientific and clinical investigations that confirm the efficacy of the transfusion of leukoreduced blood products in established patient populations. Without question, the use of leukoreduced products has a place in patient care.

As a manufacturer of automated blood processing equipment used on donor to provide transfusable blood products, and not directly involved in patient transfusion practice, Haemonetics does not have an opinion on whether 100 percent use of leukoreduced blood products should become the standard of care in the United States. However, Haemonetics is committed to offering a product mix supporting any level of leukoreduction as determined by the regulatory and standard-setting agencies.

Nevertheless, it is the opinion of our organization that whenever a leukoreduced product is prepared the product should be prepared in the manner that ensures that leukoreduction has actually been achieved. To date, only blood collectors who manufacture a leukoreduced product have the quality control testing and quality assurance mechanisms in place to demonstrate that leukoreduction has occurred. Haemonetics strongly supports that only prestorage procedures be encouraged to achieve leukoreduction.

Haemonetics believes prestorage leukoreduction is

superior to bedside filtration for the following reasons: Evidence suggests prestorage filtration may eliminate the immunomodulating effects of blood transfusion on tumor growth.

Prestorage filtration produces a product with lower levels of pro-inflammatory cytokines.

Prestorage filtration has been demonstrated to be effective in partially removing microbial contaminants that may be present.

Fewer and more adequately trained personnel are used to prepare the products. The effectiveness of the filtration procedure may be greater because of the younger age of the product.

Quality control testing performed on products prepared using prestorage procedures are standardized, and demonstrate manufacturing competency and consistency. Standardizing practice among transfusion facilities enhances the ability to maintain adequate inventories and minimizes the wastage and discard of blood components.

Haemonetics urges the exclusive use of prestorage leukoreduction procedures because we believe that leukoreduced blood components should be subject to the principles and guidelines governing good manufacturing practices and other process control reviews. Prestorage leukoreduction techniques provide for process control that

the other procedures do not because prestorage leukoreduction techniques are performed by a limited number of properly trained staff, and in an environment under the control of the collection agencies.

The training of the staff and conditions under which the other types of procedures are performed are not under the control of any one particular agency. Therefore, unless prestorage techniques are routinely used, it is difficult, if not impossible, to analyze the causes of aberrant results and to implement corrective actions easily.

Since the number of agencies performing leukoreduction procedures is limited, if exclusive use of prestorage leukoreduction techniques is mandated, it is easier to collect, compile and analyze quality control and quality assurance data. This will enable the collecting agency to better identify trends and take corrective action as appropriate. In addition, communities will be better able to use this data for inter-community comparisons.

Additionally, Haemonetics supports exclusive use of prestorage procedures that utilize filtration. Recently it has been demonstrated that the various methods of leukoreduction currently used do not produce equivalent cellular subsets in the residual products. A recent publication in the Journal of Transfusion, by Coker and associates, demonstrated that among the different

leukoreduction procedures there were distinct phenotypic differences among the white blood cells remaining in the final leukoreduced products.

It is not known whether these phenotypic differences may be important in the treatment regime of the patient. Nevertheless, given the final end product differences among the various manufacturers' methodologies, Haemonetics supports a requirement that each manufacturer should perform its own clinical evaluation to prove that that specific methodology meets the desired clinical endpoint. Regulatory approvals for clinical endpoints should not be extended to another manufacturer as a result of previous clinical evaluation endpoint success displayed by a previous manufacturer.

In addition, standardizing the procedure for preparing leukoreduced products within a community standardizes the phenotypic constituents of the end product and provides the clinician with consistent and reliable information, regardless of the institution where the transfusion is to occur.

Haemonetics stands ready to support use of prestorage of leukoreduction techniques, and to make it easier for the collections agencies to prepare leukoreduced products that consistently meet all good manufacturing practice requirements, as well as other regulations.

Previously Haemonetics has added an inline leukocyte filtration system for apheresis platelets to its product offerings. Most recently, our next generation product uses a continuous filtration system which further improves the prestorage leukoreduction process by reducing operator interface, and the numerous manual decision points currently necessary to produce apheresis platelet products which meet the current definitions of a leukoreduced apheresis platelet product.

In addition, this process has proven so effective, it leaves adequate margin to continually meet regulatory agency guidelines should future clinical evidence require a change in the definition for leukoreduction in the final product to be lowered to the 10^5 range. Haemonetics has committed its current research and development efforts to extend the same process improvement to its other product lines as well.

Thank you for your time and consideration.

DR. HOLLINGER: Thank you. I just want to run this by the committee, we have two more speakers. I would like to go ahead and do those. If somebody has to check out, you can go ahead and do it, but I think I would like to finish the last two. The next one is from Biotech, Dr. Roths and Dr. Barr. Shall we hear from Biotech?

[No response]

Well, that was a short presentation.

[Laughter]

The next one is from Terumo Corporation. I don't have a name. Is there someone there from Terumo?

[No response]

That also was a short presentation. We are roughly on time then. We are going to take a break until 1:30. We will reconvene here for the deliberations.

[Whereupon, at 12:30 p.m., the proceedings were recessed to be resumed at 1:30 p.m.]

AFTERNOON PROCEEDINGS

DR. SMALLWOOD: While we are getting started, I would just like to thank the members of the advisory committee whose term has expired. That is Dr. Jerry Holmberg, and we would just like to extend our appreciation to him for having served with us.

[Applause]

The other member that will be leaving us will be Dr. William Martone, who is not here. Dr. Martone is on travel. So, we have the same appreciation for him, and we will let him know that.

As we get our replacements, we will introduce our new members to you as they are replaced on the committee. Thank you.

Committee Discussion and Recommendation

DR. HOLLINGER: Thank you. Before we go into the committee session, is there anybody else from the public that wants to say any words about the leukoreduction? If not, then I would like to have the question put before the committee, if you would, please?

The question which we are to deal with today is, is the benefit to risk ratio associated with leukoreduction sufficiently great to justify requiring the universal leukoreduction of all non-leukocyte cellular transfusion and blood components, irrespective of the theoretical

considerations for transfusion-transmitted CJD?

So with that in mind, I would like to open up the discussion regarding this question. Well, before everybody just breaks out --

[Laughter]

-- let's deal with one issue here, and that has to do with bedside -- let me just throw that out, bedside filtration. Does anyone here feel, from what you have heard today, that bedside filtration should be done? If so, let me hear someone speak about it.

DR. ELLISON: Only if it hasn't been done before. What I mean is that I strongly think that prestorage is the way to go, but as somebody who frequently is called on to transfuse patients who have a history of febrile reactions from multiple transfusions, I always use a microaggregate filter in those people, but I would much prefer to have prestorage.

DR. HOLLINGER: Or poststorage, that is, just prior to -- within the blood center.

DR. ELLISON: Yes.

DR. HOLLINGER: I am really speaking about bedside filtration rather than, say, filtration just before administration. Yes, Mark, please?

DR. MITCHELL: Yes, I agree that if there isn't prestorage filtration bedside may be appropriate. I have

more of a question, it is not clear to me what is already going on now, you know, what percentage of bedside and prestorage filtration leukoreduction is already in practice.

DR. HOLLINGER: Yes, could somebody maybe give us some feel, at least through the blood banking community, for how much leukoreduction is being done? If you could give us sort of a percentage, and what products, and whether it is primarily at the blood center versus the bed, and so on.

