DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE

70th MEETING

December 13-14, 2001

8:10 a.m.

Thursday, December 13, 2001

Hilton Silver Spring
Maryland Room
8727 Colesville Road
Silver Spring, Maryland

MEMBERS OF THE COMMITTEE

Kenrad E. Nelson, M.D.
Chairman

G. Michael Fitzpatrick, Ph.D.

Raymond S. Koff, M.D.

Jeanne V. Linden, M.D.

B. Gail Macik, M.D.

Daniel McGee, Ph.D.

Mark A. Mitchell, M.D.

Terry V. Rice

Paul J. Schmidt, Jr., M.D.

David F. Stroncek, M.D.

Sherri O. Stuver, Sc.D.

TEMPORARY VOTING MEMBERS

Jonathan S. Allan, D.V.M.
(by telephone)

Lianna Harvath

F. Blaine Hollinger, M.D.

NON-VOTING CONSUMER REPRESENTATIVE

Katherine E. Knowles

NON-VOTING INDUSTRY REPRESENTATIVE

Toby L. Simon, M.D.

Executive Secretary

Linda A. Smallwood, Ph.D.

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1 P R O C E E D I N G S

2 DR. SMALLWOOD: Good morning. Welcome to
3 the 70th meeting of the Blood Products Advisory
4 Committee. I am Linda Smallwood, the Executive
5 Secretary. We're going to start the meeting as
6 close as possible to on time, although we don't
7 have all of the committee members here, but we do
8 have enough to constitute a quorum.

9 At this time I will read the conflict of
10 interest statement that will apply to both days'
11 session of this meeting. The following
12 announcement is made part of the public record to
13 preclude the appearance of conflict of interest at
14 this meeting.

15 Pursuant to the authority granted under
16 the committee charter, the Director of FDA's Center
17 for Biologics Evaluation and Research has appointed
18 Drs. Jonathan Allan, Lianna Harvath, and Blaine
19 Hollinger as temporary voting members. In
20 addition, the Senior Associate Commissioner of FDA
21 has appointed Dr. Michael Diamond as a temporary
22 voting member.

23 To determine if any conflicts of interest
24 existed, the agency reviewed the submitted agenda
25 and all relevant financial interests reported by

1 the meeting participants. As a result of this
2 review, the following disclosures are being made.
3 Drs. Kenrad Nelson and Paul Schmidt had
4 waivers previously approved by the agency that are
5 applicable for this meeting. The following
6 participants have associations with firms that can
7 be affected by the committee discussions: Dr.
8 Boyle, Diamond, Fitzpatrick, Harvath, Hollinger,
9 Koff, Knowles, Linden, Macik, Nelson, Schmidt, and
10 Simon. However, in accordance with our statutes,
11 it has been determined that a waiver or an
12 exclusion is not warranted for these deliberations.
13 With regards to FDA's invited guests, the
14 agency has determined that the services of these
15 guests are essential. There are reported interests
16 which are being made public to allow meeting
17 participants to objectively evaluate any
18 presentations and/or comments made by the
19 participants.
20 Related to the discussions on potential
21 concerns for Simian Foamy Virus transmission by
22 blood and blood products, Dr. Louisa Chapman is
23 employed by the Centers for Disease Control and
24 Prevention. Dr. Paul Sandstrom is employed by the
25 National HIV lab in Canada.

1 For discussions on the current leukocyte
2 reduction guidance, Dr. Linda Kline is employed by
3 the American Red Cross, Holland Labs. Her lab has
4 performed leukoreduction evaluations for and has
5 collaborated with Baxter, Hemasure, Pall, and
6 Terumo. Dr. Edward Snyder is the principal
7 investigator on research projects supported by
8 Baxter, Pall, and Terumo. He also consults with
9 Baxter. He is an ad hoc advisor for Terumo, and is
10 a member of Pall's board of directors.
11 For the discussions on human cells,
12 tissues, and cellular and tissue-based products,
13 risk factors for semen donation, Dr. Charles Sims
14 is employed as the Director of California Cryobank,
15 Inc., a sperm bank. He has financial interests in
16 Cryobank. He is a founder and a member of its
17 board of directors. He is also a member of the
18 board of governors, American Association of Tissue
19 Banks, and a member of its accreditation committee.
20 Dr. Linda Valleroy is employed at the National
21 Center for HIV, STD, and TB Prevention at the
22 Centers for Disease Control and Prevention.
23 In the event that the discussions involve
24 other products or firms that are already on the
25 agenda, for which FDA's participants have a

1 financial interest, the participants are aware of
2 the need to exclude themselves from such
3 involvement, and their exclusion will be noted for
4 the public record. With respect to all other
5 meeting participants, we ask in the interest of
6 fairness that you state your name, affiliation, and
7 address any current or previous financial
8 involvement with any firm whose products you wish
9 to comment upon.
10 Copies of waivers addressed in this
11 announcement are available by written request under
12 the Freedom of Information Act. At this time I
13 will ask if there are any additional declarations
14 by any committee members or anyone involved in this
15 meeting.
16 [No response.]
17 DR. SMALLWOOD: At this time I would like
18 to call upon Dr. Jay Epstein, the Director of the
19 Office of Blood Research and Review.
20 According to our agenda, we will have a
21 presentation of committee certificates, because we
22 have some members of the Advisory Committee whose
23 terms have expired and they will be leaving us, so
24 that we want to acknowledge them.
25 DR. EPSTEIN: Well, first I just would

1 like to extend my personal thanks, and thanks on
2 behalf of the Center for Biologics Evaluation and
3 Research, to those outgoing members of the
4 committee who have served us so well in recent
5 years. We depend a great deal on this committee
6 process to provide external scientific advice to
7 the FDA, and we feel that it is a very important
8 part of our decisional process, that we can have
9 open public meetings and fully vet the scientific
10 concerns that affect our regulatory policies.
11 So Linda is going to assist me by
12 prompting me to mention the names of those who are
13 outgoing, since I just assume you will all be on
14 the committee forever. And don't worry, we can
15 still call you ad hoc.
16 So among these are Jeanne Linden. Again,
17 my thanks. Gail Macik. Mark Mitchell. And I
18 guess Kathy Knowles, our Consumer Representative,
19 as well. So once again, our very special thanks.
20 We hope that it has been an enjoyable and perhaps
21 edifying experience, and in any case that you have
22 learned something about our organization and its
23 ways that you can carry in your other endeavors.
24 Thank you.
25 [Applause.]

1 DR. SMALLWOOD: Thank you, Dr. Epstein. I
2 just wanted to mention that there were some that
3 were absent, and I wanted Dr. Epstein to
4 acknowledge those of you who were here. John Boyle
5 and Dr. Richard Kagan, they are not here with us
6 today, but they will also be leaving.
7 And we will present certificates to you
8 before the end of this meeting, but in the interest
9 of time, we would like to proceed with the agenda.
10 Thank you.
11 At this time now I will introduce the
12 members of the Advisory Committee. Would you
13 please raise your hand as I call your name? The
14 Chairman of the committee, Dr. Kenrad Nelson.
15 Sitting to Dr. Nelson's left is Dr. Paul Schmidt.
16 Dr. Gail Macik. Dr. Michael Fitzpatrick. Dr.
17 David Stroncek. Dr. Sherri Stuver. Dr. Jeanne
18 Linden.
19 Sitting to Dr. Nelson's right we have Dr.
20 Daniel McGee. Mr. Terry Rice. Dr. Raymond Koff.
21 Dr. Blaine Hollinger. Dr. Lianna Harvath. Ms.
22 Kathy Knowles. And Dr. Toby Simon.
23 I assume that some of our members will be
24 coming in later. Dr. Mary Chamberland, Dr. Kagan,
25 and Dr. Koerper will not be in attendance at this

1 meeting.

2 With no further announcements, at this

3 time I will turn the meeting proceedings over to

4 our Chairman, Dr. Kenrad Nelson.

5 CHAIRMAN NELSON: Thank you, Dr.

6 Smallwood.

7 The first items on the agenda are a series

8 of committee updates. The first one is TSE

9 Guidance, Dr. Dorothy Scott from FDA.

10 DR. SCOTT: Good morning. I'm going to

11 review for you the new FDA draft guidance which was

12 published in August 2001, "Revised Preventive

13 Measures to Reduce the Possible Risk of

14 Transmission of CJD and vCJD by Blood and Blood

15 Products." I believe you already have this

16 document, but I'm going to walk you through some of

17 the salient features.

18 Just to quickly review, the previous

19 guidance, which is currently in effect, was

20 published in November of 1999. And that

21 recommended deferrals for variant CJD, CJD, risk

22 factors for classical CJD, and for BSE exposure

23 risk, and that particular deferral was for travel

24 or residence in the United Kingdom for six months

25 or more between 1980 and 1996, as well as for

1 injection of bovine insulin with a U.K. source.
2 Since the November 1999 guidance, there
3 has been an increasing rate of the vCJD epidemic in
4 the United Kingdom. That is, there is an increased
5 rate of onset of cases. In addition, there has
6 been an increased BSE epidemic detected in Europe.
7 There have been more countries described, and in
8 fact between the draft guidance in August and now
9 we've had four additional countries--five, actually
10 --with BSE, and more cattle in a lot of the
11 European countries have now been detected with BSE,
12 partly as a result of increased surveillance. But
13 it appears that the epidemic is increasing, and is
14 expected to peak in Europe in different countries
15 sometime between 2002 and 2005, There was also a
16 single sheep transfusion transmission of BSE that
17 was reported in the Lancet.
18 But all this tells us that there is
19 continued scientific uncertainty about where the
20 BSE epidemic is and whether it's going to be a
21 problem for blood. So we're left with the question
22 whether or not vCJD is transmitted by blood.
23 The TSE Advisory Committee last June
24 considered increased donor deferrals for variant
25 CJD risk, and this risk we base on BSE exposure.

1 They weighed the risk of the shortages of blood
2 against the need to take precautionary measures,
3 and I'm just pointing out some of the things that
4 make this kind of decision complicated.
5 First of all, the long incubation period
6 of transmissible spongiform encephalopathies, and
7 presumably variant CJD, limits the power of any
8 epidemiological studies to tell us whether or not
9 blood can transmit the disease. But if
10 transmission is possible, donor deferrals have
11 current importance.
12 Experimental studies on the infectivity of
13 blood from vCJD patients or people who are
14 incubating vCJD are limited to date. We do know,
15 though, that a blood shortage is possible if large
16 donor deferrals for travel to countries with BSE
17 are recommended.
18 The opinions and votes for new donor
19 deferrals by the TSE Advisory Committee back in
20 June were incorporated into the FDA draft guidance,
21 which you have a copy of. I'm going to go into the
22 questions about supply a little bit more later, but
23 the new donor deferrals decrease the risk based on
24 exposure days to BSE by about 90 percent, and it's
25 estimated from REDS survey data that about a 5

1 percent donor loss will occur.

