

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

**BLOOD PRODUCTS ADVISORY COMMITTEE**

**56TH MEETING**

Friday, September 19, 1997

8:10 a.m.

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P R O C E E D I N G S

**Announcements**

1  
2  
3 DR. SMALLWOOD: Welcome to the second day of the  
4 56th meeting of the Blood Products Advisory Committee. I am  
5 Linda Smallwood, the Executive Secretary.

6 Yesterday, I read the conflict of interest  
7 statement. That statement applies to today's proceeding as  
8 well. If there is any individual at this time who needs to  
9 make a declaration regarding conflict of interest, please do  
10 so.

11 Today, Dr. Blaine Hollinger will be the Acting  
12 Chairman of the advisory committee. Yesterday, I announced  
13 that Dr. Scott Swisher, the former Chairman, has resigned  
14 from the Blood Products Advisory Committee.

15 I would just like to make a brief announcement  
16 that there will be a workshop held on September 26, 1997 at  
17 the Jack Masur Auditorium. It is sponsored by the Food and  
18 Drug Administration. The subject of that workshop will be  
19 "Von Willebrand Factor Concentrates."

20 At this time, I will turn over the proceedings of  
21 this session to the Acting Chairman, Dr. Blaine Hollinger.

22 DR. HOLLINGER: Thank you, Dr. Smallwood. Welcome  
23 to the meeting today. We had a very lively session  
24 yesterday which I thought was very helpful in looking at

1 inadvertent contamination and other items.

2 Paul Mied is going to give us some committee  
3 updates on some very important topics dealing with HCV  
4 "Lookback" Guidance Document. We will start with Paul and  
5 he will provide us some information about what is going to  
6 take place.

7 **COMMITTEE UPDATES**

8 **HCV "Lookback" Guidance Document**

9 DR. MIED: Thank you, Dr. Hollinger. This is an  
10 update for the committee on the resolution of the Advisory  
11 Committee on Blood Safety and Availability regarding HCV  
12 "Lookback."

13 (Slide.)

14 On August 11 and 12, the advisory committee on  
15 Blood Safety and Availability met to discuss issues related  
16 to "lookback" for HCV. The committee addressed the  
17 questions of whether and how to focus a program aimed at the  
18 identification, notification, testing and counseling of  
19 persons who may have been infected with HCV through  
20 transfusion and, if such an effort was considered  
21 appropriate, what would be the most efficient way of  
22 identifying the largest number of HCV-infected individuals.

23 (Slide)

24 On August 12, the committee drafted a resolution

1 regarding HCV "Lookback." This resolution stated that based  
2 on the following considerations that HCV is a major cause of  
3 chronic liver disease which can progress to cirrhosis and  
4 liver failure; that an estimated four million Americans have  
5 been identified with HCV, about 7 percent by transfusion,  
6 most before 1992 when an improved screening test was  
7 licensed; that many persons are unaware of their infection;  
8 and that HCV-infected persons may benefit from treatment or  
9 behavioral interventions; and believing that persons who may  
10 be recipients of a unit from an infectious donor should be  
11 notified, the following was recommended:

12           First of all, a program to educated providers of  
13 medical care regarding the importance of identification or  
14 persons at risk for HCV infection, including recipients of  
15 transfusions prior to 1992, the date of introduction of the  
16 improved screening test; and regarding appropriate measures  
17 for prevention, counseling, diagnosis and treatment.

18           Secondly, a public education campaign to notify  
19 and test recipients of transfusions prior to 1992.

20           Thirdly, a targeted lookback program, triggered by  
21 donors detected as confirmed positive by second generation  
22 screening and supplemental testing, that is, since 1992, for  
23 prior collections extending back to January, 1987 or 12  
24 months prior to the donor's most recent negative second

1 generation screening test. This program should include  
2 tracing of recipients of previous untested or first or  
3 second generation test negative units from these positive  
4 donors.

5 This resolution has been transmitted by the  
6 advisory committee to the Department of Health and Human  
7 Services, and HHS will be considering this recommendation.  
8 FDA, which is developing a guidance for industry, will  
9 follow through with that guidance document once a decision  
10 has been made by HHS regarding the acceptance or the non-  
11 acceptance of the advisory committee's recommendations.  
12 Thank you.

13 DR. HOLLINGER: Thank you, Paul. Anybody have any  
14 questions of Dr. Mied regarding this targeted lookback and  
15 also identification? Paul, just a question I have, does  
16 this mean basically that any new person who is found to be  
17 anti-HCV positive, that there will be a targeted lookback on  
18 those patients?

19 DR. MIED: Yes, it does. This third  
20 recommendation that is for a targeted lookback has a  
21 prospective element to it, as well as a retrospective, for  
22 all positive donors back to '92 with lookback prior to that,  
23 back to '87. So, it is both prospective and retrospective.

24 DR. HOLLINGER: And it goes back only '87 -- that

1 is right, the lookback is only to '87.

2 DR. MIED: The lookback is to '87.

3 DR. HOLLINGER: In terms of looking at it, it also  
4 means that any patient that comes into an office of a  
5 primary care physician should be asked about their prior  
6 transfusion history, and if they give a prior transfusion  
7 history then, presumably, the insurance companies, if this  
8 is passed through law, will pay for their testing, either  
9 way, anti-HCV or with ALTs or whatever.

10 DR. MIED: Yes, that is correct. As I understand  
11 it, part of the public education program that will be  
12 initiated will be to notify people or to notify the general  
13 public that if they received a transfusion prior to '92 they  
14 should go to their doctor and talk about the possibility of  
15 being tested.

16 DR. HOLLINGER: Okay, thank you. Yes?

17 DR. DUBIN: Has there been any kind of fleshing  
18 out of what the public education campaign will look like, or  
19 not yet?

20 DR. MIED: I don't believe -- not yet, but what I  
21 would like to do on that, perhaps Steve Nightingale can give  
22 you a little more detail on that. Steve is here, from the  
23 PHS Office of HIV-AIDS policy.

24 DR. NIGHTINGALE: I am Dr. Steve Nightingale. I

1 am the new executive secretary of the committee. We are  
2 still in the planning stages of that but on Monday there was  
3 a conference call with ourselves and with the CDC. The CDC,  
4 as many people in the room know, do have a detailed plan for  
5 control of hepatitis -- actually, Dr. Khabbaz was also in on  
6 the conference call, our current efforts are devoted towards  
7 identifying ongoing educational activities in the non-  
8 governmental sector and trying to integrate the governmental  
9 activities, for example the teleconference which is going to  
10 be held on Saturday, November 22nd, sponsored by CDC, and  
11 already has, I think, over a thousand sites identified right  
12 now and I, parenthetically strongly recommend it to all  
13 interested parties.

14           The NIH consensus conference last March on  
15 hepatitis C would also be an important component of the  
16 campaign. Obviously, resources are not infinite. You hear  
17 that from every government official, not just from me, but  
18 the current planning within HHS and the coordination of the  
19 agencies is devoted to trying to make the best use of  
20 existing resources, and that means minimal duplication.

21           DR. HOLLINGER: I might also add that that  
22 conference on November 22nd was initiated by the Hepatitis  
23 Foundation International, and then in cooperation with the  
24 CDC it is going at least to a thousand or two thousand

1 sites. Some 50,000 people I think are set up for this  
2 conference. Thanks.

3 DR. MIED: Dr. Hollinger, I would just like to say  
4 one other thing. We have provided the committee with a  
5 draft copy of the guidance for industry document. FDA would  
6 welcome comments on that document from the committee.

7 DR. HOLLINGER: On this?

8 DR. MIED: Yes, the guidance for industry.

9 DR. HOLLINGER: Thank you. The second committee  
10 update is on HTLV-II, Dr. Elliott Cowan.

#### 11 HTLV-II Guidance Document

12 DR. COWAN: Thank you, Dr. Hollinger.

13 (Slide)

14 In December, 1996 the Blood Products Advisory  
15 Committee recommended that donations of whole blood and  
16 blood components for transfusion be screened for antibodies  
17 to HTLV-II. This recommendation was based on the possible  
18 association of HTLV-II with disease and the fact that a test  
19 kit containing HTLV-II antigens was under review by FDA.

20 In addition, the advisory committee reviewed data  
21 which suggested that some currently licensed HTLV-I  
22 screening tests exhibit a high degree of sensitivity for  
23 detection of antibodies to HTLV-II compared to a screening  
24 test that contains HTLV-II antigens. The committee,

1 therefore, recommended that currently licensed HTLV-I tests  
2 could be labeled to detect antibodies to HTLV-II following  
3 qualification by FDA.

4 In March, 1997 FDA discussed before the Blood  
5 Products Advisory Committee the development of a guidance  
6 document to recommend screening for HTLV-II antibodies to  
7 blood establishments in the implementation of that testing  
8 and, in June, presented to this committee a draft of that  
9 document. This morning I would like to update the committee  
10 on developments in this area since the last meeting.

11 (Slide)

12 On August 15, 1997 FDA licensed the first  
13 screening test for antibodies to HTLV-II, the Abbott HTLV-I,  
14 HTLV-II EIA. Concurrent with this licensure, FDA issued a  
15 guidance for industry on donor screening for antibodies to  
16 HTLV-II which was distributed for both implementation and  
17 comment.

18 (Slide)

19 In the guidance document FDA is recommending that  
20 blood establishments implement donor screening for  
21 antibodies to HTLV-II using a licensed test that is labeled  
22 specifically for this indication. Furthermore, screening  
23 for antibodies to HTLV-II should be implemented within six  
24 months of the commercial availability of the first test

1 specifically labeled for this purpose. Therefore, screening  
2 for antibodies to HTLV-II should be implemented by blood  
3 establishments by February 15, 1998. FDA is not intending  
4 to recommend that inventory u nits of whole blood and blood  
5 components collected prior to the date of implementation be  
6 rescreened for antibodies to HTLV-I and HTLV-II.

7 (Slide)

8 In addition, FDA is proposing that the testing  
9 algorithm used to screen donations, the manner in which  
10 repeatedly reactive donations are handled and  
11 recommendations for donor deferral, notification and  
12 counseling be consistent with those outlined in the November  
13 19, 1988 guidance to registered blood establishments on  
14 HTLV-I antibody testing.

15 Recommendations for quarantine of prior  
16 collections and disposition and release of units would be  
17 consistent with those outlined in the July 19, 1996 guidance  
18 to registered blood establishments on product retrieval.

19 (Slide)

20 As discussed in December, 1996, some currently  
21 licensed HTLV-I screening tests exhibit a high degree of  
22 sensitivity for detection of antibodies to HTLV-II due to  
23 crossreactivity with the HTLV-I antigens in the test.  
24 Therefore, FDA will permit a labeling claim for detection of

1 antibodies to HTLV-II for those tests for which this can be  
2 demonstrated and rigorous clinical trials which meet rigid  
3 statistical criteria.

4           Clinical trials should include testing of known  
5 HTLV-II positive samples and a prospective study of an  
6 unselected group of individuals from an HTLV-II endemic high  
7 risk population in a head-to-head comparison with a licensed  
8 HTLV-II test.

9           Secondly, the test must demonstrate a high degree  
10 of sensitivity compared to a licensed HTLV-II test on an FDA  
11 HTLV-II qualification panel consisting of known HTLV-II  
12 samples. This panel will consist of some members of the  
13 panel who discussed this in December, 1996 but will be  
14 supplemented with the HTLV-II positive samples that have not  
15 been preselected by screening with licensed HTLV-I tests,  
16 and which represent a broad spectrum of populations infected  
17 with HTLV-II.

18           FDA will require testing with three independent  
19 kit lots and will supply manufacturers of HTLV-I screening  
20 tests with a volume of each panel member sufficient to  
21 perform the testing.

22           Thirdly, the test must exhibit satisfactory  
23 performance on an FDA HTLV-II lot release panel.

24           Prior to initiation of these studies, a

1 manufacturer should submit a supplement to the IND for the  
2 licensed HTLV-I screening test. The data from the clinical  
3 studies should then be submitted to FDA in the form of a  
4 supplement to the product license application for that  
5 screening test.

6 (Slide)

7 Comments based on this presentation or the  
8 previous Blood Products Advisory Committee discussions may  
9 be directed to FDA CBER in the Division of Transfusion-  
10 Transmitted Diseases, HFM-310, 1401 Rockville Pike, in  
11 Rockville, Maryland.

12 Thank you very much.

13 DR. HOLLINGER: Thank you. Yes, Rima?

14 DR. KHABBAZ: I just wanted to point out that the  
15 testing algorithm and counseling recommendation in NNWR of  
16 1988 are outdated. The PHS document of 1993, actually, talks  
17 about confirming and differentiation I from II and that the  
18 counseling be specific to I or II. So, if you are testing  
19 HTLV-II, I think it is appropriate to go with  
20 differentiation and counseling appropriately.

21 DR. COWAN: Thank you.

22 DR. HOLLINGER: Any other comments fro the  
23 committee? Yes?

24 DR. EPSTEIN: Rima, I certainly agree with that

1 guidance but, as you well know, there are no licensed  
2 supplemental tests for HTLV-I or II, which makes it  
3 problematic for FDA to advocate it.

4 DR. HOLLINGER: Thank you. If there are no other  
5 comments, then we will start the morning with the next topic  
6 which is the effect of leukoreduction on CMV transmission  
7 through blood transfusion. To initiate this, Dr. Lee will  
8 give us the FDA perspective.

9 **Leukoreduction on CMV Transmission Through Blood Transfusion**

10 **Leukoreduced Blood Components: FDA Perspective**

11 **Jong-Hoon Lee, M.D.**

12 DR. LEE: Good morning. Just wait a few minutes  
13 until we are set up here.

14 (Slide)

15 Today I would like to discuss two topics that have  
16 been problematic for the OBRR at the Center of Biologics,  
17 FDA. As the first of the two topics this morning, we shall  
18 discuss the effect of leukoreduction on CMV transmission  
19 through blood transfusion.

20 (Slide)

21 The use of blood components that contain reduced  
22 numbers of residual leukocytes results in fewer  
23 complications of transfusion therapy. Of the many potential  
24 benefits of using leukoreduced blood components, the

1 potential decrease in the rates of cytomegalovirus, or CMV,  
2 transmission has been receiving increasing attention. The  
3 Agency is aware of the recent reports in the literature in  
4 which the investigators have concluded that leukoreduced  
5 blood components are as effective as seronegative units in  
6 minimizing the rates of CMV transmission through blood  
7 transfusion.

8           In fact, the American Association of Blood Banks  
9 recently issued a bulletin to its members with the  
10 conclusion that the leukocyte reduction level currently  
11 accepted for the reduction of alloimmunization to HLA  
12 molecules reduces transfusion-transmitted CMV to a level at  
13 least equivalent to that observed with the use of CMV  
14 seronegative units.

15           (Slide)

16           As an infectious agent capable of causing  
17 significant morbidity and mortality in at-risk patient  
18 populations, including premature infants and recipients of  
19 hematopoietic transplants, we, as the public health center,  
20 shall be remiss if we fail to take advantage of a readily  
21 available opportunity to further safeguard our blood supply  
22 against this infectious agent. If the use of leukoreduced  
23 blood components does, indeed, have the potential to replace  
24 the use of CMV seronegative units as an equivalent or

1 perhaps even superior form of transfusion therapy, it should  
2 be adequately studied to conclusively establish this role  
3 within the available armamentarium of therapeutic  
4 transfusion products. Such studies should include targeting  
5 the following questions:

6 (Slide)

7 Number one, at one level of leukoreduction does  
8 the leukoreduced unit become truly equivalent to CMV  
9 seronegative units? Can it be superior to seronegative  
10 units?

11 Number two, does this level differ with different  
12 leukoreduction methodologies? In other words, are all  
13 leukoreduction filters equivalent to each other and to  
14 cytopheresis methods of leukoreduction?

15 Number three, is the CMV transmission rate  
16 proportional to the level of leukoreduction or is there a  
17 particular threshold for leukoreduction to be effective?

18 In order to maximally protect the blood supply  
19 against the CMV, the agency awaits the manufacturers of  
20 blood and blood processing devices to seek FDA approval for  
21 labeling claims specific to CMV based on answers to these  
22 questions, gathered through well conducted studies.

23 A well constructed application which adequately  
24 addresses these concerns will allow the agency to readily

1 and confidently approve such labeling claims to further the  
2 goal of optimizing public health against CMV infection.

3 (Slide)

4 In the absence of such applications, however, the  
5 agency has thus far been unable to step beyond a labeling  
6 guidance outlined in the May 29, 1996 FDA memorandum  
7 entitled "Recommendations and Licensure Requirements for  
8 Leukocyte Reduced Blood Products," in which leukoreduced  
9 blood components are defined as units collected or processed  
10 within a rigorous GMP framework to contain  $5 \times 10^6$  residual  
11 leukocytes or fewer per unit.

12 (Slide)

13 To date, the agency is not aware of such interests  
14 from specific manufactures or blood or blood processing  
15 devices. Instead, the agency has been asked to approve  
16 labeling claims specific to CMV based on the conglomerate  
17 body of general literature that does not lend itself well to  
18 critical product review.

19 This morning will be devoted to exploring the  
20 current body of literature and public opinions relevant to  
21 CMV transmission, blood transfusion and leukoreduction with  
22 the aim of assessing their adequacy as a substitute for well  
23 designed, manufacturer-sponsored clinical studies typically  
24 required for optimal public health protection. It is hoped

1 that this aim will be realized through specific questions  
2 that will be posed to the committee following the  
3 presentations by Dr. Dzik and Dr. Sayers and the ensuing  
4 discussions.

5           Although these questions or their appropriate  
6 modifications will be discussed in detail towards the end of  
7 the topic, I would like to briefly present them at this  
8 point so that they may serve as a guide for analyzing and  
9 critiquing the presentations and discussions that will  
10 follow.

11           (Slide)

12           Question 1(a), is there sufficient evidence to  
13 conclude that leukoreduction of red blood cells and  
14 platelets to  $5 \times 10^6$  leukocytes per unit or below reduces  
15 the incidence of CMV transmission by these components?

16           (Slide)

17           Question 1(b), is there sufficient evidence to  
18 conclude that leukoreduction of red blood cells and  
19 platelets to  $5 \times 10^6$  or below is equivalent to the use of  
20 seronegative components with respect to the potential to  
21 transmit CMV?

22           (Slide)

23           Question 2, is there sufficient evidence to  
24 conclude that all of the methods of leukoreduction discussed

1 are equivalent in their ability to reduce the incidence of  
2 transfusion-transmitted CMV infection, provided that the  
3 final leukocyte content of each component is  $5 \times 10^6$   
4 leukocytes per unit or fewer?

5 Thank you very much. Dr. Dzik will follow this  
6 presentation with an overview of leukoreduction.

7 **Overview of Leukoreduction Technology and**  
8 **Clinical Indications for Leukoreduced Blood Components**

9 **Walter H. Dzik, M.D.**

10 DR. DZIK: Dr. Hollinger, members of the  
11 committee, good morning and thank you for an opportunity to  
12 speak before the BPAC committee. I will kind of rudely turn  
13 my back to you because the content of the slides is a little  
14 more important than the appearance of my face, but the way  
15 we are going to set up, I am going to do that. So, I  
16 apologize.

17 (Slide)

18 What I would like to do in the time before me is  
19 to try and give you an overview of the technology of  
20 leukocyte reduction, some of its applications which are not  
21 related to CMV but then, in the second part of my talk,  
22 begin to focus on the issue of CMV and, in this way, I hope  
23 to prepare you for the following speaker, Dr. Sayers, who  
24 will devote his time to the issue directly.

1 (Slide)

2 Just to give you a sense of the amount of  
3 leukocyte reduction going on nationally, these are some  
4 estimate data from industry of use of leukocyte reduction in  
5 the United States. This is total red cell distribution in  
6 the United States, about 14 million units a year. Half are  
7 collected by the Red Cross. Half of the transfusions of red  
8 cells are given for quite urgent reasons, either in  
9 operating rooms or in the emergency rooms or in a trauma  
10 setting, for which things like leukocyte reduction don't  
11 really apply because these are quite urgent. Pediatric  
12 care, which is a big issue for CMV, as we will come to in a  
13 moment, however, only represents a small number of total  
14 units in the United States.

15 So, this is kind of the baseline of what is going  
16 on. Of those transfused, about 10 percent of red blood  
17 cells are leukocyte depleted. What is important to  
18 recognize for the committee, because this topic will come up  
19 repeatedly in the course of our talks I think, is that  
20 currently about 2 million of the units are leukocyte  
21 depleted at the bedside and 850,000 are done in the blood  
22 center. This is an issue because of a major difference in  
23 these two locations for performing leukocyte depletion. It  
24 has to do with the opportunity for kind of quality control,

1 which is easier to do in a blood center type setting than it  
2 is at a bedside setting.

3 (Slide)

4 With respect to platelet transfusions, there are  
5 similarities and differences here. The platelets in the  
6 United States, there are 10 million individual units, but it  
7 is important to see that there is a very large component of  
8 platelet production in the United States which comes from  
9 apheresis technology. These are the ones collected by a  
10 single donor on a machine.

11 The difference that is important is that a higher  
12 proportion of platelets are leukocyte depleted compared with  
13 red cells. That is because platelets are used to support  
14 bone marrow transplant patients and leukemia and oncology  
15 patients for whom leukocyte depletion has several  
16 advantages. So, in the world of platelets there is a large  
17 amount of leukoreduction going on.

18 (Slide)

19 This slide just kind of gives you a history of  
20 some of the techniques that have been used to remove donor  
21 leukocytes from blood. When I entered the field in the 70s,  
22 really all we had was methods of trying to spin down the  
23 leukocytes or trying to use washing and these are not very  
24 effective and have long been discarded.

1           What was then developed as a way of getting rid of  
2 leukocytes is the use of frozen deglycerolized blood; and  
3 then the introduction in the '70s of microaggregate filters.  
4 These are filters which are not extensively used any more  
5 today because they have been replaced by better technology.  
6 But microaggregate filters, which were later referred to as  
7 second generation -- by the way, first generation just  
8 simply being something that removes clots from blood; a  
9 simple screen. So, the clot removal is the first  
10 generation. Second generation filters, these microaggregate  
11 filters, could not remove individual donor leukocytes but  
12 could remove the aggregates, these small aggregates of  
13 leukocytes, clumps of them which develop in refrigerated  
14 blood. So, in the '70s that is what we had.

15           This was then replaced in the last two decades by  
16 what are now kind of called third generation filters or high  
17 performance filters, which are capable of removing not only  
18 those microaggregates of leukocytes but are also capable of  
19 removing individual cells -- and I will show you some  
20 pictures in a minute -- so that you can attract and capture  
21 individual leukocytes on the filters.

22           During the development time of these filters there  
23 was also a parallel development in the platelet apheresis  
24 world of better technologies and better instrumentation for

1 the development of extremely clean platelets that have very  
2 low numbers of leukocytes in them. So, both of these  
3 technologies are capable of generating low numbers of cells.

4 (Slide)

5 Those kinds of cells are shown on this slide,  
6 which kind of gives you a summary of the numbers of the  
7 development of this technology over time. So, if we were to  
8 take a pint of blood out of your arm right now and look at  
9 the white count in it, there are about two billion donor  
10 leukocytes in a whole blood unit, a fresh whole blood unit.  
11 And there are lots of ways to begin to knock them down. To  
12 call your attention to the right, they go down in kind of  
13 logarithmic type jumps and people talk about log reductions  
14 in the number of cells present in the blood.

15 What you can see is that saline washing,  
16 microaggregate and deglycerolization technology, these kind  
17 of '70s and '80s technologies, were capable of knocking this  
18 down by about 1 log, from  $10^9$  to about  $10^8$ .

19 If we kind of draw a little line here, we move now  
20 into the realm of third generation filters, these high  
21 performance filters. An early one that was developed and is  
22 not used any more because it has been supplanted by better  
23 ones is the Imugaard filter, which was capable of maybe 1.5  
24 to 2 log reduction to get you down to this  $10^7$ . This would

1 not be acceptable as leukocyte-depleted blood now but in its  
2 day it was a first start.

3 I pause on this one because we are going to come  
4 back to this particular filter later on. In an important  
5 randomized, controlled study that was done in neonates with  
6 respect to CMV infection, I will jump ahead to mention that  
7 that particular study showed a benefit for the prevention of  
8 CMV using this filter which, I remind you, by today's  
9 standards is no longer adequate.

10 The current group of filters, and here are just  
11 three kind of brand names of filters which are produced by  
12 the Pall Corporation, though there are other companies which  
13 have also created filters of equivalent powers and  
14 technology, but these filters are able to get things down at  
15 first to the  $10^7$  and now to  $10^6$  and below range.

16 This is where I want you to understand the  
17 numbers. The two important numbers on this slide are  $5 \times$   
18  $10^6$ , which is the definition and cutoff level for leukocyte  
19 reduction in the United States, and  $10^6$  or one million,  
20 which is the cutoff number for leukocyte reduction in  
21 Europe.

22 (Slide)

23 So, to kind of summarize things, it is kind of  $10^9$   
24 down to  $10^6$  or about a 1000-fold reduction.

1           There are two ways to achieve this level of  
2 depletion. As I have already stated, there are filters and  
3 apheresis. I want to give you just a little bit more  
4 background on those before I get into some of the clinical  
5 studies.

6           (Slide)

7           To talk about the filters for a second, this is a  
8 filter that is designed for use in the laboratory. They are  
9 much larger than the kind of typical clot filter. You can  
10 see that there is a receiving bag down here, to give you a  
11 sense of the size of these things.