DR. GILCHER: Ron Gilcher. As I stated earlier, in our system the platelets are all leukoreduced. There is no bedside leukoreduction of platelets. But within our system, and we have surveyed our hospitals, there is almost the same amount of bedside leukoreduction filtration that is going on as prestorage. So, if we were to look at the total number in our system, it currently comprises almost 35-40 percent of all red cells that are transfused, roughly half being prestorage and half bedside filtration.

DR. HOLLINGER: And how about other places? I mean, you have talked to others who are doing this, or can you give us an idea. I think Steve Kleinman and some of the others are gone, but can you give us a feeling?

DR. GILCHER: Well, it is hard to say for sure what is going on, but from talking with my friends around the country, similar figures, perhaps lower total numbers, 10-15 percent on prestorage and then 10-15 percent on

bedside. But I think that currently in the United States -- and perhaps the manufacturers of the filters could actually speak to this more effectively, but I think the numbers would be pretty close to being equal but, clearly, as we see the data being presented, the movement is clearly going to be toward prestorage because that really benefits the patient.

DR. HOLLINGER: Okay. Yes, Corey Dubin?

MR. DUBIN: I come at this from two angles. In terms of hemophilia, I think it affects us. For instance, one of our board members had dual knee replacements and needed 4 units. He is HIV- and HCV-infected, and probably should have had blood that had gone through this process. He didn't have that choice at the time. I think for our people that are having surgery -- I think people may not be aware of the level of hip and knee replacements that go on in hemophilia in my age group, 35-50. So, I think in that sense it will benefit hemophilia.

I think in the larger perspective, regardless of CJD which is obviously a separate issue, we have fallen a little behind in standards. I don't think the United States is the leader of the pack, so to speak, any more as we have been in the past in standards. This came up with the Blood Safety and Availability Committee, and I think it is high time we did things to at least be equal to where Europe is

and we, of course, would like to see us take the lead again.

So, I think this has been a long time coming. It should have been done -- should do it, would do it, but whatever happened, I think we can afford to do it. I think we have heard from people like Dr. Gilcher a fairly persuasive argument and I strongly support it even outside just the narrow view of benefiting those with hemophilia who are going to need units, who are immune compromised and having surgeries.

DR. KAGAN: Can I expand upon that a little bit?

DR. HOLLINGER: Yes, please.

DR. KAGAN: As a surgeon, I would also like to add to what Corey said. There are many patients, immunosuppressed or otherwise -- cancer patients, trauma patients, millions of patients, who undergo surgical procedures, and I don't know to what degree the surgical community as a whole in this country is aware of potential problems from transfusions. I know in most academic medical centers they are. But, are we expected to ask emergency room doctors, transfusing patients coming into the emergency room, a traumatologist, to call a blood bank and say, yes, we want pre-filtered versus whatever you got off the rack? I think that is a bit much to expect. I think that there is an expectation that when they order blood it is going to be the best thing for the patients, and this can even extend to

the elective community for cancer patients, and the like, as well.

So, I think from the perspective of the patients requiring surgery that pre-filtration of as much of the blood supply as possible is going to help those patients because there is going to be a uniform standard for the blood that comes off the shelf, but not as much of a need for an individual surgeon or an individual blood bank to make many, many people aware of decisions that need to be made because, that way, every physician, every time he orders blood, has to sit down and think, okay, do I want this? Do I want filtered? Where do I want it filtered? I think that is too much to expect. I think there needs to be a uniform standard that simplifies it, and with the patient's safety in mind.

DR. HOLLINGER: Yes?

MR. DUBIN: Well, I think there is an important anecdote to that. Terry had his knees done in Brigham and Women's and the doctor was so concerned about infection that he suited up the entire surgical team in essentially the light weight NASA suits. You know, I mean, here was a doctor that was so concerned and, yet, he didn't think about leukodepleted units. He gave Terry regular units. And, here is a doctor that you would think would know because he was suited up the whole surgical team to prevent infection.

So, I think your point is really important. I saw Terry just before I left and he said, you know, Corey, I should have had leukodepleted. There was a real risk there. So, I think you are right, to expect everyone to know -- it is much better if we just set a standard and that becomes the standard and, you know, we work from there.

DR. HOLLINGER: I just want to ask you, Dr. Kagan, one thing. You know, as a surgeon, a lot of discussion here and in the literature that was sent about postoperative infection secondary to this, and working on a clean colorectal surgery, and so on, in which most of them get antibiotics to start with, prophylactically, what is your take on the information that you either heard or that you read about, particularly written by -- was it Blumberg?

DR. KAGAN: Right.

DR. HOLLINGER: Give me some feeling on what you thought about most of that data.

DR. KAGAN: Actually, I had an opportunity to review some of those papers, as well as the bibliography where there is an awful lot of surgical literature from trauma centers, burn centers, and the like, and where you are dealing with patients who are probably going to be immunocompromised anyway by nature of surgery alone, even an elective procedure -- cancer patients probably have some degree of immunocompromise, trauma patients -- I think you

have a set up for infection with all the prophylaxis possible. If you look at some of the literature in elective colorectal surgery where there is sufficient mechanical preparation of the bowel, there are systemic antibiotics, in some cases even gut antibiotics administered, and you find that just the issue of transfusion versus no transfusion makes a difference in wound infection rates and length of stay.

If you look at the cost of that issue alone, ten extra days in the hospital, maybe in an intensive care unit, maybe some ARDs with sepsis, with ventilator support, the cost of that is outrageous compared perhaps to the cost of, (a) not transfusing if you can help it and, (b) if you do have to transfuse, transfusing the safest product that is going to as little as possible cause further immunocompromise in the patient. So, I think the cost benefit on the other side will be in decreased hospital costs, and decreased morbidity for patients, even though it may cost a little bit more on the upside.

DR. HOLLINGER: Norig, anything you want to add to that?

DR. ELLISON: I agree with what he said. I think that the surgeons and anesthesiologists are becoming more aware of this risk, and I don't think many of them are aware that by leukoreduction we can decrease that.

DR. KAGAN: I would even further add that when somebody comes in and needs, you know, 100 units of blood over the next 3 hours in the operating room, it is kind of hard to pump that stuff in with all those filters going if it hasn't been pre-filtered. You will find that people at that point of time are saying, "he needs blood; screw the filters," and you are pumping it in as fast as you can. I mean, you have to get the patient off the table first.

DR. ELLISON: Dr. Gilcher, I was just going to tell what you said earlier to me privately about the fact that if you do this prestorage one filter lasts a lot longer than it does if you are taking regular units of blood that you have to pump, and every four or five units you have to change it.

DR. GILCHER: May I comment?

DR. HOLLINGER: Yes, please.

DR. GILCHER: Actually, I had just put my hand up to make this comment. There is an additional side benefit that I didn't talk about this morning because it is not something that blood centers, in fact, want to have happen. The reality is that there is a certain number of units that we collect that will have clots in them, and we will not detect those clots. They will be detected by the end user when they are not filtered.

But when we do the prestorage filtration, the

reality is we can pick up every single one of those. So, now if you talk about purity and potency of a product, unquestionably, the product that has gone through the leukocyte reduction filter, regardless of the leukocyte reduction aspect -- I am talking about what comes through the filter in terms of the product itself -- clearly, it has far fewer other contaminants, if I can say it that way, you know, looking at a clot as creating a problem in the operating room or the end user point, and taking that out up front. Now, that is not the reason to do it but it is another additional benefit that is going to make life a lot easier for the nurse, the surgeon, the anesthesiologist, and obviously in a critical situation you are not going to stop up the filters. That is what we were talking about.