2 There are some things written into the
3 guidance that are designed to help attenuate the
4 impact on supply. The first is phased
5 implementation, so not all the donor deferrals have
6 to go into effect at once. Phase 1 will begin in
7 May, and Phase 2 in October of 2002--at the end of
8 May and the end of October, by the way.

9 We've also recommended pilot studies for
10 establishments which wish to institute more
11 stringent deferrals than those that we have
12 recommended. And finally I'll talk about the
13 differential deferral for blood and blood
14 components and source plasma with regard to the
15 European donor deferral.

16 So first I'm going to just list for you
17 the deferrals that we're recommending. In Phase 1
18 we have implementation beginning on May 31, 2002,
19 and these are the Phase 1 deferrals. These Phase 1
20 deferrals capture most of the risk or most of the
21 BSE exposure, and they have to do mainly with the
22 consumption of British beef.

23 The first one is for residence in the U.K.
24 for three months now, rather than six months, still
25 between the periods 1980 and 1996--still between

1 the years 1980 and 1996. The second is for France,
2 residence for five years or more between 1980 and
3 the present, and this is because France was a large
4 importer of British beef, and as you all know,
5 France now has five variant CJD cases.
6 Third, for residence on U.S. military
7 bases for the time periods that I've shown here,
8 between '80 and '90 north of the Alps and '80 and
9 '96 south of the Alps. And this is because people
10 who lived on these military bases ate British beef
11 under the British Beef to Europe program, and it's
12 estimated that, worst case, they may have consumed
13 35 percent British beef. That's a substantial
14 amount.
15 And, finally, we have recommended deferral
16 for recipients of transfusion in the United
17 Kingdom.
18 I just want to mention something about the
19 time period of 1980 through 1996 for donor deferral
20 for people who have lived in the U.K., and the
21 reason there's a cut-off at 1996 is because the
22 U.K. implemented measures to prevent entry of BSE
23 into the human food chain by 1996. And if you want
24 to know a lot more about these, they have a web
25 site where they go into great detail about their

1 inspections and enforcements of all of these food
2 chain controls.
3 I've just listed some, well, most of them
4 here, the important ones. They have a specified
5 risk material ban, so that brain, spinal cord,
6 intestines, and other tissues with potentially high
7 titers of the BSE agent can't enter the human food
8 chain. They are removed at slaughter. They have
9 also banned mechanically recovered meat from
10 vertebral columns because this can contain a lot of
11 contaminating neural tissue. And they have
12 instituted the over-30-months scheme, whereby
13 animals over 30 months can't be consumed, with rare
14 exceptions, under the beef assurance scheme.
15 And I just wanted to mention that we
16 anticipate or we think it's likely that the TSE
17 Advisory Committee/BPAC combined meeting in January
18 of 2002 will have a review of the food chain
19 controls in the U.K. and Europe.
20 Now I'm going on to Phase 2, and we have
21 recommended implementation of this donor deferral
22 on October 31, 2002, and this is deferral of blood
23 donors who have lived in Europe for five years or
24 more between 1980 and the present, again for the
25 consumption of beef. But in this case for the most

1 part in other European countries, most of the beef
2 consumed was their own, but they now have their own
3 epidemics of BSE, which are, I should point out,
4 considerably less than the U.K. epidemic, probably
5 on the order of several percent in terms of size
6 relative to the U.K. epidemic.
7 However, donors of source plasma for
8 plasma derivatives remain eligible to donate, and
9 that's what I want to talk about next, why source
10 plasma is an exception. First of all, we know now
11 from publications in peer-reviewed journals that
12 model TSE agents are partitioned and removed during
13 plasma fractionation, and there are several
14 different kinds of steps which are capable of
15 accomplishing this. Secondly, the European risk of
16 vCJD is likely to be low because they have a small
17 BSE epidemic.
18 The magnitude of risk reduction achieved
19 by fractionation at a minimum is likely to be
20 several logs greater than that possibly achievable
21 by donor deferral. It is believed that the effects
22 on nationwide and worldwide plasma supplies are
23 potentially severe if we have this pan-European
24 donor deferral, not because we have so many donors
25 that donate plasma who have lived in Europe for

1 five years or more, but because of the perception
2 of the safety of European plasma and the demand for
3 U.S. plasma that might ensue.
4 And, finally, I just want to point out
5 that the highest estimated risk deferrals remain in
6 place for donors of source plasma, that is, the
7 U.K. deferral, the deferral for residence in
8 France, the military donor deferral, and
9 transfusion in the United Kingdom.
10 I also want to say something about source
11 versus recovered plasma, because this has been a
12 worrisome issue for establishments. We have
13 recommended that source plasma from donors with
14 European residence may be used, but recovered
15 plasma may not be used. And this is not due to any
16 perception that recovered plasma is less safe than
17 source plasma, but rather these are differentiated
18 to prevent potential accidental use of blood
19 components from donors who are deferred for
20 residence in Europe.
21 And I also want to say that this
22 particular source plasma recommendation will be
23 reevaluated continually, really, in light of
24 additional epidemiologic evidence, transmission
25 studies, and advances in the validation of removal

1 of TSE agents by manufacturing.

2 I want to talk a little bit now about
3 supply and the anticipated supply effects. Our
4 recommended deferrals, and I am contrasting those
5 later with some other industry initiatives or
6 another industry initiative, are estimated to
7 result in the deferral of 5 percent of blood
8 donors, based on the REDS study. However, there
9 will be a greater proportion of deferrals likely in
10 coastal cities, perhaps double the amount, 10
11 percent.

12 In addition, 35 percent of the New York
13 Blood Center supply may be affected, and this is
14 because about 25 percent of their supply comes from
15 the Euroblood program, and they also are expected
16 to have a higher than 5 percent deferral of donors
17 for travel.

18 There has been also an industry-proposed
19 and now implemented deferral, which is three months
20 in the United Kingdom and six months in Europe, and
21 an industry survey suggests that 3 percent of their
22 donors would be deferred under this set of
23 deferrals. The REDS study estimated 9 percent. We
24 expect that the actual rate of deferral is likely
25 to be somewhere in between.

1 The TSE Advisory Committee proposed that
2 before new donor deferrals are implemented, that a
3 national recruitment campaign and a system to
4 monitor adequate blood supply be instituted. I
5 just want to mention again the efforts that we have
6 made to attenuate the effect of the new donor
7 deferrals: The phased-in plan. Recommending pilot
8 studies for establishments who wish to institute
9 more stringent deferrals, and this is in the
10 guidance; we have recommended that they institute
11 first a pilot program which includes donor
12 recruitment schemes, evaluation of donor loss, and
13 end points for the pilot donor deferral study. And
14 that they monitor their recruitment efforts and
15 fluctuations in hospital demands. Also, the
16 implementation dates are skipping the summer, so we
17 hope that that will also be useful in terms of the
18 potential for shortage.
19 Before I finish, I just want to mention
20 non-European BSE, because we don't have deferrals
21 for any countries other than Europe, but the first
22 case of BSE in a non-European country that appears
23 to be endemic was documented in September 2001 in
24 Japan, and this was confirmed by testing in the
25 United Kingdom. The USDA announced an import ban,

1 also in September 2001, for bovine materials from
2 Japan.
3 Now, meat and bone meal from the United
4 Kingdom was shipped to many non-European countries,
5 and these are now presumably at risk for BSE also.
6 So it appears that the BSE epidemic is likely to be
7 globalized, and the shipments, while not officially
8 published, shipments of meat and bone meal from the
9 U.K. during the BSE epidemic before they stopped
10 shipping, these shipments went to South American
11 countries, African countries, and other Asian
12 countries.
13 So it isn't likely that Japan itself is
14 going to be singled out as the only non-European
15 country with BSE. However, we feel the need to
16 assimilate the current donor deferrals, but we will
17 probably in the future consider additional
18 deferrals after weighing the risk and benefit of
19 any new donor deferrals for possible exposure to
20 BSE.
21 What is the future of the draft guidance?
22 Well, we have collected and evaluated the comments.
23 The comment period ended on October 28th. We
24 anticipate issuance of a final guidance with
25 revisions in the very near future, and the

1 revisions are the result mainly of many comments
2 that we received and which we found very helpful.
3 In addition, a plan to monitor the blood
4 supply which was initiated by HHS is in effect, and
5 that's being led by Dr. Nightingale, and this is
6 already up and running and will be in place, of
7 course, as these recommendations are effected.
8 Just to mention how is the final guidance
9 likely to be different from the draft guidance that
10 you have, we've accomplished some streamlining of
11 donor questions. We've clarified product
12 retrievals and reporting requirements. We are
13 going to have summary tables and a list of
14 definitions, and we've updated the science and the
15 epidemiology.
16 So I thank you very much.
17 CHAIRMAN NELSON: Thank you, Dr. Scott.
18 Are there any questions from the committee, or
19 comments?
20 The Red Cross donor deferral is already in
21 place?
22 DR. SCOTT: That's what we understand,
23 yes.
24 CHAIRMAN NELSON: Are there any data from
25 New York, since you singled out that important

1 Euroblood--I guess that won't occur until May of
2 next year, though, so we won't know anything.
3 DR. SCOTT: That's correct. I understand
4 they're working hard on absorbing these, and there
5 are commitments for them to obtain blood and some
6 assistance that's being provide from other
7 organizations.
8 CHAIRMAN NELSON: Okay. Thank you very
9 much.
10 The next presentation is by Dr. Robin
11 Biswas, talking about the--I got an old one. Okay.
12 It's Mark Weinstein, summary of a CDC workshop on
13 Factor VIII.
14 DR. WEINSTEIN: Thank you. The
15 availability of Factor VIII has been problematic
16 and highly erratic for most of 2001. In March,
17 April, May, and July of this year, recombinant
18 Factor VIII distribution was 15, 50, 25, and 60
19 percent respectively below the historical monthly
20 average. In June, August, and September,
21 distribution was 60, 32, and 39 percent above
22 average.
23 On October 3rd the Centers for Disease
24 Control and Prevention and the FDA held a national
25 workshop in Atlanta, Georgia to discuss issues