12          (Slide)

13          If you were to open one up and look inside, there  
14 is a kind of media in here. These are just cut marks, but  
15 there is a material inside and the materials are different  
16 for the different companies' products though they share a  
17 lot of similarities as well. Among the most striking things  
18 of these media is that this is not a woven fiber like the  
19 clothing you are wearing but, rather, is a web of very small  
20 synthetic microfibers. All the major manufacturers are  
21 using synthetic microfibers that provide a very large  
22 surface area and can have a controlled porosity so as to  
23 capture individual cells.

24          (Slide)

1           This is a different company's filter, not the one  
2 I just showed you. This is a filter from Asahi and Baxter.  
3 It is a nice picture because it shows the kind of things  
4 that can be done. This is a filter designed for red cells,  
5 in the top panel. This is a very large microaggregate. We  
6 already talked about them earlier. You can see this is a  
7 clump of leukocytes captured on a rather coarse portion of  
8 the filter with rather open spaces. Then as you go deeper  
9 into the filter you come to a range where there are very  
10 fine microfibers which are able to trap and capture  
11 individual leukocytes. It is by combining the technologies  
12 to get rid of both microaggregates as well as individual  
13 cells that the high performance of these technologies was  
14 achieved.

15           (Slide)

16           You can also get high performance filtration by  
17 apheresis technology, as I mentioned. There are a number of  
18 companies, again, that have techniques to do this. The Cobe  
19 Company in the United States is probably the most widely  
20 used and has some of the best technology for generating  
21 leukocyte-depleted platelets by apheresis. A typical  
22 product that would come off this machine without any  
23 filtration would have, for example, a million platelets per  
24 microliter but less than 1 white cell per microliter. So,

1 that is a million-fold differential between the number of  
2 platelets delivered to the patient and the number of  
3 leukocytes. So, this is an alternative way to make  
4 leukocyte-depleted platelets.

5 (Slide)

6 Now, a key issue is the issue of where is this  
7 done. I mentioned this earlier and I want to highlight this  
8 again. With respect to filtration, it can be done at the  
9 bedside or it can be done in a laboratory and there are some  
10 practical things that fall out when you consider it.

11 Bedside filtration, which is done by nurses at  
12 the point of transfusion, since there are many nurses and  
13 many patients there are many users. When you do it in the  
14 lab it tends to be concentrated in the hands of the blood  
15 manipulating personnel and so there are fewer users and some  
16 people, including myself, believe that makes it a little  
17 easier to get a good outcome.

18 You can certainly control the conditions of  
19 filtration a little bit more easily in the lab than you can  
20 at the bedside where often there are urgent situations going  
21 on with the care of the patient.

22 A key issue, and one that I would just want to  
23 highlight as the most important one is that you can easily,  
24 of course, sample the filtered product in the laboratory and

1 then do a leukocyte count on it to see whether the process  
2 worked or not, and you can periodically check your process.  
3 This is a little more problematic at the bedside because, of  
4 course, if you dilute the blood into the patient's veins you  
5 can't get that blood back again to see what you actually  
6 delivered. So, you can't actually do a straight QC at the  
7 bedside setting although, of course, you can mimic a bedside  
8 transfusion. You can create conditions which are extremely  
9 similar to bedside transfusion and give it into a bag and  
10 then sample from that bag. So, it is not impossible to do  
11 bedside quality control; it is just a little bit more  
12 difficult.

13           Another issue is that in-lab filtration is  
14 increasingly being done on relatively fresh blood. By that,  
15 I mean within the first day or two of collection. Whereas,  
16 bedside filtration tends to be done on any storage age.

17           (Slide)

18           On to the clinical information, what are the  
19 indications for leukocyte depletion for probably most  
20 American hospitals? I have kind of broken them up into kind  
21 of "definites" and "possibles."

22           The possible indications of leukocyte depletion  
23 are really not the topic today. They are very interesting  
24 biologic and scientific issues, and have to do with the kind

1 of curious thing of whether or not transfusion can cause an  
2 effect on the recipient's immune system and I am not going  
3 to discuss it any further because it is really not our  
4 focus.

5           This technology is definitely currently being used  
6 to decrease the episode of febrile non-hemolytic transfusion  
7 reactions, and I will show you some information about that  
8 in a second. There is very good data and definite evidence  
9 that it can increase HLA sensitization. There is also very  
10 good data and definite evidence that it can decrease the  
11 incidence of CMV transmission. What is on your plate is to  
12 decide whether you feel it is equivalent to an alternative  
13 methodology but there is no doubt that it can decrease CMV  
14 transmission, and I will show you some of that data also.

15           (Slide)

16           So, we will start with febrile reactions. These  
17 are the most common immunologically acute mediated  
18 reactions. They occur in about one percent of transfusions.  
19 They occur in people who have been multiply exposed to blood  
20 and develop antibodies to them, and represent -- you know,  
21 this is a non-fatal problem but an important morbidity of  
22 transfusion, and this whole problem has had a huge degree of  
23 resolution, particularly in the setting of red cells, by the  
24 use of leukocyte reduction.

1 (Slide)

2 What is shown on this slide as evidence for the  
3 ability of this to work is data from Milan, where there is a  
4 very large cohort of patients with thalassemia who are  
5 heavily transfused and multiply exposed, and for whom  
6 febrile reactions are very common. This is the reaction  
7 rate for the patients and this is per transfusions.

8 What is shown here is a decline over time in the  
9 incidence of these febrile reactions with the introduction  
10 of different kinds of leukocyte removal filters.

11 "BC" here is just simply centrifugation to remove  
12 the buffy coat, and that is kind of where we were back in  
13 the old days.

14 This is that Imugaard filter that I mentioned,  
15 which was an early kind of leukocyte removal filter which  
16 would not make today's standards but was a significant  
17 advent of its time.

18 This is the microaggregate filter, the second  
19 generation filter. Then these are two of the more recent  
20 third generation filters, although even these have been  
21 replaced by even more powerful third generation filters  
22 since their time.

23 You can see there has been basically a wipe-out of  
24 the febrile non-hemolytic transfusion reactions.

1 (Slide)

2 The second area is the issue of HLA sensitization,  
3 and this is just to remind you that all patients who are  
4 exposed to donor leukocytes become then exposed to antigens  
5 which are on the donor cells. This is meant to be the donor  
6 and this is the recipient. Among those antigens are the HLA  
7 antigens which can cause a recipient then to make HLA  
8 antibodies. So, it was logical to expect that if you could  
9 get rid of the donor leukocytes you could get rid of this  
10 HLA stimulus, and a large number of studies have now been  
11 done to support that.

12 (Slide)

13 This is one slide that just compiles a group of  
14 different studies that look at the frequency of the  
15 development of HLA antibodies as they were plotted against  
16 the number of white blood cells that were in the component.  
17 So, here is our  $10^9$  figure, which is very fresh whole blood,  
18 and here we are, moving in the direction of  $10^6$  or  
19 leukodepletion. And in a number of independent trials there  
20 is very strong evidence that if you provide leukocyte-  
21 depleted blood to patients you will not expose them to  
22 leukocytes and, thus, not expose them to HLA and you will  
23 not stimulate them to make HLA antibodies.

24 This is important in oncology because the patients

1 who make HLA antibodies then become very resistant to  
2 regular platelet transfusions. It is also important in the  
3 world of kidney transplantation because if you are exposed  
4 to HLA antibodies, of course, then you cannot receive an  
5 allograft from a donor who bears those antigens. So, you  
6 basically wipe yourself out from the opportunity for a  
7 kidney transplant.

8 (Slide)

9 Kind of the strongest evidence in support of the  
10 use of this technology for the prevention of HLA was the  
11 recently completed TRAP trial, which was an NIH-sponsored  
12 trial that involved some very large and very good  
13 institutions and randomized a very large number of patients  
14 to four kinds of groups. All of these patients received  
15 leukocyte-depleted red cells. The study was designed to  
16 examine various kinds of options for platelets.

17 What you should focus on here is one option which  
18 was the control arm. These were non-leukocyte-depleted  
19 platelets. Then there were two other arms of the study that  
20 involved leukocyte-depleted platelets.

21 (Slide)

22 The study involved a good number of patients in  
23 each arm. For some of the epidemiologists on the committee,  
24 N of 100 is not something you think is a big number but this

1 is a very large effort to do this in patients with leukemia  
2 and bone marrow transplantation who get large quantities of  
3 blood products. This was a real tour de force actually.

4 (Slide)

5 The bottom line on this study is to show that the  
6 patients who received non-leukocyte-depleted platelets had  
7 this level of HLA immunization, whereas the other arms that  
8 received leukocyte-depleted products had a significantly  
9 lower incidence. This is about as good as we have had in  
10 clinical medicine for this topic.

11 (Slide)

12 Finally, to finish, I want to focus now on the  
13 issue of CMV which is the third major area in which  
14 leukocyte depletion has had an impact. This is a biopsy  
15 from the GI tract of an immunosuppressed patient who had  
16 reactivation of CMV, not transfusion-related CMV. And these  
17 are the CMV inclusion bodies that you see that occur. CMV  
18 causes tremendous morbidity in immunocompromised people.  
19 For example, in patients who suffer HIV and AIDS it can  
20 cause CMV retinitis and blindness; in patients who have had  
21 bone marrow transplantation or are frequently subjected to  
22 CMV pneumonitis, which can be very difficult to control and  
23 can often be fatal. The great bulk of CMV infection which  
24 is occurring in immunosuppressed patients is, of course,

1 reactivation of their own disease. More than half of the  
2 people in this room have CMV in your body. I know I do. If  
3 we become immunosuppressed as a result of disease or as a  
4 result of treatment, what happens is that our immune system  
5 breaks down, the CMV reactivates and this kind of morbidity  
6 occurs.

7           So, while I think we can use technologies, and we  
8 have technologies to try and protect patients who currently  
9 do not have CMV from exposure through transfusion, I think  
10 we must recognize that the great majority of CMV disease is  
11 still going to occur because it is reactivation disease.

12           The bug was recognized in 1891, actually when a  
13 kidney was examined from a stillborn child and these  
14 inclusion bodies were seen. It was first cultured in 1954.  
15 In the '60s there was recognition of a syndrome of what was  
16 called then heterophile negative infectious mononucleosis  
17 but was recognized to be actually CMV disease, some by  
18 transfusion, some by reactivation.

19           Then from the '70s, '80s and '90s there have been  
20 a whole host of studies on this topic, looking at the  
21 prevention of CMV transmission by different technologies,  
22 and that is where we are headed.

23           (Slide)

24           So, the bug is a large DNA-based virus. It is

1 very tissue-tropic, and I think that is key here. With  
2 respect to blood, which is of interest to all of us here, it  
3 is in the blood tissue and what we mean by that is that it  
4 is found in the blood leukocytes.

5           Originally there was a lot of attention on the  
6 presence of CMV in polymorphic nuclear cells because that is  
7 where it was first found. But it was first looked for in  
8 sick patients and it is now recognized, I think, that why we  
9 find it in poly's in sick people is that poly's are eating  
10 the bug and so you find it in the cytoplasm of poly's.

11           When examined in healthy donors, more relevant to  
12 our concerns, it appears to be mostly localized to monocytes  
13 and to some of the lymphocyte populations rather than more  
14 in the granulocytes. But it probably exists in both kinds  
15 of leukocytes.

16           It is not just in leukocytes, however. The virus  
17 in someone like me who was previously infected with it  
18 lingers in a latent state in all kinds of tissue,  
19 particularly actually in the oropharyngeal tissue, and  
20 people like me go through episodes of reactivating the  
21 disease and excreting it in the saliva. I am a "normal" by  
22 the way. And it is found in 30 to as much as 100 percent  
23 seropositive normals. It is a marker of age. As you get  
24 older and meet people, you become exposed. So, if you look

1 in all populations, the further out you go in age, the  
2 higher the percentage is. It is also a little more common  
3 in crowded populations than in places where people are not  
4 brought together. As I said, it is a virus that lives long  
5 and goes through periods of latency and reactivation.

6           Importantly, its transmission by transfusion  
7 depends a lot more on the status of the recipient than it  
8 does on the status of the donor. If I were transfused today  
9 for some reason, I would have no consequence from CMV. If a  
10 person who was otherwise healthy and had a normal immune  
11 system but was CMV unexposed or transfused with CMV-positive  
12 blood that person would also not get sick from CMV. The  
13 people who get sick from transfusion are the people who have  
14 a disordered immune system, as we will come to right now.

15           (Slide)

16           So, who are these patients at risk? There are a  
17 couple of very key and important groups: allogeneic bone  
18 marrow transplant patients, particularly in the situation in  
19 which the recipient has never been exposed to CMV and the  
20 bone marrow donor is CMV negative -- if both the recipient  
21 and the donor is CMV negative, then these are the people who  
22 might get exposed as a result of transfusion because they  
23 are not going to get it from their allograft.

24           I would point out that this is an unusual

1 combination. Typically, people who are coming in for a bone  
2 marrow transplant, the patient is already CMV positive. In  
3 those instances where the patient is CMV negative, if the  
4 donor of the bone marrow is CMV positive transfusion is not  
5 an issue because that person is going to get CMV from the  
6 donor material. So, transfusion is an issue where both the  
7 donor and recipient is negative.

8           A second major group are very low birth weight  
9 premature infants, that I will come to in a minute. It was  
10 recognized a couple of decades ago that these babies, these  
11 newborns under 1500 grams or 1200 grams, babies you can hold  
12 in one hand easily who are born prematurely and have a  
13 premature immune system are unable to deal well with CMV,  
14 delivered at the time of transfusion, and these little  
15 babies are often transfused because they are very sick. So,  
16 they are at risk for getting CMV by transfusion.

17           In the case of solid organ recipients, again, when  
18 both the recipient and the donor are negative and have never  
19 been exposed there is some risk from transfusion, although  
20 it is quite a bit less compared to allogeneic BMTs because  
21 solid organ patients are not so strongly immunosuppressed.  
22 In my hospital where we do liver transplants, which is a big  
23 operation and gets a lot of blood and there is a lot of  
24 immunosuppression, obviously, involved we actually don't

1 concern ourselves with CMV from transfusion because even in  
2 a setting of donor negative and recipient negative we have  
3 never had a death due to CMV from transfusion, and have had  
4 actually very little morbidity. That is because the  
5 cyclosporine that these folks get is not huge  
6 immunosuppression compared to what goes on in these upper  
7 categories.

8 I mentioned CMV retinitis. It is a terrible  
9 complication and for those patients who are HIV positive but  
10 CMV negative, they are at risk, high risk, because of their  
11 disordered immune system, for getting transfusion-related  
12 CMV and its terrible consequences. So, this is an  
13 important group to keep an eye out for. Unfortunately, most  
14 patients who are HIV positive are CMV positive and so they  
15 have already been exposed and their retinitis occurs as a  
16 result of reactivation. It has nothing to do with  
17 transfusion.

18 So, there are two methods to try to take care of  
19 these patients. The two methods are serologic testing and  
20 leukocyte reduction. To close, what I would like to do is  
21 discuss the failures of each of these methods and the  
22 success.

23 (Slide)

24 I will start with the CMV serology first. CMV

1 serology has its own problems. It is not a perfect  
2 technology. It is an antibody test and so it is unable to  
3 pick up early phase infection, like any antibody test would.  
4 So, it has its own infectious window, which is highly  
5 discussed at these meetings.

6           Of course, the test is not perfect and I will show  
7 you some data in a minute, and the test has false negatives,  
8 meaning that people who are truly antibody positive would  
9 test negative.

10           Then there is another problem of people who are  
11 antibody negative. This is not a false-negative test  
12 because they are truly antibody negative but, in fact,  
13 harbor the virus anyway.

14           Finally, a very important thing to consider, and  
15 again I think some of the epidemiologists would recognize  
16 this immediately, is that when we look at these clinical  
17 studies that we are about to look at and you see situations  
18 where there are failures or breakthrough, you must recognize  
19 that the clinical studies include protocol violations in  
20 which recipients receive the product that was not intended,  
21 according to the protocol, and were thus exposed. In fact,  
22 it is my own feeling that protocol violations account for  
23 many of the failures that have popped up in some of the  
24 clinical trials that occur.

1 (Slide)

2 So, the serologic testing isn't perfect. To get a  
3 sense of what serologic tests do, one of the problems is we  
4 say seronegative as if that were one test. Of course, there  
5 are a bunch of different ways to test for the serology of  
6 CMV and these tests have varying degrees of performance, not  
7 only when done in ideal expert hands but when done in the  
8 field. I put sensitivity in quotes. These measurements of  
9 sensitivity, which have been reported in the literature, are  
10 defined as based on concordance of these tests. Studies  
11 have been done in which three, four or five of these tests  
12 were simultaneously done on a bunch of samples and if  
13 something reported out at 96 percent sensitivity, it meant  
14 that on samples Latex tested negative but the other tested  
15 positive. So, it was a kind of common voting. Since there  
16 is no gold standard for the test, there is no real sense of  
17 the true sensitivity. So, I just want to caution you that  
18 this word is not actually being used perfectly correctly in  
19 the literature.

20 (Slide)

21 Then there is this issue of what if you test  
22 negative but you actually have the virus? There have been  
23 three studies now, and these are very small numbers but  
24 three intriguing studies in which donors, healthy people who

1 are CMV seronegative have had PCR done and were found to be  
2 PCR positive. In aggregate, about a quarter of individuals  
3 in these small numbers of donors who have been looked at who  
4 are CMV seronegative actually test positive for the virus in  
5 a DNA-based test.

6 (Slide)

7 What about some of the successes? Serologic  
8 testing has been used for a long time in medicine to try and  
9 prevent the transmission of CMV, and there have been a  
10 number of studies in these very low birth weight neonates.  
11 That was kind of the initial group looked at. Ann Yeager,  
12 at Stanford, really got this whole business going, and a  
13 whole series of studies, the best one of which was a  
14 randomized, controlled trial in 1981 in which very low birth  
15 weight infants were randomized to receive CMV serologically  
16 tested blood or CMV unscreened blood, that these were the  
17 results in these low birth weight infants -- not big numbers  
18 but at Stanford it took quite a bit of effort to find a  
19 bunch of babies who were less than 1200 grams. These are  
20 very little babies; it is not your average birth. For term  
21 pregnancies it is probably no issue here; it is just for the  
22 little guys.

23 Then there was a whole series of studies that  
24 followed over the years which basically confirmed the fact

1 that if babies were given CMV-unscreened blood that there  
2 was a continuous attack rate for these very low weight  
3 infants. Although it has been repeatedly pointed out that  
4 over the years, for kind of unclear reasons, the attack rate  
5 in low birth weight infants exposed to unscreened blood just  
6 seems to be dropping. That may be due to the fact that  
7 there is greater conservatism in transfusion in general;  
8 that babies in the '90s, very low birth weight infants, are  
9 simply exposed to fewer donors than they were back in the  
10 '70s. There is not a huge number of randomized, controlled  
11 trials though which actually support the use of serologic  
12 testing, even though it is certainly something that is done  
13 every day.

14 (Slide)

15 What about bone marrow patients? Miller, from  
16 Minneapolis, published a very nice study which I think was  
17 the best one to look at the value of serologic screening in  
18 the setting of BMTs. There were 64 patients randomized to  
19 receive serologically tested products and 61 to receive  
20 untested products. Then they looked at the infection rate.  
21 You can see that if the donor of the bone marrow was  
22 positive there is no help here because the patients are  
23 getting sick because the donor of the bone marrow is  
24 positive. But if the recipient was negative -- all the

1 recipients were negative -- and if the bone marrow donor was  
2 negative, so you have a double negative combination, then  
3 there was an advantage to receiving CMV-negative blood  
4 compared to the blood that was untested for CMV. This just  
5 gives you where these two positive ones were found.

6           What is interesting is that there was no impact on  
7 survival and, in fact, there was a concern raised in this  
8 paper about a higher rate, a statistically higher rate of  
9 gram-negative bacteremias in the patients who received sero-  
10 tested blood. It is kind of an intriguing thing. We don't  
11 understand that and someone will have an idea to tell me  
12 afterwards. In the paper it was brought up that when you go  
13 to serotested blood, CMV-negative blood, you shift your  
14 donor population to a younger age group because the older  
15 you get the more positives you have. The concern was that  
16 when you went to a younger age group these donors had less  
17 antibacterial antibodies in them. So, you were providing  
18 less passive immunity because you were getting younger  
19 donors who had had less exposures to bacteria. So, the  
20 patients had less antibacterial capability.

21           That was never really followed up on and it is an  
22 intriguing issue. I bring it up just because there are  
23 always hidden things that go on in medicine when you make a  
24 decision about something; you don't know about another

1 impact and that is something to think about.

2 (Slide)

3 Finally to finish on the issue of leukocyte-  
4 reduction, there are ways in this technology can fail as  
5 well. One could be an early phase infection in which there  
6 is free virus in the plasma because, remember, with this  
7 technology we are just removing the leukocytes; we are not  
8 addressing the issue in the plasma, and we don't know much  
9 about this.

10 There is also the issue of process failure. You  
11 can not get the intended outcome. So, then you might not  
12 get the intended prevention. Of course, protocol violations  
13 are the same way.

14 (Slide)

15 Just to address the middle section on process  
16 failure, you might not get the intended outcome. This is a  
17 study by Ledent, in 1984, in which they looked at a bedside  
18 filter. This, by the way, is the same filter used in the  
19 very large Bowden trial that you will be hearing about  
20 later. They used a bedside filter and used it quickly, and  
21 gave the blood in 10 minutes into a bag; or they transfused  
22 it slowly, over a number of hours, into a bag. They found  
23 that the failure rate, judged by the number of leukocytes  
24 that came through, was considerably higher when they gave it

1 slowly through the bag. This made them think that maybe the  
2 fact that it was given slowly allowed the blood to warm up  
3 and reach a higher temperature, and that that change in  
4 temperature might have had an impact on the performance of  
5 the filter. When, on the other hand, they tested a very  
6 large number of units with a higher performance filter  
7 designed for in-lab use, and did that in a cold setting,  
8 they had extremely good outcome in a large number.

9 (Slide)

10 This issue of temperature was confirmed in a  
11 subsequent study by another group in which they deliberately  
12 looked at the impact of temperature, and again found that if  
13 you transfused the blood slowly, over more than an hour and  
14 a half, and allowed it to warm up to room temperature, there  
15 was a failure rate; the number of leukocytes was greater  
16 than  $5 \times 10^6$  and, in fact, 10 X greater than  $10^6$ . So,  
17 temperature I think plays an important role in some of the  
18 devices in terms of how well they work for removal.

19 (Slide)

20 What about the successes of the filtration? Here  
21 is a summary of studies, again in very low birth weight  
22 infants, of the ability of leukocyte reduced blood to  
23 prevent CMV transmission. It was started in the late '80s  
24 when these filters came into place.

1           This was an initial study using just saline  
2 washing, which was kind of a very early method. It doesn't  
3 work very well, and 2/20 babies were infected.

4           This is a whole group of studies done using frozen  
5 blood, which again was an interim earlier technology, and  
6 even frozen blood actually had a very good track record for  
7 the prevention of CMV.

8           This is a second generation microaggregate filter  
9 plus a kind of third generation. This study was published  
10 in '92 and covered a time period in which they made a  
11 transition from second and third generation. When they  
12 reported their data, they split the report and both methods  
13 worked fairly well for the prevention of CMV transmission.

14           Finally, there is a study by Gilbert, in '89,  
15 which was a randomized, controlled trial using that Imugaard  
16 filter that I referred to earlier, which was kind of one of  
17 the early third generation filters. That study is really  
18 one of the best ones done in babies.

19           (Slide)

20           I am going to show you a slide on that study  
21 because I don't think this is ever going to get done again  
22 because doctors and patients will not allow little babies to  
23 get CMV-positive blood that is in no way protected any more.  
24 That is exactly what was done in this Australian study in

1 which hundreds of babies were registered and enrolled. Then  
2 when you break it through, you find among the babies who  
3 were CMV negative and were known to be given CMV-positive  
4 blood -- there were 59 such babies where no protection was  
5 provided at all. So, these were unmodified red cells; not  
6 filtered and the blood was CMV positive. There were 42  
7 babies who received CMV-positive blood. The babies were at  
8 risk, and they got it through this early filter.

9           If you further break it down and look at the very  
10 at risk group, the small babies who got CMV-positive blood,  
11 29 and 24, 9 of these 29, about a third of them, became  
12 infected with CMV and none of these became infected.

13           As I said, we are not going to be able to do this  
14 any more because no mom and no dad either is going to allow  
15 their small birth weight baby to get CMV positive blood  
16 which has not been leukocyte depleted. So, the control arm  
17 won't be done.

18           (Slide)

19           In the setting of bone marrow transplantation,  
20 there was a bunch of studies in the 1980s looking at  
21 patients at risk undergoing bone marrow transplantation:  
22 Important details of where the filtration is being done, in  
23 the lab versus filtration at the bedside; good evidence,  
24 again, of prevention of CMV transmission in the treatment

1 arms, the filtration arms, and in those studies that had a  
2 control arm transmission continued to occur in the control  
3 arms.

4 (Slide)

5 In the '90s, there have now been three studies,  
6 one of them a randomized, controlled trial which I will not  
7 discuss because you will hear more about this in a minute,  
8 and then two preceding trials in the '90s, again, bone  
9 marrow transplantation patients, filtration being done in  
10 controlled settings, and these were not randomized studies  
11 so the treatment arm that got leukocyte depleted blood had  
12 no evidence of CMV transmission in this at risk group.