DR. HOLLINGER: Ron, while you are up there, you were saying that you do yours mostly by 20 hours, by and large. Do you have an upper limit that it ought to be done by? Do you think 20 hours is the upper limit, or do you think 48 hours would be the upper limit? What are your thoughts after looking at all the data?

DR. GILCHER: The upper limit in our institution is 20 hours. We try to have completed all units that we are going to label before 20 hours. We picked 20 hours mainly because of the granulocyte dissolution that occurs after about 24 hours. That also gives us time in our current

situation to do the testing, have the test results and then do the leukoreduction, and be more "cost effective."

DR. HOLLINGER: Is there a lower level that you think is probably too quick?

DR. GILCHER: Well, there are arguments on this, whether continuous filtration technology or machine-based technology is too fast or not. I think that those are arguments are going to be very hard to debate.

Let me say that there potentially might be an advantage in filtration, in reducing bacterial contamination if the bacteria were introduced at the time of the phlebotomy. In reality, there are two major sources of bacteria in blood. One is the bacteremic donor, and those are going to come out either way. The other is where the bacteria are introduced at the time of collection. There are some technological ways to take those out in addition that I won't go into, but one of those is, in fact, if we were to allow a certain storage period to occur those bacteria could be phagocytized. There is some evidence to support that in the literature.

DR. HOLLINGER: And, the data would suggest how long does it take for phagocytosis to occur?

DR. GILCHER: That is hard to say but somewhere probably between zero and four to six hours.

DR. HOLLINGER: Thank you. Yes, Dr. Nelson?

DR. NELSON: It seems like a lot of arguments have been made for using filtered blood, and I agree with them and they are persuasive. The one thing I have some question about, and data was presented on, is CMV. Presumably, what was shown was a comparison between CMV-negative donors and CMV-positive donors who had been leuko-filtered. But there was no comparison group of CMV positives who hadn't been leuko-filtered and, presumably, that would have been 100 percent but I don't know.

The issue is I wonder if you are giving a million white cells in a patient who is likely infected with CMV, how much does filtration really reduce the risk? It clearly doesn't go to zero but I would be interested if there is any data. Because that is obviously one of the arguments, that we would like to prevent CMV, HTLV and unknown leukocyte-associated viruses. So, if you are giving one unit or more than one unit of blood intravenously, it seems like a pretty big challenge.

DR. HOLLINGER: Anyone have any thoughts about that or any information on that?

DR. KAGAN: I have some parallel comments. Years ago I looked at the incidence of CMV infection in burn patients, and looked at transfused units as well as allogeneic skin grafts that patients may have received. Those of you who aren't aware of this, most burn patients

have severe immunosuppression if they have significant burn injuries. We found that in that pool of patients, over 50 percent of the patients, if they had significant burn injuries, they had reactivation of latent virus merely from the immunosuppression of their injuries. You know, they were sick enough that they needed transfusions; they were sick enough that they needed all these other avenues. And, we couldn't find a link to blood or the allogeneic skin.

Now, there have been some people who have also recently looked in burn care at CMV-positive versus CMV-negative allograft skin for the care of extensively burned patients, and although they have some interesting data, clinically it doesn't seem to make a difference because, unfortunately for us in this country, most of the donors are over the age of 35 years and they are CMV positive, and if you work in a pediatric burn center facility most of your patients are CMV negative.

To try to maintain adequate supplies of CMV-negative skin means that you have a very small and very fortunate donor pool available. So, practically it doesn't seem to make a difference, or be appropriate for tissue banks. It doesn't seem to make any difference in the clinical response of the patients at all whether they have a primary CMV infection or develop reactivation of latent virus.

DR. HOLLINGER: Dr. Busch?

DR. BUSCH: Yes, two comments, one to Ken's question on CMV seropositive blood. You know, about 50 percent of our donor pool is seropositive. When that is transfused, less than 1 percent of the recipients of seropositive blood who, themselves are susceptible seronegative become infected. Those rates are really not well documented. The latest studies are from Canada, probably not over 10 years ago, and it seemed to decline in the 80's from rates of 3 or 4 percent, and which of these seropositive donors are transmitting is unclear, and studies I think are ongoing now to see if perhaps PCR could discriminate the seropositive transmission. But seropositives almost certainly harbor the virus some place in their body because they will reactivate if they become immunosuppressed. The rate at which they are viremic and would transmit is quite low.

Just another comment in terms of reactivation, the viral activation transfusion study, which was mentioned earlier, has completed enrollment of about 550 patients who are randomized to get prestorage filtered leukodepleted blood versus standard blood components. It is looking at the effect of transfusion of filtered versus non-filtered not only on HIV reactivation, but all these patients are also CMV positive and we are monitoring for CMV viremia over

time post-transfusion and end-organ disease. So, that is a study which should have results completed within about a year, I think, in terms of all results and data analysis. It should answer the question whether reactivation, triggered by donor leukocytes, occurs with respect to both HIV and CMV.

DR. HOLLINGER: And, Ken, I think the other thing too is that as blood ages, even if you leukoreduce it, as you know, the probability is that transmission markedly goes down with CMV, and that probably is playing another additional role. Yes, Celso? And, while you are up there, you might just tell us how much you do in terms of leukoreduction at the New York Blood Center, by and large, yourselves.

DR. BIANCO: By and large, about 20 percent of the cells distributed in New York City are leukoreduced. So, the number is not very large.

DR. HOLLINGER: Okay.

DR. BIANCO: But the question I was going to ask, because I know there are several aspects around it as we are talking about CMV, is HTLV. There is pretty good documentation that HTLV is totally cell-associated. Could we think, as we balance everything, that leukoreduction could preclude screening for HTLV? Dr. Khabbaz?

DR. KHABBAZ: Good question. I don't have an

answer. I think you are right that HTLV is cell-associated and there is no transmission from leukocyte-free products.

DR. BIANCO: I am just thinking that as we look at the entire picture maybe we can divide benefits on one side and other things on the other side where, ultimately, for the whole healthcare system we could find the cost benefit that we are looking for.

DR. OHENE-FREMPONG: From a hematologist and patient point of view, when you order red cells for a patient you expect to give red cells. We go through a lot to make sure that the red cells we are giving are matched to the patient's red cells as closely as possible. Because of the technology, we have sort of lived with the idea that if you order red cells you get white cells and platelets that you didn't match that you don't cause problems for the patient.

I think if technology is making it possible so that at least we can separate the components and give the components we want, as matched as possible, we should be heading that way. So far, we haven't heard of any advantage to a patient who is going to get a red cell transfusion -- we haven't heard any advantage that the white cells, or platelets, or plasma products that may be in there would give that particular patient. So, it seems to me, from that point of view alone, and also knowing that we have heard of

a lot of potential risks, from the patient's point of view this is the ideal product that one would want for the patient. If cost and other considerations make is such that we are not able to implement it right away, at least we should commit ourselves to implementing it as soon as we can. But it is hard to argue that in the face of everything else we know there is going to be benefit to not doing so.

DR. HOLLINGER: Yes, Dr. Khabbaz?

DR. KHABBAZ: Yes, since the question is benefit to risk, and I understand that the risk is minimal, I would like to see us explore a little bit the question of risk, and only to make sure that I understood and have that clear.

With regard to the hypotensive reactions, I understand that they are mostly associated with rapid resolution. Have there been any deaths? Any reports of, you know, deaths related to any reaction? No? Okay.