1 related to managing life- or limb-threatening
2 emergencies for persons with hemophilia, should
3 shortages of clotting factors significantly worsen.
4 Among those attending the workshop were 120
5 representatives from manufacturers, hemophilia
6 organizations, Federal agencies, home health care
7 companies, and hemophilia treatment centers.
8 While the worldwide demand for recombinant
9 Factor VIII has rapidly increased, manufacturing
10 problems have delayed the capacity to meet the
11 demand. Further unforeseen events or unplanned
12 manufacturing restrictions could create dangerous
13 shortages, especially for individuals who suffer
14 life-threatening bleeding episodes and must receive
15 clotting factor within one to two hours of such an
16 episode. CDC data indicate that approximately 100
17 such episodes occur each year among the 13,000
18 patients with hemophilia in the United States.
19 That's hemophilia A in the United States.
20 Inventories of plasma-derived Factor VIII
21 have decreased significantly since March, as more
22 plasma-derived products were distributed to
23 partially make up for the recombinant Factor VIII
24 shortage. This decrease of inventory further
25 reduces the flexibility of the distribution system

1 to react to unforeseen emergencies.
2 During the Atlanta workshop, speakers
3 discussed issues related to developing a
4 contingency plan for managing the supply of
5 clotting factor to meet any life-threatening
6 emergency throughout the country. Important issues
7 included when should such a plan be implemented;
8 where and how should the emergency factor inventory
9 be maintained, that is, should this inventory be
10 stockpiled or set up as a virtual system; what
11 criteria warrant individual use; how is inventory
12 tracked and distributed; what communication
13 channels are available; and how will expenses be
14 met.
15 As part of the workshop, Dr. Keith Hoots
16 presented the recommendations of the National
17 Hemophilia Foundation's Medical and Scientific
18 Advisory Council, or MASAC, concerning management
19 of the current short supply of recombinant Factor
20 VIII in the United States.
21 There was general agreement that at
22 present the short supply is being managed by
23 MASAC's recommendations to limit Factor VIII usage
24 and by cooperation among the hemophilia treatment
25 centers in informal product transferring. It was

1 recognized that further disruption of the supply
2 would require much more planning and action, and
3 attendees agreed to work toward developing a
4 contingency plan, with the hope that it would never
5 need to be used.
6 Initial thoughts concerning the plan were
7 that in case of severe shortages, the immediate
8 need would be for local emergency supplies to treat
9 life-threatening episodes for 24 hours, with
10 subsequent national redistribution of factor to
11 accommodate the emergency. Thus, it was thought
12 that a virtual inventory would be most effective,
13 that is, one that does not require a separate
14 distribution channel from the ones already in
15 place. Such an inventory would rely on an
16 independent information clearinghouse operated 24
17 hours a day to field requests and to pinpoint the
18 nearest location of factor needed in an emergency.
19 The workshop adjourned with a renewed
20 spirit and feeling of cooperation among the various
21 groups represented to try to accomplish this goal
22 for the continued safety and health of the
23 hemophilia community.
24 Subsequent to this workshop, the National
25 Hemophilia Foundation issued a resolution on

1 November 18th, resolving that a depot network be
2 set up to provide immediate, 24-hour access to
3 clotting factor for hemophilia patients seeking
4 emergency treatment around the country. It was
5 recommended that all efforts be made to use
6 existing locales such as hemophilia treatment
7 centers where clotting factor is already present.
8 It was also recommended that the emergency
9 depot system provide a single, toll-free number for
10 use around the country that would allow an
11 emergency physician to have access to factor within
12 two hours. The same toll-free number should
13 facilitate dialogue between the emergency physician
14 and the hemophilia treatment center physician, to
15 ensure that the emergency physician can obtain
16 accurate and timely medical advice about the
17 management of the patient. Further discussions
18 among interested parties will be needed to
19 facilitate implementation of this resolution.
20 Thanks for your attention.
21 CHAIRMAN NELSON: Comments or questions?
22 Dr. Koerper isn't here. So thank you very much.
23 The next presentation is the disaster
24 response. I assume that means September 11th,
25 synonymous terms, lately. Dr. Alan Williams from

1 the FDA.
2 DR. WILLIAMS: Thank you. Like the
3 Kennedy assassination and the Challenger shuttle
4 disaster, most of us know exactly where we were
5 when the events unfolded on September 11th. I was
6 in a room like this, learning how to be a Federal
7 supervisor, but soon found myself with colleagues
8 around a large conference table in the Office of
9 Blood, trying to gather as much information as
10 possible about the unfolding events by working the
11 telephones and e-mail and so forth.
12 Basically, on September 11th FDA and its
13 many entities monitored developments closely and
14 tried to anticipate the range of blood supply and
15 supply scenarios that could unfold, recognizing
16 that we had very little information in the early
17 stages. We didn't know if these events could be
18 occurring at multiple sites or just what the final
19 impact might be.
20 We readily established close contact with
21 blood organizations, manufacturers, the Department
22 of Defense, and other HHS agencies, and based on
23 information gathered in the early hours, issued a
24 policy statement in the evening of September 11th
25 allowing for modifications within the existing

1 regulatory framework that would allow training and
2 certification of emergency staff members coming
3 from a health care environment, who could be
4 trained to collect blood in a safe manner.
5 Also, we made provisions for release and
6 use of units that may have to be transfused prior
7 to completion of all testing. In fact, this was
8 not used to any great extent, but provisions were
9 made so that this could happen if supply shortages
10 occurred that really indicated that.
11 Because of the lines of donors that were
12 there, that presented to donate blood to help in
13 the disaster situation, we allowed that shipping of
14 unlicensed blood components could be done in
15 interstate commerce providing that adequate
16 labeling was provided. And to monitor all
17 collections and blood shipments that were occurring
18 under these modified policies, we required product
19 identification and record-keeping for each of the
20 collections and distributions occurring during that
21 time period.
22 Within really a day to a day and a half,
23 it became clear that the need for blood was not
24 what the potential could have been, and by
25 September 14th a revised policy statement was

1 issued, essentially returning policy regarding
2 collection and distribution to a relative state of
3 normalcy. Training and certification of emergency
4 staff was revised to allow some necessary use of
5 urgently trained staff where indicated, but for the
6 most part it returned to normal.
7 We asked for quality assurance
8 investigations within 72 hours for all units
9 collected during that time period, to make sure
10 that they met all current safety and regulatory
11 requirements. The release of units that were not
12 fully tested was revised, as was the shipment of
13 unlicensed blood components in interstate commerce,
14 which was discontinued. And now the emergent
15 scenario was the fact that the airlines were shut
16 down and supplies and test reagents were becoming
17 limited in some areas, so we made provision for use
18 of alternative FDA-registered laboratories to allow
19 continuity of testing.
20 The transportation disruptions in fact did
21 prove to be somewhat challenging, and in the course
22 of the several days following September 11th we
23 needed to take measures to assure continuing
24 availability of supplies, reagents, which involved
25 lot release measures and looking into means in

1 which samples could be shipped in a reliable manner
2 not using the airlines, which were not working.
3 At the end of this experience, and
4 actually throughout the experience, we instructed
5 staff to formalize records in terms of the
6 interactions with industry and the steps that we
7 were taking and the inquiries that were made in to
8 the Office of Blood. And this formal documentation
9 of these experiences really became the first
10 component of what has developed as our new
11 emergency response strategic plan within the
12 office, and I'll say more about that in a moment.
13 Then came anthrax. In October, while many
14 of us were at the AABB annual meeting, some
15 remaining FDA staff were meeting extensively with
16 scientific experts to determine appropriate
17 policies in the event that potential blood donors
18 might be exposed to the anthrax agent. And it was
19 agreed that no known risk of transmission would be
20 there from blood collected from asymptomatic donors
21 who may have been exposed to bacteria or spores, as
22 long as those donors were healthy.
23 This resulted in issuance of a guidance in
24 October entitled "Recommendations for the
25 Assessment of Donor Suitability and Blood and Blood

1 Product Safety in Cases of Possible Exposure to
2 Anthrax," with the provisions included in this
3 guidance that in cases of proven anthrax, donor
4 deferral should be mandated or recommended until
5 completion of appropriate treatment, and that
6 quarantine and retrieval of in-date products should
7 occur. This is in case of proven anthrax
8 infection.
9 In instances where there is demonstration
10 of colonization or suspected skin lesions, donor
11 deferral should be accomplished until an alternate
12 diagnosis is established or a course of treatment,
13 appropriate treatment, is completed. And in cases
14 where there is potential exposure but with an
15 unconfirmed diagnosis, medical discretion is
16 advised in terms of donation.
17 Subsequent to these events, like many
18 other organizations, both Federal and non-Federal,
19 FDA has been working hard on an emergency response
20 strategic plan. In general terms it boils down to
21 four different elements, the first being actions to
22 treat or protect affected individuals by looking at
23 potential blood products or components or
24 derivatives that might be appropriate for
25 treatment.

1 And the second entity, actions to protect
2 the blood supply, bioterrorism or other terrorist
3 activities that might limit blood donors or
4 facilities or reagents or staff that would be
5 available to collect blood, we're trying to
6 anticipate different scenarios and develop
7 emergency procedures that could be brought into
8 place. And the special emphasis here is of course
9 bioterrorism agents.
10 Third, we're taking actions to assure
11 continued supply availability, again anticipating
12 potential scenarios, looking at ways to monitor the
13 blood supply, working with HHS, and in general just
14 anticipating factors that could compromise supply
15 and trying to preempt those.
16 And then finally, extensive outreach
17 activities. The major blood organizations and
18 manufacturers are developing contingency plans of
19 their own, and we're working carefully with those
20 external and agency-related components to develop a
21 working plan that hopefully will form the basis of
22 a well-coordinated emergency plan. And there are
23 several meetings coming up in the ensuing months,
24 including the PHS Safety and Availability
25 Committee, which will be extensively discussing

1 some of these aspects of the emergency plan.
2 CHAIRMAN NELSON: Thank you.
3 David?
4 DR. STRONCEK: Well, good luck with your
5 planning. I think it's going to be very difficult.
6 You know, it's easy to decide on these things if
7 you know there's an emergency. But what happened
8 on September 11th, everyone thought there was going
9 to be an emergency with the blood supply and there
10 really wasn't. So then the blood was collected, I
11 think in many centers under practices that would
12 not be--they didn't use their normal SOPs.
13 And so what happens when you don't have
14 the emergency, you have all this blood, are you
15 going to address that issue? So you collected
16 blood under emergency SOPs, but then there's no
17 emergency.
18 DR. WILLIAMS: Well, as I mentioned
19 earlier, the emergency SOPs were put into place
20 because it was an unknown situation, and they were
21 in place if we needed them. In response to the
22 safety of the blood collected, we did require a
23 complete audit of those units collected. In terms
24 of over-collection, this is not an area that FDA
25 has any direct control over.