13 (Slide)

14 To finish, I just want to point out that to see  
15 the failure rates you need big numbers. I think you will be  
16 hearing something about this in a second. But if you  
17 consider 250 patients who were to get 100 units, or 25,000  
18 donor exposures in the study, if this is the process success  
19 rate, the success rate kind of being a global idea that  
20 includes the concerns that I have talked about of false-  
21 negative serologic testing of these PCR-positive donors, or  
22 filtration failures or protocol violations -- if these are  
23 your success rates and if the attack rate of CMV is one of  
24 these three, this would be the number of infections you

1 would expect to see. In fact, I think they were kind of in  
2 these ranges. When you do these big studies you see things  
3 in the 3-6 range, meaning that probably for each of these  
4 methods of serologic testing and filtration we have a  
5 success rate around here and an attack rate that is around  
6 here. Obviously, if you are more immunosuppressed your  
7 attack rate goes up; if you are less immunosuppressed your  
8 attack rate goes down. But you need these big studies to be  
9 able to see any numbers at all.

10 (Slide)

11 Just to close, I want to mention that this issue  
12 that is before you has been addressed by others. The  
13 current guide is the 1995 guide to use quality controlled  
14 leukocyte depleted components, and the Council of Europe  
15 regards that leukocyte reduced blood, if reduced to this  
16 level because the Europeans use  $10^6$ , can be considered  
17 equivalent to CMV serotested blood. As mentioned by Dr. Lee  
18 at the outset, the AABB, in its 1997 bulletin, also felt  
19 that the use of leukocyte reduced blood, if reduced to this  
20 level because that is the America standard, would be  
21 considered to CMV serotested blood as well.

22 Thank you very much for your attention, and good  
23 luck with the rest of the day's deliberations.

24 DR. HOLLINGER: Thank you, Dr. Dzik. Dr. Sayers

1 is going to talk about the clinical consequences of CMV  
2 infection and a comparison of leukoreduced and CMV  
3 seronegative blood components.

4 **Clinical Consequences of CMV Infection and**  
5 **a Comparison of Leukoreduced and CMV Seronegative**  
6 **Blood Components**

7 **Merlin Sayers, M.D., Ph.D.**

8 DR. SAYERS: I would like to say thank you to the  
9 Blood Products Advisory Committee for this invitation.  
10 Actually, it is only standing up here that I find out that I  
11 was sitting in a section which is restricted to FDA  
12 employees. If any of you suspect that this reveals some  
13 undeclared allegiance or affection on my part, your  
14 suspicions are unjustified. They are the regulators; I am  
15 just one of the regulated.

16 (Laughter)

17 In an attempt to give myself some credibility as  
18 to what I am going to discuss, let me just say this by way  
19 of a preface: My current affiliation is with a community  
20 independent blood center in Dallas, but previously I was at  
21 the Puget Blood Center in Seattle and the University in  
22 Washington, and it was there that the blood program, in  
23 conjunction with the Fred Hutchinson Cancer Research Center,

1 was particularly interested in CMV transmission in marrow  
2 transplant patients, and we enjoyed a long and profitable  
3 collaboration with Dr. Raleigh Bowden. Some of his studies  
4 have been referred to.

5 I am going to start my presentation here with a  
6 case discussion and, obviously, one needs to disguise  
7 identities of cases that are being presented.

8 (Slide)

9 So, let me just say that Father JP is a well-known  
10 and well-loved cleric who is currently employed as the head  
11 of a large religious organization, head-officed in Rome.

12 (Laughter)

13 (Slide)

14 Some years ago this gracious man was recognizing  
15 the adulation of a throng in St. Peter's Square, and he was  
16 a victim of an awful and terrifying assassination attempt.

17 (Slide)

18 He was shot on a number of occasions. He had  
19 wounds to his abdomen; he had wounds to his hand. He was  
20 hospitalized. He underwent emergency surgery, and during  
21 the course of that surgery he was transfused. He had  
22 colonic resection. He underwent a splenectomy.

23 (Slide)

24 To say that his postoperative course was stormy is

1 an understatement. He developed pneumonia; developed  
2 respiratory failure. I would love to say that this is,  
3 indeed, the papal thorax but I suspect that if I claim that  
4 I will probably be struck by lightning!

5 (Laughter)

6 This is a representative x-ray of an individual  
7 with the condition that the Holy Father suffered -- evidence  
8 of consolidation and infiltration.

9 (Slide)

10 Then he also went into liver failure. He had  
11 wildly fluctuant liver enzymes and the liver biopsy revealed  
12 this characteristic. In fact, Dr. Dzik has already shown a  
13 colored version of this feature. I think it is just a  
14 reminder that the organization with which Dr. Dzik is  
15 affiliated, Harvard Medical School, probably plays, at least  
16 as far as illustrations are concerned, less attention to the  
17 not-for-profit motive than my community blood program does.

18 (Laughter)

19 Nonetheless, this is the biopsy which revealed  
20 what, in fact, the Holy Father had contracted, which was  
21 transfusion-transmitted cytomegalovirus disease.

22 This was highly unusual, and I want to emphasize  
23 that point -- highly unusual for an immunocompromised  
24 individual to suffer such profound and debilitating

1 complications of cytomegalovirus disease. As Dr. Dzik  
2 pointed out, we are more used to recognizing severe CMV  
3 disease, at least transmitted by the transfusion route, in  
4 the immunocompromised individuals. I will point out as to  
5 why the Holy Father nearly died as a result of transfusion-  
6 transmitted disease, CMV disease, a little later.

7 (Slide)

8 We have emphasized that immunocompromise is the  
9 major risk for CMV infection. There are a number of  
10 categories of immunocompromised. We can talk about  
11 temporary or natural immunocompromise in the fetus, the  
12 premature newborn, the low birth weight infant. We can talk  
13 also about acquired immunocompromise as happens in  
14 individuals with, for example, infection with HIV.  
15 Certainly there is iatrogenic compromise. Goodness knows  
16 the extent to which transplant candidates are bullied and  
17 bludgeoned with pharmacologic insults and irradiation as  
18 part of their conditioning therapy prior to transplantation.

19 (Slide)

20 Who are those patients then that are at risk for  
21 transfusion-transmitted CMV infection? Again, I am echoing  
22 something that Dr. Dzik has said. In fact, this is the  
23 second time this year that I have spoken after Dr. Dzik, and  
24 quite often find what I have to say dissolving into

1 repetition and redundancy, but it does give us an  
2 opportunity to emphasize some of the more salient features  
3 of this topic. I also take consolation speaking after him  
4 from the fact that when there is overlap between what he  
5 says and what I say, I can refer all the questions to him.

6           So, these then are the patients who are at risk,  
7 where the risk is well established: CMV seronegative  
8 pregnant women; premature infants. We have some review of  
9 experience with those categories of patients. CMV  
10 seronegative recipients of marrow transplants; and CMV  
11 seronegative patients with acquired immune deficiency.

12           (Slide)

13           Then there is a category of patients where the  
14 risk is less well established, but it is sufficient to merit  
15 consideration or interventions that would reduce the risk of  
16 transfusion-transmitted CMV. I have these bullets here but  
17 I think many of us would concede that a number of these  
18 patient categories have already shifted over into those  
19 patient categories where there is no longer any doubt as to  
20 those patients' candidacy for CMV screened products.

21           So, we have here CMV seronegative patients  
22 receiving tissue transplants from negative donors; patients  
23 who are potential candidates for marrow transplantation;  
24 autologous marrow transplant recipients; patients with

1 evidence of infection with HIV rather than AIDS itself.  
2 Then here, back to the Holy Father, CMV seronegative  
3 patients undergoing splenectomy. There are a few studies  
4 which point to the fact that it is highly likely that  
5 transfusion transmission of CMV at the time of infection  
6 results in a course of disease much more profoundly  
7 complicated by risk than in individuals who are otherwise  
8 immunocompetent. It looks as if splenectomy superimposed  
9 very rapidly a relative immunoincompetence on otherwise  
10 normal individuals who are then, as a result, at risk of  
11 profound transfusion-transmitted CMV disease.

12 (Slide)

13 I need to say something about how we classify  
14 post-transfusion cytomegaloviral infection, and it is  
15 against the background that this infection is a primary  
16 infection in individuals who have never been exposed to the  
17 virus before. So, seronegative individuals, seronegativity  
18 being a hallmark of the fact that they have not been exposed  
19 to the virus, are at risk of primary infection.

20 Infection is secondary in these two sets of  
21 circumstances: If latently infected patients undergo  
22 reactivation, or if they undergo reinfection with perhaps a  
23 different strain of the virus that they are already latently  
24 infected with. So, the categories of infection are in

1 primary and secondary, with secondary being divided into  
2 reactivation and reinfection.

3 (Slide)

4 How do we reduce the risk of transfusion-  
5 transmitted CMV? As has been pointed out, the early studies  
6 relied on the transfusion of CMV seronegative blood and  
7 components. As an example, here was a study by Raleigh  
8 Bowden some ten years ago. She showed that 4/104 marrow  
9 transplant patients, compared with 60 percent of historical  
10 controls, developed primary infection from screened blood  
11 and components. Screen the blood, reduce the infection of  
12 transfusion-transmitted primary CMV disease.

13 It was also pointed out, and this is true as  
14 revealed in a number of studies, that there is a failure  
15 rate of about 1-4 percent. Dr. Dzik has hinted at what that  
16 failure rate is attributable to --insensitivity in the  
17 screening assays; falling antibody titers; protocol  
18 violations and such like.

19 (Slide)

20 We have spoken about some of the background to  
21 this. What is the rationale for leukocyte reduction of  
22 blood and components? Bear in mind that after the primary  
23 infection CMV infection does become a chronic state. There  
24 is a latent state of infection established in individuals

1 who are otherwise healthy, whose only evidence for latency  
2 of the disease is that they are CMV seropositive.

3           It is not known where the sites of this latent  
4 infection are. As was pointed out, 50 percent of us here  
5 have this latent infection. But we do know the virus is  
6 cell associated.

7           There is something else that we know. We know  
8 that non-cellular components, such as plasma and  
9 cryoprecipitate, do not transmit CMV regardless of the  
10 donor's status. How do we know that? Well, one of the  
11 studies that we did in Seattle looked at marrow transplant  
12 recipients who were recipients of AB/O incompatible marrow  
13 who, as part of their management prior to transplantation  
14 with the incompatible marrow, had plasma exchange, exposing  
15 them to many, many liters of plasma. These were marrow  
16 transplant candidates at risk of primary infection. They  
17 had never been exposed to the virus before, and the plasma  
18 that was used in their exchange was from unscreened donors,  
19 some of whom, perhaps 50 percent of them, were latently  
20 infected.

21           We were able to show that with exposure to plasma  
22 from many hundreds of donors latently infected there was no  
23 seroconversion in these candidates who were at risk of  
24 primary infection by transfusion of plasma. So, on the

1 strength of that, we are confident that non-cellular  
2 components are, indeed, CMV safe.

3 (Slide)

4 What, then, has the early experience with  
5 leukocyte reduction by non-filtration methods been? It is  
6 true that there really is scant little new under the sun.  
7 This is a study that was done twenty years ago by Lang and  
8 coworkers. They showed that CMV seroconversion in cardiac  
9 surgery patients was reduced from 67 percent to 13 percent  
10 merely by the use of whole blood from which the buffy coat  
11 had been removed by centrifugation. A simple procedure  
12 designed to ineffectively reduce the concentration of  
13 residual white cells and, in fact, the procedure reduced the  
14 white cell burden by only about 60 percent. Nonetheless,  
15 they were able to show that that modest intervention did  
16 interrupt in some patients transmission of CMV by  
17 transfusion.

18 CMV seroconversion in the neonates was 1-2 percent  
19 following transfusion with saline washed red cells. This  
20 was a study by Naomi Luban about ten years ago. This  
21 procedure reduced the white cell burden by about 90 percent.

22 Both of these procedures are certainly relatively  
23 less effective by comparison with the efficacy of the third  
24 generation filters when it comes to reducing the white cell

1 burden.

2           Then we have, as we know, frozen deglycerolized  
3 units. Freezing and deglycerolization really is a  
4 reasonably competent way to reduce the white cell burden of  
5 red cells. We know that those units do not transmit CMV in  
6 the hemodialysis and in neonatal transfusion settings.

7           (Slide)

8           So, much for the non-filtration but reasonably  
9 successful attempts to reduce the likelihood of transfusion-  
10 transmitted CMV. Let's say something now about those  
11 studies that have investigated leukocyte depletion employing  
12 either partially or exclusively some form of third  
13 generation filtration.

14           These studies by Verdonck, in 1984 and 1985, were  
15 studies which looked at marrow transplant recipients. I  
16 haven't shown here what the follow-up periods are, but these  
17 are follow-up periods of 12 months in this study and 100  
18 days in this study. The workers in the 1984 study used  
19 filtered red cells. The donors were unscreened. Those  
20 donors had a CMV seroprevalence, prevalence of latent  
21 infection of something like 63 percent. The filter that was  
22 used was an Organon filter and it removed something like 98  
23 percent of the white cells, and the platelets were from CMV-  
24 negative donors and they did not reveal any transfusion-

1 transmitted CMV.

2           In the 1985 study, the same group of donors, the  
3 same seroprevalence of latent infection, filtered red cells,  
4 platelets from CMV seronegative donors, and extension of the  
5 earlier experience and, again, those interventions -- the  
6 combination of filtration and donor screening -- were able  
7 to interrupt the likelihood of CMV transmission in these  
8 patients.

9           The study by de Graan-Hentzen and coworkers, in  
10 1989, looked at centrifuged and filtered red cells and  
11 centrifuged platelets again in unscreened donors. The  
12 prevalence of CMV in this donor group was less than in the  
13 Verdonck studies. It was some 37 percent. The filter that  
14 these workers in The Netherlands used was a Sepacell filter  
15 from the Asahi Medical Corporation, in Japan.

16           What they pointed out was that there was  
17 significant donor exposure here. These patients who were  
18 leukemia and lymphoma patients were exposed on average to  
19 something like 160 patients and, nonetheless, in spite of  
20 those significant donor exposures no patients had  
21 transfusion-transmitted CMV.

22           The authors conceded that there were problems with  
23 their control group, and their control group consisted not  
24 of the same category of leukemia or lymphoma patients but of

1 coronary-artery bypass patients, coronary-artery bypass  
2 patients who averaged 9 donor exposures.

3           Some of the problems that are associated with  
4 these studies include the fact, as this study exemplifies,  
5 that control patients quite often had scant relevance to the  
6 nature of the interventions or the categories of patients  
7 who were being investigated for interruption of transfusion-  
8 transmitted CMV disease. I mean, here we are comparing  
9 leukemia and lymphoma transplant patients with coronary-  
10 artery bypass patients and certainly there are opportunities  
11 like that to criticize some of these studies. The control  
12 groups are poor. The study size leaves a lot to be desired.  
13 Quite often the residual white cell counts were conducted by  
14 inaccurate methods. They were expressed as percentages.  
15 This study too suffers from the fact that there was no  
16 randomization. Nonetheless, the authors did concede, those  
17 criticisms aside, that filtration did appear to be a good  
18 alternative to CMV serological screening of donors.

19           (Slide)

20           Let me continue with some of these studies that  
21 investigated leukocyte depletion of blood and components.  
22 Here is a study by Raleigh Bowden, in 1989. These were  
23 marrow transplant patients. They were followed for 50 days.  
24 The filters that were used were the Pall filters. Donor

1 exposures were something like 150 on average for these  
2 marrow transplant patients. As you can see, there was one  
3 individual who failed to be protected from transfusion-  
4 transmitted cytomegaloviral disease as a result of  
5 filtration of both red cells and platelets provided by  
6 unscreened donors.

7 I have another Bowden study here. Although I had  
8 hoped to emphasize in this illustration and the previous one  
9 the role of filtration, this was just a reminder that in  
10 this study by Bowden's group the red cells were from  
11 seronegative donors. The platelets were merely centrifuged.  
12 You could be pardoned for thinking that this 1991  
13 publication, by comparison with this 1989 filtration  
14 publication, implied that the Fred Hutchinson Cancer  
15 Research Center took a step back from filtration and went to  
16 centrifugation as a way to intercept CMV disease. On the  
17 contrary, the reason why this earlier study was published,  
18 and this was material that had been accumulated many years  
19 before, was because we really believed that it was important  
20 to remind clinicians that a ruthlessness in leukocyte  
21 reduction was certainly not absolutely necessary when it  
22 came to intercepting transfusion-transmitted cytomegaloviral  
23 disease. Certainly mere centrifugation, which we assumed  
24 removed something like 99 percent of the white cells, was

1 effective, as witnessed by no infection in 35 recipients,  
2 and was effective in also helping prevent transfusion-  
3 transmitted CMV infection.

4           There was a study in 1990, by de Witte, using  
5 filtered red cells and centrifuged platelets. This was an  
6 NPBI filter. The residual white cells in the red cell  
7 products were less than  $1 \times 10^7$ . The residual white cells  
8 in the platelet product were less than  $1 \times 10^8$ . Each  
9 individual averaged something like 216 donor exposures.  
10 They were able to show that these interventions were  
11 effective in reducing the likelihood of transfusion-  
12 transmitted CMV infection.

13           Dr. Dzik has already referred to this study by  
14 Eisenfeld. In fact, this is actually not a homogeneous  
15 group of individuals. Some of them had spin-cooled filtered  
16 red cells and others had products that were filtered in the  
17 Sepacell or Erypur filter. Filtration removed like 98  
18 percent of the white cells, and the spin-cooled filter  
19 maneuver removed something like 94 or 95 percent of the  
20 white cells. But both of them seemed to be efficacious in  
21 this small study.

22           (Slide)

23           The major study which looked at a third generation  
24 filter was a study which was conducted by this mob of

1 investigators from the Fred Hutchinson Cancer Research  
2 Center, the blood center where I was in Seattle, and the  
3 Department of Medicine and Bone Marrow Transplant program at  
4 the University of Minnesota.

5 This was a comparison of filtered leukocyte  
6 reduced and cytomegalovirus seronegative blood products to  
7 prevent transfusion-associated CMV after marrow  
8 transplantation. This was an earnest, diligent, labor-  
9 intensive study which earned a good deal of national and,  
10 for that matter, international scrutiny, and enjoyed a  
11 certain degree of controversy and provoked a number of very  
12 perceptive questions.

13 Filtration in this study was at the bedside. The  
14 filters that were used were the Pall filters. For platelets  
15 there was a PL-100 or PL-50 filter, and for red cells there  
16 was the Pall RC-100 filter.

17 (Slide)

18 Let me describe to you some of the aspects of this  
19 study. These are the characteristics. There were 502  
20 patients that were randomized into 2 groups, those receiving  
21 screened blood and those receiving filtered blood. There  
22 were about 250 patients in each of these arms. Ages were  
23 comparable at 28 and 31. The proportion of males to females  
24 was very similar, and so were the underlying diagnoses. You

1 can see the numbers here for the indications for the  
2 transplantation, ALL, ANL, CML, lymphoma and some other  
3 indications.

4 (Slide)

5 Then the type of transplantation, again, was  
6 reasonably comparable between the screened blood arm and the  
7 filtered blood arm with regard to whether they were  
8 allogeneic related transplants, allogeneic unrelated,  
9 autologous or twin transplants.

10 Other features of these patients were also  
11 investigated to look for differences between the groups, and  
12 those differences did not emerge. Here is an example,  
13 graft-versus-host disease in the allogeneic patients. Here  
14 are the gradings and they are reasonably comparable in the  
15 two arms.

16 (Slide)

17 What about the preparatory regimens? We have  
18 already referred earlier to the fact that preparatory  
19 conditioning regimens account significantly for iatrogenic  
20 immune incompetence in this category of patients. Total  
21 body irradiation and Cytosan, busulfan and Cytosan. Total  
22 body irradiation along with other chemotherapy, only  
23 chemotherapy and some other regimens. Indeed, it was very  
24 comparable between the screened blood and the filtered blood

1 groups. As far as the prophylaxis for graft-versus-host  
2 disease was concerned, there was either methotrexate or  
3 methotrexate with cyclosporine and some other regimens and,  
4 indeed, groups that were reasonably comparable.

5 (Slide)

6 Could we say that the patients were exposed to an  
7 equivalent number of donors? Bear in mind that the  
8 seroprevalence in the donors is going to determine the  
9 extent to which patients are exposed to the "Trojan horse"  
10 white cells of these latently infected donors. There is the  
11 screened and the filtered arm again. The mean number of  
12 platelet units, together with the range -- platelets were  
13 provided either as random donor concentrates or as apheresis  
14 platelets, and the apheresis platelets were either community  
15 donors or they were family donors. Again, we have groups  
16 that are largely comparable. The number of red cell units  
17 is shown here, 18 exposures in both the screened and in the  
18 filtered blood.

19 (Slide)

20 What, then, was the incidence of CMV infection and  
21 disease in each study arm? One of the criticisms of this  
22 multicenter study was the fact that at the outset the  
23 authors had decided that there were going to be primary and  
24 secondary analyses of the results. The primary analysis

1 referred to events from days 21 after transplantation to  
2 100. The secondary analysis included an analysis of all  
3 events, infection and disease, from the outset at the time  
4 of transplantation to the end of the study at day 100. The  
5 reason why this primary and secondary analysis was decided  
6 on was that patients with infection fewer than 21 days from  
7 study entry could have had a recent prior infection with  
8 CMV. They might not have had time to seroconvert or,  
9 alternatively, they might not have a reproducible level or a  
10 reproducibly identifiable concentration of CMV antibody.  
11 Indeed, patients who were in the period of time between 0  
12 and 21 days did include individuals who on some occasions  
13 were seropositive for CMV antibodies and on other occasions  
14 were CMV negative. The primary and secondary analyses were  
15 part of the study protocol. It was decided on, as I said,  
16 at the outset of this investigation.

17           Here we have the seronegative arm and the filtered  
18 arm. If we look at the primary analysis, 2 individuals  
19 having CMV seronegative blood and 3 individuals receiving  
20 filtered blood fell into this category of "all CMV  
21 infections and disease." There was no CMV disease in the  
22 seronegative arm. The 3 cases in the filtered arm all went  
23 on to disease.

24           What was the difference between CMV infection and

1 CMV disease? Infection was a serologic outcome. CMV  
2 disease was biopsy evidence of tissue invasion.

3 In the secondary analysis, bearing in mind all  
4 individuals that were included, including those individuals  
5 that were infected between days 0 and 21, thereby including  
6 those individuals in whom we suspected there probably was  
7 preexisting CMV disease, 4 and 6 in the negative and  
8 filtered arm went on to have infections with or without  
9 disease. Once again, there was no disease in the  
10 seronegative arm and all 6 individuals who had received  
11 filtered blood went on to develop disease.

12 It was difficult to explain why the disease, in  
13 spite of the fact that we could not statistically  
14 demonstrate differences between these two groups, why  
15 individuals who went on to develop disease were individuals  
16 who appeared in the filtered blood arm. The thinking really  
17 is that disease reflects not how transfusion-transmitted  
18 infection is acquired so much as disease reflects the immune  
19 status of the transfusion recipient. We had examined the  
20 two arms exhaustively to try and get a clue as to whether  
21 there was a difference in the immune status between those  
22 receiving screened and those receiving filtered blood and we  
23 were unable to reveal any of those differences.

24 (Slide)

1                   Were there differences in the number of exposures  
2 in infected individuals and non-infected individuals? You  
3 can see that in the infected individuals receiving random  
4 donor platelets, community apheresis platelets and family  
5 apheresis platelets and mean number of red cells there was  
6 no significant difference in the number of donor exposures  
7 when one compared infected patients and the non-infected  
8 patients.

9                   (Slide)

10                   What were the conclusions from this study? The  
11 conclusions were that filtration of blood and components is  
12 as effective as CMV seronegative blood and components in  
13 reducing the risk of transfusion-acquired CMV infection in  
14 allogeneic or autologous marrow transplant.

15                   The second conclusion was that more CMV disease  
16 occurred in the filtered group when patients infected prior  
17 to day 21 were included in the analysis. This was a  
18 statistical observation, and I have already said to you that  
19 we were hesitant to include individuals who were infected  
20 prior to day 21 because we believed that they may well have  
21 been harboring CMV infection prior to their transplant.

22                   Then we also emphasized that what we really need  
23 is a gold standard test for CMV serology. Dr. Dzik has  
24 pointed out that there is not good concordance when you look

1 at the various methods for identifying CMV antibody  
2 seropositivity in donors.

3           Ironically, what we really need is an assay of the  
4 truly infectious donor. I mean, 50 percent of donors in our  
5 community in the Pacific Northwest are CMV seropositive but  
6 probably fewer than 10 percent, or maybe well fewer than 10  
7 percent of those 50 percent of antibody positive donors are  
8 truly infectious. The economical way to address  
9 transfusion-transmitted cytomegaloviral infection in immune  
10 compromised patients, the effective and cost efficient way  
11 would be to have a test, maybe PCR, but then goodness knows  
12 what that would cost, but to have a test which identifies  
13 the truly infectious donor.

14           We also have to conclude, disappointingly, that  
15 neither filtration nor screening eliminates the risk of  
16 transfusion-transmitted CMV infection. If you look at all  
17 the experience internationally, something like 1-4 percent  
18 of individuals, despite filtration or despite CMV screening  
19 of donors, do go on to develop CMV infection.

20           (Slide)

21           What is going on in the real world? At the Fred  
22 Hutch screened and leukofiltered blood and components are  
23 regarded as equivalent, and I would add, more recently, that  
24 platelets from unscreened donors that have been leukoreduced

1 by virtue of being collected on the improved pheresis  
2 equipment, which also have a reduction in the white cell  
3 content without having been filtered, are also regarded as  
4 equivalent to leukofiltered blood and to CMV screened blood.