The other question is, is it correct -- again, in interpreting Dr. Popovsky's presentation -- that the hypotensive reactions are mostly associated with bedside?

DR. HOLLINGER: Yes.

DR. POPOVSKY: That is correct. Other than that initial survey that I alluded to that we published the data from, in 1996, if you look at the literature summary that I then presented, the subsequent 42 cases, those were all exclusively associated with bedside and, to my knowledge,

did not involve mortality -- morbidity only.

DR. KHABBAZ: And, also you included that the incidence is not well defined. Any efforts going on to try to address or collect information on incidence?

DR. POPOVSKY: Not to my knowledge. I mean, that is difficult data to get. One would need to basically know what that denominator is and be able to prospectively follow and track the number of cases that are occurring either in an institution or multiple institutions and, to my knowledge, there are no data that are being collected in a formal way.

DR. KHABBAZ: Thank you.

DR. NELSON: So, to extend the argument, if there were routine leukoreduction in the blood bank this risk might be reduced if it is associated with bedside, presuming that there was no further bedside filtration, which I guess is an assumption that may not be true but it should reduce the risk if it were done under controlled circumstances.

DR. VERTER: I would make a few comments. From my perspective as a non-blood banker, the presentations were excellent but when I think of risk/benefit I become very quantitative, and I am very upset at the lack of quantitative data today. Of course, I have made the statement before to those from FDA sitting around here. In fact, at another FDA panel session that I was on, they now

call me "the show me the data guy."

[Laughter]

In this one, unlike some of our other presentations, there really is data. There were two trials. I understand from the presentations today and from the package that we received this morning that there are probably many other trials. I got a chance to look at the two that were presented. One was in CABG patients and one in colorectal patients, both surgery trials. Both seemed to imply, although I had some questions about the design and the analysis, that infection, for whatever that is worth, is reduced. In the CABG there was no difference in mortality and in the colorectal trial there was actually a two-fold increase in mortality in the leukoreduced group, but it was not significant and the numbers were quite small.

So, I have a plea, and unfortunately I am going to direct this more to the FDA folks although certainly anyone who presents in the future maybe should hear it also, if there are trials that are out there that are relevant and germane to the subject that we are going to discuss, could we either see the reprints included in the package, or have someone in the FDA give us -- and I am not going to use the "M" word -- and overview? I don't want to see any summary of odds ratios or relative risk.

I will go ahead and volunteer to help you do that

because, to me, I am at a real disadvantage. The presentations were clearly in one direction today, and that is probably where they should be but there are risks, and the risks were alluded to but there is really no greater data for risks; most of it was anecdotal.

As one of the two presenters indicated, where is the denominator? No one can tell us exactly what the denominators are. However, you know, I am willing to concede that relative to the 14 million or so transfusions, and I don't know how many products are given every year, it is relatively small but I feel somewhat uncomfortable -- I mean, I am pretty sure I know how I am going to vote, but uncomfortable in that I don't have the data. I really don't.

DR. HOLMBERG: First of all, I want to shift gears a little bit here but, Dr. Gilcher, what is your plan for implementing 100 percent at your facility? Is it a phased approach?

DR. GILCHER: Very clearly it is an educational approach, and it is also working with our hospitals to find ways to reduce the use of blood so we are focusing on utilization. I can do that as a transfusion medicine specialist and clinician, and then also focusing on outcomes. That is why we do need the reports of these various trials because I think the outcome analysis will

show that this is cost effective.

Also, if we can reduce what I call the unnecessary utilization -- there always is some, and there are ways that we can do that, that will help reduce the overall costs of operating a transfusion center so that we can put in new technology that can benefit the patient. That is really the approach we are using.

DR. HOLMBERG: We talked about the bedside filtration before, a year ago when we were talking about the CMV issues, and I think all of us realized that there are a lot of disadvantages to that uncontrolled infusion rate and also the temperature, the time and what-not. But I think over the years why facilities have gone to that bedside filtration is the ease of use, and also some facilities not wanting to relabel a product, and the labeling issue there of the claim of a leukoreduced product.

I want to shift a little bit though to the QC aspect of it. Again, Dr. Gilcher, I think you brought up some good points on the QC. First of all, I guess I would like to ask the FDA to give me a refresher on how we came up with the 5×10^6. It was also very interesting to hear that with the U.K. going to 90 percent -- well, 90 percent at 10^6 and all the product had to be below 5×10^6.

DR. HOLLINGER: Who can provide the information about the number that was sort of selected, this 5×10^6,

less than 5 X 10^6? Yes, please state your name.

DR. HOLWITZ: I am Les Holwitz, from FDA, CBER. The number of 5 X 10^6 was decided on at the workshop in March, in 1995, basically, after much discussion of the workshop participants.

DR. HOLLINGER: Yes? Could you use the microphone, please?

DR. FREEDMAN: The number 5 X 10^6 comes from the work in 1981, I think, by Klas, in Holland, who did experiments in mice and he arrived at the figure of 5 X 10^6 and that has been accepted ever since.

DR. HOLMBERG: I guess I would also raise some issue as far as the way the current guideline is written with the amount of QC. I think that as we talk about vendor qualifications being part of GMPs, and the amount of testing that the vendor must do, the manufacturer of these filters, I think that they carry with them a labeling message that they can reduce down to a certain level. I just question the need for a 1 percent sampling. I think that I would like to hear some discussion on the sampling for the QC, and also the methodology. When we talk about the different methods that are presented in the guidelines, it actually gave leeway for any other methodology that could demonstrate measurement or counting of white cells. But, you know, even with the Nageotte chamber that is so difficult to do and,

yet, where are the quality controls on the Nageotte chamber? So, if I could hear some discussion on the concept of sampling and what the sampling size should be?

DR. GILCHER: Well, in part I attempted to address that this morning because we, as I stated earlier, have quality control for 100 percent of the platelets, not the red cells but the platelets. So, it has given a chance to really look at all these platelet preparations. Very clearly, if you look at the numbers, about 97 percent of our platelets were below 1 X 10^6. In fact, they are virtually uncountable. They are from 3-5 X 10^4, and basically you have heard that number repeatedly.

What I did say that I think is important is that we were able to predict the outliers. I think that is very important. I think that needs to be defined within the guidelines when there is data that can predict where the outliers are going to be. Either you don't label those products as leukoreduced or, if you want to do that, then you must actually QC those products. I think that will inherently improve the products overall. So, I think that needs to be incorporated into whatever guidelines are developed for the sampling procedures.

DR. HOLMBERG: Do you label your products if they are over 5 X 10^6?

DR. GILCHER: They are not labeled as a

leukoreduced product or they are, in fact not distributed, one or the other.

DR. HOLMBERG: But what is your feeling on sample size? Do you think it is necessary to leukocyte counts on every platelet product?

DR. GILCHER: No, I don't think that it is necessary to do it on every platelet product. I think, again, we are clearly going to move away from that. That is very expensive overall to do, and it is unnecessary once you can predict where the outliers are going to be. That is part of the reason why we have done so many platelet QC products.

I think that the amount of QC that is done -- I think there are a couple of factors that are important here. One is that in order for your staff to be competent in whatever procedure you pick, there is a certain number they have to do or they won't be competent at it. We have found that whether it is flow cytometry, spatial laser imaging or, certainly, the Nageotte counting. I think those institutions where they won't be doing enough probably need to find some place else that can do the testing for them where they, in fact, do the testing with quality. But really it is the training of these people and the numbers that they do that is important. I think from that we can determine what the numbers are that need to be done, whether

it is 1 percent, more or less. But 1 percent of the total number is not a bad number to pick. It probably is enough in a large institution to keep the staff competent but it is clearly not enough in a small institution.