1 DR. STRONCEK: But it's clear that units
2 that were collected on September 11th, 12th and
3 13th were collected with people screening blood
4 donors that were not trained to do that, and those
5 units then went into inventory. I know you asked
6 that people audited everything, but still, you
7 know, if you went back and looked and there was no
8 emergency, nobody would say those units were
9 collected in a way of their normal SOPs. So then
10 all of a sudden, you know, you're using those units
11 a month later when there's an excess of blood, and
12 what happens if one of those units really shouldn't
13 have been collected at all?
14 DR. WILLIAMS: Well, we are aware of some
15 reports where the audits turned up a proportion of
16 units that did not meet current standards, and
17 those units were removed from distribution. And
18 the whole idea of an audit is that the safety and
19 usability of units should be documented and
20 demonstrated, and then they are appropriate for the
21 normal supply.
22 DR. FITZPATRICK: Alan, my question was
23 about just that thing. Was there an increase in
24 variance reports to the FDA? Is there an analysis
25 being done on what happened to the audits of those

1 units collected after the incident? Did you see
2 increased product recalls or withdrawals? And
3 what's being done by the agency to examine the
4 impact of your policy?
5 I want to commend you on being proactive
6 and developing a policy and putting it out, and
7 dealing with the anthrax and responding to the
8 incident, but what's being done now to analyze the
9 impact of those things that you did? How many
10 products were shipped in an unlicensed state, and
11 that sort of thing?
12 DR. WILLIAMS: The data regarding use of
13 the alternate policies that were put into place at
14 that time, we have primarily results collected I
15 would say anecdotally in terms of results of
16 audits. We don't have that currently on a
17 universal basis. I think it would be appropriate
18 to obtain that, and I think it probably is
19 something which would be determined at the end of a
20 current collection year, but we have not in a
21 uniform way attempted to collect that information.
22 I think it's a good point.
23 CHAIRMAN NELSON: Was there any evidence
24 of increased infectious markers during--donors
25 during that period, or are the numbers too small to

1 look at that?
2 DR. WILLIAMS: The numbers aren't too
3 small. The numbers are actually quite large. I
4 think the difficulty is, the mix of first-time and
5 repeat donors changes, and potentially the mix of
6 demographics of the incoming donors changes. There
7 are studies underway, including REDS, and I know
8 some individual blood centers that are looking at
9 marker rates. Preliminary data that has been
10 shared with us indicates no higher rates above what
11 would be anticipated when corrected for the first-time donor
12 status.
13 MS. KNOWLES: I understand that there was
14 actually a fair number of hepatitis C cases
15 uncovered as a result, too.
16 DR. WILLIAMS: That's correct, and in fact
17 the rates of hepatitis C infection are higher in
18 first-time donors. Rather than being attributable
19 to the emergency outpouring of blood donors, it is
20 probably more due to the fact that it's an incoming
21 population that has not been previously screened.
22 DR. MITCHELL: Now with the bioterrorism
23 issue I know that the post office is moving toward
24 irradiation of the mail and that that might be a
25 problem. What is the FDA doing to address that

1 issue?

2 DR. WILLIAMS: Could you develop that a

3 little further?

4 DR. MITCHELL: Okay. My understanding is

5 that the shipment of some of the testing components

6 through the mail, that the irradiation might affect

7 the viability of some of the test kits, and that's

8 what I was wondering.

9 DR. NAKHASI: I think at this point we

10 don't--thank you for bringing it to our attention--we don't

11 know anything about it. We'll look into

12 it. So at this point we don't have any

13 information.

14 CHAIRMAN NELSON: Mark, do you have any

15 other information on this?

16 DR. NELSON: No. No, that's all.

17 CHAIRMAN NELSON: Other comments? Thanks.

18 Dr. Ed Tabor is going to discuss a summary

19 of the NAT workshop December 4th and 5th.

20 DR. TABOR: A workshop sponsored by FDA

21 was held on December 4th and 5th, 2001, at the

22 National Institutes of Health, with the title

23 "Application of Nucleic Acid Testing to Blood Borne

24 Pathogens and Emerging Technologies." A number of

25 challenging regulatory issues were discussed

1 concerning the implementation of NAT screening of
2 blood and plasma to detect viruses.
3 I will try to highlight some of the
4 difficult or controversial issues that we
5 discussed. However, interested persons should
6 check the FDA web site for the transcript, which
7 should be available on line by the end of the
8 month, to read the text of the talks on such topics
9 as the development of reference standards and other
10 aspects of assay validation for NAT, the detection
11 of emerging pathogens, and the use of DNA
12 microarray chips and other new technologies to
13 enhance NAT screening.
14 In addition to preventing window period
15 transmission of blood borne viruses, NAT screening
16 can prevent rare cases of transmission by atypical
17 carriers. In an opening summary at the workshop,
18 Dr. Busch mentioned several anti-HCV negative
19 donors who were NAT positive and transmitted HCV to
20 recipients over a long period of time. Dr.
21 Neubling described HIV transmission by three NAT-positive,
22 p24 antigen negative, and anti-HIV
23 negative individuals.
24 The workshop also included a session on
25 the possible substitution of NAT screening for

1 various tests that are currently licensed. One
2 such issue was whether NAT screening for HIV could
3 permit elimination of the screening test for p24
4 antigen, a test that was originally recommended as
5 an interim measure in 1996.
6 Dr. Stramer reported that since 1996, the
7 test for p24 antigen has only detected six units
8 donated to the American Red Cross and nine units
9 donated to America's Blood Centers that would not
10 have been detected by tests for anti-HIV. In all
11 of the data presented at the workshop, HIV NAT was
12 more sensitive than p24. No one reported any
13 instance in which a unit that was anti-HIV negative
14 and p24 positive would not have been detected by
15 NAT.
16 Dr. Conrad and Dr. Stramer both described
17 studies in which NAT on minipools of 512 units
18 detected every sample that was positive for p24.
19 Dr. Stramer reported studies in which NAT on
20 minipools of 128 units or 16 units detected p24
21 negative samples that would not have been detected
22 without NAT. These data suggest that licensed NAT
23 screening might make p24 screening unnecessary in
24 the future.
25 Dr. Kleinman presented an excellent

1 summary of data indicating that HBV NAT on
2 minipools would not permit the elimination of the
3 currently recommended anti-HBC screening of whole
4 blood donations or the replacement of the required
5 HB-sAg testing of all blood and plasma donations.
6 There is sufficient evidence that a very
7 small number of donor samples are HB-sAg negative,
8 anti-HBC positive, and have detectable HBV DNA, but
9 the HBV DNA copy number is very low, less than 100
10 copies per mL. These samples are presumably
11 infectious but would not be detected by HBV NAT on
12 minipools.
13 Thus, only the development of very
14 sensitive single unit NAT screening might permit
15 the elimination of anti-HBC screening of whole
16 blood donations. Further, reports of HB-sAg
17 positive donations that were NAT negative but were
18 found to be NAT positive when larger volumes of
19 plasma were tested, combined with the long history
20 of HB-sAg screening of blood donations, makes it
21 unsafe to consider eliminating HB-sAg screening
22 simply because of NAT minipool screening.
23 Further consideration of this issue will
24 require data from a large study using sensitive
25 assays to detect HBV DNA and quantitate HBV viral

1 load, in which follow-up samples from the donors
2 are also obtained and tested, and in which the
3 focus is on single unit NAT. Of course, it is
4 hoped that using NAT to test individual units
5 rather than to test minipools will eventually be
6 technologically possible and cost-effective. This
7 would make NAT screening far more sensitive.
8 Nevertheless, it was not clear from
9 presentations at the workshop exactly how long it
10 will be before single unit NAT is available.
11 Clearly, most of the companies working on
12 developing minipool NAT are also working on and
13 evaluating single unit NAT, but it appeared from
14 the workshop presentations that a cost-effective
15 single unit NAT is still not available.
16 NAT screening for parvovirus B19 and NAT
17 screening for hepatitis A virus were discussed in a
18 session of the workshop, and more extensively in
19 the panel discussion at the end of the second day
20 of the workshop. NAT systems for these two viruses
21 are usually discussed together because of similar
22 regulatory issues, even though there is no
23 scientific similarity.
24 FDA has permitted NAT screening to detect
25 parvovirus B19 and HAV in minipools as in-process

1 control testing rather than as donor screening.
2 NAT assays geared to detect only high
3 concentrations of parvovirus B19 are expected to
4 detect between one positive unit in 1,000 and one
5 positive unit in 13,000 blood donations or source
6 plasma donations, based on the results of testing
7 reported by the American Red Cross, Alpha, Aventis,
8 Baxter, and Bayer.
9 The number of HAV positive units is
10 expected to be from 1 in 1 million blood donations,
11 based on Red Cross testing, to between 1 in 100,000
12 and 1 in 400,000 source plasma donations, based on
13 the results of testing reported by Aventis and
14 Baxter. NAT for parvovirus B19 now has been
15 initiated voluntarily by all four major
16 fractionaters as an in-process control.
17 Some but not all of the fractionaters are
18 screening for HAV, or will be doing so by early
19 2002. They are doing screening for parvovirus B19
20 according to standards that they expect FDA to
21 recommend, namely, to keep the titer of parvovirus
22 B19 below 10,000 international units per mL in all
23 manufacturing pools for plasma derivatives.
24 Screening for parvovirus B19 was reported at the
25 workshop to remove about 10 logs of virus from the

1 production pool.

2 Dr. Stramer said that the American Red
3 Cross plans a two-phase introduction of screening
4 blood donations for parvovirus B19 and HAV by NAT.
5 Phase one will involve screening minipools that are
6 larger than those for NAT screening of HIV and HCV,
7 and will involve doing so after 42 days have
8 elapsed. This will be in-process control testing.
9 Effectively, this will amount to screening
10 recovered plasma. Since all cellular components
11 will be outdated at the time of testing, any
12 positive pool will be discarded entirely without
13 identifying the specific positive unit. In phase
14 two the testing protocol would be modified in a way
15 that would incidentally make donor notification
16 possible, and this could amount to donor screening.
17 The Red Cross expects to have further discussions
18 with FDA about this phase.