5 In the real world, and I am referring back to the  
6 experience in Seattle, filtration is carried out at the  
7 blood center for quality control reasons that Dr. Dzik has  
8 referred to. It is also true that CMV screened blood and  
9 components are ordered preferentially, only if the CMV  
10 inventory is depleted of filtered products or leukoreduced  
11 by pheresis technology products, and patients with febrile  
12 reactions are an exception.

13 One thing I would like to say in conclusion is  
14 that in Utopia we really could argue for additional clinical  
15 trials. But I think those that really hope for such trials  
16 should arm themselves for disappointment. There is a  
17 general acceptance by clinicians that CMV safety or relative  
18 safety is achieved by third generation filtration in  
19 general, and protection of the patient is not necessarily an  
20 outcome which is exclusively attributable to one brand of  
21 filter rather than to another.

22 With breakthrough infections occurring with the  
23 lack of frequency that they do, it is a daunting prospect to  
24 consider clinical trials, having to involve many hundreds of

1 individuals before there is any likelihood that statistical  
2 significance is achieved. These clinical trials, in  
3 addition to being a labor-intensive challenge, are obviously  
4 going to be an economic challenge as well.

5 Many thanks, and if there are any questions, as I  
6 said, I will refer them to Dr. Dzik.

7 (Laughter)

8 DR. HOLLINGER: Thank you, Merlin. We are going  
9 to take a break actually right now until 10:15. There are  
10 several people who wish to speak in the open public hearing  
11 so we will begin that at 10:15. Thank you.

12 [Brief recess]

13 DR. HOLLINGER: We are going to open this portion  
14 of the session, the open public hearing. The first speaker  
15 that we are going to have, who has asked to speak today, is  
16 Roger Dodd who will speak on behalf of the AABB.

17 **OPEN PUBLIC HEARING**

18 **Roger Y. Dodd, Ph.D.**

19 DR. DODD: Thank you, Dr. Hollinger, members of  
20 the committee. I am Roger Dodd, and I am speaking on behalf  
21 of the American Association of Blood Banks. I am a member  
22 of the Board of Directors of the Association.

23 The AABB is the professional society for almost  
24 8500 individuals involved in blood banking and transfusion

1 medicine. It also represents more than 2200 institutional  
2 members including community and Red Cross blood collection  
3 centers, hospital based blood banks, and transfusion  
4 services as they collect, process, distribute, and transfuse  
5 blood and blood components. Our members are responsible for  
6 virtually all of the blood collected and more than 80  
7 percent of the blood transfused in this country. Throughout  
8 its 50-year history, the AABB's highest priority has been to  
9 maintain and enhance the safety of the nation's blood  
10 supply.

11           The AABB appreciates the opportunity to comment on  
12 the effect of leukoreduction on CMV transmission through  
13 blood transfusion. Over the past year, an ad hoc committee  
14 of the Association has reviewed the issue in detail and  
15 essentially all of the data reviewed by this committee has  
16 been presented to you by the two major speakers today. The  
17 ad hoc committee has reported that both retrospective and  
18 prospective data support the conclusion that the leukocyte  
19 reduction level currently accepted for reduction of  
20 alloimmunization to HLA molecules, that is, to fewer than 5  
21  $\times 10^6$  leukocytes per transfused component, reduces  
22 transfusion-transmitted CMV to a level at least equivalent  
23 to that observed with the use of CMV-seronegative  
24 components. The data supporting this conclusion reflected a

1 number of different studies, encompassing a wide variety of  
2 technical approaches to leukocyte reduction. These studies  
3 are reviewed in some detail in AABB's Association Bulletin  
4 97-2, dated April 23, 1997, and entitled "Leukocyte  
5 Reduction for the Prevention of Transfusion-Transmitted  
6 Cytomegalovirus, TT-CMV." A copy of the Association  
7 bulletin has been provided to committee members.

8           The AABB, therefore, endorses the use of  
9 leukoreduced components as a measure to reduce the risk of  
10 transmission of CMV to susceptible patients. The  
11 Association encourages the use of procedures which can be  
12 performed in a fashion which assures that current standards  
13 for leukoreduction are consistently achieved. Thank you.

14           DR. HOLLINGER: Thank you, Roger. The second  
15 speaker is from Hemasure, Hans Heiniger.

16                           **Dr. Hans Heiniger**

17           DR. HEINIGER: Thank you, Mr. Chairman. I would  
18 like, as a former member of the Council of Europe Expert  
19 Committee, to fill you in on the situation of how it evolved  
20 in Europe.

21                           (Slide)

22           As you know, the first studies, and they were  
23 presented today by the two speakers in the morning, were  
24 done in Europe by the Dutch groups. They came to the

1 conclusion that, indeed, leukoreduction helps to prevent CMV  
2 transmission. However, the studies were not controlled.

3           The members of the Expert Group of the Council of  
4 Europe started to closely follow in their sessions the  
5 development of CMV. Then, as you know and as was discussed,  
6 in 1989 came the dramatic study which probably couldn't be  
7 done today any more. But this was a very-well controlled  
8 study, with very clear-cut outcome. In the control arm, if  
9 I remember correctly, 3 children or 9 children, anyway,  
10 something like 9 percent became infected. The prevalence  
11 was 46 percent in the donor population. In the filtered arm  
12 none of the children became infected.

13           (Slide)

14           Based on those dramatic results and the previous  
15 not very well controlled studies, the Committee on Blood  
16 Transfusion of the Council then developed a consensus  
17 opinion. It consisted of two representatives of each  
18 Western European countries at that time. You can read it  
19 yourself. The opinion was written into the protocol. Blood  
20 components used in premature and young children, in  
21 immunocompromised patients and patients undergoing organ  
22 transplantation should be routinely filtered, using filters  
23 able to reduce the leukocyte content sufficiently. The  
24 example given that now comes to European philosophy is that



1 DR. SAYERS: I am Merlin Sayers, representing  
2 America's Blood Centers. ABD is an association of 70  
3 independent blood centers that provide almost half of the  
4 nation's volunteer donor blood supply. We are pleased to  
5 have the attention of the Blood Products Advisory Committee  
6 on the issue of preventing transfusion-associated CMV  
7 infection.

8 CMV infection is a potentially serious  
9 complication of blood transfusion to selected  
10 immunoincompetent patients. Current practice demands  
11 serological screening of blood donors for antibody to CMV  
12 and provision of seronegative components to at-risk  
13 recipients to prevent this infection. Serologic screening  
14 presents logistic difficulties in the provision of adequate  
15 products to some patients, particularly in geographic  
16 settings with a high prevalence of CMV infection in the  
17 donor population.

18 In addition, serological screening is redundant  
19 for many of the at-risk patients who already receive  
20 leukoreduced components for other medical indications.

21 The laboratory and clinical data support the  
22 conclusion that the leukocyte reduction level currently  
23 accepted for product labeling by the FDA, that is, less than  
24  $5 \times 10^6$  residual leukocytes per product, reduces



1 previous speakers, but I will try to restrict my remarks to  
2 ten minutes or less.

3 (Slide)

4 Most of this background material has been well  
5 covered by Sunny and others in their presentation. The  
6 problem is CMV positivity in the donor supply, and the  
7 various studies that have been done over the years are  
8 fairly consistent. The rate of CMV seropositivity varies  
9 from 50-80 percent in the United States, and is about the  
10 same in most developed nations, perhaps higher in the Third  
11 World countries.

12 Of the studies that have documented the  
13 seroconversion, i.e. infection rate, the two outstanding  
14 studies have been conducted by Contreras and Gilbert, one in  
15 a general population of immunocompetent adults in a tertiary  
16 care setting; the other in neonates. With little surprise,  
17 the numbers are fairly consistent for infection. We are not  
18 talking about disease now. Somewhere between 20-25 percent  
19 is the generally acknowledged number.

20 (Slide)

21 Roger Dodd has alluded to the Association's  
22 Bulletin 97-2, the American Association of Blood Banks, with  
23 guidelines for the transfusion of either CMV-seronegative  
24 blood or CMV-leukocyte reduced blood to the standards that

1 we have been talking about. It basically groups people into  
2 the categories that you see here: Category I, in which there  
3 is no precaution taking, representing the major portion of  
4 currently hospitalized and transfused patients; and Category  
5 II through V, representing people at increased risk of CMV  
6 disease and their serological status at the time. I will  
7 not belabor this slide since the Association bulletin has  
8 been given to all of the members of the committee for their  
9 perusal.

10 (Slide)

11 The highlight studies, and by no means complete  
12 studies, that support the equivalency and use of CMV-  
13 seropositive blood have been presented in detail. Just to  
14 summarize some of the studies that I think are the most  
15 germane to this morning's proceedings are the three you see  
16 here that encompass a six-year period of time, and encompass  
17 studies performed in the United States and Europe as well.

18 I think that what is impressive is that these  
19 encompass 338 bone marrow transplantation patients at  
20 extremely high risk of CMV seroconversion, infection,  
21 disease, pneumonitis and death. There were 338 patients and  
22 transfusion of not quite 25,000 platelet products and over  
23 5000 red blood cell products. In the historical data in  
24 three studies performed by Bowden, the risk of infection to

1 routinely screened product would be estimated to be between  
2 104 percent. What we see here are 3 infections in 338  
3 patients, well below that statistic and highly statistically  
4 significant -- again, supportive data for the equivalency of  
5 the leukoreduction technique.

6 (Slide)

7 These are the same data in a neonatal population,  
8 probably the three most pertinent studies. Certainly the  
9 Eisenfeld and Gilbert studies have been touched upon. There  
10 are lower numbers because it is a more difficult study to  
11 put together but, again, it is equally impressive with 93  
12 patients in the filtered group and 54 patients receiving  
13 unscreened, unknown if you will, components. None of the  
14 patients seroconverted or developed disease in the filtered  
15 group and, of course, 1/3 or 33 percent of the patients in  
16 the control group -- rather impressive statistics.

17 (Slide)

18 Just one area that I would like to introduce, the  
19 second question that has been distributed by the FDA for the  
20 committee to consider is the definition of leukocyte-  
21 reduction, and is  $5 \times 10^6$  for all blood products independent  
22 of the way they are manufactured equivalent? We do not have  
23 the answer as to whether or not they are clinically  
24 equivalent. That answer is not in since all products and

1 all technologies have not been put to the acid test yet,  
2 which is the clinical trial.

3           What I would like to share with you is some data  
4 that has been developing and is submitted for publication  
5 from our laboratories. What you see here is a  
6 representation of 20 units of blood, 10 leukoreduced by a  
7 machine technique, 10 reduced by a filtered technique. The  
8 residua is the same in both. The white cell residua is 10<sup>5</sup>.  
9 But what is consistently striking from unit to unit is the  
10 phenotypic fingerprint of the method used. The filtered  
11 method gives you a 3-cell population that is exclusively  
12 lymphocytes, T4, T8 and B lymphocytes, with no granulocytes  
13 and no monocytes whatsoever. The machine produced product,  
14 although it gives you the same leukocyte residua, gives you  
15 a consistent population of monocytes and granulocytes coming  
16 along in that population too.

17           Is it of significance clinically? Again I  
18 underscore the fact that we do not have that answer,  
19 however, it is a question worth considering. One of the  
20 articles I would direct you to is that of Kondo and  
21 colleagues, "Human CMV Latent Infection of Granulocytes and  
22 Macrophage Progenitors." It is fairly well universally  
23 accepted that the monocyte is a very rich area of the virus  
24 achieving latency. The ability of granulocyte transfusions

1 in years gone by to transmit CMV is well documented.

2           If I can leave a take-home message with this  
3 slide, the take-home message is that the products currently  
4 on the market are not generic products. We believe that,  
5 like pharmaceutical reagents, a non-generic product should  
6 have its own clinical endpoint.

7           (Slide)

8           Returning to Category I, the patients that the  
9 AABB says require no special precautions for transfusion of  
10 CMV positive or CMV negative blood. You can see the  
11 patients included in that list. The rationale for this, of  
12 course, is that these are immunocompetent patients and,  
13 therefore, if infected the virus will achieve latency and  
14 these people will not progress to disease, and that there is  
15 little or no historical evidence to support the fact that  
16 this particular group of patients is at increased risk of  
17 disease.

18           I would like to point out that it ignores several  
19 considerations. The first is it implies a degree of  
20 clairvoyance in who will become immunologically compromised  
21 in the future. What we are doing with this policy, if we  
22 believe the numbers that have been documented, is causing 22  
23 percent of our transfused patients to seroconvert. If these  
24 patients become immunocompromised either by disease or

1 iatrogenically in the future and have latent infection, this  
2 infection which we have now transfused to them poses a  
3 secondary and, in my opinion, unnecessary risk.

4           The second thing that the recommendation does not  
5 take into consideration is that there are 34 published  
6 studies documenting fatal and non-fatal CMV infections in  
7 immunocompetent individuals. Certainly Merlin Sayers  
8 presented data on the Pope and his bout with CMV infection  
9 and at that time, although splenectomized, he was not  
10 considered an immunocompromised recipient of a seropositive  
11 unit.

12           (Slide)

13           It also ignores the fact that there are a number  
14 of reports of neurological complications of CMV. must  
15 underscore that is not transfusion acquired CMV. This is  
16 CMV acquired as a wild infection in the population but,  
17 nonetheless, multiple neurological reports from many  
18 authors, and I represent four, that show immunocompetent  
19 patients at increased risk for either meningoencephalitis,  
20 encephalitis or transverse myelitis from CMV. So, I think  
21 with that kind of body of evidence, closing the door on the  
22 fact that CMV is only a risk factor of the immunoincompetent  
23 is a little bit too severe a statement. It certainly is a  
24 major risk factor in the immunocompetent and a minor risk

1 factor in other populations.

2 (Slide)

3 Finally, and we are coming to the end of the  
4 slides and I thank you for your patience, atherosclerosis  
5 and CMV is becoming a hotly debated issue. There are more  
6 than 70 articles in the last 20 years associating CMV  
7 infection and latency with adverse outcomes in  
8 cardiovascular procedures, in cardiac transplantation  
9 procedures and in the atherogenic process itself. A 5-year  
10 cohort study that you can see here, by Nieto and his  
11 colleagues, concluded that CMV has a consistency with a  
12 causal role in atherosclerosis. Authors as prestigious as  
13 De Bakey are represented here, making similar statements,  
14 property of CMV consistent with involvement at several  
15 levels of the atherogenic process. I think, at best, we do  
16 not know the long-term risks of CMV infection in the  
17 immunocompetent individual.

18 (Slide)

19 Two other risks deserve our consideration this  
20 morning, and that is two other Herpes viruses, Herpes virus  
21 type 8 and HTLV-I. Blackburn, for the first time in Lancet,  
22 has documented the occurrence of Herpes type 8 virus in 1/11  
23 otherwise healthy, normal donors. Herpes virus type 8 has  
24 no screening test at the current time, is potentially

1 transmissible in the blood supply and is the agent known to  
2 be associated with Kaposi's sarcoma.

3           Although not direct proof in a following article,  
4 Lefrere has shown that in 19 blood recipients transfused  
5 more than 6000 units of leukocyte reduced blood, reduced by  
6 filtration techniques, not a seroconversion to the Herpes  
7 virus type 8 occurred. Is this belt and suspenders?  
8 Perhaps, but it is one of the unknown dread threats. HTLV-  
9 I, a little bit more complex. We do have a screening test  
10 but Dr. Dorothy Zucker-Franklin, past president of the  
11 American Society of Hematology, has recently published that  
12 in randomly screening 11/100 donors, these donors were found  
13 to be negative for the antibody for HTLV-I by positive by  
14 PCR for the tax genome to the virus. The tax genome is the  
15 transforming, transactivating viral gene that expresses  
16 itself and exerts effect not only on HTLV-I but on a host of  
17 other viruses, including the virus associated with AIDS. It  
18 has been shown as far back as 1993 that both the pol and the  
19 tax genome can be eliminated from these units by simple  
20 leukocyte filtration.

21           (Slide)

22           In closing, I would like to pose the following  
23 questions? Given a universal means of removing leukocytes  
24 and reducing the CMV viral latency rate in the donor

1 population, do we really need to triage the blood supply by  
2 some serological technique in 1997? Since we cannot predict  
3 who will be immunocompromised in the future, are we really  
4 right in allowing people to seroconvert due to the  
5 transfusion practice when there are safeguards that can be  
6 put in place to minimize that risk?

7           As a practicing physician and as a former blood  
8 bank director, one that really disturbs me is that the  
9 current state-of-the-art is on demand to screen units for  
10 their serological status to CMV. Those units that are found  
11 to be CMV negative are labeled and distributed  
12 appropriately. Those units found to be CMV positive are not  
13 labeled and are put back into the general supply. I am not  
14 sure that finding a virus in the blood and not informing the  
15 recipient is either ethical or constitutes a complete  
16 informed consent process, regardless of how small the risk.

17           I question whether good manufacturing processes  
18 should demand a disclosure of what is known about the unit  
19 at the time that it is screened. If it is positive, it  
20 should be labeled so. Whether or not precautions should be  
21 taken is an open question. My personal opinion, of course,  
22 is known.

23           (Slide)

24           Finally, there are new potentially pathogenic

1 viruses, such as HHV type 8 and HTLV-I tax genome, that have  
2 been documented to be present in our blood supply for which  
3 we do not have adequate screening tests or a procedure to  
4 exclude. Given the fact, again, that there is a literature  
5 that implies protection, does informed consent require that  
6 the physician and the recipient be given these alternatives?

7           In closing, I would point out that France, Austria  
8 and Norway has cautions because of all of the potential  
9 risks above and have committed to some respect to a  
10 universal leukoreduction program. The major blood banks in  
11 Austria and Norway have already committed by the end of  
12 1997, beginning of 1998, to leukoreduce their entire blood  
13 supply. France currently leukoreduces 40-50 percent of all  
14 their blood and has expressed intent and desire to go to 100  
15 percent. I ask the members of the committee if the blood  
16 recipients in the United States are really less worthy and  
17 should not receive the same type of consideration. Thank  
18 you.

19           DR. HOLLINGER: Thank you. Is there anyone else  
20 in the audience that wishes to speak in this open public  
21 hearing today? If not, I wonder, Dr. Lee, if you would  
22 present the questions again to the committee so that we can  
23 open up our discussion?

24           I might just mention to the speakers, particularly

1 Dr. Wenz, it would have been useful for the committee to  
2 have had many of these publications provided to us before  
3 you are here. It is pretty hard to digest things without  
4 having the data to look at, although I think there are some  
5 very intriguing questions that you bring up. But in order  
6 to allow one to provide some sort of a guidance to the FDA  
7 or others, having that data ahead of time would have been  
8 very useful.

9 **Presentation of Questions**

10 **Jong-Hoon Lee, M.D.**

11 DR. LEE: Thank you. After that series of insight  
12 from the presentations we received this morning, I would  
13 like to simply re-read the questions that we began this  
14 discussion with.

15 (Slide)

16 Question number 1, is there sufficient evidence to  
17 conclude that leukoreduction of red blood cells and  
18 platelets to  $5 \times 10^6$  leukocytes per unit or below reduces  
19 the incidence of CMV transmission by these components?

20 (Slide)

21 Question 1(b), is there sufficient evidence to  
22 conclude that leukoreduction of red blood cells and  
23 platelets to  $5 \times 10^6$  leukocytes per unit or below is  
24 equivalent to the use of seronegative components with

1 respect to the potential to transmit CMV?

2 (Slide)

3 The final question, is there sufficient evidence  
4 to conclude that all of the methods of leukoreduction  
5 discussed are equivalent in their ability to reduce the  
6 incidence of transfusion-transmitted CMV infection provided  
7 that the final leukocyte content of each component is 5 X  
8  $10^6$  leukocytes per unit or fewer?

9 **Committee Discussion and Recommendations**

10 DR. HOLLINGER: Thank you, Dr. Lee. So, we will  
11 open this up to the committee for discussion. Dr. Linden?

12 DR. LINDEN: Before we get into a discussion, I  
13 have three questions for Dr. Dzik. One, in your  
14 presentation you presented figures on leukoreduction done at  
15 the bedside and in the blood center. What about by hospital  
16 blood banks doing in-laboratory filtration? Do you have  
17 those figures?

18 DR. DZIK: Yes, actually in my own hospital we do  
19 it in the laboratory. So, I am familiar with that process.  
20 I left that out just to try and make something complicated a  
21 little simpler. My impression from our own experience is  
22 that filtration done in the hospital blood bank is really  
23 quite similar to that done in the blood center in the sense  
24 that the critical issues, this temperature issue, again, is

1 done in a cold setting, at least the way we do it in the  
2 hospital. You take the blood out of the refrigerator and  
3 run it through the filter and it goes through in short  
4 order, about 10 minutes or so. So, the blood doesn't have a  
5 chance to warm up during the process of filtration.

6           One kind of administrative challenge for filtering  
7 blood in a hospital is that you are going to enter the unit  
8 in order to do that, unless you use a sterile connecting  
9 device system which is not cost effective for us to do. So,  
10 we really filter it upon demand. So, if someone says I need  
11 a bag of red cells, we say, okay, you are going to have to  
12 wait 15, 20 minutes while we actually do the filtration. If  
13 it is done in a blood center environment so that the  
14 hospital then purchases it already leukodepleted, of course,  
15 you can then just hand it out. We do it the way we do it  
16 because we wind up only filtering those units that need to  
17 be filtered and so we save a few dollars doing it that way.

18           By the way, the performance, which is the element  
19 of your question, when you do a QC on that process it  
20 appears to be the same as the QC results that you would get  
21 in a blood center setting. So, we do not see that problem  
22 of breakthrough filtration failures in a hospital-based  
23 program. I think that is because it is cold.

24           DR. LINDEN: Thank you. That leads into my next

1 question which regards the efficacy of bedside filtration,  
2 which I am personally a little nervous about because of the  
3 potential of operator error and lack of uniformity, as well  
4 as the temperature question that you brought up. I believe  
5 you said for the RC-100 filters that the reduction could  
6 range down to  $10^6$  to  $10^7$ . Do you know what percent of the  
7 time bedside filtration would be able to achieve this  
8 proposed limit of  $5 \times 10^6$  per unit?

9 DR. DZIK: No, I don't. There have really been  
10 precious few studies of the quality control of the  
11 performance of bedside filtration. Of course, as I said  
12 before, you can't do it on a unit that actually goes into a  
13 body because the blood has already been filtered and goes  
14 into the recipient so you can't capture the blood cells in  
15 order to count the number of leukocytes that are there. So,  
16 what you can best do is mimic bedside filtration in which  
17 you kind of set up the transfusion set and run it through  
18 and pretend it is going into the patient, but it is going  
19 into a receiving bag, and then sample that bag. In a couple  
20 of studies that were done, as I showed you the data, there  
21 were some concerns about slow filtration of red cells. I  
22 don't think that issue comes up in the setting of filtration  
23 of platelets, by the way, because those filters are designed  
24 for a room temperature product. So, there isn't a lot of

1 data on the quality control performance at bedside.

2 DR. LINDEN: I guess one concern would be if the  
3 recommendation is that, yes, you do it provided you meet the  
4  $5 \times 10^6$ . How do we know that at the bedside that is being  
5 met?

6 DR. DZIK: That is a very good question. I think  
7 that it would be up to users to perhaps show that data. One  
8 approach could be to again try and mimic the bedside setting  
9 though, again, whether or not in actual practice, in the  
10 heat of battle of caring for patients, people would perform  
11 as your mimic would imply. That is one reason why we are  
12 not doing it at my hospital that way.

13 DR. LINDEN: Thank you. My last question relates  
14 to Dr. Heiniger's presentation where he said that the  
15 European limit was  $1 \times 10^5$ .

16 DR. DZIK: Good pick up, Jeanne. I think that was  
17 a typo. It is  $10^6$ . I think it was simply a typographical  
18 error.

19 DR. LINDEN: Because a 50-fold difference would be  
20 huge.

21 DR. DZIK: Yes. No, the European standard is  $10^6$   
22 and the American standard is  $5 \times 10^6$ .

23 DR. LINDEN: Thank you for clarifying that.

24 DR. NESS: I have a question for the FDA. We are

1 going to be asked, at least in part, to compare  
2 leukodepletion as a means of achieving CMV-safe blood as  
3 opposed to using screened blood. I would be interested to  
4 know what the regulatory status of screening tests for CMV-  
5 negative blood is in view of the data we have heard that  
6 implied that different methods come up with different  
7 results, and have clear-cut failures as well.

8 DR. WILSON: I am Leonard Wilson, from the Office  
9 of Blood. I will try to answer that question. In December  
10 of 1995, all CMV tests which were currently being used for  
11 testing donor blood were required to be relabeled  
12 specifically for use in testing donor blood. So, those  
13 products that were on the market prior to December of '95  
14 were not specifically cleared for use in blood screening.  
15 They were being used because they were available. All the  
16 test kits, five or so, were submitted and the relative  
17 sensitivities were evaluated based on those 510(k)  
18 submissions, and the range, sensitivity-wise, was 97.8  
19 percent to about 99-plus percent. So, that was based on the  
20 data that the manufacturers had submitted based on donor  
21 populations. So, they were a little bit higher than what  
22 was on one of the previous slides but I did note that the  
23 data from those previous slides were from 1985 or so. Some  
24 of the data that were submitted I think were not absolutely

1 current, but the data did reflect in thousands of donors in  
2 each test studied that approximate relative sensitivity  
3 compared to the other tests that are on the market. Does  
4 that answer your question?