DR. HOLLINGER: But, Ron, along those same lines, 1 percent is nothing. I mean, how are you going to pick up anything? Once you have something established that is below a certain level and you do 1 percent when you only have 2 percent that are above that level, you are never going to pick them out. Then, what if you find that this sample which you are using, whether it is 1 percent a month or 4 a month, whatever the number, is elevated above that level, does that mean only that sample is going to be labeled as not leukoreduced? What about all the samples before then? I mean, how are you going to make those decisions on that basis?

DR. GILCHER: When your QC on a sampling basis, where you are not doing 100 percent, is not where it is expected to be or within the guidelines, then it tells you that your process is no longer in control. The process by which you are performing -- that is what that says to me -- the process by which you are performing this leukoreduction is out of control.

DR. HOLLINGER: And, how far back do you go with the samples of the product before that then?

DR. GILCHER: Well, i don't know the answer to that. What I am saying is that you must bring that process into control, and that means you are going to have to do more and, obviously, up front you have to validate the process. And, you validate the process not by doing 1 percent but by doing a large number to determine that your process, in fact, can be validated and stay in control, and it is the QC that really is showing that that process stays in control.

DR. HOLLINGER: As I look at it, I guess I would say if you have a good process that is going on you would probably have to do some but, I mean, you might as well not do any if you are just going to do 1 percent, and I am not sure that that really is bad.

DR. GILCHER: Well, I think you have to do enough -- and I am not going to define "enough," but you have to do enough to show that your process is, in fact, valid; that it stays in control. It would take, I think, some statisticians -- perhaps Larry, you can comment on the exact number that one would need to verify that your process is in control.

MR. DUMONT: Larry Dumont, from COBE, but I want to speak though as one on the authors of the best guidelines that Dr. Williamson referred to earlier. That was a group that put together a paper and some approaches to try to

answer those difficult questions.

I think, first of all, most of those questions would be moot points if we had a very, very simple analytical method to count white cells, which we don't have. If it was as simple as doing a CBC we would just say, "just go, do it," and we will move on and think about other things. But it is difficult. You have to do flow cytometry or Nageotte counts, or something that is expensive and complex.

So, in that approach we actually took kind of your classical SPC quality control approach that has been around since before World War II to say you can't really look at every product. What you need to do is you need to control the process. So, you start out with a process that is well designed and validated, and that is the manufacturer's responsibility. Then you bring that process into your blood center and you validate that with an appropriate number of samples. It is more than 1 percent. It depends on the process. Then you do some type of ongoing monitoring to verify that the process is stable. That is a fairly rational way to approach it.

As far as the 1 percent question, anybody in statistics knows that a percentage sampling really doesn't mean a whole lot. It is better than nothing. Sometimes it is very helpful and sometimes it is not. So, it is really

more important to look on a consistent basis.

So, that was the approach. People can also take the other approach. I know Dr. Gilcher did this for a while at least, at OBI, where he said we are just going to count every one. So, that is kind of the background. It doesn't answer all the questions because those are tough questions.

DR. HOLLINGER: Thank you. Yes?

DR. WENZ: I am Barry Wenz, from the Pall Corp., and I don't even look like Judy Angelbeck --

[Laughter]

-- I can give you some data on our experience with the Canadian program where we currently are monitoring 500 leukoreduced products per month on an ongoing basis. We asked the same question, and we didn't have the answers so we turned to a group of statisticians at the University of Stony Brook. They came in and they analyzed the problem. Much like Larry described, they set up a program that we can use. The program, known as Komagorov-Smirnov Analysis, basically establishes a database, and we have a database on products now, some of which exceeds 8000 data points. The database basically with two-tail analysis and negative binomials, and all sorts of other considerations that go beyond my being able to mouth them, and not understand them, sets up a curve that has a frequency distribution and a shape for the expected results and the accomplished results.

This is monitored on a real-time basis.

What this permits you to do -- the generic "you" and what our experience has been to date is to detect a shift or a change in the shape of the curve even before the process is out of control. It alerts you to the fact that something has changed in that center. On a real-time basis before we exceed the magical 1 X 10^6, we can say, "wait a second, this doesn't look like the other 5000 data points that the last 20 points on this curve fit to." It allows us to go in, and with the supervision and help of the experts at the center, reanalyze the process and, in each and every instance so far, identify something that has changed in the process and put it back into the curve. We are doing this on the basis of 1 percent sampling, as was presented, so that these 500 data points, grouped over individual centers, fit to their individual curves, and over time each one of them revalidates their curve with progressively increasing numbers. So, this is the approach we have taken.

DR. HOLLINGER: Thank you. Yes, Dr. Boyle?

DR. BOYLE: I want to put together what Corey and Joel said because, on the one hand, I am persuaded that I like this direction and I think that it will benefit patients and patients at risk, and I am persuaded by what I read, but I also think, given my interest, that my standard of evidence isn't all that high. And, in looking through

some of the data, for instance, one of the real benefits pointed out is the reduction in the febrile transfusion reaction. Or, when I read the Canadian document, it rates five of the six studies as poor in terms of its design.

So, I am happy to move forward here because I am convinced by what is available here that it is a good thing. But I think when it moves to the next step where we are not talking about benefit/risk but we are talking about cost benefit people are going to be holding it to different standards. And, I think we had better get that information together now if we are going to be successful at the next step.

DR. LINDEN: I have a question for FDA about the question. The question has to do with requiring universal leukoreduction. By what mechanism would FDA propose doing that as opposed to recommending it? Are you talking about a regulation?

DR. EPSTEIN: We would move progressively. First we would recommend the product standard. We would examine approved products that don't satisfy the label requirements. We would solicit resubmissions for labeling. Ultimately, we would follow it with regulation. So, you know, we have our ways!

[Laughter]

DR. LINDEN: So, there would presumably be

opportunity then for increasing experience, perhaps gathering data along the lines of this process.

DR. EPSTEIN: I think, Dr. Linden, you are suggesting that perhaps the committee would want to recommend a gradual approach. For example, there may be some patient groups in whom the benefit is thought to be better established than in others, and one might make a practice recommendation for those groups but encourage that there be rigorous studies in those groups to try to, as Dr. Verter said, establish benefit with better quantitation. So, yes, I mean, we have asked a black and white, up and down vote but if that is not possible, then I think, you know, we would seek advice on the next steps. And, it is, of course, possible to do additional studies.

DR. KHABBAZ: I am glad to hear us moving in that direction because I am sitting here, on one hand, agreeing with my colleagues and it is a beneficial thing by and large. That is probably something that we are moving towards, and probably should because there are no benefits from those leukocytes and there are proven benefits, as I have heard, for subpopulations. I have been sitting here, bothered by the FDA wording, requiring universal. I am thinking it is probably good but, you know, I have not really heard the evidence, the data. So, I am happy to see us consider maybe a gradual recommendation, and maybe

starting with populations of patients.