19 Dr. Bianco said that America's Blood
20 Centers probably will perform in-process NAT
21 minipool testing for parvovirus B19 and HAV. In
22 addition, America's Blood Centers plan to identify
23 units with low levels of parvovirus B19 and to use
24 only these, or preferably only negative components,
25 for transfusing high-risk recipients such as

1 pregnant women. However, comments made by other
2 meeting participants indicate that some internal
3 discussion about such selective screening will be
4 likely to occur.
5 It should be emphasized that screening by
6 NAT for parvovirus B19 and HAV are considered by
7 FDA to be in-process control testing because only
8 minimal public health benefit would be expected to
9 result from donor or recipient notification within
10 the time frame that testing is currently being
11 performed. It is current thinking at FDA that any
12 testing for parvovirus B19 or HAV that was done in
13 real time, and at the same time identified specific
14 donors who are infected with either virus, would
15 constitute donor screening because it would permit
16 donor or recipient notification or targeted
17 donations that would have a public health benefit.
18 Such donor screening would be subject to the same
19 types of requirements as other donor screens.
20 There was a substantial and fascinating
21 session in the program on the use of DNA microarray
22 technology to enhance NAT screening. However, the
23 panel discussion after the session revealed that
24 application of this technology for blood screening
25 is still 5 to 10 years away. At present,

1 microarray methods are not suitable for use by
2 routine or non-research labs because of a variety
3 of factors that can interfere with proper testing.
4 However, the technology is constantly improving.
5 One workshop attendee pointed out that
6 microarray technology is designed to test a small
7 number of samples for up to 50,000 genes. In
8 contrast, blood bank testing needs a technology to
9 test thousands of samples for a half dozen to a
10 dozen genes. It was suggested that HLA screening
11 might be most suitable for the first blood bank use
12 of microarray technology. Once a testing format
13 such as this is in place in the blood centers, it
14 becomes much easier to modify it for new screening
15 purposes thereafter.
16 Dr. Hewlett pointed out that at the 1994
17 NAT workshop, skepticism was expressed concerning
18 the utility of NAT for blood bank testing, and that
19 five or six years later NAT was being widely used
20 for just that purpose. She urged that we reserve
21 judgment on how fast microarrays could be
22 introduced into blood and plasma screening, since
23 the technology can rapidly evolve.
24 Thank you.
25 CHAIRMAN NELSON: Comments or questions

1 for Dr. Tabor? Yes?

2 DR. FITZPATRICK: Ed, is there a process

3 for the elimination of a test like p24?

4 DR. TABOR: Well, I think the tests have

5 to be discussed in two different categories: tests

6 that are recommended and tests that are required.

7 p24 was recommended, and as I said, it was

8 recommended as an interim measure. I think we were

9 anxious to give the blood supply as close to a zero

10 risk as possible at the time, and it was recognized

11 that better tests would be available in the future.

12 A recommended test has inherent in the

13 recommendation the understanding that any applicant

14 can come to FDA with an alternative way to approach

15 screening, and so if a group has sufficient

16 evidence that NAT screening would be of equal or

17 greater sensitivity as for instance p24 testing

18 without any loss in specificity, that FDA would

19 consider those data and could permit the

20 substitution of NAT screening for p24 by that

21 applicant.

22 DR. FITZPATRICK: So the applicant has to

23 come to you with the information, rather than you

24 withdrawing the recommendation once it's licensed?

25 DR. TABOR: I assume that if we had--first

1 of all, we have to have the data brought to us
2 because the data is almost always generated outside
3 of FDA. I would assume that if we had sufficient
4 data to withdraw the recommendation, we would be
5 able to do so.
6 DR. FITZPATRICK: Okay, and just one other
7 comment. I understand the cost-effective issue of
8 single unit testing, but we have been doing single
9 unit NAT for a year and a half now on all our
10 specimens, and Chiron has all that information and
11 all that data.
12 DR. TABOR: Just for the benefit of both
13 myself and the audience, could you elaborate on
14 that a bit? When you say "we", do you mean all
15 military--
16 DR. FITZPATRICK: The Army and Navy. Army
17 is doing all testing for the Navy, so the Army and
18 Navy units collected have been tested by single
19 unit NAT since--
20 DR. TABOR: For HIV and HCV?
21 DR. FITZPATRICK: Yes.
22 DR. TABOR: And for how long ago?
23 DR. FITZPATRICK: Since we started, which
24 is about a year and a half now.
25 DR. TABOR: And where is it actually being

1 conducted?

2 DR. FITZPATRICK: At Fort Hood, Texas and

3 at Fort Knox, Kentucky.

4 DR. TABOR: So all samples are sent there?

5 DR. FITZPATRICK: Right.

6 DR. TABOR: And you're doing it with

7 Chiron, it sounds like you said?

8 DR. FITZPATRICK: Yes, and then the Air

9 Force is contracting with local civilian, so that

10 their samples are being done by minipool. And

11 Chiron has that information and the results.

12 CHAIRMAN NELSON: Dr. Epstein has a

13 comment.

14 DR. EPSTEIN: Well, I wanted to comment

15 upon the p24 issue. Regarding the single unit--can

16 I be heard in the back? Can you raise your hand?

17 No? Maybe I'll move to a new mike.

18 Can I be heard now? Okay. With regard to

19 single unit testing, you know, it falls to the

20 manufacturer to submit data to the agency to

21 support a licensing claim, so unless and until such

22 data is reviewed and approved in product

23 application, we would regard continued use as

24 investigational. In other words, it should be

25 under and IND. But nothing prevents Chiron or any

1 other company that has gathered such data from
2 making a submission to the agency, so that's the
3 pathway.
4 With regard to p24, what Dr. Tabor said is
5 correct, but let me also mention that FDA has
6 issued a final regulation which became effective
7 December the 10th on donor testing, and it says
8 that the agency periodically in guidance will
9 recommend which tests are deemed adequate and
10 suitable to reduce the risk of transfusion
11 transmitted infections.
12 And that's a paradigm shift, because in
13 previous regulation we enumerated certain agents
14 for which one had to test, and indeed certain
15 tests. So, for example, the HB-sAg was mandated in
16 the regs as serologic test for syphilis, antibody
17 to HIV. Those were the only tests enumerated in
18 the regs. Everything else was under
19 recommendations.
20 However, under the paradigm of the new
21 regulation we specify etiologic agents, and then we
22 indicate that we will through guidance establish
23 which test technology is appropriate. So
24 basically, at a certain point in time it may be
25 possible for us to decide that the HIV-1 p24 is no

1 longer necessary to adequately and appropriately
2 reduce the risk for transfusion-transmitted HIV.
3 What has happened, as described, is that
4 in the first license, which was for NAT for source
5 plasma by National Genetics Institute, and then a
6 corresponding license supplement from Alpha
7 Therapeutic Corporation for implementation, we did
8 approve an NAT minipool method both for HCV and for
9 HIV, and in that same approval we approved
10 discontinuing the HIV-1 p24 upon implementation of
11 the HIV-1 NAT. So we do regard it as a case-by-case
12 decision based on the data submitted for the
13 HIV NAT. And so then, you know, it would convey to
14 the approved user. If they are using the test
15 approved with that condition, then they can drop
16 the HIV-1 p24 NAT.
17 CHAIRMAN NELSON: Has that happened?
18 DR. EPSTEIN: I don't know if it has been
19 implemented yet. In other words, we have approved
20 it, but I don't actually know whether they have
21 implemented. Perhaps there is a representative
22 here who could comment.
23 DR. FITZPATRICK: On the single-unit
24 testing, Jay, since resolution of a minipool that
25 comes up positive has to be done by single-unit

1 testing, isn't there sort of an inherent licensure
2 of a single-unit test within that?
3 DR. EPSTEIN: Well, no, because the
4 performance characteristic of a single-unit test
5 when used for mass screening could be different.
6 In other words, when you use it to secondarily test
7 a pre-screened set of presumptive positives, you
8 get a higher positive predictive value than if you
9 simply use it randomly screening. So I think what
10 you're suggesting is that the added work to
11 validate it might be a lot less than if you had,
12 you know, no previous experience, and I would agree
13 with that.
14 And we have had some dialogue with the
15 companies about the possibility to establish the
16 single-unit test with the labeling for the
17 minipool, provided that a small trial shows it to
18 be non-inferior. And then later, presumably phase
19 four, one could then establish the exact
20 performance characteristic, already knowing that it
21 is as good or better than what it was originally
22 labeled to be.
23 So there are ways that we can try to
24 expedite the progress here, but I would contend
25 that the use as a secondary test does not have the

1 same performance characteristic as the up-front
2 use.
3 CHAIRMAN NELSON: Yes? Could you identify
4 yourself?
5 MR. HEATON: Yes. Good morning. I'm
6 Andrew Heaton with Chiron Corporation. I wanted to
7 confirm to the committee that we have submitted
8 material to allow the replacement of p24 antigen
9 testing with nucleic acid testing, and that
10 information was submitted to the agency
11 approximately 12 weeks ago. In addition, to answer
12 Colonel Fitzpatrick, we have also compiled the U.S.
13 military individual donor testing data which has
14 been collected over the past 18 months, where I
15 might add individual donor testing has performed
16 extremely satisfactorily, and that data has also
17 been submitted to the agency within the last two
18 weeks. We believe this should allow individual
19 donor testing.
20 CHAIRMAN NELSON: You're not testing NAT
21 for HBV, right? Just HIV and hepatitis C?
22 MR. HEATON: No, just HIV and hepatitis C.
23 MS. WAGNER: Hi. I'm Tori Wagner with
24 Alpha Therapeutic, and we have discontinued the p24
25 antigen testing.