5 DR. NESS: Yes.

6 DR. NELSON: I am not sure I understand 97-99  
7 percent. In comparison to what? Was it a culture PCR? Was  
8 there a reference test? What are you talking about?

9 DR. WILSON: The 510(k) clearance process is the  
10 real basis of your question. The clearance of the products  
11 is based on substantial equivalency to other products that  
12 are on the market. So, the cross-comparisons were based on  
13 those donor studies. But that is the regulatory level at  
14 which CMV test kits are right now because they are not  
15 required for blood donor screening; they are elective for  
16 blood donor screening. If they were required for blood  
17 donor screening they would likely be elevated to a product  
18 license application and more of those types of studies would  
19 be conducted.

20 DR. NESS: But it is fair to say, for those of the  
21 committee who don't understand, that there really is no gold  
22 standard to which they are compared, and there is no known  
23 comparison to true infectivity of a donor for any of the  
24 screening methods that we currently use for serologic

1 diagnosis.

2 DR. WILSON: Yes, I think that is fair to say,  
3 although I would add that there is no perfect standard for  
4 any diagnostic test; it is more like gold-plated --

5 (Laughter)

6 -- but there are not at the same level of  
7 performance as a product license application licensed test,  
8 or at least they are not reviewed to that level and the  
9 performance data is based on cross-comparison to other  
10 tests.

11 DR. VERTER: I have two things. I would like to  
12 ask Dr. Dzik a question and then I have a critique of the  
13 paper, if that is okay.

14 When you were going through your slides, and I am  
15 referring to the Miller study and I didn't get a chance to  
16 look at the Lancet article, but at the very end I thought I  
17 saw some numbers which implied that the study really had  
18 something like 500 people randomized into the trial, not  
19 just the 30 and 30 in the LBW group.

20 DR. DZIK: Miller or Gilbert?

21 DR. VERTER: Did I get the two studies mixed up?

22 (Slide)

23 DR. DZIK: This is the Miller study. Is that the  
24 one you wanted?

1 DR. VERTER: Maybe I am getting too confused. The  
2 middle one I understood. But then there was another slide  
3 where I thought I saw 500.

4 (Slide)

5 DR. VERTER: Yes, that one, 600.

6 DR. DZIK: I am glad you asked. The Gilbert  
7 study, which Dr. Heiniger referred to also, is the study  
8 which I thought really won't get done again. It really was  
9 a big study and did, as you correctly note, involve  
10 randomizing almost 600 babies to be studied. Many of the  
11 babies were already born CMV seropositive because the mom  
12 was seropositive. Remember, many people are CMV  
13 seropositive. So, if a mother is CMV seropositive when she  
14 gives birth the baby is also born seropositive because of  
15 transfer of maternal antibody. Many people believe that in  
16 a mature term infant that maternal antibody is, in fact,  
17 protective from that baby acquiring any further CMV from any  
18 other source because the baby has kind of passive immunity  
19 from mom.

20 When they then went and broke it down and looked  
21 at the next level, which is the babies who are born of CMV  
22 seronegative mothers, many of those babies happened to get  
23 some CMV-seronegative blood. So, they are not of interest  
24 either because even though they were negative they happened

1 to get negative blood. So, there is no issue.

2 So, when you break it down to the negative babies  
3 who got CMV-positive blood we get to the heat of battle. I  
4 am still on the second line. So, we have negative babies  
5 born from negative mothers. So, they are at-risk children,  
6 who are known to have received CMV-positive blood. So, the  
7 blood bank knew that they were giving out positive blood to  
8 these at-risk children, and there were 59 who got non-  
9 filtered blood and 42 who got filtered blood.

10 The outcomes of those children are further broken  
11 down. Basically, the children who were normal term, nothing  
12 happened to them. All the disease was focused in the low  
13 birth weight CMV-negative babies who got CMV-positive blood.  
14 So, now there are 29 and 24. Then a third of the babies who  
15 got unfiltered blood, who were tiny babies at risk, a third  
16 of them got infection and none in the filtered arm got  
17 infected. So, you had to start with 600 to get 29 and 24  
18 who were the real focused group.

19 DR. VERTER: I guess I have to read the article,  
20 but of the original 600 only 9 wound up with an infection?

21 DR. DZIK: That is correct, attributed to  
22 transfusion. Well, of the original 294, we should say. Of  
23 the 294 who received unfiltered blood, on the left-hand  
24 side, only 9 of them got sick. That is right. This is not

1 wiping out babies left and right. You have to do big  
2 studies to catch this in a baby.

3 DR. VERTER: Thanks. Can I go to the other  
4 question? I think that what Dr. Sayers presented on the  
5 Bowden study is kind of interesting in a couple of respects.  
6 In one respect, it points out, at least to me, the problem  
7 of all the other studies that were addressed, other than the  
8 two randomized ones that Dr. Dzik talked about. That is,  
9 they were all so small that the fact that you get zero out  
10 of something is nice but so what? You need hundreds of kids  
11 to even see one or hundreds of adults. So, it is reassuring  
12 but it shouldn't be that convincing. They were woefully  
13 underpowered and poorly designed, but given the resources  
14 available they probably contribute something. So, for me it  
15 comes out to three studies, the two that Dr. Dzik presented  
16 and the Bowden study.

17 I have some serious problems with the Bowden  
18 study, some of which were reported in the letter in Lancet  
19 but I would like to go a little bit further. First of all,  
20 I think they violated some principles of clinical trial  
21 reporting. Number one, there were 521 patients actually  
22 randomized in that trial. They excluded 19. They give the  
23 reasons why these were excluded but, indeed, it turns out  
24 that they were disproportionate, 6 in the regular group and

1 13 in the filtered group. You know, you can see the reasons  
2 in the paper. They may be justified; they may not. In my  
3 mind, once randomized you are in and in intention-to-treat  
4 you should be reporting the results.

5 I don't agree with the idea that this study, in my  
6 own opinion, convincingly states that filtered is equivalent  
7 to seronegative, and there are a couple of issues on that.  
8 Number one, from the way they wrote the design section it is  
9 unclear to me that the study was actually designed to test  
10 equivalence rather than perhaps "efficacy."

11 I did a few calculations late last night and,  
12 depending on the assumptions you want to make, an  
13 equivalence trial is probably not doable. It would require  
14 somewhere between 1500 and 5000 patients at the levels that  
15 they are talking about. So, it may be the best we can do  
16 given the resources that are available, or maybe we could  
17 change some design assumptions to do one. In any case, it  
18 was unclear to me what exactly this was designed for.

19 The fact that they did the actuarial rather than  
20 Fisher's Exact Test, which Landau note indicates has a p  
21 value of 0.1 for the 0 versus 6 I think is intriguing and  
22 possibly speaks to the fact of censoring. If you read the  
23 article, you will notice that only 50 percent of the  
24 patients were available for evaluation at 100 days. That

1 means that over the course of the 100 days we have lost half  
2 of those patients for a variety of reasons. So, the actual  
3 incidence of CMV disease at 100 days is only an estimate  
4 based on the statistical technique. I would argue that 50  
5 percent censoring is quite large. So, that is another issue  
6 that I had a problem about. That probably sums it up.

7 DR. HOLLINGER: Merlin, while you are coming up,  
8 there is something else I will ask also on the same issue.  
9 They received 6 units of blood or more. That was in non-  
10 study transfusions. It doesn't say how many received less  
11 than 6. Obviously, that means that a number of patients  
12 received 1, 2, 3, 4 or 5, which could have resulted in a  
13 disease. There are no comments about it at all in the  
14 study. Could you respond to these questions?

15 DR. SAYERS: Sure. I said by way of a preface  
16 before presenting that study that this was an investigation  
17 which, albeit done with diligence on the part of the  
18 investigators, was a study which was subjected subsequently  
19 to withering scrutiny and to a significant degree of  
20 criticism. Dr. Verter has brought out reasons why that  
21 study and the statistical interpretation and the protocol,  
22 indeed, do deserve criticism.

23 All I can stand back and say though is that in an  
24 attempt to compare filtration with serological screening of

1 donors that is the largest study, flawed as it is, that we  
2 have. Certainly, there are other opportunities for  
3 interpretation of those results. Larry Pitts, in a letter  
4 to Blood, brought up a number of his criticisms for the  
5 interpretation of that study. I am not saying this as a  
6 defense at all, but it is the largest study looking at  
7 filtration and screening.

8 I believe with regard to your question, I do not  
9 have an answer to that at my fingertips and, obviously, it  
10 is not going to be relevant to this discussion because I  
11 wouldn't be able to get it in time but I can certainly go  
12 back and find out what the answer was.

13 DR. HOLLINGER: Thank you. Yes, Rev. Little?

14 REV. LITTLE: I would just like to comment on the  
15 first question. I have two comments. The first, I would  
16 like to ask the FDA for some help. What constitutes  
17 sufficient evidence according to your definition?

18 The other thing is, the way the question is  
19 phrased, I can only respond to evidence that has been  
20 presented to us so I don't know what exists beyond the  
21 material that I have been given and the material that has  
22 been presented, and I have no idea how much more evidence  
23 there is or how wide the pool is. Maybe someone can help me  
24 out.

1 DR. LEE: The material that was circulated prior  
2 to the meeting and the speakers that were invited was based  
3 on an attempt to cover the waterfront of what is known about  
4 CMV reduction by blood transfusion and leukoreduction. So,  
5 I believe that all the major pieces of information that we  
6 should consider have been presented at this meeting.

7 DR. LINDEN: I have a question for you also about  
8 the questions. They all refer to  $5 \times 10^6$  leukocytes per  
9 unit, which is fine for apheresis platelets and for red  
10 cells but for platelet concentrates, according to the AABB  
11 proposal, it is per pool. Can we interpret the question  
12 loosely to mean unit or pool, or do you really mean unit?

13 DR. LEE: Yes, please interpret it loosely. The  
14 memorandum actually mentions  $8.3 \times 10^5$  per particular unit,  
15 which is then going to be pooled in a 6-pool unit.

16 DR. HOLLINGER: Just on that same issue, and  
17 perhaps somebody else also could reply, I get the  
18 impression, just looking at all the data that is out there  
19 and the different techniques when you start from the early  
20 generations to the present, there is a fairly wide amount of  
21 safety there and as you get down to the  $10^7$  even, down in  
22 that range, there were still very few infections. Am I  
23 correct in that sort of assumption that this level was  
24 chosen because it was approachable? That is one question.

1           The other question is whether there is a  
2 difference in filtration based on the age of the product,  
3 blood say in the first 7 days versus something that is old.

4           DR. DZIK: You are correct, it is our reading of  
5 the literature, both Dr. Sayers and myself, that there is a  
6 fairly strong level of comfort there that, in fact, a lot of  
7 the earlier technology, whether it be simple centrifugation  
8 or frozen deglycerolization or some of the early models of  
9 third generation filters, even a study done that used that  
10 second generation microaggregate filter, all had actually  
11 favorable results in these trials, small as the trials were.  
12 So, there are zeros followed by a denominator that is not  
13 huge.

14           So, yes, the number of  $5 \times 10^6$  which is used as at  
15 standard in the United States was not selected on the basis  
16 of CMV at all. That  $5 \times 10^6$  was based on preliminary early  
17 studies using the technology to prevent HLA sensitization.  
18 So, it became the standard for leukocyte reduction where the  
19 goal of the technique was to prevent HLA stimulation of the  
20 recipient. That goal was then later adopted as the same  
21 goal to be used for the prevention of CMV. So, rather than  
22 set different goals for different indications, which would  
23 get a little bit confusing for everyone, the  $5 \times 10^6$  number  
24 was not selected based on an attempt to find what was safe

1 for CMV. In fact, it seems like CMV is easier to prevent  
2 than HLA alloimmunization. The  $5 \times 10^6$  number was picked  
3 for alloimmunization.

4           Regarding the timing of filtration and the age of  
5 the blood, it is also a very difficult issue to study and  
6 have good facts about because the ability to count the  
7 residual leukocytes in filtered blood, which has been stored  
8 for a long time and is old, is a strong technical challenge  
9 because the cells begin to degenerate during storage and it  
10 is simply hard to visualize or enumerate by any technology  
11 in stored blood. So, the best studies that have looked at  
12 kind of counting of residual leukocytes have focused on  
13 fresh blood because you can most correctly count the cells  
14 in that setting. Leukocytes deteriorate dramatically in a  
15 refrigerated environment so the feeling is that when you  
16 work with stored and older blood you are probably going to  
17 do at least as well as you do with fresh blood, but there  
18 isn't really hard data on taking a one-month old unit of red  
19 cells out of the refrigerator and trying to get really good  
20 numbers on the leukocyte counts on those units. So, most of  
21 the numbers that I gave to you were based on kind of a worst  
22 case scenario working with fresh blood.

23           DR. HOLLINGER: In that same regard, when they  
24 looked at very low birth weight neonates there was much

1 interest in using fresh blood. As new anticoagulants and  
2 other things came along, this seems not so important. It  
3 used to be, particularly with hepatitis, that blood that was  
4 more than seven days old was less likely to transmit  
5 hepatitis, you were less likely to see it than with fresh  
6 blood. Is that sort of still the feeling, that as blood  
7 ages there is much less probability, whether filtered or  
8 not, of transmitting CMV?

9 DR. DZIK: I think that is a very good point. We  
10 move from data to kind of more conjecture and feeling with  
11 this. It was felt that a product that was very likely to  
12 transmit CMV to an at-risk recipient was, for example,  
13 granulocyte transfusion, which is always given fresh. You  
14 cannot store granulocytes. So, the freshness became  
15 attached to the granulocyte topic. Of course, in the  
16 granulocyte transfusion you are giving a product that is  
17 hugely rich in leukocytes which harbor the CMV. So, we may  
18 be mixing concepts there that we don't know about.

19 I do know that leukocytes deteriorate during  
20 storage, and to the extent that they deteriorate in a  
21 refrigerated environment, you do begin to get as much as 40,  
22 50 percent decline in the leukocyte content and you are  
23 starting to get the levels that are similar to those of  
24 those early centrifugation and washing techniques. So,

1 there may be an impact of storage, although I don't think we  
2 should focus on that because there really isn't good  
3 information.

4           The point is quite relevant about babies though.  
5 Nowadays babies are not restricted to receiving fresh blood  
6 in most major hospitals. What that means is that you can  
7 take a donor unit and use that same unit for that baby for a  
8 month of the course of the baby's care, and the impact of  
9 that is that the baby now gets exposed to fewer different  
10 donors. In the old fresh days, you know, you would give him  
11 your unit, and then your unit would no longer be fresh so we  
12 would have to give him his unit, and then we would give the  
13 baby that person's unit. So, the baby would get three donor  
14 exposures. Now babies are getting fewer donor exposures  
15 because we can use that single unit and reserve it for the  
16 baby and take off aliquots over the course of a month. That  
17 may contribute to the decline that we are seeing even in  
18 unscreened settings in the neonatal setting, just fewer  
19 donor exposures.

20           DR. HOLLINGER: I thought that once you opened a  
21 donor unit it had to be used within a certain period of  
22 time. How is that done?

23           DR. DZIK: Two ways. There are packs you can make  
24 that have multiple connected bags, bags with lots of little

1 bags hanging off of it and they just kind of run them in and  
2 they are sterilely separated; or you can use a sterile  
3 connecting device, a little device that does a tubing weld.  
4 So, that is good for babies, actually.

5 DR. VERTER: I need someone to help me with the  
6 question. I am actually going to pay you a compliment also.  
7 If the Miller and Gilbert articles, which I haven't been  
8 able to get a hold of, are as well written and have all the  
9 data to allow me to critique them the way I critiqued your  
10 study, Dr. Bowden's study and yours, then I am faced with  
11 the following dilemma: The three trials which are the best  
12 data we have appear to show that the leukoreduction  
13 techniques may be effective in LBW babies but may not be  
14 beneficial in people undergoing bone marrow transplant.

15 DR. HOLLINGER: You mean versus seronegative  
16 blood?

17 DR. VERTER: Right.

18 DR. KHABBAZ: That is a good question. I think in  
19 commenting on the limitation of the serologic test you  
20 mentioned some antibody negative who are responsive. What  
21 do we know of viremia and PCR studies in assessing the role  
22 of viremia?

23 DR. DZIK: Yes, in doing a review for this I came  
24 across those studies and just felt compelled to make you

1 aware of them. But I am glad you asked the question because  
2 it gives me a chance to emphasize the fact that these  
3 findings that who people test as seronegative but PCR  
4 positive -- these are really new studies, new data, small  
5 numbers and we really know nothing about the infectivity of  
6 those units. So, I don't think you should attach any  
7 impression that someone who tests as seronegative and PCR  
8 positive -- that that has been studied evidence of a cause  
9 of transmission. It is one potential cause but it is really  
10 too new to anything about that.

11 DR. KHABBAZ: PCR positivity in cells or cell  
12 free?

13 DR. DZIK: Yes, I am sorry. The PCR positivity in  
14 cells -- that is an important question, yes -- if you just  
15 take some plasma and PCR it, you are not going to get  
16 something but what they took was cells. In fact, this study  
17 was used to find which cells among healthy donors are likely  
18 to have PCR positive material and found, for example, that  
19 it was really the monocytes and some of the lymphocytes that  
20 more likely had PCR positive material. If in situ is looked  
21 at, you would have to see it in the nucleus, which is where  
22 you would kind of expect to see it. When you look at sick  
23 patients, ill patients, you find actually PCR positive  
24 material in the cytoplasm of polys, and it is felt that

1 polymorphonuclear cells have kind of swallowed up the virus,  
2 the virus has been engulfed by the poly not the stuff that  
3 is latently infected in the nucleus.

4 DR. NELSON: Are there no studies comparing PCR  
5 and culture?

6 DR. DZIK: Not that I am aware of, no. A  
7 technical difference to be aware of in the studies -- it  
8 could be that very low birth weight infants are, indeed,  
9 different from marrow transplant patients. Indeed, marrow  
10 transplantation patients are among the severest challenge  
11 because they are really assaulted by total body irradiation  
12 and heavy chemicals and get a chimeric immune system, and  
13 they are really sick customers. But it is also important to  
14 recognize that in the Gilbert study the filtration was done  
15 in the laboratory and in the Bowden study it was done at the  
16 bedside. It may not have been the recipients; it may have  
17 been the process by which the blood was done.

18 DR. HOLLINGER: There have been some studies  
19 looking at in plasma with PCR and it has not generally been  
20 successful in plasma.

21 DR. DZIK: Yes.

22 DR. NELSON: My question was relating to what  
23 proportion of PCR positives in cells were culture positive.

24 DR. DZIK: I am sorry.

1 DR. HOLLINGER: How much are these filters, by the  
2 way?

3 DR. DZIK: I can tell you, and maybe Dr. Dodd has  
4 a follow up.

5 DR. DODD: I just wanted to comment, Kenrad, that  
6 I think many careers have been lost over the years in trying  
7 to isolate CMV from donor samples, and only just now are we  
8 beginning to see PCR data. I just reviewed a couple of  
9 papers, and I would say they were random papers rather than  
10 a systematic evaluation, but they are suggesting that of  
11 seropositive donor samples less than one to perhaps a few  
12 percent might be PCR positive. If you look carefully, the  
13 implications of the data are that in seropositive donors,  
14 when this happens you probably have one genome copy per  
15 several thousand cells. So, you are very far down. We  
16 don't know how this relates to, as Sunny said, infectivity  
17 but it has been a fraught area in dealing with donors.

18 DR. DZIK: Dr. Hollinger asked about the price of  
19 the filters and I really don't have data on national  
20 pricing; there are people here in the room who do. The  
21 acquisition cost of a filter for a hospital is higher than  
22 the acquisition price for doing a CMV test. So, the filters  
23 are a more expensive technology than serotesting. However,  
24 I think the real question with regard to economics is to

1 remember that nearly all the patients for whom CMV is an  
2 issue are patients who are going to have to get leukocyte-  
3 depleted blood anyway for other clinical reasons, like the  
4 HLA alloimmunization. So, what we are really discussing is  
5 the cost of the filtration experience and whether or not to  
6 add on to that the pricing required for serologic testing.  
7 So, that is probably the best way to think about the  
8 economic question.

9 DR. HOLLINGER: Thank you. Yes, Beatrice?

10 MS. PIERCE: I have a question for Dr. Sayers. In  
11 terms of the latent CMV with the filtered, do you have any  
12 additional information about that? Is there anything else  
13 available? It may have just been clarified but I just  
14 wanted to clarify whether those were bedside leukoreduced or  
15 if those were leukoreduced in the lab or blood bank.

16 DR. SAYERS: They were bedside leukoreduced and,  
17 you know, I missed the first part of your question. I am  
18 sorry.

19 MS. PIERCE: The latent CMV in the filtered,  
20 patients who received filtered blood, seemed to be a little  
21 higher. I know there are not a lot of numbers here. I  
22 wondered if there was any additional information available.

23 DR. SAYERS: No, there isn't.

24 DR. DZIK: A little bit of an afterthought to

1 follow up on your question about the PCR issue. There is a  
2 paper I didn't present, which may or may not be relevant;  
3 again, it is small, looking at the PCR signal in a CMV  
4 positive unit and then the effect of filtration on that.  
5 Filtering PCR positive blood resulted in the blood then  
6 becoming PCR negative. On that PCR is ethidium bromide gel.  
7 If you have done PCR in gels, there are limitations in that.  
8 So, it was not done Southern blotted and probed, which would  
9 give you a little more sensitivity. I don't know whether  
10 they didn't do that because they can't do blotting or  
11 because they didn't want to do blotting. But I do know that  
12 a clearly positive gel signal was rendered negative by using  
13 a third generation filter. So, I share that with you. I  
14 don't know what that means.

15 DR. HOLLINGER: Dr. Sayers brought up a couple of  
16 questions that the FDA may be interested in our talking  
17 about if someone has some comments. That is, not just about  
18 leukoreduction but, if the questions are so answered, about  
19 the adequacy and sufficiency of the filtration procedures,  
20 whether some comment should be made about that. Anyone have  
21 any comments about that in terms of the product itself? No  
22 comment?

23 Why don't we then go ahead and put the questions  
24 up? Yes, Bill?

1 DR. MARTONE: Just a comment, and it may be a  
2 misperception but I get the general feeling that the studies  
3 in the neonates look better than the studies in the  
4 immunocompromised patients. If that is true, I am wondering  
5 if that might not be due to volume and, by extrapolation,  
6 number of white cells that the two groups receive during the  
7 course of a treatment. If that is true, I wonder if further  
8 reductions in the number of white cells might be even more  
9 efficacious.

10 DR. NESS: I think the other fact though gets back  
11 to the question you were talking about, the conditions of  
12 filtration. In neonates, by definition since these are  
13 whole units of blood and these are very small recipients,  
14 they have to be filtered at the blood center or in a blood  
15 bank and then, as Dr. Dzik described, aliquots are then  
16 given. So, the filtration is done in a relatively  
17 controlled process. In some of the transplant studies some  
18 of the data comes with pre-storage filtration in the blood  
19 center. The Bowden study came with bedside filtration.  
20 While it is probably true in a relatively stable patient at  
21 the bedside that a well-trained nurse can filter and achieve  
22 that, anybody who has gone to see the bedside of a bone  
23 marrow transplant patient or a liver transplant patient in  
24 which these units are being given at the bedside, knows that

1 many of these transfusions have to be delayed by the  
2 infusion of antibiotics. The blood bag hangs there while  
3 the amphotericin is running in or the growth factors are  
4 being given, etc. So, it is a relatively chaotic experience  
5 and I am sure that the clinical experience would indicate at  
6 Hutchinson that that would occur. So, the filtration  
7 conditions I think can be very different.

8 DR. HOLLINGER: Thank you. Dr. Gilcher, I saw you  
9 nodding your head. Do you have exception to that?

10 DR. GILCHER: With all due respect to my friend,  
11 when the Bowden study came out there was a lot of concern  
12 and criticism exactly on what Dr. Ness said, in fact, in the  
13 original presentation. The abstract was written in the  
14 reverse. That is, it was written that the filtration did  
15 not produce good results but, in fact, when they presented  
16 the paper they showed that it did -- the same data that Dr.  
17 Sayers showed.

18 But the concern and criticism which has hung for  
19 years now is that that study was a bedside filtration study  
20 and, very clearly, the panel here has not focused on the  
21 importance of bedside, which is totally uncontrolled, versus  
22 the filtration either in the blood bank or at the blood  
23 center, the data which Dr. Dzik showed that clearly shows  
24 that process control is a critical part of the leukocyte

1 reduction. We don't really know in the Bowden study how  
2 many white cells went into the patient. There was no QC on  
3 any of the units, whereas, at least there is QC in the blood  
4 center or in the hospital blood bank and, of course, there  
5 is temperature control and so forth. I think that is a very  
6 critical issue here.

7 DR. HOLLINGER: So, what is the issue? What is  
8 the resistance to having it done one place or the other?  
9 Why is there an issue here?

10 DR. GILCHER: No, the issue is process control.

11 DR. HOLLINGER: I understand the issue. Doing it  
12 in the blood bank there is better control, I agree.

13 DR. GILCHER: Blood bank versus bedside.

14 DR. HOLLINGER: Right. But what is the reason why  
15 it shouldn't be done in the blood bank? I mean, I would  
16 agree if it is better controlled that is probably where it  
17 ought to be done.

18 DR. GILCHER: It should be.

19 DR. HOLLINGER: But why is there then this issue  
20 of why it should be done at the bedside?

21 DR. GILCHER: The reason why it shouldn't be done  
22 at the bedside is that there is no process control. There  
23 is no quality control. You have no quality assurance in the  
24 process. You really filtering with many variables. You

1 really do not know then how many white cells ultimately go  
2 into the patient.