DR. TUAZON: I share the concern of Dr. Verter in terms of the lack of the denominator. I think so far the major consensus has been on the prevention of febrile reaction. I think the major impact of this would be in the postoperative infections if we can confirm the data, especially the cardiac surgery. But I think the data presented to us so far is really insufficient, and the data also, you know, is related to the number of transfusions in the cardiac patients, the difference between the leukoreduced and the non-leukoreduced. If you think about those patients, those are the patients who had numerous transfusions and these are also the patients who are probably more complicated and have had prolonged durations of surgical interventions in the OR and, therefore, exposure to high risk of infection, aside from the factor of blood transfusion alone. So, I think the bottom line is really that we need more data in those areas.

DR. HOLLINGER: Thank you. Yes, Dr. Mitchell?

DR. MITCHELL: I am very concerned, I guess, about people with sickle cell, particularly children with sickle cell who may be receiving up to four units of blood a month on a regular basis. If the chance for febrile reaction is 20 percent, to me, that seems very, very high and we should be doing all we can to reduce that. I mean, people with

sickle cell, that is almost 50 units a year for children, every year for the rest of their lives presumably. So, I think that is the group that is arguably most risk for problems from transfusions, and I think we need to do what we can to protect this group.

I think that we need better data on what the endpoint should be. We have heard, you know, five million WBCs versus one million, and it looks like the technology is going so that we should be able to remove that even below the one million mark. But I would love to see us start to move in this direction and to try to perhaps require even greater amounts of leukoreduction.

DR. BUSCH: Just one response to that. We were interested in doing some studies in terms of leukodepletion in sickle cell and thalassemia patients, and came to quickly learn that all patients in the United States, all sickle cell and thalassemia patients get leukodepleted blood already. We had to do the study in Brazil to get the population that was not leukodepleted.

DR. HOLLINGER: thank you. Yes, Corey?

MR. DUBIN: I don't have a problem with "require." In fact, I will be perfectly honest, I mean, I sat down, saw the question and said, "hmm, about time; about time we said we don't recommend." There are some of us that think that the agency recommended a little too much over the last ten

years and didn't require enough for certain things to be done. So, I agree that we need to see more data, but I think we can see that data and move at the same time, and the committee can weigh in that way, but I think it is pretty clear that the benefit is going to be to move this way and to require it. It is going to move the equation and that is what we want to do.

DR. HOLLINGER: Okay. Dr. Koerper?

DR. KOERPER: Speaking as a pediatric hematologist, I take care of at least four of the groups of patients that have been mentioned for whom leukoreduction is mandatory, namely, sickle cell, thalassemia and severe aplastic anemia. When I write the orders my patients get leukoreduced blood that is being reduced -- what is it, at the Pacific? It was Urban Blood Bank for 20 years and I can't remember this new name. Anyway, when I write the orders it is done right.

But the problem is that I also cover oncology and some of my patients need to be admitted to the hospital as well, and we have house staff. And, it might be three o'clock in the morning and I might not be the person on call who got the phone call to say, "yes, you'd better transfuse because there is a chest syndrome happening here." The house staff and the oncologists who might be covering for me don't always have this firmly in mind that, "oh, yes, we'd

better order leukoreduced blood." So, I can make sure that my patients get what they need but I can't be there all the time, writing the orders all the time and, for my patients in particular, I would feel more comfortable knowing that whatever was written for that came out of our blood bank was going to be prestorage leukoreduced, rather than hoping that somebody remembers to put a filter in once they are hanging at the bedside.

DR. ELLISON: I would echo that and say that the only way we are going to be sure that the patients that need leukoreduction are going to get it is if they are all that way.

DR. DUBIN: That is right.

DR. ELLISON: I like Dr. Williamson's description of the precautionary principle which was applied in Great Britain, and I think instead of America sort of catching up I think we should catch up and be a leader rather than follower.

DR. HOLLINGER: Dr. Gilcher?

DR. GILCHER: There is one point that I would like to make from the standpoint of being a blood center director, and that is the worst thing for us is to inventory two products when they are 50-50. As we move up, it becomes very difficult. It clearly adds additional cost to the system. It is much better, both for the hospital blood bank

which also has that issue and for the blood center, to not have to inventory two products when one product, in fact, would suffice.

DR. HOLLINGER: One of the things we talked about was refractoriness of platelets following alloimmunization of a recipient. But, you know, I have not been able to see in the data that has been provided to us -- I know, clearly, you get patients whose platelets go down to 30,000 or so and you give them platelets and they don't rise, but I haven't got the feeling for whether this is a real problem or not. We all know that even if normal levels weren't 50,000 if you have good functional platelets you can be pretty low and still prevent bleeding and other things. I would like to have some feeling from either you or other people here in the audience who have experience. Can you give me some idea whether these are real risks that we face?

DR. GILCHER: Well, the first issue with refractoriness is that not all of it is immunologically induced. In fact, since we have been doing a lot of platelet immunological work where we look for platelet-specific HLA antibodies in patients who are refractory -- and we have a definition for refractoriness, what we are actually finding is that about 60 percent are non-immunologic, at least as far as we can determine, and only about 40 percent are immunologic. Those are the only ones

where this would be applicable. But in that 40 percent that are immunological, then what we are resorting to is platelet cross-matching and/or HLA identical platelets. In particular, we use the cross-matching because we can cross-match against what is in stock and provide a platelet, hopefully, in most cases immediately. Whereas, with HLA we would have to bring the donor in. So, that is really one of the approaches.

I think something that was brought up this morning by one of the presenters that is important is whether we are dealing with primary refractoriness or secondary refractoriness. I think the primary refractoriness can be significantly reduced by using leukoreduced products up front, whereas, with the secondary I think it is going to be less likely because the patients are all already alloimmunized against selected HLA antigens, and if they are presented those antigens, even without antigen-presenting cells, they probably will have an anamnestic response.

DR. HOLLINGER: Did you want to say something?

DR. SNYDER: Ed Snyder, from Yale. Being in a transfusion service, we have used over the past several years less and less HLA-matched and cross-matched platelets which we use almost exclusively for patients who are refractory, and the levels have dropped commensurate with our using leukoreduction filters almost exclusively for

oncology patients.

The comment that was made about not always being able to be there, we have problems if someone has an oncology patient and is admitted to another floor -- if someone is admitted to the oncology floor and they don't request leukoreduced CMV negative, we trip to it because it is on the oncology floor, but if they are on another floor because the oncology floor is full, unless we are told -- we are not mind readers. So, in that sense I agree with you.

Being refractory and not being able to get platelet count up is a serious problem. The percentage of individuals at Yale that suffer from this is getting smaller because we are using leukoreduction filters more, but a lot of people may come in for surgery and get blood that is not leukoreduced when they are 20. They will come in 70 years later with a cancer and they present already alloimmunized. That has always been a soft argument. People say, "yeah, well, you know, because it's guns or butter" --

[Laughter]

-- but I think we know enough now. Perhaps the phase-in concept that I hears is appropriate in order to allow us to get more data but to move off the dime, as Corey has said. It is a problem, but not enough of a problem to say, yes, we absolutely have to have universal leukoreduction because of all the refractory patients that

are bleeding. It is not a large number but for those who treat those patients it is a very difficult problem. You wind up with platelet drips. Our drip is now three units every four hours around the clock until something happens, either the patient gets better or has a more untoward outcome.

Just one caution. Bedside leukoreduction is not the best. We have talked about that, but I certainly would not want to do away with the option of having it available in some circumstances for certain reasons. It is not the best but it is certainly better than not having a bedside opportunity to leukoreduce at all.

DR. HOLLINGER: Thank you. Dr. Ogamdi?