1 CHAIRMAN NELSON: Okay. Well, we've got a
2 rare event. We're way ahead of time. Next was
3 supposed to be a break, but I think it's a little
4 early for--yes?
5 DR. DAVEY: I'm Richard Davey. I'm the
6 chief medical officer of the New York Blood Center,
7 and I'd like to make just a few comments related to
8 the September 11th events and the disaster comments
9 that Dr. Williams made, and also some observations
10 that we are noting in the current blood supply
11 situation.
12 I guess as you know, we were the blood
13 center at the epicenter of the events on September
14 11th, and we've learned a lot from that experience,
15 and we're looking with great anticipation to the
16 Advisory Committee on Blood Safety and Availability
17 meeting on January 31st and February 1st which is
18 going to evaluate disaster response in the blood
19 community in much more detail.
20 Very briefly, we observed very quickly
21 that it was very important to assess the medical
22 need around the catastrophe. We sent 600 units
23 within one hour of the first attack to the downtown
24 New York hospitals, and unfortunately even that
25 amount of blood was not needed, but it was unclear

1 for a day or two. The communications were down.
2 And we did find very quickly, and we want
3 to talk about this more at the end of January, that
4 communication is so essential. We fortunately had
5 cell phones that operate on some wave phase, I
6 don't know the technology, but they worked when
7 everything else was down. All the other cell
8 phones and telephones were gone. And those phones
9 were critical for us to manage our response to the
10 catastrophe.
11 Transportation was clearly a problem, and
12 we quickly were able to get the police and fire to
13 help us move blood around, but that was an issue
14 with the planes and bridges and tunnels closed.
15 There were clearly issues in managing the
16 influx of donors. We within two days decided that
17 we were going to ask people to come back. Just a
18 bit of data on that, which isn't really tight at
19 the moment, but we asked approximately 24,000 to
20 25,000 people to please come back, that we had
21 enough blood. We have contacted or attempted to
22 contact all 25,000-plus people.
23 We've had over 8,000 folks have signed up
24 to donate blood. About 2,500 of those have
25 actually shown up to donate, and we've had about

1 2,000 usable units. So about 9 percent of the
2 24,000 or 25,000 people that we did ask to come
3 back have actually come back and donated. I'm not
4 sure that that's bad or good. We haven't teased
5 out how many of those are first-time donors, how
6 many are repeat donors, but that's our experience
7 thus far.
8 By the way, Dr. Mitchell, at this meeting
9 in January the post office will be invited. They
10 are already on the docket. Another concern, by the
11 way, which is interesting for that meeting--I'm
12 diverging a second--is smallpox immunizations, if
13 they are recommended nationally, could possibly
14 impact the blood supply because there is a deferral
15 for live vaccines, and if a lot of people are
16 vaccinated, it could have an issue. These are
17 spin-offs that are very interesting in terms of the
18 September 11th episode.
19 Another repercussion that we are noting is
20 a worrisome trend now in terms of our donor base.
21 We had this great surge in donations, very
22 heartwarming, but now we're seeing a very worrisome
23 downturn in our donations. We look at the
24 efficiency of our donor drives, the number of
25 people who actually show up vis-a-vis the bookings.

1 We usually run 100 or 110 percent because there are
2 a lot of walk-ins. We are down to about 80
3 percent.
4 The Police Academy of New York, for
5 instance, yesterday cancelled a 500-unit drive
6 because the police have been, the cadets have been
7 on the streets. They have to come back and get
8 some lessons. They can't accommodate a donor
9 drive. We have noticed other corporations, a
10 little bit of a burnout, whatever. Obviously there
11 has been negative media attention about the surplus
12 and how it was handled.
13 And we think this is a nationwide trend.
14 I believe there are several blood centers on appeal
15 right now. So I think the blood supply is very
16 volatile, very unstable at the moment, and the
17 repercussions of September 11th, not only the
18 immediate repercussions, the disaster response, but
19 the short- to medium-, maybe even long-term effects
20 on the blood supply are yet to be determined. Of
21 course the vCJD deferrals will not help, and we are
22 impacted, as you know, most significantly by those
23 deferrals.
24 So we have a lot to learn. I think the
25 meeting in January is going to be very useful, and

1 I think the caution flags are flying right now in
2 terms of the donor base, its volatility, and
3 perhaps the decline in donors that we're seeing.
4 Thank you.
5 CHAIRMAN NELSON: Maybe you could, maybe
6 you or some other blood bankers could tell, what
7 was the change in the proportion of first-time and
8 repeat donors in the period around September 11th?
9 DR. DAVEY: We're looking at that. We
10 haven't looked at that yet, Mr. Chairman, but we
11 are trying to tease it out. That's very important
12 information.
13 We have found, though, as I think Alan
14 mentioned, that our marker rates in the people that
15 did show up after the 11th were essentially
16 identical to the marker rates that we have
17 identified in a normal mix of donors that present
18 at our donor centers.
19 CHAIRMAN NELSON: So normally about 30
20 percent are first-time donors? Is that about
21 right?
22 DR. DAVEY: That's about right, 25, 30
23 percent.
24 DR. FITZPATRICK: I'm sorry. I had one
25 more question for Dr. Tabor. On the hepatitis A

1 and the parvo B notification and recall, when you
2 made the comment that all cellular products would
3 be expired by the time you knew the test results,
4 I'd just like to remind the agency that there is a
5 resurgence of interest in frozen red cells, and
6 those cells would not be expired by the time you
7 got those results, so you need to make a
8 consideration for that during your deliberations.
9 DR. TABOR: Yes. Thank you. We are aware
10 of that, and I left that out of the discussion just
11 for simplicity. But the point being that if tests
12 in situations that Dr. Stramer had discussed in
13 their phase one, where the testing is done at a
14 point after most of the components or all of the
15 components have expired, obviously notification is
16 not relevant unless there were a situation where
17 there were frozen components.
18 DR. SCHMIDT: Mr. Chairman, earlier agenda
19 notices that we received indicated that in this
20 committee report section we would have a report on
21 consent decree update, and that has disappeared
22 from the agenda. Is there any comment on that?
23 DR. SMALLWOOD: If you will notice, on
24 your agenda it's scheduled for Friday morning. The
25 presenter was unable to make this session, so

1 that's why it was moved.

2 DR. SCHMIDT: Thank you. Excuse me.

3 DR. SMALLWOOD: And that's why we have

4 more time.

5 CHAIRMAN NELSON: Well, I would think

6 that--is Dr. Kahn here? Yes? No? How about Dr.

7 Chapman? Okay. I wonder if we could--Dr. Nakhasi,

8 do you think we could move in to begin discussion

9 on the Simian Foamy Virus issue?

10 DR. NAKHASI: Right now?

11 CHAIRMAN NELSON: Yes.

12 DR. NAKHASI: I think we could, but I

13 think Arifa Kahn is going to be presenting the--

14 CHAIRMAN NELSON: Okay. Right. So it

15 doesn't make sense to start.

16 DR. NAKHASI: That's the problem.

17 CHAIRMAN NELSON: Okay. I guess then

18 we'll have a half-hour break, unless somebody has a

19 speech to make. So we'll come back at 10 o'clock.

20 [Recess.]

21 DR. SMALLWOOD: May I ask all of the

22 committee members to please return to your seats?

23 We are ready to reconvene. We're sorry about the

24 delay, but you know that the Blood Products

25 Advisory Committee meetings are always unique, and

1 we try to live up to our reputation.
2 Dr. Nelson, whenever you're ready.
3 CHAIRMAN NELSON: The next group of
4 presentations is on the Simian Foamy Virus and the
5 issue of transmission by blood and blood products,
6 which I think the virology may be more interesting
7 than the transfusion risk, but it is an interesting
8 virus. I think we all will agree with that. And
9 to introduce the topic, Dr. Hira Nakhasi from the
10 FDA.
11 DR. NAKHASI: Thank you, Dr. Nelson. I
12 want to apologize to all the committee members for
13 the delay here, because I thought we will get
14 started earlier, but traffic and other things don't
15 let you. Mother Nature doesn't want it to be that
16 way. So I again want to apologize, and let's get
17 started with the topic.
18 Today I am going to present in front of
19 you the topic, which is basically the potential
20 concerns for Simian Foamy Virus transmission by
21 blood and blood products. The issue here is to
22 seek advice from the Advisory Committee to assess
23 the possible transfusion risk from SFV. I will
24 sort of build up the issue, why we are concerned
25 and why we brought this issue to the Advisory

1 Committee meeting here.
2 As a way of background, and you will hear
3 a little bit more about the background and the
4 pathogenesis of this virus by Dr. Arifa Kahn in the
5 presentation following mine, however, just to give
6 you a little bit brief introduction to this virus,
7 Simian Foamy Virus belongs to the Retroviridae
8 family, and the prevalence of SFV infection in wild
9 animals is very high. Seroprevalence is higher in
10 captive animals versus the wild animals. Precise
11 mode of transmission is not clear. However, we
12 believe to start that it is transmitted by the
13 saliva when the animals bite other animals or
14 animals bite humans.
15 The infection, in several pathogenesis
16 models using the small animals like rabbits and
17 mice, they found out that they get infected by the
18 respective Simian Foamy Viruses, but without any
19 evidence of pathology in those animal studies.
20 With regard to infection in humans, SFV
21 infection is not believed to be prevalent in human
22 population. However, humans who are handling or
23 are occupationally exposed to non-human primates
24 can be infected by SFV. There have been several
25 studies done where they have shown, in the past

1 there were several studies done where they showed
2 that several diseases such as myasthenia gravis and
3 some other diseases I cannot even pronounce,
4 multiple sclerosis, there has been some association
5 with this foamy virus. However, that association
6 was tenuous. However, further analysis of those
7 studies, they are using several methodologies like
8 Western blot, PCR, IFA, it turned out to be there
9 was no association between foamy virus infection
10 and these diseases.
11 Then a current concern for us is basically
12 on the following studies, which you will hear more
13 from both CDC presentation as well as from Health
14 Canada presentation, that in an unlinked CDC
15 serosurvey of North American zoo workers, they
16 found out that 4 out of 322 individuals who were
17 tested were positive for this SFV infection. And I
18 would like to emphasize here, out of 322, 133 were
19 potentially people who had handled the non-human
20 primates, and all the four were positive from that
21 group, whereas they had 189 people who had not
22 handled, and none of the infections were in that
23 group. From these studies and other studies, the
24 seroprevalence of this infection is between 1.8 to
25 3 percent among the people who are occupationally

1 exposed to non-human primates.
2 Another study about which you will hear
3 from Health Canada, a recent study which was done,
4 again unlinked serosurveillance of non-human
5 primate handlers, they found 2 out of 46
6 seroreactive people, and one of them was very
7 strongly positive for the antibody on the Western
8 blot, and one was weakly reactive. That prompted,
9 basically that prompted Health Canada to sort of
10 ask CDC and FDA what can be done.
11 They were thinking at that time, can there
12 blood people who will be deferred donors? These
13 non-human primate handlers can be deferred for
14 donation. However, at this point you will hear
15 from Health Canada they are not considering that at
16 the moment. But then again, this is again a
17 seroprevalence study, very limited.
18 Not only that, they found that SFV can be
19 isolated from humans, these workers who are exposed
20 to non-human primates. And in another look-back
21 study which was done by CDC and Atlanta Red Cross,
22 where basically you will hear more of that in
23 Louisa Chapman's presentation, where they found out
24 one positive person who had donated over I guess
25 several years, and seven donations from that person