3 DR. HOLLINGER: It is more subtle than that maybe.  
4 I understand that there is a big difference between the two  
5 but why would then anyone want to do it at the bedside?  
6 That is the issue. I mean, is there a problem because the  
7 blood banks can't handle it and, therefore, it is easier to  
8 send it to the bedside, or is it that the nursing staff  
9 feels that they can do this quicker, or is it money? What  
10 is the issue?

11 DR. GILCHER: I think ultimately it comes down to  
12 exactly the last point that you said, which is money. There  
13 are filter manufacturers who are pushing to do bedside  
14 filtration because the blood center or the blood bank  
15 chooses to uses a different filter.

16 DR. HOLLINGER: There are different filters?

17 DR. GILCHER: There are multiple filters on the  
18 market and we have, in our own laboratories at the Blood  
19 Institute, assessed these and the truth is whether you use a  
20 Pall, a HemaSure or an Asahi filter we can achieve  
21 essentially the same degree of leukocyte reduction in the  
22 laboratory under controlled conditions, that is, process  
23 control in place, regardless of which filter is used. So,  
24 if a blood center chooses to use one filter, the

1 manufacturers of the other filters will, in fact, go into  
2 the hospitals and promote bedside filtration.

3           This practice is going on throughout the country.  
4 It clearly is happening in our area. I will not remark on  
5 which filter we use but the other manufacturer has gone into  
6 the hospitals and is selling the filter at a very low price  
7 and advising the hospitals to use bedside filtration. Our  
8 point is there is no process control. I do not believe that  
9 this committee realizes the importance or understands that.  
10 There are clearly members on the committee, Dr. Ness,  
11 certainly Dr. Dzik, and Dr. Sayers, who can I think discuss  
12 exactly the points that I am making, but I think this is a  
13 critical issue.

14           DR. HOLLINGER: Thank you, Dr. Gilcher. Jay wants  
15 to comment.

16           DR. EPSTEIN: The issue that you raise, which is  
17 of course legitimate, exists at two levels of potential  
18 control. One is regulatory and the other is practice of  
19 medicine.

20           Now, with respect to the regulatory control, you  
21 currently have filters that are being approved more or less  
22 generically as devices that do not have restrictive labeling  
23 and that have not been approved for specific efficacy  
24 claims, particularly for CMV prevention. Our thrust here is

1 whether we can move towards specific labeling for efficacy  
2 for CMV prevention.

3           We could also at the same time move towards  
4 restricted device labeling which would say, you know, to be  
5 used in a quality control environment, and the language in  
6 the insert could explain that we don't think that is the  
7 bedside.

8           But I think that the practice of medicine issue  
9 also needs to be addressed, but that is through other  
10 venues.

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

12           DR. NELSON: Well, my interpretation is really  
13 that the standard of care now is to screen blood, and that  
14 is what blood banks do. So, what is really happening is  
15 that screened blood is now being filtered by some  
16 oncologists, some transplant surgeons, some neonatal, etc.,  
17 and we haven't really discussed that except that one of the  
18 presenters mentioned that probably the use of both  
19 techniques is probably more efficacious, in other words,  
20 screening and filtering in an extremely high risk situation.  
21 There is no data on that. There will probably never be.  
22 But it makes sense that the two might be additive at least.

23           DR. HOLLINGER: Dr. Sayers?

24           DR. SAYERS: Dr. Hollinger, thanks. Just in

1 response to the comments about the Bowden abstract from ex-  
2 friend, Dr. Gilcher --

3 (Laughter)

4 -- if there was general detraction, confession and  
5 revision, then certainly we would have revisited that  
6 abstract. Dr. Gilcher was 100 percent right, that abstract  
7 which was produced under the heat of a deadline was put out  
8 before the final statistical review had been carried out,  
9 and the abstract did lean in favor of seronegative blood  
10 rather than filtered blood. Certainly that was not the  
11 final message that the authors felt was a correct  
12 interpretation after more thorough statistical review, as it  
13 was iterated in the paper.

14 That aside, I don't want to sound discouraging or  
15 defeatist by some courage has to be taken when it comes to  
16 making recommendations in the knowledge that it is not going  
17 to be possible to conduct the clinical trials that are  
18 reasonably suggested by the evidence that is at hand. I  
19 mean, we have been trying to understand, I believe  
20 legitimately, the scientific method and the clinical trial  
21 process. But when it comes to understanding how to reduce  
22 the likelihood of low incidence side effects, and here the  
23 Bowden study is symptomatic of that problem when it comes to  
24 understanding how best to do those studies and to be able to

1 design those studies, there are significant limitations. I  
2 do suspect some clinical recommendations will have to be  
3 made without, as I say, being able to perform the clinical  
4 trials that legitimately are provoked or are suggested by  
5 the questions that are raised.

6 DR. HOLLINGER: Thank you. Yes, Dr. Linden?

7 DR. LINDEN: Dr. Sayers, before you sit down, in  
8 terms of the bedside filtration in the Bowden study, was  
9 that done in a very small hospital unit with a very small  
10 number of people who may potentially have been more trained  
11 and had better uniformity than you would generally find in  
12 hospitals using bedside filtration?

13 DR. DZIK: I think Dr. Ness hit the nail on the  
14 head. This was a multicenter study. It was done at a  
15 number of different locations. One only has to sample the  
16 hurly-burly of the average marrow transplant unit to  
17 recognize that, as Dr. Gilcher said, process control is an  
18 illusory goal in those units.

19 DR. HOLLINGER: If there is no further discussion,  
20 we have the first question up there. I will read the  
21 question and then we will vote on it.

22 Is there sufficient evidence to conclude that  
23 leukoreduction of red blood cells and platelets to  $5 \times 10$ <sup>6</sup>  
24 leukocytes per unit or below reduces the incidence of CMV

1 transmission by these components? Yes, Joel?

2 DR. VERTER: I need a clarification there -- as  
3 compared to what?

4 DR. HOLLINGER: As compared to unscreened blood.

5 DR. VERTER: But that is the next question.

6 DR. NELSON: As compared to unfiltered blood.

7 DR. HOLLINGER: Unfiltered, I mean. Unfiltered.

8 DR. NELSON: Unscreened, unfiltered.

9 DR. HOLLINGER: Okay. The first two questions are  
10 similar. All those in favor of this, raise your hand.

11 (Show of hands)

12 All those opposed?

13 (One opposed)

14 Abstained?

15 (Show of hands)

16 Paul?

17 DR. NESS: I would vote yes.

18 DR. HOLLINGER: And Violet?

19 REV. LITTLE: I will abstain.

20 DR. HOLLINGER: Any comments about the opposition?

21 DR. NELSON: I voted no because it says is there  
22 sufficient evidence and I didn't see the evidence compared  
23 to nothing.

24 DR. HOLLINGER: All right.

1 DR. NELSON: Although I suspect it is true.

2 DR. SMALLWOOD: The results of the votes for  
3 question number 1(a) are 8 yes votes, 1 no vote, 2  
4 abstentions. The industry representative agrees with the  
5 yes vote; the consumer representative abstained.

6 DR. HOLLINGER: I presume the abstention was  
7 because of lack of evidence?

8 DR, MARTONE: I just didn't think we were holding  
9 this question to the same standard to which we might hold a  
10 drug.

11 DR. HOLLINGER: All right. May we have the second  
12 question, please? The second question is, is there  
13 sufficient evidence to conclude that leukoreduction of red  
14 blood cells and platelets to  $5 \times 10^6$  leukocytes per unit or  
15 below is equivalent to the use of seronegative components  
16 with respect to the potential to transmit CMV?

17 All of those that agree, that are in favor of this  
18 question, raise your hand.

19 (One response)

20 All those opposed?

21 (Show of hands)

22 Abstaining?

23 (Show of hands)

24 Paul?

1 DR. NESS: I would agree with the yes vote.

2 DR. HOLLINGER: And Rev. Little?

3 REV. LITTLE: I would say no.

4 DR. SMALLWOOD: Results of voting to question  
5 1(b), 1 yes vote, 7 no votes, 3 abstentions. The industry  
6 representative agrees with the yes vote; the consumer  
7 representative agrees with the no vote.

8 DR. HOLLINGER: Yes, Joel?

9 DR. VERTER: No one actually responded to the  
10 question I asked earlier. I did vote no, but I am concerned  
11 that there may be evidence in some subpopulations where it  
12 is effective.

13 DR. HOLLINGER: All right. The next question is,  
14 is there sufficient evidence to conclude that all of the  
15 methods of leukoreduction discussed are equivalent in their  
16 ability to reduce the incidence of transfusion-transmitted  
17 CMV infection provided that the final leukocyte count of  
18 each component is  $5 \times 10^6$  leukocytes per unit or fewer?

19 All those in favor of that question, raise your  
20 hand.

21 (No response)

22 All those opposed?

23 (Show of hands)

24 Abstaining?

1 (Show of hands)

2 Dr. Ness?

3 DR. NESS: I would vote no.

4 DR. HOLLINGER: Rev. Little?

5 REV. LITTLE: No.

6 DR. SMALLWOOD: Results of voting for question

7 number two, there were no yes votes, 9 no votes, 2

8 abstentions. The industry representative agreed with the no

9 vote; the consumer representative agreed with the no vote.

10 DR. HOLLINGER: This concludes the morning

11 session. This afternoon we will start at 1:30 and the

12 session will be on cryoprecipitate-depleted plasma. Thank

13 you.

14 [Whereupon, at 12 o'clock p.m., the proceedings

15 were recessed, to be resumed at 1:30 p.m.]

1 AFTERNOON SESSION

2 DR. HOLLINGER: We will begin the session this  
3 afternoon on cryoprecipitate-depleted plasma. Before we  
4 start, I think one or two of the committee members wanted to  
5 make a comment about their vote this morning. So, I am  
6 going to allow for the record. Jeanne?

7 DR. LINDEN: I would just like to clarify because  
8 I don't think my vote really reflects my opinion. On  
9 question 1(b), my opinion is that leukofiltration performed  
10 in the blood bank or blood center would be an acceptable  
11 alternative to CMV testing. I wasn't really happy with the  
12 way the question was worded. Had it been worded differently  
13 I would have said yes.

14 DR. HOLLINGER: Thank you. Yes, Jerry?

15 DR. HOLMBERG: I didn't have an opportunity to  
16 really express myself earlier, and I do appreciate what Dr.  
17 Gilcher mentioned earlier about the variability with the  
18 temperature and where the filtration is taking place.  
19 Again, the evolution of this is that all of us have used  
20 some form of filtration in the past where it was easier to  
21 dispense a filter from the blood bank versus relabeling a  
22 product. I think we have moved past that point where it  
23 would be better to do it in the donor center or the  
24 transfusion service, to have a lot more control over it.

1                   But it goes back to the issue of if that is done  
2 in the laboratory, then you have to have the quality  
3 controls there to say that this qualifies the product. This  
4 was, even in my personal experience, a limitation, that is,  
5 I would then have to relabel the product and it was easier  
6 and more convenient at the time, and we are talking about  
7 six, seven years ago, to go ahead and just issue the filter.  
8 But we have moved past that, and that is primarily the  
9 reason I voted the way I did on those issues also.

10                   Again, I do appreciate what Joel mentioned about  
11 the study, pointing out some of the weaknesses with the  
12 Seattle study. Again, that also reflected the way I voted  
13 on that.

14                   DR. HOLLINGER: Thank you very much. In that  
15 case, I think we will begin then the session this afternoon.  
16 Dr. Lee is going to initiate this with some background  
17 information.

18                   **Cryoprecipitate-Depleted Plasma**

19                   **CDP: A New Plasma Component?**

20                   **Jong-Hoon Lee, M.C.**

21                   (Slide)

22                   DR. LEE: Thank you and welcome back to the last  
23 topic of this meeting.

24                   (Slide)

1           Recently plasma has been recognized as a critical  
2 element in successfully treating patients with thrombotic  
3 thrombocytopenic purpura, or TTP, a rare systemic disease of  
4 unknown etiology in which platelet aggregates form  
5 throughout the microcirculation. The rapid institution of  
6 plasma exchange using fresh-frozen plasma, or FFP, as a  
7 replacement fluid has resulted in high rates of remission  
8 for a disease which is typically fatal if untreated.

9           (Slide)

10           The plasma fraction remaining after the removal of  
11 the cryoprecipitate fraction has been receiving increasing  
12 attention in the treatment of TTP. Based on theoretical  
13 considerations, the use of cryoprecipitate-reduced fraction,  
14 also referred to in the literature as cryoprecipitate-  
15 depleted plasma, cryopoor plasma and cryosupernate, may  
16 offer an advantage over using FFP.

17           Of the nearly 800 reports in the literature about  
18 TTP in general over the last ten years, however, only a few  
19 directly support such theoretical considerations in a  
20 clinical comparison of cryoprecipitate-reduced plasma and  
21 fresh-frozen plasma. Although the relative effectiveness of  
22 cryoprecipitate-reduced plasma and fresh-frozen plasma in  
23 treating TTP has been receiving increasing attention, there  
24 has been little interest, if any, in exploring in controlled

1 clinical trials the role of plasma in treating TTP under  
2 which both FFP and cryoprecipitate-removed plasma belong.

3 (Slide)

4 The Code of Federal Regulations defines plasma as  
5 the fluid portion of one unit of human blood intended for  
6 intravenous use which, in a closed system, has been  
7 collected, stabilized against clotting, and separated from  
8 the red blood cells. Towards establishing product standards  
9 the regulations state that plasma shall be separated from  
10 the red blood cells within the expiration date of the whole  
11 blood unit from which it originates, and shall be stored at  
12 -18 C or colder.

13 (Slide)

14 Additionally, the CFR states that it is possible  
15 to separate cryoprecipitate AHF from plasma and that the  
16 remaining plasma may be labeled as Plasma, with a capital  
17 "P".

18 (Slide)

19 Thus, the current regulations do allow the use of  
20 cryoprecipitate-reduced plasma. However, the term  
21 cryoprecipitate-reduced plasma has not been recognized by  
22 the FDA thus far as a distinct product name.

23 The agency approval of a new drug or an existing  
24 drug for a new clinical indication typically requires the

1 submission of adequate data which demonstrate the product's  
2 safety and efficacy, as well as the appropriate labeling and  
3 product information. In the current situation, the agency  
4 has been asked to approve a new entity, called  
5 cryoprecipitate-reduced plasma, for the indication of  
6 treating TTP based not on a manufacturer's submission of  
7 data and labeling but on the general experience with the  
8 product over the last decade.

9           The agency seeks public advisory opinions about  
10 the adequacy of the recent general experience to serve as a  
11 substitute for rigorous data, collected directly in support  
12 of a product license application. In attempting to make  
13 this determination, it is requested that the following  
14 specific questions be kept in mind as we review the recent  
15 experience with TTP and cryoprecipitate-reduced plasma. As  
16 before, these questions will be posed to the committee for  
17 consideration following all discussions.

18           (Slide)

19           Question number one, is there sufficient evidence  
20 to conclude that the use of CDP offers a clinical advantage  
21 over the use of FFP in treating thrombotic thrombocytopenic  
22 purpura?

23           (Slide)

24           Question two, based on current knowledge and

1 experience, should the FDA recognize CDP as a new plasma  
2 component, subject to licensure for interstate distribution,  
3 with the indication for treating TTP? In other words, is  
4 the evidence available sufficient for the FDA to begin the  
5 development of licensing criteria for TTP?

6 Thank you very much, and I believe that Dr. Moake  
7 will now follow this with a discussion about TTP.

8 **Clinical Indications for CDP and a Comparison of FFP**

9 **Joel L. Moake, M.D.**

10 DR. MOAKE: Thank you, Dr. Lee. Thank you for  
11 inviting me. My intention in the next few minutes would be  
12 to speak briefly about cryoprecipitate and cryoprecipitate-  
13 depleted plasma contents, and then make a few comments about  
14 thrombotic thrombocytopenic purpura and its different types,  
15 and review what modest information is available regarding  
16 the use of cryoprecipitate-depleted plasma in different  
17 situations that are TTP-related.

18 I have no stake in the question; I am just a  
19 provider of information. I am not a blood banker. I am a  
20 clinical hematologist and hemostasis laboratory person, with  
21 an interest in TTP.

22 (Slide)

23 This slide just reviews what is known to be  
24 present in cryoprecipitate, a considerable amount of Factor

1 VIII which, as most everyone in the room knows, ordinarily  
2 is complexed to von Willebrand factor polymers or multimers;  
3 a considerable amount of Factor VIII, as well as some of the  
4 fibrinogen, some of the Factor XIII. These molecules are  
5 precipitated whenever plasma is frozen and then slowly  
6 thawed. There is fibronectin; some immunoglobulins,  
7 particularly IgM, the largest of the immunoglobulins; some  
8 platelet fragments, detectable in cryoprecipitate.

9           The component that perhaps is most relevant to our  
10 discussion here is that in cryoprecipitate the largest  
11 plasma von Willebrand factor multimeric forms are present.  
12 In fact, most of the large plasma von Willebrand factor  
13 multimers are precipitated by this cryoprecipitation  
14 technique.

15           (Slide)

16           The yields are quite variable and not rigorously  
17 standardized. This means then that if one looks at  
18 cryoprecipitate-depleted plasma there are, as follows,  
19 reduced quantities of Factor VIII, fibrinogen, Factor XIII,  
20 fibronectin, IgM, a little bit less IgG. Most of the large  
21 plasma von Willebrand factor multimeric forms are absent.

22           In addition, there is present in cryoprecipitate-  
23 depleted plasma, as there is present in plasma, a component  
24 that appears, on evidence recently published, to be a

1 protease capable of breaking down the largest von Willebrand  
2 factor multimeric forms. But for our discussion, I think  
3 the most important concept on this slide is that the largest  
4 plasma von Willebrand factor multimeric forms are absent in  
5 cryoprecipitate-depleted plasma.

6 (Slide)

7 This is an example of cryoprecipitate-depleted  
8 plasma. On the left are cryosupernatant as compared with  
9 normal pooled plasma, on the right. By the way, this  
10 technique was developed by Mark Weinstein, who is in the  
11 room, and it has been nurtured by various people since. If  
12 normal plasma is not reduced but is mixed with sodium  
13 dodecylsulfate and urea and then is electrophoresed into  
14 very porous agarose, one percent agarose, fixed there and  
15 then reported by radiolabeled antibodies to von Willebrand  
16 factor, what you see is on the right side there.

17 On the left is cryosupernate. You can see that  
18 almost all of the largest, that is, the multimeric forms at  
19 the top of the gel are missing.

20 (Slide)

21 So, cryoprecipitate-depleted plasma contains  
22 reduced quantities of several coagulation factors and  
23 proteins -- contains reduced quantities, let's say, in some  
24 preparations but no von Willebrand factor multimeric forms.

1           I would like to speak just for a few moments about  
2 thrombotic thrombocytopenic purpura.  Until -- well, it is  
3 so old now but when I was in medical school there was one  
4 kind of thrombocytopenic purpura.  It was a kind that people  
5 got and they didn't live through it.  Everyone died of this  
6 disorder.

7           In the late '50s and through the '60s and '70s,  
8 empirically people were treated with exchange transfusions  
9 and then, as we will talk about in a few minutes, plasma,  
10 and many people began to live through episodes of thrombotic  
11 thrombocytopenic purpura, which is a disease where extensive  
12 platelet clumps form all around the microcirculation, block  
13 the microcirculation causing ischemic problems in the brain,  
14 in the heart, in the kidneys, and in the '50s 100 percent  
15 mortality.

16           As people began to be treated with whole blood  
17 exchanges and then plasma infusions and exchanges,  
18 individuals began to live through these episodes, to the  
19 present time where perhaps 60 or 70 percent of individuals  
20 who have TTP episodes will survive them.

21           This led to observations that TTP, indeed, comes  
22 in several different forms.  Here they are.  Some people,  
23 indeed, will have a single episode of TTP out of the blue,  
24 idiopathic, and if they survive it they will never have

1 another.

2           Occasionally people have these kinds of single  
3 episodes that, if they survive, they will have another after  
4 taking one of several different types of drugs,  
5 cyclosporine, ticlopidine, mitomycin C and perhaps others.  
6 But most people will have the single episode and, if they  
7 recover, they will not have the disease again.

8           About a third of individuals who have TTP will,  
9 indeed, if they survive the episode go on to have relapses.  
10 Those relapses are very unpredictable in terms of timing,  
11 but a third or so of people will have episodes repeatedly,  
12 every year, every several months, maybe only every several  
13 years, but they will have repeated episodes.

14           The rarest type, chronic relapsing TTP, at the  
15 bottom here, has been truly a laboratory for observations  
16 about TTP. It is a disorder almost exclusively of children,  
17 children who get TTP and, if it is recognized, and if it is  
18 treated successfully, they will then have relapses of the  
19 disorder approximately every three weeks, every 21 or 22  
20 days, a really amazing disease process.

21           There are perhaps a dozen of these children known  
22 in the United States, a few in Canada, a similar number in  
23 Europe, and quite a lot has been learned about this disease  
24 by observing these children in terms of pathophysiology and

1 a little bit about therapy.

2 (Slide)

3 In terms of pathophysiology, let me just make a  
4 couple of comments because a few things have been learned in  
5 the '80s and '90s. If one looks at the platelet clumps in  
6 the microvasculature of individuals with TTP, there is a  
7 very striking presence of von Willebrand factor antigen in  
8 the platelet clumps, very little fibrinogen, very of other  
9 alpha granular markers but von Willebrand factor is very  
10 heavily stained in platelet clumps of individuals with TTP.  
11 There is very little fibrin present. This is almost the  
12 opposite of what one sees in disseminated intravascular  
13 coagulation. This is truly a systemic platelet clumping  
14 disease of the microvasculature, and it appears as if von  
15 Willebrand factor is somehow involved in the clumping of the  
16 platelets.

17 (Slide)

18 This cartoon summarizes some observations of the  
19 last decade. It shows that von Willebrand factor, which is  
20 indicated as red subunits linked together into different  
21 size polymers or multimers. The multimeric series that  
22 circulates in the plasma is shown on the left. It is  
23 demonstrated in this cartoon that endothelial cells contain  
24 within their granular contents von Willebrand factor

1 multimers of unusually large size. These are normally put  
2 backwards into the subendothelium where there are very good  
3 honing sites for platelets when endothelial cells are  
4 disrupted, and the von Willebrand factor multimers are put  
5 antegrade as well into the circulation where something  
6 causes them to break down into the slightly smaller forms  
7 that circulate. The ultra-large forms, if they remain in  
8 the circulation or if they are put into the circulation in  
9 excess of the capacity of the plasma component that  
10 ordinarily breaks them down, have the propensity to clump  
11 platelets as the cartoon demonstrates. These ultra-large  
12 forms are very much more likely to bind to platelet  
13 receptors for von Willebrand factor and clump the platelets.

14 (Slide)

15 So, this slide summarizes a decade of  
16 observations. No one knows exactly what happens to the  
17 endothelial cells. There is recent published, and about to  
18 be more published, about the possibility that endothelial  
19 cells undergo some apoptotic event when they are exposed to  
20 TTP plasma. Exactly what that is that initiates that event  
21 is unclear, but the apoptosis signaling and result is being  
22 defined by several different groups. So, there is some sort  
23 of endothelial cell alteration or damage that occurs, and  
24 the endothelial cells then are capable of leaking their

1 contents into the plasma.

2           The von Willebrand factor story that we are  
3 discussing here has to do with the subsequent platelet  
4 clumping that causes the obstruction to the microvasculature  
5 and the ischemic events in the brain, heart and elsewhere.

6           Both the ultra-large von Willebrand factor  
7 multimeric forms from endothelial cells and the largest  
8 plasma forms participate once the process of von Willebrand  
9 factor attachment to platelet begins.

10           (Slide)

11           Let me turn to what modest information is  
12 available regarding cryoprecipitate-depleted plasma versus  
13 plasma in the treatment of TTP. This is a notation from a  
14 paper in the last '70s, by John Byrnes and his colleague,  
15 Dr. Khurana at the University of Miami, where they studied a  
16 young lady who had a very prolonged, multiple relapsing  
17 course of TTP. She had a single episode which then relapsed  
18 over and over again for a period of time in excess of a  
19 year. During the course of this observation and treatment  
20 of this young lady, the authors wrote what you see here,  
21 that deep into the course of this young person they gave her  
22 as a plasma infusion, not a plasma exchange,  
23 cryoprecipitate-depleted plasma at a time when her disease  
24 was in relapse and she apparently responded to this

1 infusion. All of us will admit that is a very dangerous  
2 concept to ascribe success to the last thing tried. We  
3 worry about this all of the time but, nevertheless, this is  
4 from this New England Journal paper, one of the first, maybe  
5 the first, to observe cryoprecipitate-depleted plasma  
6 effects in a young lady with multiple relapses of TTP.

7 (Slide)

8 When one looks in current pediatric textbooks for  
9 what one should do in the treatment of chronic relapsing TTP  
10 of children, here the literature consists of anecdotal  
11 information, perhaps five papers at the most, on European  
12 and American children who have been treated with fresh-  
13 frozen plasma infusions or cryoprecipitate-depleted plasma  
14 infusions -- no plasma exchanges, just infusions. So, the  
15 suggestion is that they are being given something that they  
16 don't have or that they have inhibited.

17 My own personal experience with this is five  
18 American children treated with either FFP or  
19 cryoprecipitate-depleted plasma, responding equally to these  
20 infusions apparently. But these comments are anecdotal.