DR. OGAMDI: I just wanted to emphasize the fact that we have heard a lot about the positives, especially in some patients, to be able to go forward with this. My concern is that the more we get data we will also see a lot of positive things, especially with HTLV and other things. So when we look for data, we are not just looking for data to see some negatives. We know that we may see more positives coming out of this if we begin to ask them questions. I want to see whether someone may comment about the positive and negative filters. Is there anything going on with regards to that, whether we are changing or moving towards eliminating one type of filter or advising against

one.

DR. HOLLINGER: Any thoughts about the positive or negative filters, or whether that is critical for removing certain contaminants.

DR. SNYDER: This is not my area. There are people in the room whose area it is. The positive or negative relates, again, to the surface tension. And I don't know anything about how the Pall Corp. or Asahi makes their filters but you can't just change a positive to neutral or negative and still have it remove the cells you want it to remove with the same efficiency. That would require a good deal of effort. It is probably easier to leukoreduce prestorage and not have to worry about the bradykinin concern than it is to try to redesign an entire filter. But, again, this is not my area.

DR. HOLLINGER: Dr. Holmberg, you have a question?

DR. HOLMBERG: Yes, I would just follow up with Dr. Snyder's comment about not doing away with bedside filtration, but I do appreciate what Dr. Epstein said, that there should be a progressive approach and that eventually we can replace the bedside filtration with prestorage.

I also have a question, when the comment came up about sickle cell, I am concerned also with the effects of filtration on the blood from those donors that have sickle cell trait. Does anybody have any experience with that?

Dr. Gilcher, do you?

DR. GILCHER: Yes, my technical director reminded me they don't filter. We have tremendous problems if we inadvertently have a donor who comes through who is a sickle trait, and we currently do test all of our blank donors for sickle trait. We notify them of that if we find it but, in fact, these units do not filter. We have a very high loss of red cells in the filter, giving you an unacceptable result.

DR. HOLLINGER: Dr. Williamson?

DR. WILLIAMSON: I am very interested to hear that because we are wrestling with the same question. There have been reports over the years in the literature of difficulty filtering sickle-positive donors. Since we have a fair number, particularly in the London region, who are regular donors we plan to do some prospective studies with different types of filters under different processing conditions to see if there are any circumstances in which we would be able to keep these donors.

DR. HOLLINGER: Thank you. Dr. Gilcher?

DR. GILCHER: One other quick point on that which relates to bedside filtration, we clearly have had units sent back to us that went to the hospitals not leukoreduced, and when they attempt to leukoreduce these at the bedside they really won't filter there. The pH is lower, and so

forth, because the units are older. So, they even pick them up at a higher rate, so to speak. They won't filter.

DR. HOLMBERG: Dr. Gilcher, what are you doing with your donor population that are sickle cell trait? Are you redirecting them into your apheresis program or plasma?

DR. GILCHER: Exactly. We are attempting to convert as many of those donors to, say, non-red cell donations -- that is the term that we use, and it includes in our system apheresis platelets and apheresis plasma. If that is not acceptable, we will continue to draw the donor but we are offering other alternatives for donations, and it is amazing how many of these donors are willing to do what I will call non-red cell donations.

DR. OHENE-FREMPONG: This is so interesting. This implies that in people with sickle cell trait, after donation either the pH of the blood or the level of oxygen is so low that the hemoglobin begins to polymerize and the cells begin to sickle. I don't remember that being demonstrated in any fashion. Is there any understanding why?

DR. GILCHER: Well, I think very clearly it does happen and, remember, your pressure of oxygen will reduce; your pH will go down. Remember, theoretically that reverses when the unit is transfused. So, if it goes through a big enough pore size filter, it will go on through. The cells

would revert to a normal shape. They are not irreversibly sickled in that situation. But when they get to the smaller pore size filters, because there is an increase in the conversion from normal to a sickle shape, they just won't get through that filter.

DR. BIANCO: That is true even with the frozen cells, and you have to be very careful when you thaw the cells. Just the sheer forces of the washes lead to a much increased rate of lysis.

DR. OHENE-FREMPONG: My original issue though was a follow-up to the issue about sickle cell disease patients and what type of blood they are getting. I would be very surprised if most sickle cell patients in the country receive leukodepleted cells. I think at comprehensive sickle cell centers where there are large numbers of patients who are on chronic transfusion therapy for stroke and other complications, they may be getting leukodepleted blood but most sickle cell patients in the country are not cared for at centers like that. Even at those centers we arrived at using leukodepleted red cells not because we thought theoretically they would do better, but because patients suffered through years of febrile reactions, and they were sort of gradually advanced through regular red cells to leukocyte poor to leukodepletion. So, these are patients who suffered through, and it is almost as if we

held the best product out for those who had developed complications.

We have shown at Children's Hospital in Philadelphia that some of our patients have become immunized against platelets, sickle cell patients. Now there are patients with sickle cell disease who are being transplanted with bone marrow transplantation. Some of you may know that the few fatalities we have had post-transplantation have been in patients whose platelet counts cannot rise with platelet transfusion. This is maybe because they were immunized against platelets when they were being given red cells. So, I think most patients with sickle cell disease who are transfused on an episodic but, albeit, increased rate than normal people are not receiving depleted cells and they should be receiving leukodepleted cells.

DR. HOLLINGER: Dr. Nelson, did you have something or has it been answered?

DR. NELSON: This is very interesting. I just wondered if there were any other either hemoglobinopathies or other donor characteristics were leukoreduction could be a problem. I can certainly see why sickle cell but I just wondered are there any other donors in whom the blood would be damaged or could not be transfused or used because of the leukoreduction process.

DR. SNYDER: I am not aware of any other.

Thalassemia trait I don't think would be a problem. Many of these donors don't have a high enough hematocrit to be able to donate, anyway.

There is one point I would like to make, which Dr. Nelson raised. When we talked about people who become alloimmunized when they are younger and then appear later, as long as this is on the record, and there are people from the NIH listening, I think one area that is appropriate to pursue in women's health issues is the risk of alloimmunization that occurs as a natural actor in parturition. We need to be able to modify the immune system. It is not simply just sneaking up behind it and trying to get around it, but actually being able to manipulate somehow the immune system so that either prevention of alloimmunization during parturition -- somehow deal with this problem, and it is not something that is easily solved but I think if the federal government were to put out certain initiatives we might be able to get some evaluation in this area, which I think is a serious problem for never-transfused women who would come to need a blood transfusion and wouldn't be able to get a platelet count up, or would need a transplant and couldn't get a platelet transfusion that worked.

DR. HOLLINGER: Yes, Dr. Bianco?

DR. BIANCO: In response to the question about

other groups that could have a problem, I can think of neonates when the neonatologists don't like to use red cell preservatives, like Adsol and these substances, because it is much more difficult to filter a red cell if it is not diluted to a lower hematocrit. So, that would be a problem if that requirement is there.

DR. HOLLINGER: Yes?

DR. POPOVSKY: Actually, I have a question and a point of clarification that does not relate to this immediate question, if that is okay and I may proceed?

At the beginning of the session this morning, I believe a question was asked by an industry representative regarding the issue of processes through apheresis techniques that would lead to leukoreduction, and was that considered in the question of this debate today because, looking at that question on the board, it deals with leukoreduction and most of the discussion for the last half hour has dealt with the obvious advantages of prestorage versus bedside filtration.