1 were transfused, and four were basically traced
2 back, and those four people who had got the
3 transfusion from this positive donor did not show--are
4 negative for the last 1.7 to 7 years post-transfusion, so
5 obviously they are not infected.
6 So, however, based on these observations,
7 which are the studies I presented to you, the CDC
8 study which you will hear more detail, the Health
9 Canada study you will hear more in detail from, and
10 other studies from the literature survey, it looks
11 that there is insufficient data to exclude the risk
12 from transfusion at this time.
13 So the topics we will be discussing this
14 morning will be the review of SFV biology and
15 pathogenesis by Arifa Kahn, and she will educate us
16 all about what this SFV--I mean how this
17 pathogenesis of SFV takes place. Then we will hear
18 a review of investigation on human infections from
19 SFV and proposed human studies from Louisa Chapman
20 from CDC. And then we will hear the review of risk
21 assessments from Paul Sandstrom from Health Canada.
22 And then the last, we will hear the
23 proposed animal study which FDA is proposing,
24 especially Arifa Kahn is proposing. And in
25 collaboration with Arifa Kahn, we would like to ask

1 the question: Can this SFV be transmitted through
2 the blood?
3 Therefore, while you are listening to
4 their presentation, I would like you to please pay
5 attention to these following questions. The three
6 questions we will be asking to the committee are:
7 One, does the committee agree that the currently
8 available data are insufficient to determine
9 whether SFV can cause adverse health effects in
10 humans? That's one.
11 Number two, does the committee agree that
12 the currently available data are insufficient to
13 determine whether SFV can be transmitted by blood
14 transfusion?
15 Number three, we would request your
16 comments on the adequacy of the proposed study to
17 evaluate SFV transmission by blood transfusion?
18 So at this point I would like to ask Dr.
19 Arifa Kahn to present the first part of the talk.
20 DR. KAHN: Good morning. Today I would
21 like to describe to you a group of retroviruses
22 that are distinct from other retroviruses in many
23 of their properties, as well as different from HIV
24 and HTLV, which you are quite familiar with.
25 Foamy viruses form a unique genus called

1 Spumavirus, due to their unique biological and
2 genetic properties, which include an extremely
3 broad host-, tissue-, and cell-tropism. To date
4 there is no known cell line that is resistant to
5 infection by Simian Foamy Virus. Also, in most
6 situations in culture these viruses are highly
7 cytopathic. However, there is no known
8 pathogenicity to date with this group of viruses.
9 Simian Foamy Viruses share many of the
10 genomic structural features of other viruses, such
11 as LTRs at both ends of the viral genome, as well
12 as structural genes gag, pol, env. However, they
13 are distinct from the simple retroviruses in that
14 they have open reading frames, such as tas and orf-2, of
15 which the tas is known to encode a
16 transactivating protein which is necessary for
17 transcriptional activation of the two promoters
18 that are shown in the figure.
19 All right. So therefore these viruses are
20 considered complex retroviruses because of the
21 additional open reading frames. However, foamy
22 viruses have properties that are distinct from
23 other retroviruses and are similar to the family of
24 Hepadnaviridae, in that the infectious particles
25 have been shown to have associated linear DNA

1 genomes. Also, persistently infected cells contain
2 very large amounts of linear DNA.
3 This is showing a diagrammatic figure of
4 the replication cycle of foamy viruses. The virus
5 cycle is complex because it does share certain
6 features of retroviruses and others of
7 Hepadnaviridae. However, what I would like to
8 focus is that like all retroviruses, foamy viruses
9 do have the critical step in their life cycle of
10 integration, which leads to persistence of stable
11 viral DNA in the host. So therefore these
12 sequences reside in the life of the host, or
13 throughout the life of the host, and it is this
14 critical feature of retroviruses that make this
15 class of retroviruses of special safety concern in
16 biologics.
17 Foamy viruses are highly prevalent in a
18 wide variety of species. They have been identified
19 in simian, bovine, equine, ovine, feline, murine,
20 and otariidine. In non-human primates, foamy virus
21 infection is widespread. In whatever species that
22 has been looked at, foamy virus can be isolated,
23 for example in New World primates, Old World
24 primates, including macaques, African green
25 monkeys, baboons, as well as in apes.

1 The natural infection in non-human
2 primates, some of the distinct features are
3 described here. There are 11 serologically
4 distinct subtypes of foamy virus, and these are
5 identified in the variety of species that I showed,
6 the non-human primate species. Seroprevalence is
7 high in captivity. And again you will see
8 throughout my presentation that the studies done on
9 foamy viruses are limited, so basically we have to
10 extract whatever information we can based upon
11 these studies, and this is very unlike what you see
12 in the literature for HIV and some of the other
13 retroviruses.
14 In the natural situation there is a report
15 that it may be as high as 70 percent, and there is
16 higher incidence in adults than in infants, and
17 this is again based on this one study that's
18 indicated here. The sequences, however, are
19 genetically stable, and this is I guess expected
20 because the virus is white cell-associated, and it
21 does not have a high replication efficiency as you
22 are aware of in the case of HIV, where there is a
23 lot of mutations due to high reverse transcriptase
24 activity.
25 There is very broad tissue distribution.

1 In one study in African green monkeys it was
2 reported that viral DNA was found in all of the
3 tissues in the animal that were looked at
4 extensively. However, the infection is latent and
5 persistent, and viral RNA in this same study was
6 only detected in the oral mucosa. This is one of
7 the reasons, or this study is one of a few studies
8 based upon which it is believed that the virus is
9 transmitted through the saliva.
10 However, it should be noted that humans
11 are not the natural host of foamy viruses. The
12 human foamy virus that is in the literature has
13 been confirmed to be of chimp origin. This is the
14 new designation of this virus. And this has been,
15 I guess based upon the sequence analysis, is
16 believed to be acquired by cross-species infection
17 from a chimpanzee. And as Dr. Nakhasi mentioned
18 earlier, based upon seroprevalence studies and I
19 guess limited analysis in various human
20 populations, there is no known foamy virus
21 infection in the natural situation.
22 However, accidental infection of humans
23 occupationally exposed to non-human primates has
24 been reported, and you will hear more about this in
25 the subsequent presentations. SFV infection in

1 non-human primate handlers and zookeepers has been
2 shown due to exposure to African green monkeys,
3 chimpanzees, baboons, and macaques, and Dr.
4 Sandstrom will talk more about this today.
5 The infection is persistent. In one case
6 that I'm aware of, infectious virus was isolated at
7 least 30 years post exposure to the animal, and
8 based upon limited sequence analysis, the sequences
9 were shown to be almost identical to the virus that
10 was present in the original animal. This is work
11 from the CDC.
12 Latent virus infection has been I guess
13 observed in all of the human infections, based upon
14 the fact that there is no evidence of plasma
15 viremia, and virus has been isolated in co-culture
16 from PBLCs. However, there has been no evidence of
17 virus transmission in close contacts, and no signs
18 of any foamy associated disease in the individuals.
19 And again, these will be, this aspect will be much
20 more elaborated in the next two presentations.
21 In terms of the host range of Simian Foamy
22 Virus, as I have mentioned earlier, the host range
23 is exceptionally broad. I have listed here various
24 species ranging from chicken, avian species, to
25 feline here, various tissues of origin. In all

1 cases Simian Foamy Virus was shown to replicate
2 with CPE.
3 In terms of primate species, there are a
4 variety of cell types, fibroblast, epithelial,
5 macrophage, lymphoid cells, in both monkeys and in
6 humans; various tissues of origin. I all cases the
7 in vitro studies on Simian Foamy Virus have
8 resulted in virus replication, and in almost all
9 cases also CPE, cytopathic effect.
10 Based upon the published reports on Simian
11 Foamy Virus in vitro studies, the infection is
12 productive. Either it's acute, in which case there
13 is variable amounts of extracellular virus
14 produced, and there is cytopathic effect seen
15 either due to lysis or apoptosis; and in some cases
16 based in other cell lines you can have chronic
17 infection, in which case you have low level virus
18 production and no cytopathic effect.
19 Now, it should be noted that the studies,
20 all the in vitro studies that I have described are
21 based upon using prototype Simian Foamy Viruses,
22 mainly SFV-1, -2, or -3, and in many cases also the
23 Human Foamy Virus, which is the simian, chimpanzee
24 isolate actually. So all of the studies thus far
25 have been based upon these prototype viruses which

1 have had extensive passage in a variety of
2 different species for a different number of
3 passages.
4 And the reason for this primarily was to
5 create working virus stock. The virus replicates
6 very poorly, so in order to generate some, you
7 know, I guess, material with enough virus titer,
8 the propagation may have been done. This is again
9 historical. This is what I think the reason might
10 be.
11 However, these lab-adapted viruses may not
12 represent the properties of the naturally occurring
13 parent viruses. Therefore, it is important that
14 the properties of naturally occurring Simian Foamy
15 Viruses be studied to understand the mechanism of
16 Simian Foamy Virus infection in humans, such as
17 transmission, persistence, as well as pathogenic
18 potential.
19 In order to investigate this aspect, my
20 lab had initiated studies a few years ago in which
21 we isolated foamy viruses from rhesus and pigtail
22 macaques by very limited in vitro passage, and we
23 have extensively characterized the replication
24 kinetics of these limited passage, low passage
25 macaque isolates and compared them with the

1 prototype lab-adapted viruses in a variety of
2 different cell lines of different species,
3 different tissue origins, including a wide variety
4 of deployed transformed as well as tumor human cell
5 lines.
6 And I'm just going to summarize our
7 results in the next slide. What we have found is
8 that the naturally occurring viruses also have the
9 broad host-, tissue-, and cell-tropism as do the
10 lab-adapted viruses. However, in all cases the
11 macaque isolate showed slower replication kinetics
12 than the prototype lab-adapted virus, for example,
13 SFV-1. And the order of the kinetics of
14 replication was the same with the viruses
15 regardless of which cell line we tested.
16 Interestingly, there was a wide difference
17 in the replication efficiency of the different
18 macaque isolates. Some of them were extremely poor
19 in their replication regardless of the cell line,
20 and some of them were much better, however, not as
21 good as the prototype viruses.
22 Interestingly, all the macaque isolates
23 that we tested showed unique characteristics from
24 the prototype SFV, in that non-productive infection
25 was seen in the case of a human tumor cell line,