21 (Slide)

22 In the late '80s, a small group of us looked at a  
23 very small group of patients with TTP who were refractory to  
24 fresh-frozen plasma exchange. The experience with TTP

1 patients, either their first episode or relapse, that do not  
2 respond over several weeks to fresh-frozen plasma exchanges,  
3 or sometimes even shorter periods of time than that, they  
4 will die of this disease, just as everyone died in the '50s.  
5 So, a small group of patients from the University of Miami  
6 and the Texas Medical Center in Houston were accumulated  
7 over a period of several years.

8           These are the results. This is not any kind of  
9 prospective, randomized, anything. These are just TTP  
10 patients refractory to plasma exchange. There were seven in  
11 total. Amazing to us, six of these seven improved within  
12 one to two days after being switched to cryoprecipitate-  
13 depleted plasma exchanges. One took a little longer, took  
14 five days. All of the seven patients achieved remission.

15           Please, I realize that this is an anecdote, but  
16 this was published in 1990. Then the Canadian Apheresis  
17 Group conducted a little bit larger trial.

18           (Slide)

19           Before describing that, let me just show a couple  
20 of these patients. Again, I have no stake in the outcome of  
21 what we are discussing. Here are the patients. There are  
22 only two of these examples. This is a 27-year old woman,  
23 transient hemiparesis, fever, microangiopathic hemolysis,  
24 platelets of 17,000. After 3 days of plasma pheresis and

1 infusion of whole plasma as fresh-frozen plasma, the  
2 platelet count rose to 180,000/mcL, as you can see on the  
3 far left on the bottom. However, she quickly relapsed.  
4 After 20 additional daily plasma pheresis with the infusion  
5 of 2 L of fresh-frozen plasma, vincristine and splenectomy  
6 her TTP had not responded. Substitution of cryosupernatant  
7 for fresh-frozen plasma on day 38 was associated with prompt  
8 increase in the platelet count to normal and resolution of  
9 the other manifestations of TTP. In other words, the last  
10 thing she got was cryoprecipitate-depleted plasma and she  
11 recovered. I realize that.

12 (Slide)

13 Here is one other. You can see that that last  
14 patient got both exchange and infusion of cryoprecipitate-  
15 depleted plasma or cryosupernatant. This other patient, a  
16 20-year old woman, neurological disturbances,  
17 microangiopathic hemolytic anemia, platelets of 21,000,  
18 little response was obtained with 3-liter plasma exchanges  
19 performed consecutively on days 6 through 19. On day 20  
20 vincristine was given, cryosupernatant was substituted for  
21 FFP. These are cryosupernatant exchanges. On the fifth day  
22 thereafter neurologic improvement began, the platelet count  
23 rose, continued plasma pheresis with cryosupernatant was  
24 associated with full recovery. A very small study.

1 (Slide)

2 Last year the Canadian Apheresis Group reported  
3 the conduct of a trial that they had overseen over the  
4 course of '93 to '95, or thereabouts, involving 6 of their  
5 centers, Ottawa, Vancouver, Toronto. Perhaps most  
6 interesting to me and it can be discussed whether it is the  
7 most important, but they had 18 patients that were  
8 refractory to fresh-frozen plasma exchanges. Their study  
9 defined refractoriness as non-response neurologically, no  
10 significant platelet count increase after 7 days, 7-8 days,  
11 of fresh-frozen plasma, whole plasma exchange.

12 There were 18 patients who were in that category  
13 and 11 of them responded to cryoprecipitate-depleted plasma  
14 exchanges when those were substituted for whole plasma  
15 exchanges, and 15 of those patients were alive at 1 month.

16 These observations led the Canadian group to  
17 conduct a small trial of previously untreated patients, that  
18 is, to use cryoprecipitate-depleted plasma up front in these  
19 6 centers. They reported 40 patients and 30 of those  
20 responded within 7 exchanges. All but 2 were alive at a  
21 month.

22 This was not any kind of prospective, randomized  
23 trial. What they did, they looked back at the same 6  
24 centers and the patients that they had contributed for an

1 FFP exchange trial that had been conducted in the '80s.  
2 That is shown at the top, 29 patients had been contributed  
3 by these same centers and almost half of them responded by  
4 day 7 of FFP exchange, and three-quarters of them were alive  
5 at 1 month.

6 (Slide)

7 This slide is not any kind of editorial comment.  
8 it is simply taken from a recent textbook of hemostasis and  
9 thrombosis. The suggestion is that fresh-frozen plasma  
10 exchanges be used up front in TTP unless evidence  
11 overwhelming to the contrary emerges, but the suggestion is  
12 that in people who are refractory to FFP exchanges, the  
13 evidence, though slim, does suggest that in these people,  
14 who will otherwise surely die, cryoprecipitate-depleted  
15 plasma is appropriate therapy. Exactly how long one should  
16 be exchanged with FFP before one switches to  
17 cryoprecipitate-depleted plasma is a subject for debate, but  
18 I think one could make a point that if a person worsens on  
19 FFP plasma or develops new neurological symptoms, that there  
20 are easily defined clinical situations where it could be  
21 stated that the individual is refractory to fresh-frozen  
22 plasma exchange. In that situation the use of  
23 cryoprecipitate-depleted plasma in people refractory to  
24 whole plasma exchange is supported almost solely by the

1 anecdotal type of information that I have presented.

2           A number of centers around the United States have  
3 switched to cryoprecipitate-depleted plasma as up front  
4 therapy in TTP. The justification for that is entirely this  
5 non-prospective, non-randomized Canadian Apheresis Group  
6 trial that I described, so far as I am aware. Thank you  
7 very much.

8           DR. HOLLINGER: Thank you. We have no one who has  
9 specifically requested time in the open public hearing.  
10 There seem to be only two groups who have published and we  
11 have heard from one. Is there anyone out in the audience  
12 who would like to comment at all on this? Yes, Dr. Gilcher?

13                                   **OPEN PUBLIC HEARING**

14                                   **Ronald Gilcher, M.D.**

15           DR. GILCHER: We have been using cryopoor plasma  
16 in TTP patients for quite some time, and we prepare it from  
17 our jumbo plasmas, that is, our apheresis fresh-frozen  
18 plasma, which is a 500 30 ml product which we then  
19 cryoprecipitate. We use the apheresis cryoprecipitate  
20 within our system. That is currently being submitted for  
21 licensure as a cryoprecipitate by FDA. But the cryopoor  
22 plasma then is used by our group, which is part of the  
23 University of Oklahoma, Dr. James George, and we have  
24 currently about 145 patients whom we have diagnosed with a

1 TTP syndrome. That includes the whole spectrum from HUS on  
2 one end to TTP.

3 We do not yet know whether this product is as  
4 efficacious as is reported, but what I think is very  
5 important is that it is not not efficacious. We have not  
6 seen any patient deteriorate by using the cryopoor plasma.  
7 I think that is the other side of it, Dr. Moake. So, we are  
8 in that randomized trial with Dr. Zigler, in Pittsburgh, to  
9 really look at the two products. But, clearly, the use of  
10 cryopoor plasma in no way is detrimental to these patients.  
11 If anything, it is advantageous to use it, but we don't have  
12 enough data at the moment to support that.

13 DR. MOAKE: It is at least as good.

14 DR. GILCHER: It is absolutely at least as good.

15 DR. HOLLINGER: Thank you, Ron.

16 **OPEN COMMITTEE DISCUSSION**

17 **Presentation of Questions**

18 DR. HOLLINGER: With that said, we are going to go  
19 to the open committee discussion. Dr. Lee, could you put up  
20 the questions again?

21 DR. LEE: I would just like to make a comment  
22 about the questions. I would like to point out that these  
23 two questions are independent questions and they should be  
24 considered separately. To address that point, actually it

1 may make more sense to consider the second question first.

2 DR. HOLLINGER: Let's have the second question  
3 then.

4 DR. LEE: The second question, which is now the  
5 first question reads, based on current knowledge and  
6 experience, should the FDA recognize CDP as a new plasma  
7 component, subject to licensure for interstate distribution,  
8 with the indication for treating TTP?

9 DR. HOLLINGER: Comments?

10 **Committee Discussion and Recommendations**

11 DR. NESS: I guess I have a question for the FDA.  
12 If you were to do this, and I am not sure it is indicated to  
13 do it, how would it be suggested that those criteria be  
14 defined? I mean, how do you define suitability by the  
15 absence of something when we don't even know what we are  
16 trying to deplete or measure?

17 DR. LEE: We have certainly struggled with that  
18 question, but one method might be to establish standards for  
19 processing, such as standardize the method with which  
20 cryoprecipitate is removed, and to what extent you have to  
21 subject it to precipitation measures. I don't know for  
22 sure, but if you were to subject a unit of blood to two  
23 rounds of cryoprecipitate generation, you may get more out  
24 of it than just one round, which is typically done now. So,

1 those are questions that can be addressed from a  
2 standardizing criteria standpoint.

3 DR. NESS: Yes, but the obvious problem, as Dr.  
4 Moake showed very well in his slides, is that when you make  
5 cryo the yields are very variable. This is a long-term  
6 problem and there is some process control by most people who  
7 make it and, yet, the yield -- you know, we remove, we  
8 think, 25-50 percent of von Willebrand factor or such when  
9 we do it. It just seems that by trying to come up with  
10 criteria, either by a specific assay or by process control,  
11 that you are asking for a very difficult definition.

12 DR. HOLLINGER: Dr. Moake, could you comment on  
13 that?

14 DR. MOAKE: I really like both those comments and  
15 agree with them. To me, it seems as if there is a standard  
16 for making cryoprecipitate. I would be careful about  
17 tampering with that standard because we don't know anything  
18 about repeated cryoprecipitation. It may turn out that that  
19 is even better, but we don't know anything about that yet.

20 We know, though, that those places that make  
21 cryoprecipitate by a standard procedure, that what is left  
22 is a product that appears to be effective in some refractory  
23 TTP patients, and no less efficacious. So, I would suggest  
24 that we not make this too complicated, nor too expensive

1 because we don't want this product to disappear for possible  
2 use by those people who have refractory TTP. It is not very  
3 many but it is several hundred people in the United States  
4 each year. So, I would suggest that the processing is what  
5 we look at because even though the CBER artist drew a nice  
6 cartoon about von Willebrand factor, let's don't pretend  
7 that we know more than we do. So, I think it would be  
8 dangerous to try to assay something, either something  
9 present or something absent, yet. But I think we would be  
10 comfortable overseeing the procedure: make cryoprecipitate,  
11 what is left is defined as cryoprecipitate-depleted plasma.  
12 We have to admit that we don't know much more than that at  
13 this point for certain. That would be my suggestion.

14 DR. HOLMBERG: That is exactly the question I  
15 would like to lead to. If you call it cryoprecipitate-  
16 depleted plasma, then you are implying that you have  
17 depleted the plasma of something. I have heard FDA use two  
18 different phrases here, cryopoor plasma or cryodepleted  
19 plasma. What is the term we are going to be using?

20 Also, as far as the variability in the amount of  
21 cryo that has been removed, you are exactly right, there is  
22 a lot of variability. When you do make cryoprecipitate  
23 there can be a variation in the technique and after you take  
24 the plasma out after you have refrigerated it, and where you

1 take it to a 4 degree water bath or at refrigeration. Also  
2 there is a variability based on AB/O blood group type, and  
3 the amount of Factor VIII that is present there. So, there  
4 is variability there and, first of all, I am confused on  
5 what terminology we are going with.

6 DR. HOLLINGER: Are there other questions from the  
7 committee? Yes, Bill?

8 DR. MARTONE: Am I correct in hearing that there  
9 is a randomized clinical trial ongoing now, looking at this  
10 product versus plasma?

11 DR. NELSON: Dr. Lee, could you explain the  
12 terminology?

13 DR. LEE: The terminology CDP in the agenda is  
14 somewhat by chance. It could have been just as easily CRP  
15 for cryoreduced or CS for cryosupernate. We just wanted to  
16 get the concept across, recognizing from a licensure  
17 standpoint the product that is remaining after the  
18 generation of a product that is recognized, the  
19 cryoprecipitate AHF. Whether that specific term should be  
20 decided here, at this sitting, is probably not as important.  
21 I guess the preferred term is cryoprecipitate-reduced. I  
22 understand that there are some labeling initiatives which  
23 attempt to standardize terminology and I think the favored  
24 term right now is cryoprecipitate-reduced in keeping with

1 the way we handled the leukoreduction issue.

2 DR. NELSON: Are there standards for production of  
3 cryoprecipitate? If there are, then couldn't there be  
4 standards for the cryoreduced plasma too?

5 DR. LEE: I guess if you simply use the standard  
6 for the generation of the removed product as the same  
7 standard in a complementary way for what is remaining, that  
8 is the simplest option of recognizing licensing criteria.

9 DR. MARTONE: Am I correct in my understanding  
10 that the proposed CDP is now called Plasma, with a capital  
11 "P"?

12 DR. LEE: No, in terms of the CFR definitions of  
13 plasma, plasma is recognized as a category that encompasses  
14 both fresh-frozen plasma and any other plasma which can be  
15 cryoprecipitate-depleted plasma, if we choose to also  
16 recognize that as a more specialized form of plasma. So,  
17 from a unit of whole blood you generate, the fluid portion  
18 is obviously the plasma, but then if you subject that to a  
19 cryoprecipitation procedure, are you left with a special  
20 product called cryodepleted plasma, or is what is left  
21 simply a unit of plasma that is not much different from the  
22 parent plasma unit?

23 DR. HOLMBERG: So, Dr. Lee, are you telling us  
24 that you would use the same standard that you use for the

1 preparation of cryoprecipitate, in other words, the 80 IU?  
2 That any plasma that came from that product could be labeled  
3 as cryoreduced or cryodepleted?

4 DR. LEE: I don't think I am proposing that. We  
5 were simply asking a question, whether or not the  
6 recognition of this special product should be done at this  
7 point. If the answer is clearly yes, then it is clear that  
8 we should begin work on what criteria should go into  
9 defining such a product. One alternative is that, but I  
10 think it deserves more consideration and discussion.

11 DR. MARTONE: I guess I am still confused. What  
12 do we have now? We have fresh-frozen plasma and then we  
13 have plasma. What is currently called plasma is what you  
14 are proposing to call CDP or something else, or it could be  
15 either.

16 (Slide)

17 DR. LEE: This slide might help. When I made this  
18 slide I didn't really think it would add a whole lot, but  
19 maybe it will. At the top you have the whole blood unit  
20 from which you pull off the cellular components, and what is  
21 left is the fluid component called plasma. That is  
22 recognized as a licensable product, with a capital "P". If  
23 you were to subject that unit of plasma to further  
24 processing and generate the cryoprecipitate fraction off of

1 it, then are you left with a distinct product called CDP,  
2 and I put CDP in with a question mark to emphasize the fact  
3 that this is not a licensable product now but the question  
4 is should it be?

5 Of course, if you proceed from the original unit  
6 of plasma directly to freezing within eight hours without  
7 further processing, then you have a special product called  
8 fresh-frozen plasma because it has the added limitation that  
9 the unit of plasma you collected has been frozen within a  
10 well-defined time limit.

11 DR. MARTONE: Then my question is if you don't  
12 freeze it and you don't cryoprecipitate what is it called?

13 DR. LEE: Plasma. If you don't freeze it and  
14 don't cryoprecipitate, it is called liquid plasma.

15 DR. MARTONE: So, in this case plasma could be two  
16 different things, an adulterated plasma and an unadulterated  
17 plasma.

18 (Laughter)

19 Processed plasma and unprocessed plasma.

20 DR. HOLLINGER: I think that is a good point; it  
21 is a very important point because if you do cryoprecipitate  
22 it, it is still called plasma that somebody gets but it is  
23 really not the same as the plasma above, in that it doesn't  
24 have several of the factors in it. Fibrinogen is depleted,

1 Factor VIII, Factor XIII and so on. So, it is different  
2 and, yet, it still could be called plasma to somebody. I  
3 don't know how that happens in the blood bank. Maybe  
4 somebody here could say. I mean, if that is sent out by  
5 order? If I am a physician and I order plasma, is it  
6 conceivable that somebody will send me a plasma that has  
7 been reduced or not? Tell me, Paul.

8 DR. NESS: We make plasma as FFP. Then we also  
9 have a lot of requests for cryosupernatant and cryodepleted  
10 plasma, cryopoor plasma, whatever you want to call it. But  
11 those are very different products and would not be used  
12 interchangeably.

13 MS. GUSTAFSON: Mary Gustafson. The issue is that  
14 from a regulatory standpoint, maybe not in common use but  
15 according to our regulations, plasma encompasses all  
16 different kinds of plasma. In terms of labeling, we only  
17 have a licensing distinction for fresh-frozen plasma or  
18 liquid plasma. Years, and years, and years ago the regs.  
19 required that the product be labeled if you had taken the  
20 platelets off or if you had taken the cryoprecipitate off.  
21 That was changed maybe fifteen, twenty years ago, saying  
22 that there was no difference, that plasma would encompass  
23 plasma that had been frozen sometime close to the dating  
24 period, or plasma that had had platelets removed, or plasma

1 that had had the cryoprecipitate removed.

2           So, what has happened in more recent years, blood  
3 banks have wanted to make a specific labeling claim for  
4 cryodepleted, cryopoor, cryoreduced. Until we license a  
5 product there is no proper name, sanctioned name. So, we  
6 are talking conceptually, not the actual name that would be  
7 given. But they want to make a specific labeling claim and  
8 ship the product in interstate commerce as a licensed  
9 product for use in treating TTP.

10           We are faced with the dilemma that we have not  
11 been able to get anyone to do carefully controlled clinical  
12 trials that would support licensing of this as a specific  
13 product. However, we know that it is being labeled that  
14 way. We also know that if it is being sold for that use the  
15 circular of information should address it whether it is yea  
16 or nay. We are bringing it to you as a dilemma before us at  
17 this point in time, trying to get as much information as  
18 there is, which is why we invited Dr. Moake to speak today.  
19 Is that any clearer, that it is kind of a regulatory dilemma  
20 right now?

21           DR. MARTONE: Yes.

22           DR. NELSON: One issue is that it is difficult to  
23 define the quality of this product as to what essential  
24 component is present or actually missing, or has been

1 removed. I wondered if it might not be possible to do that,  
2 if the von Willebrand complexes, or what-have-you, could be  
3 measured and quantitated. It could be that the von  
4 Willebrand is not the issue; that this is a surrogate marker  
5 but we have dealt with surrogate markers before, the ALT and  
6 the Hepatitis C. But I would think that even though we  
7 don't know completely the pathophysiology it would be  
8 possible to set some sort of standard, that it is below a  
9 certain amount of some kind of complement. That would make  
10 it easier to monitor as to whether or not one unit of this  
11 cryodepleted plasma has the same clotting factors absent, or  
12 absent to the same level as another unit. Therefore, it  
13 might be possible to assign a quality score even though we  
14 don't, for sure, know whether that is the critical quality  
15 issue or not.

16 DR. EPSTEIN: I understand that comment, but I see  
17 it taking us down a very difficult path and really asking a  
18 different question than the one we are asking the committee.  
19 Certainly, we would rather have better scientific data on  
20 the mode of action for the specific indication, TTP, and,  
21 certainly, we would prefer to have product controls that  
22 directly measure whatever aspect of the product it was that  
23 caused its potency. That, of course, is the normal paradigm  
24 for drug approval.

1           The problem that we have at this point in time is  
2 that there is clinician acceptance, which evolved largely  
3 because of unregulated intrastate use; that there is in the  
4 literature and anecdotal evidence that this may, in fact, be  
5 a benefit to patients, in the absence of prospective,  
6 randomized, controlled trials and in the absence of clear  
7 underlying scientific knowledge that tells what the active  
8 principle is and how to measure it, whether that is presence  
9 or absence of some factor.

10           What we are asking the committee is can we take  
11 the operational approach? Can we say that cryoprecipitate-  
12 reduced plasma, whatever product name we give it, made in  
13 the "conventional way," that is to say as it has been done  
14 in the past, has efficacy. If the answer is yes, then we  
15 have reason to recognize it. The product standards would be  
16 purely operational and they would reflect the kinds of  
17 conventional procedures for making cryoprecipitate that are  
18 already acknowledged under regulation, and that are typical  
19 of the institutes that have made products where they have  
20 generated use that is efficacious.

21           So, this is not an uncommon situation in  
22 biologics, where we may not know how something works and we  
23 have to come to a decision whether it can be made  
24 consistently in such a manner that we believe that we can

1 make it work even though we don't know why. Of course, we  
2 are happier when we know why and, of course, we would not  
3 discourage future study that might make the product better  
4 or more consistent on the basis of measurements related to  
5 its underlying mode of action.

6           But that would be a different question. See, if  
7 the way you direct us is don't license it now because you  
8 don't know how it works and can't measure the right  
9 variable, that would be a vote against the scheme that we  
10 are asking, and that is okay if that is your considered  
11 opinion. But we are asking you to weigh the current  
12 evidence and advise us whether we could, at this point in  
13 time, define and label a product. As Mary suggested, and  
14 some of you probably caught it and some of you didn't, how  
15 it changes the landscape it then becomes legal to label and  
16 ship in interstate commerce.

17           DR. NELSON: I am not suggesting that the very  
18 important clinical observations be ignored. I think they  
19 are very important, and often clinicians have the answer  
20 long before there is a clinical trial. And clinical trials  
21 give examples of where a clinical trial saw something that,  
22 in fact, the clinical impression was wrong but I would guess  
23 that 90 percent of the time the clinical impression was  
24 correct. Therefore, given the difficulty of doing this

1 clinical trial perfectly, I would think that we should  
2 consider licensure or making this available to the patients  
3 and clinicians that need it. I think that is very  
4 important.

5 But I would think, at the same time, that it might  
6 be possible to study what is the variability in the product,  
7 just by looking at some cryodepleted plasma, what is the  
8 variation in what is there. I don't think it would be  
9 impossible to take both steps at the same time, license it  
10 or make it available to the patients, the rare patients that  
11 need it but, at the same time, study the product a bit more.

12 DR. MARTONE: I will take the opposite tack. I  
13 think it probably already is available, and if it weren't we  
14 wouldn't be seeing these uncontrolled clinical trials. I  
15 don't think it would be difficult to do a study.

16 DR. HOLLINGER: I think one of the issues that he  
17 mentioned though, from the blood banking situation, has to  
18 do with being able --

19 DR. MARTONE: Right, it is made within the state  
20 and distributed within the state.

21 DR. HOLLINGER: Yes, interstate distribution.

22 DR. MARTONE: Right.

23 DR. HOLLINGER: Paul, did you have your hand up?

24 DR. MCCURDY: Yes. If we were to recommend that

1 this be licensed, would that necessarily change the label of  
2 fresh-frozen plasma? I think I can see that this could be  
3 an acceptable alternative to fresh-frozen plasma but I don't  
4 see any data at all, and my own experience would suggest  
5 some difficulties in obtaining that data unless you do a  
6 well-designed trial that it has an advantage over fresh-  
7 frozen plasma other than that it doesn't deplete your fresh-  
8 frozen plasma supply. You can use that for people with  
9 clotting deficiencies.

10 DR. NESS: I have a couple of questions. One is,  
11 if the committee recommends against licensure would such a  
12 vote inhibit the availability of this product? Because it  
13 currently is available by blood centers and is used for  
14 those patients in whom clinicians seem to need it. I would  
15 hope a negative vote would not make it less available. That  
16 would be one concern.

17 The other concern is, feeding on Dr. McCurdy's  
18 question, if, in fact, it is going to be licensed I guess I  
19 would urge the FDA to allow us to call it what it is because  
20 I think the current restrictive labeling on plasma that we  
21 now have available to us doesn't really tell the blood bank  
22 nor the clinician what is really there. So, I would urge,  
23 as part of a labeling licensing process, if that happens,  
24 that somehow the various products be clarified such that

1 transfusion services and physicians and, therefore, their  
2 patients would really know what is in this bag of what we  
3 are now calling Plasma, with a capital "P".

4 DR. HOLMBERG: That is exactly what is happening  
5 with the interstate. People don't know what to call it and  
6 they don't know how to label it. The dilemma is that it  
7 will still be prepared but we will still have the problem of  
8 how to label it.

9 Dr. Moake, I heard several people comment about  
10 why we don't have randomized studies. Would you care to  
11 discuss that?

12 DR. MOAKE: Well, the Canadians took a decade to  
13 get the number of patients that I showed you, and they have  
14 a very tightly-knit, or at least some of the centers are  
15 tightly grouped together under the Canadian clinical  
16 research system. There has been an effort to conduct a  
17 clinical trial in the United States since the early '80s.  
18 In that trial there has always been a suggestion that the  
19 products be assayed for a variety of different components.  
20 The funding for that trial has never been achieved, and I  
21 don't see that it will be in the current climate.

22 So, I am very pessimistic. I think all the  
23 comments here are right on the mark but I would be very  
24 distressed if it were to become illegal to use

1 cryoprecipitate-depleted plasma, as little as we know of it,  
2 in people who have not responded to FFP exchanges because  
3 they will die. I don't mean to be too maudlin about this  
4 but that is the truth.

5 I think that in the next several years, maybe  
6 before the millennium, it may be possible to know what is  
7 present and what should be absent and then the product can  
8 be assayed. That is not true presently. So, I think the  
9 issue can be revisited but the conduct and completion of a  
10 large-scale prospective clinical trial that meets the  
11 criteria ordinarily considered at these sessions I think is  
12 unlikely.