I want to return to that point because Dr. Snyder, in his presentation this morning, made one very brief comment dealing with fresh-frozen plasma, that there are various processes involved in the manufacturer of fresh-frozen plasma, some of which are associated with higher levels of white cells than others. I guess my question for

the group to consider is that in voting affirmatively today, is the panel, in fact, voting in favor of having fresh-frozen plasma or frozen plasma products leukoreduced by filtration or, in fact, would they consider processes that produce those levels of leukocytes that meet FDA standards to be satisfactory for patient needs?

DR. HOLLINGER: Paul, did you have a question about this, or did you want to respond to this?

DR. MCCURDY: I would presume from the response that was given this morning to the question about pheresis machines that gave a low leukocyte preparation that the issue is the number of leukocytes that are in the final product, not how you get there. The issue of leukoreduction in fresh-frozen plasma I don't think has really been addressed. There certainly are leukocyte fragments in fresh-frozen plasma, and they are probably going to be for a long time unless there is something done, either by spinning them out or by leuko-filtering fresh blood.

I was going to make other comments. The TRAP study has gotten a fair amount of discussion today. There are a couple of parts of it, however, that I would like to mention, and be sure that the panel understands. Number one, the frequency of refractoriness to platelet transfusion, by very strict definition of what is refractoriness, was very low even in the control group. It

was on the order of 10-15 percent, and refractoriness really wasn't different between the 3 test arms and the control arm.

Frequency of alloimmunization to HLA antigens was very much higher in the control group that got standard platelets. The others were essentially the same. The frequency of refractoriness due to alloimmunization was much lower, and was much closer together between the groups, although the 3 test arms had a little bit of an advantage. The p values on those were very close, and one can raise a question as to how clinically significant they are.

TRAP, in view of today's discussion, suffers from the fact that the platelets were leukodepleted in the blood bank with quality control, but just prior to transfusion. So they were not prestorage leukodepleted.

Finally, the frequency of febrile transfusion reactions in the TRAP study was virtually identical in all 4 arms. The control which was standard platelets, and the others which were leukodepleted or UV irradiated. We saw one study, that I think Ed Snyder showed, that failed to demonstrate a difference between leukodepletion and non-leukodepletion in febrile transfusion reactions, but he had an explanation for that.

Are there studies for which you don't need an explanation? In other words, do we have satisfactory

controlled studies that demonstrate what "everybody knows," namely, that get removing the leukocytes will get rid of the febrile transfusion reactions?

To shift gears a minute, we do have, as was mentioned, a viral activation by transfusion study. In that, the blood components were leukodepleted shortly after collection. So, it is what currently is state-of-the-art. I think all of the components that were transfused were quality controlled, so we will have a pretty good idea of how many leukocytes actually went in.

We also looked very carefully at the frequency of transfusion reactions. So, we will have those data when it is available, in addition to the primary endpoint, namely, demonstrating whether there is or is not leukodepletion.

I think, again shifting gears, that those data probably won't be available for another three to six months at the very best. We will make them available as quickly as we reasonably can.

Finally, I sympathize with everybody here who wants more data. I think we all want more data. But I seriously question whether we are ever going to get more data. In the first place, there are a lot of believers out there who are leukodepleting either routinely or for all of their patients, or something like that. So, to randomize would be very difficult, and to get the number of patients.

I suspect we are going to come out -- at least I am coming out with a sort of a gut reaction that adding everything together is likely to improve transfusion practice and safety, but it is going to be damnably difficult to prove or to recognize before and after.

DR. HOLLINGER: If there are no other burning questions on the committee here, I would like to call for the question. Yes, Paul?

DR. MCCURDY: There is one other thing a propos of the sickle cell trait. Studies many years ago, I think in the 60's or thereabouts, demonstrated that sickle cell trait blood stored for 21 days, in I think either ACD or CPD solution, had a normal post-transfusion survival, the same as people who did not have sickle cell trait.

On the other hand, I can tell you from personal experience that you are probably bleeding in your blood banks a few patients who have sickle cell hemoglobin C disease and sickle thalassemia because they will have hematocrits that are within the normal range, and they will meet all of the other criteria that you have for blood donors. When I was involving with running a blood bank with a large black donor population, I did some screening for a while and, indeed, found one of each in, I guess, somewhere between 500 and 1000 donors.

DR. HOLLINGER: All right, I think we will go

ahead and vote on the question. I want to read it again. It says, is the benefit to risk ratio associated with leukoreduction sufficiently great to justify requiring the universal leukoreduction of all non-leukocyte cellular transfusion blood components irrespective of the theoretical considerations for transfusion-transmitted CJD? I emphasized the cellular because I think their question has to do with blood and platelets.

So, with that in mind, all those who agree with that statement, please raise your hand.

[Show of hands]

All those opposed?

[No response]

Abstaining?

[Show of hands]

Comments, please from anyone?

DR. VERTER: I would like to comment. The abstention is so I was consistent with my earlier statements. I basically feel like I am on the Titanic and there is an iceberg ahead, and I hope we avoid it but I don't see anyway of stopping before we reach it. So, I have a feeling that within the next year that 20 percent is likely to be 80 percent leukoreduced. However, I have been involved in trials that, going in, the community was pretty much convinced that we had a winner and most of the time --

some of the time they were neutral but occasionally losers. So, that is why I voted that way.

DR. HOLLINGER: Anyone else?

DR. TUAZON: I stated my reason.

DR. HOLLINGER: Okay. I do think that Joel has a very important point. It is critical that we don't get summaries; that we get perhaps critical papers that are important for making these decisions to look at, and particularly for our statisticians. I think that is one reason we have them on the committee -- and we are going to miss you. And, what are you standing up there for?

[Laughter]

DR. BIANCO: Mr. Chairman, just a clarification.

DR. HOLLINGER: Okay.

DR. BIANCO: Does this mean that the recommendation implied, let's say, the rate of implementation of such a process, or something of that order?

DR. HOLLINGER: I can ask from the rest of the committee. I did not get that impression. They felt it was important that there is progress on this; that it is not slow but there is certainly progress, and they did not seem to think that there was a time element placed on that. Now, the committee is certainly free to make any statements about that if they would like, but I am not sure that we have the

information where we could really say. It is a real logistical problem. I think there are issues being raised already by the AABB regarding this issue. That will be important. I think the FDA will clearly benefit by seeing that document. So, I think those are going to be important as well. Yes, please, Linda?

DR. SMALLWOOD: The results of voting are as follows: There were 13 "yes" votes; there were no "no" votes; there were 3 abstentions. It was noted that the industry representative agreed with the "yes" vote and the consumer representative left a statement, which I will read: On the question regarding universal leukoreduction, I would agree that the benefit/risk ratio would justify universal leukoreduction.

DR. HOLLINGER: Thank you. Yes, Dr. Boyle?

DR. BOYLE: Before we close, could I ask one procedural question? When somebody submits written testimony but is not able to complete that testimony because of time limitations, does the full testimony become part of the record? The reason I ask is because somebody complained that they got cut off in the previous session and that their written statement did not become part of the record.

DR. SMALLWOOD: I would like to answer that question. I always request in advance that we be given copies of the presentations. So, therefore, if an

individual, unfortunately, is cut off we would hope that we have received copies of that presentation so that it is made available and will be complete.

DR. BOYLE: Thank you.

DR. HOLLINGER: Thank you. We are adjourned until three months from now.

DR. SMALLWOOD: The next meeting is tentatively scheduled for December 10 and 11.

[Whereupon, at 3:02 p.m., the proceedings were adjourned.]

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CERTIFICATE

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

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