13 DR. VERTER: If someone could enlighten me a  
14 little bit, I keep hearing that this stuff is out there  
15 being used, and all I have heard I guess is the results of  
16 two basically anecdotal type studies. Are we seeing some  
17 literature bias? Are we only getting the reports of those  
18 cases where it appears to be beneficial? By the way, I can  
19 concede that all products, all therapies, all interventions  
20 can't necessarily be done by a clinical trial -- orphan  
21 drugs and things like that, they just can't. So, you just  
22 do the best you can. But what I am concerned about is the  
23 potential that there is some literature bias here and we are  
24 not seeing everything.

1 DR. HOLLINGER: Joel, do you have a comment?  
2 Because I think it is an important issue, if somebody uses  
3 it on two patients or three patients and they don't get a  
4 response --

5 DR. MOAKE: I think absolutely. I would be  
6 stunned if that were not the case. I don't intend to leave  
7 the impression that I would consider that 7/7 patients in  
8 the next trial are going to respond to cryoprecipitate-  
9 depleted plasma. I just don't believe that. I do believe  
10 that it is useful in certain patients. I do believe that  
11 there is a profound bias, and I think that probably the  
12 data, the very limited data that I reviewed here probably is  
13 an overestimate of the usefulness of the product. I believe  
14 it is useful but I think this was an overestimate. I think  
15 you are exactly correct.

16 DR. MARTONE: Currently you do have a name for the  
17 product. It is called plasma. I think my suggestion is  
18 that that is not a very descriptive term for what it is.  
19 Why don't we change the name of it to CDP?

20 DR. HOLLINGER: I think that is the issue.

21 DR. MARTONE: But without all this other stuff.

22 DR. HOLLINGER: Well, the only other stuff, as I  
23 understand it --

24 DR. MARTONE: Is the labeling.

1 DR. HOLLINGER: -- the labeling, but also  
2 standardization.

3 DR. MARTONE: What I am proposing is that you  
4 change the name of it, without the claim of efficacy.

5 DR. KHABBAZ: I have a question for Dr. Moake.  
6 The table that you showed from a textbook about the use of  
7 cryoprecipitate-depleted plasma, as I saw it, was only for  
8 refractory TTP, or is it recommended for use as first-line?

9 DR. MOAKE: In my opinion, which is just that, it  
10 is indicated for refractory TTP. That is when our team uses  
11 it. I think there are some data to support that use,  
12 however limited and however biased they are. However, it  
13 has gotten rather away from that and many centers have gone  
14 the next step and presumed that if CDP is better for  
15 refractory TTP, why not just use it up front. The data to  
16 support that are entirely the data from this limited  
17 Canadian trial conducted over five or six years. But the  
18 indication, in my opinion, is for TTP refractory to FFP  
19 exchange. However, it has gotten away from that and I don't  
20 think the data really support general use for CDP.

21 DR. KHABBAZ: Yes, I would support Dr. Martone's  
22 suggestion. I think I would feel very comfortable saying,  
23 yes, let's label it as what it is, but in terms of the  
24 indication for treating TTP I am concerned that that may be

1 taken as endorsing it as first-line treatment with absence  
2 of the data. That leaves me more uncomfortable.

3 DR. EPSTEIN: I guess I would like to comment from  
4 a regulatory point of view what it means if we license a  
5 product. We license products under the Public Health  
6 Service Act, Part 351. Biologics are regulated under that  
7 section as drugs subject to the FD&C Act. The bottom line  
8 is that we do it when they are found safe and effective for  
9 indicated use.

10 Now, it is certainly true, indeed, it is almost a  
11 tautology that we could just name it for what is  
12 operationally. I have no quarrel with that logic. There is  
13 nothing illogical about calling it, you know, cryoreduced  
14 plasma. That is not where the issue lies. The issue is  
15 whether a product given that name has been found safe and  
16 effective under the Public Health Service Act, Part 351.  
17 That is the question, and that is what it takes for us to  
18 license it for interstate commerce. So, I don't think that  
19 the FDA has the luxury of ignoring the question of whether  
20 there is a clinical indication. If there is no clinical  
21 indication it is not possible for us to license it. Okay?

22 So, it is not a semantic issue. I think that  
23 there is a mistake being made around the table that the  
24 issue is semantic. It is not a semantic issue. The

1 question is whether we have adequate data on safety and  
2 effectiveness, and no one has actually doubted safety here,  
3 and the whole focus has been on whether there is efficacy.  
4 I think that what we have heard is that the best available  
5 clinical trial data were from the Canadian study and that  
6 was a study that took a decade. We know that the patients  
7 occur infrequently. We know that the trials would be  
8 difficult. That is not to say that they are impossible.  
9 But the issue is whether we can make a decision today or  
10 whether we are going to hold out for further trial data.

11           On the question of availability though, we are  
12 aware that the product is being made available. However, it  
13 is being made available intrastate, which does not have  
14 license requirements under the Act. That creates an  
15 inconsistency which we would like to address.

16           DR. NESS: We may be confusing the efficacy issue  
17 by trying to compare this to FFP because the data where you  
18 compare CDP to FFP, obviously, are scant and anecdotal. To  
19 the extent that FFP is now considered efficacious in TTP, I  
20 would not be uncomfortable and certainly would advocate  
21 calling CDP efficacious also in TTP, but not getting into a  
22 discussion, which we can't answer, as to which is better and  
23 for what indication specifically within the subset of TTP.

24           DR. HOLLINGER: Paul, on that issue though, I mean

1 as I look at some of the data here, even from the Canadian  
2 study they reported 11/18 patients, 61 percent, who were  
3 refractory to FFP exchange responding within 7 days. To me,  
4 that sounds like it was effective, at least in those  
5 patients. That is quite a few. I mean, it is not a huge  
6 number but it sounds efficacious.

7 DR. NESS: Yes. We have used a lot of it at  
8 Hopkins and we have published previously, about the time of  
9 the first Canadian study, a series of about 100 patients who  
10 had been treated with FFP exchange and with a pretty good  
11 survival rate. We have used some of it. I don't know  
12 anecdotally at this point, because I haven't analyzed the  
13 more recent data, as to whether it is any better than FFP  
14 but certainly I don't think we have any evidence that it is  
15 any worse. So, if that gets us off that dime, I would be  
16 very comfortable saying both work.

17 DR. EPSTEIN: I agree, Paul, and that is why you  
18 have two different questions in front of you. One says is  
19 it approvable as a stand-alone product? The other says do  
20 we know if it is any better than FFP? They are two separate  
21 questions.

22 DR. FINLAYSON: I do this with fear and trembling  
23 as a decided non-blood banker, but I would sort of like to  
24 come to, I would say, the rescue of Dr. Martone --

1 DR. MARTONE: I need rescue.

2 (Laughter)

3 DR. FINLAYSON: The product made in this way is  
4 licensed right now and it is called plasma. Presumably,  
5 there are some indications for plasma. I am certainly not  
6 going to enter into that one. But whatever they are, they  
7 are. So, it seems to me that one could change the name of  
8 it, if the committee so recommended, and leave the  
9 indications exactly as the indications for plasma as they  
10 are currently, if that were an option that the committee  
11 wished to recommend.

12 DR. DUBIN: Coming at it from the way I look at  
13 it, I think you, Blaine, said some things that are important  
14 for people confronted with what is in many instances fatal,  
15 who are obviously reacting negatively, some of them, and now  
16 you have some evidence, not a large study, not a lot, but  
17 you have some pretty tangible evidence that this makes a  
18 difference. It seems to me, at least from my perspective,  
19 that is a pretty good step and we ought to really look at  
20 taking care of these people, and there doesn't seem to be  
21 any downside to it at this point, so there doesn't seem to  
22 be any big risk in taking that step.

23 I almost think the debate is getting lost. I  
24 would like to refocus it and find out how we do that. I

1 mean, maybe in the big picture there is not "enough" data  
2 but there is enough, it seems to me, to do something to make  
3 this available in an interstate way; to rectify what Jay is  
4 talking about that FDA has to deal with. So, I want to come  
5 down on that side.

6 DR. NESS: Just in response to the suggestion that  
7 this be labeled plasma and be indicated for all uses of  
8 plasma. That would be absolutely incorrect. We can't do  
9 that because this product would not be useful for somebody  
10 with DIC or an acquired coagulopathy or congenital  
11 coagulopathy. It would be wrong to do that.

12 DR. LINDEN: I think this is clearly a different  
13 product, and it is one that appears to have some utility and  
14 I think it is to the benefit of the patients who have a  
15 very, very serious disease to try and make it available if  
16 there is even a chance that it might help them.

17 There may be a misperception that this is readily  
18 available intrastate even if it is not licensed. Some of  
19 the blood center systems that operate over multiple sites  
20 don't make this product at every site. So, really it is not  
21 available everywhere unless it can be licensed, and I think  
22 it should be licensed and labeled as such.

23 My one question really relates to the indications  
24 and the issue of simply administering the product versus

1 plasma exchanging. I wonder if Dr. Moake could elaborate.  
2 I know this issue about the multimers may just be sort of a  
3 hypothesis at this point. If you are removing them and  
4 replacing with deficient plasma, that makes sense to me.  
5 But why would infusing be helpful, and is infusion of this  
6 product really an appropriate indication or is it just for  
7 plasma exchange?

8 DR. MOAKE: For the children plasma infusion alone  
9 works. The reason for that is that children lack protease  
10 for unusually large von Willebrand factor multimers. There  
11 is only one publication for children, all Swiss, but the  
12 other children who have been examined also lack this  
13 protease. So, they are not getting something that is  
14 probably not good for them, and they are getting something  
15 that apparently is.

16 DR. LINDEN: So, in your opinion the indication  
17 then in adults would be for plasma exchange and for children  
18 for infusion?

19 DR. MOAKE: Yes. The protease is present both in  
20 plasma in cryoprecipitate-depleted plasma. The group that  
21 benefits from having this, as you have just discussed again,  
22 are the people who don't respond to fresh-frozen plasma  
23 exchange. That is a small group, maybe 1200 or 1500  
24 patients a year in North America, maybe 300 or 400 of those

1 don't respond to fresh-frozen plasma exchange. They will  
2 all die. A few of those will be saved by cryoprecipitate-  
3 depleted plasma exchange. I don't know how many. I am sure  
4 it is not the number that we have talked about, but it is  
5 some. My guess is that 50 percent of those that don't  
6 respond to FFP exchange will respond to cryoprecipitate-  
7 depleted plasma exchange.

8           Ultimately, I think there will probably have to be  
9 some sort of assay of maybe more than one thing in  
10 cryoprecipitate-depleted plasma, but right now if we require  
11 assays the first thing that will happen is that my  
12 laboratory will benefit hugely because we can do these  
13 multimers and we can do this protease activity. But those  
14 might not be the right things, and we might run people off  
15 from making this stuff if we make them assay things that we  
16 don't know, for sure, are related to effectiveness.

17           I would make a plea for simplicity at this point  
18 and common sense, and subsequently this can be revisited if  
19 there is really evidence that this is a protease that has to  
20 be there and we can assay it, and come back.

21           DR. MARTONE: Can I ask the FDA if the product  
22 termed plasma is available for interstate commerce?

23           MS. GUSTAFSON: Yes, plasma is available for  
24 interstate commerce. It was licensed years and years ago.

1 DR. MARTONE: Am I also correct that if you  
2 changed the name of it to CDP it would be available for  
3 interstate commerce?

4 DR. MCCURDY: It is not necessarily the same  
5 product.

6 DR. MARTONE: This product, right down here, to  
7 the bottom right, is that available for interstate commerce?

8 MS. GUSTAFSON: No, only under the name of plasma  
9 without any additional claim.

10 DR. MARTONE: Under the name of plasma it is  
11 available for interstate commerce. Is that correct?

12 MS. GUSTAFSON: That is right.

13 DR. MARTONE: So, if the name of that were changed  
14 to CDP would it be available for interstate commerce?

15 MS. GUSTAFSON: CDP is a subset of plasma. The  
16 reason why people are making CDP and wanting to label it as  
17 CDP is the additional claim for treatment of TTP.

18 DR. MARTONE: No, I think they are making CDP  
19 because they want some cryoprecipitate, and what they are  
20 left with is plasma.

21 MS. GUSTAFSON: And they can label it as plasma.  
22 The issue is that they specifically want to ship a product  
23 that is labeled --

24 DR. MARTONE: Okay, but that is a different issue,

1 what they want. I am trying to determine what exists now.  
2 What exists now is a situation where you get cryoprecipitate  
3 and then you are left with a product which you label plasma,  
4 which is available for interstate commerce.

5 MS. GUSTAFSON: But also there is plasma that has  
6 simply not had anything happen to it --

7 DR. MARTONE: I understand that.

8 MS. GUSTAFSON: -- and it is still labeled the  
9 same way.

10 DR. MARTONE: What I am saying is that the term  
11 plasma, in that box in the lower right-hand corner, is not a  
12 descriptive term because you have changed it; you have taken  
13 something out of it. I guess now you want to know what my  
14 ulterior motive is.

15 (Laughter)

16 It is just that I feel very uncomfortable using  
17 medieval standards to license a product.

18 DR. NELSON: But if there is a patient who is  
19 dying in Rhode Island and across the border in Massachusetts  
20 there is this lab that has made this -- whatever you want to  
21 call it, cryodepleted plasma -- and the numbers of units  
22 that were given in these seven patients that recovered were  
23 substantial. It wasn't just one unit; it was quite a few.  
24 I can see where you could run out of this stuff, and right

1 now that isn't kosher; it isn't legal, and what the FDA is  
2 asking is for the ability to do this, to ship cryodepleted  
3 plasma interstate for whatever indication.

4           It seems to me that, given the outcome -- we are  
5 not talking about rhinovirus and colds here, we are talking  
6 about kids dying.

7           DR. MARTONE: How many kids are dying because they  
8 can't get this stuff? Do you have the answer to that?

9           DR. NELSON: No, I don't.

10          DR. MARTONE: If they are asking us to vote on  
11 this question there must be a problem.

12          DR. NESS: If the FDA determines that I can't send  
13 cryodepleted plasma across state lines, then there is a  
14 problem.

15          DR. MARTONE: Can you do it now?

16          DR. NESS: Not officially. I have to call it  
17 plasma, which is not helpful because it then comes in a box  
18 to a transfusion service across the state line, and maybe I  
19 stick a yellow sticky on it saying this is really  
20 cryodepleted, but I don't think anybody thinks that is a  
21 good idea.

22          DR. MARTONE: So, if the name were changed would  
23 that help you?

24          DR. NESS: Yes, but I think we have heard many

1 discussions that they can't just change the name.

2 DR. MARTONE: No, I haven't heard that, that they  
3 can't just change the name.

4 DR. NESS: I think that is what Jay said.

5 DR. EPSTEIN: We can't just change the name!

6 (Laughter)

7 Again, I am repeating what I said before but if we  
8 recognize a product, a new product name under license we are  
9 asserting that it has met the standard of the PHS Act, which  
10 is that it has been found safe and effective in clinical  
11 studies. That is the standard. So, that is what it means  
12 to change the name. We don't merely change the name.  
13 Nobody is quarreling that we can give it any name we want.  
14 That is not the point.

15 The point is that to change the name and recognize  
16 it as a licensed product, legal in interstate commerce, is  
17 to make a finding that it is safe and effective based on  
18 clinical studies.

19 DR. MARTONE: And the only thing I was saying is  
20 that the term that you are using for it now is not  
21 descriptive for that particular product. It is not  
22 descriptive and it may not be what people think they are  
23 getting.

24 DR. HOLLINGER: Exactly.

1 DR. DUBIN: So, we would change the name and it  
2 would be labeled for the treatment of TTP.

3 DR. HOLLINGER: Well, that is another issue right  
4 now.

5 DR. DUBIN: But it needs to be labeled for  
6 something to go into interstate commerce. Correct? You  
7 can't just put a new label on it. Am I right about that?

8 DR. NESS: Yes.

9 MS. PIERCE: Let me just clarify with Jay, so, if  
10 we do this we say that it is a new plasma component; it is  
11 subject to licensure; the indication is for TTP. What  
12 additional things have to be done to actually have that  
13 happen, to actually be granted licensure? Because there are  
14 not clinical studies here, besides the Canadian one. These  
15 are mainly anecdotal. So, does that mean that based on what  
16 we have heard today those will be considered the studies and  
17 it will be approved?

18 DR. EPSTEIN: Yes. An affirmative vote to  
19 question two means that if an establishment requests a  
20 license to ship plasma, cryoprecipitate-reduced in  
21 interstate commerce we will not ask them for a de novo  
22 clinical trial. We will accept by reference to the existing  
23 literature that safety and effectiveness have been  
24 established. The answer is yes. Yes, we would license it

1 on the basis of the data you are reviewing today. That is  
2 the point. That doesn't in any way mean that we could not  
3 encourage further studies. I mean, I think we have all  
4 heard that that is desirable.

5 MS. PIERCE: And you don't have the missing piece  
6 of those cases where it has been used and not been  
7 effective. We don't have that, that may be missing from the  
8 literature. That is the unknown.

9 DR. HOLLINGER: I am going to call the question.  
10 Let's have the second question up, if we can have that one  
11 first, please?

12 (Slide)

13 Based on current knowledge and experience, should  
14 the FDA recognize CDP as a new plasma component, subject to  
15 licensure for interstate distribution, with the indication  
16 for treating TTP?

17 All those that are in favor of this, so signify by  
18 raising your hand.

19 (Show of hands)

20 All those opposed?

21 (One response)

22 Abstaining?

23 (No response)

24 Paul?

1 DR. NESS: Yes.

2 REV. LITTLE: Yes.

3 DR. SMALLWOOD: The results of question one,  
4 formerly question two, there are 9 yes votes, 2 no votes, no  
5 abstentions. The industry representative and the consumer  
6 representative both agree with the yes votes.

7 DR. HOLLINGER: The first question which is up  
8 there is, is there sufficient evidence to conclude that the  
9 use of CDP offers a clinical advantage over the use of FFP  
10 in treating thrombotic thrombocytopenic purpura?

11 We can open this up for a little bit of question.  
12 I will make a statement of my own, I would much prefer if  
13 that went on and said over the use of FFP in treating  
14 thrombotic thrombocytopenic purpura not responsive to FFP."  
15 I would add that at the end because that is where the data  
16 really is, and I would like to at least have a vote on that.

17 Those in favor of adding that as a part of that,  
18 raise your hand.

19 (Show of hands)

20 Opposed?

21 (One response)

22 Abstaining?

23 (Show of hands)

24 Paul?

1 DR. NESS: I would have left the question the way  
2 it is.

3 DR. HOLLINGER: And Rev. Little?

4 REV. LITTLE: I would have changed. Can I hear  
5 why Paul --

6 DR. HOLLINGER: Yes, I was going to ask him.

7 DR. NESS: The data we have seen, and I think it  
8 is important to recognize that the plural of anecdote really  
9 isn't data --

10 (Laughter)

11 -- the data that we have seen is post hoc or  
12 proctor hoc reasoning. Whereas, it may very well be true  
13 that the patients who received X numbers of exchanges with  
14 fresh-frozen plasma and then were shifted to cryopoor plasma  
15 and got better, it may have been because of, but it may have  
16 been in spite of also. I just don't think we have the data  
17 to tell us that. I think it is an acceptable alternative.  
18 I do not accept that it is impossible to do a controlled  
19 trial. I think it would be possible if people didn't  
20 believe in one thing or another making it undesirable for  
21 them to randomize.

22 DR. HOLLINGER: In my response to that, I guess as  
23 I read this it says it offers a clinical advantage over  
24 fresh-frozen plasma in treating TTP and I have not see that

1 in any of these studies here. What I have seen from the  
2 Canadian study is that it appears to have an advantage in  
3 people who are not responsive to FFP. They seem to respond.  
4 I would assume it may be equally as well, but a clinical  
5 advantage, I haven't seen that.

6 DR. VERTER: Actually, thinking about it, the  
7 truth is -- I don't know about truth but the fact is that  
8 there were only 18 patients that we were presented with,  
9 with any relevancy to anything here. I am concerned that  
10 there are 150 patients out there that we didn't have any  
11 data for. If the truth is really that in patients who are  
12 not responsive to FFP, who are almost certainly going to  
13 die, using CDP will reduce that risk, even if it only a 20  
14 percent reduction, I would argue, yes, that is great. I  
15 mean, how many 20 percent reductions do we see in many  
16 things we do? The point is we don't have the data today.

17 So, whatever the vote is here, I would strongly  
18 urge the FDA, industry, whoever can get together to get some  
19 registry together to get the data that is out there. It is  
20 being used. Let's get some data.

21 DR. HOLLINGER: We have had a vote on the change.  
22 So, I take it there was a vote to make the change. Is that  
23 correct?

24 DR. SMALLWOOD: Yes, the vote to make the change,

1 there were 8 yes votes, 1 no vote, 2 abstentions, and both  
2 the industry and consumer rep agreed.

3 DR. HOLLINGER: No, no, Paul disagreed.

4 DR. SMALLWOOD: I am sorry. Correction, the  
5 consumer representative agreed with the yes votes; the  
6 industry representative agree with the no vote.

7 DR. HOLLINGER: So, the question then would say is  
8 there sufficient evidence to conclude that the use of  
9 cryoprecipitate-depleted plasma offers a clinical advantage  
10 over fresh-frozen plasma in treating thrombotic  
11 thrombocytopenic purpura not responsive to FFP.

12 REV. LITTLE: I am getting a little confused. If  
13 we were saying no to this question, how does that relate  
14 then to having said yes to the licensing? There is no  
15 relationship?

16 DR. HOLLINGER: No.

17 DR. NELSON: I voted for this change because I  
18 felt that I didn't think there was sufficient data to know  
19 whether cryoprecipitate-depleted plasma or FFP would be  
20 efficacious in a randomized trial. On the other hand,  
21 stated this way, we have already defined that FFP fails.  
22 So, therefore, unless we vote yes for this there is really  
23 no indication for cryoprecipitate-depleted plasma, which is  
24 not the impression that I had. So, this is kind of a tricky

1 question.

2 DR. VERTER: It is actually a simple question.

3 DR. EPSTEIN: I think we have to fix a logical

4 inconsistency in the question if it is to be revised.

5 Blaine, I think what you would prefer to ask is whether

6 there is sufficient evidence to conclude that use of

7 cryodepleted plasma is indicated in treating TTP not

8 responsive to FFP. You cannot logically ask whether it has

9 an advantage.

10 DR. HOLLINGER: Right, I agree.

11 DR. EPSTEIN: The suggested modification makes the

12 question internally inconsistent.

13 DR. HOLLINGER: Okay. Tell me what you have

14 written.

15 DR. EPSTEIN: Is there sufficient evidence to

16 conclude that the use of cryoprecipitate-depleted plasma is

17 indicated, or may be indicated, in treating thrombotic

18 thrombocytopenic purpura, and then add the words, not

19 responsive to FFP.

20 But I am confused on what the previous vote was.

21 Was that a vote on the revised question or was that a vote

22 whether to revise it?

23 DR. HOLLINGER: No, no, a vote on the revised

24 question.

1 DR. EPSTEIN: But the revised question isn't  
2 meaningful.

3 DR. HOLLINGER: Well, we will take another vote.

4 MS. PIERCE: I have a question in terms of that.  
5 If we change this the way we are proposing to, what does  
6 that do to the first question we voted on when we said the  
7 indication for treating TTP? We didn't qualify --

8 DR. HOLLINGER: No, we are just defining it a  
9 little further.

10 DR. NELSON: It is a separate question.

11 MS. PIERCE: It is a separate question but in the  
12 first one it is licensed for TTP, and then where does it  
13 come that the indication is going to be for those non-  
14 responsive? See, I am seeing two different indications.

15 DR. HOLLINGER: The revision that Jay put up  
16 there, I will throw it open for another vote as it was  
17 revised by Dr. Epstein. I will read it again. It says, is  
18 there sufficient evidence to conclude that the use of  
19 cryoprecipitate-depleted plasma may be indicated in treating  
20 thrombotic thrombocytopenic purpura not responsive to FFP?

21 Those in favor of the revision --

22 DR. MARTONE: Could you read it once more?

23 DR. HOLLINGER: Yes, I will. Is there sufficient  
24 evidence to conclude that the use of cryoprecipitate-

1 depleted plasma may be indicated in treating thrombotic  
2 thrombocytopenic purpura not responsive to FFP?

3 DR. MARTONE: Maybe.

4 DR. HOLLINGER: All those in favor of the  
5 revision?

6 (Show of hands)

7 Those opposed?

8 (No response)

9 Those abstaining?

10 (No response)

11 Dr. Ness?

12 DR. NESS: The revision is okay.

13 DR. HOLLINGER: Rev. Little?

14 REV. LITTLE: Yes.

15 DR. HOLLINGER: Now we will vote on the question.

16 All those in favor of the revised question, raise your hand.

17 (Show of hands)

18 Those opposed?

19 (Show of hands)

20 Dr. Ness?

21 DR. NESS: Yes.

22 DR. HOLLINGER: And Rev. Little?

23 REV. LITTLE: Yes.

24 DR. HOLLINGER: Would you please read the results?

1 DR. SMALLWOOD: The vote on the revised question  
2 reads 9 yes votes, 2 no votes, no abstentions. Both the  
3 industry and consumer representatives agree with the yes  
4 vote.

5 I would also like to make a correction for the  
6 record. The results of voting on the first question were  
7 read incorrectly. There were 9 yes votes, 2 no votes and no  
8 abstentions.

9 DR. HOLLINGER: Thank you for that correction. I  
10 believe this concludes our meeting for today. We are out  
11 early. The next meeting is December 11-12. The site has  
12 not yet been selected but it will probably be in Washington.

13 [Whereupon, at 3:05 p.m., the proceedings were  
14 concluded.]

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