1 the A549 cell line. This is quite unique in the
2 sense that thus far all these studies have shown
3 that foamy viruses replicate productively.
4 In this case we showed that using the
5 naturally occurring viruses, we did get non-productive
6 infection in one particular cell line,
7 whereas in this cell line the prototype virus
8 replicated efficiently. There was no evidence of
9 virus replication of the naturally occurring
10 viruses by a variety of parameters, including
11 reverse transcriptase activity, by the traditional
12 assay as well as by a PCR-based RT assay which is
13 highly sensitive. There was no protein expression,
14 particle production, or unintegrated viral DNA by
15 Southern blot.
16 However, by DNA PCR we did demonstrate
17 that in all cases the viruses did enter and were
18 present in the host DNA even at 60 days post-infection. So
19 these viruses could enter, but after
20 entry they remained quiescent. And in the case of
21 one of the isolates, we did show that the infection
22 was latent, in that we were able to recover virus
23 after co-culture. So we are continuing to
24 investigate this system further to see in terms of
25 analyzing it as a model of latent foamy virus

1 infection in humans.
2 To switch gears now and talk a little bit
3 about SFV pathogenesis, or I guess I should say
4 lack of, SFV, as Robin Weiss indicated in 1999,
5 still remains "A Virus in Search of a Disease."
6 There have been limited studies to investigate the
7 pathogenesis, and I'll just mention them briefly
8 here, based upon whatever information we have.
9 These are experimental infections, and these
10 studies again have been done with prototype
11 viruses, lab-adapted viruses.
12 In immunocompetent rabbits and mice,
13 persistent infection can be achieved. Transient
14 immunosuppressive effect is seen in both species.
15 However, there is no sign of any disease and no
16 pathology associated.
17 There is another study, one study in which
18 transgenic mice which expressed, I guess, certain
19 of the orf proteins, the tas and the bet, for this
20 particular virus, were found to have some pathology
21 which was described to be probably due to the
22 presence of the structural genes. However, virus
23 replication was not demonstrated. And this
24 pathology was associated with the cerebellar
25 nervous system.

1 However, it should be noted that in terms
2 of the transgenic mouse system, here we are looking
3 at experimental results in which all these cells
4 are expressing proteins probably at much higher
5 levels than what you would see in the natural
6 infection. However, this does indicate a possible
7 pathological effect if the virus were to be able to
8 replicate to high levels, which we have not seen
9 yet in the natural situation.
10 In summary--and again, the difference in
11 the bullets does not signify any importance. It's
12 a glitch of the PowerPoint. There has been no
13 evidence of any disease in non-human primates due
14 to naturally occurring viruses, and it should be
15 mentioned that the transmission in this situation
16 is probably due to the saliva. In small animal
17 models using prototype lab-adapted viruses, no
18 disease was seen in immunocompetent rabbits or
19 mice. However, some pathology was seen in
20 transgenic mice due to protein expression.
21 And there has been no evidence of disease
22 in SFV-infected humans. However, it should be
23 noted that there has been no evidence of foamy
24 transmission by blood due to the lack of relevant
25 animal studies, and this will be further discussed

1 in the proposed study.
2 And I think I will just like to stop at
3 this point and thank everyone for their attention.
4 CHAIRMAN NELSON: Questions for Dr. Kahn?
5 DR. STRONCEK: You had a slide here, I
6 don't know if you showed it, you talked about SFV
7 viruses in dogs and cats.
8 DR. KAHN: Yes.
9 DR. STRONCEK: Do you know the prevalence
10 of those, and does anybody know if--it seems, you
11 know, to put this into context, do those transmit
12 from dogs and cats to humans?
13 DR. KAHN: In terms--well, I should
14 mention that from the literature there is a
15 statement which indicates that the prevalence in
16 the other species is similar to that in non-human
17 primates. I don't believe the host range in other
18 species has been as extensively looked at as in the
19 case of the Simian Foamy Viruses. One may expect
20 it may be the same. In terms of the feline
21 situation, and I see Dr. Folks standing up, I think
22 he may be able to comment about some of his data in
23 looking at that.
24 DR. FOLKS: Yes, I'll just make a comment.
25 We looked at about 300 individuals that are feline

1 practitioners and have been over a long period of
2 time scratched and chewed up pretty bad by cats,
3 and we saw no transmission of feline foamy.
4 DR. KAHN: But it should also be mentioned
5 that there has been no evidence for transmission of
6 feline leukemia viruses, either, and that has
7 always been a mystery to me.
8 CHAIRMAN NELSON: I think one of the early
9 cases in humans was a person with a nasopharyngeal--
10 DR. KAHN: That was the Human Foamy Virus.
11 CHAIRMAN NELSON: Right. How many people
12 with--how often has this been looked for in people
13 who have nasopharyngeal carcinoma? One would
14 expect that if there was any pathology, it would
15 relate to where the virus might replicate. If the
16 virus is latent, it's hard to imagine a pathology,
17 and you mentioned the saliva and etcetera. Have
18 focal studies been done on this subset of patients?
19 DR. KAHN: I'm not aware of that. I don't
20 believe so.
21 DR. FITZPATRICK: In the humans that have
22 evidence of the virus, I missed it if you said what
23 cell lines in those individuals are infected.
24 DR. KAHN: Well, lymphocytes have been

1 looked at, and virus, infectious virus, can be
2 recovered from the lymphocyte. And I think Dr.
3 Chapman may shed more information on the patients,
4 but it's clear that it's in the lymphocytes.
5 DR. NEUMANN-HAEFELIN: To comment on the
6 nasopharyngeal carcinoma question--
7 CHAIRMAN NELSON: Could you identify
8 yourself for the record?
9 DR. NEUMANN-HAEFELIN: Yes. I am Dieter
10 Neumann-Haefelin from Freiburg, Germany. To
11 comment on that question concerning nasopharyngeal
12 carcinoma, at the time of the detection of this so-called
13 Human Foamy Virus, intensive studies have
14 been carried out on NPC patients, and no
15 seropositivity has been found at that time. And
16 that was the only possibility to trace foamy virus
17 infections.
18 DR. KAHN: Thank you.
19 CHAIRMAN NELSON: Thanks for your comment.
20 DR. NAKHASI: Dr. Nelson, I would like to
21 at this point take the opportunity to introduce, we
22 have two, actually three experts on SFV in the
23 audience here. I think, I don't know whether you
24 know them. Dr. Neumann-Haefelin has introduced
25 himself. Dr. Tom Folks. And we have one person on

1 the telephone, Dr. Jonathan Allan, also. so if you
2 need any clarification or things like that, please
3 ask. We can ask these gentlemen.
4 CHAIRMAN NELSON: Thank you. Other
5 comments? Okay. Thanks very much, Dr. Kahn.
6 Dr. Louisa Chapman from CDC.
7 DR. CHAPMAN: Thank you. I'm going to be
8 talking about a body of work that has been done out
9 of the Division of AIDS, STD, and TB Laboratory
10 Research, HIV and Retrovirology Branch primarily.
11 Dr. Folks, who just spoke, is the chief of that
12 branch. I want to thank the BPAC for the
13 opportunity to present this body of largely
14 unpublished and actually, due to the cancellation
15 of the foamy virus international meeting that was
16 scheduled for September, at this point largely also
17 previously unpresented data on Simian Foamy Virus
18 infections in humans.
19 The work I present was led by the HIV and
20 Retrovirology Branch, NCI, CDC, but involves a
21 large number of collaborators both within and
22 outside of CDC, and I'm not going to attempt to
23 acknowledge all of those collaborators because of
24 the time limitations and the nature of the
25 presentation. But I just want you to know it's

1 composite data, largely out of the HAR Branch, and
2 largely both unpublished and unpresented at this
3 point.
4 I'm going to summarize the studies that
5 have been done and are being done there before I
6 talk about the one on this slide. Though let me go
7 back and talk about one that Dr. Folks alluded to,
8 that we had decided not to put into this
9 presentation, but since it has come up, the study
10 Dr. Folks mentioned, looking at over 300 feline
11 practitioners, is a study that has been done, has
12 been completed, and is published in the Journal of
13 the Veterinary American Medical Association.
14 Dr. Sandstrom, Sal Butera, and I, and I
15 think Dr. Folks are all co-authors on that. I
16 don't remember who the first author is. Are you,
17 Paul, or Sal? It was initiated by Paul Sandstrom
18 when he was at CDC, and finished up by Sal Butera,
19 and one or the other is the first author, but you
20 should be easily able to find it with a MedLine
21 search.
22 And again, it was over 300 highly exposed
23 feline practitioners, multiple injuries, multiple
24 years of exposure to sick cats, no evidence of any
25 of the feline retroviruses we looked for, but of

1 specific interest here was Feline Foamy Virus.
2 Now, the studies that we did plan to talk
3 about, this is a completed study that again is
4 published. It was an unlinked serosurvey of zoo
5 workers, an unlinked serosurvey of 322 North
6 American zoo workers which was published in the
7 Lancet in 2000, the year 2000, identified four
8 seropositive samples using a Western blot assay
9 containing combined antigens from three
10 antigenically distinct Simian Foamy Viruses.
11 The four reactive sera were subsequently
12 tested against antigens from SFV-6, chimpanzee,
13 SFV-3, African green monkey, and SFV-2, macaque,
14 separately. They were tested separately. The
15 single antigen testing indicated that all four were
16 infected with SFV originating from chimpanzees.
17 All four were from the 133 workers whose jobs
18 involved potential contact with non-human primates,
19 and none of the 189 workers whose jobs did not
20 involve potential contact with non-human primates
21 were seroreactive.
22 We have several ongoing studies that I'll
23 summarize for you. We have three specific ongoing
24 studies relative to potential for SFV transmission
25 by transfusion. The first is the "Voluntary

1 Seroprevalence Study of Non-Human Primate
2 Retrovirus Infections Among Occupationally Exposed
3 Workers."
4 It was developed in response to a need to
5 define the prevalence of SIV infection, Simian
6 Immmunodeficiency Virus infection, among
7 occupationally exposed persons. It was therefore
8 originally designed many years ago, at this point,
9 to enroll institutions that employed persons
10 exposed to either non-human primates, to their
11 biologic materials, or to Simian Immunodeficiency
12 Virus, SIV, and to survey the entire worker
13 population for evidence of SIV infection.
14 The current study has been modified
15 through the years to allow enrollment of self-selected
16 workers within these institutions or
17 potentially exposed individuals who are tested for
18 a variety of simian retroviruses. And let me stop
19 and say of course when we enrolled institutions,
20 individuals within that institution had the right,
21 as human research subjects always do, to refuse
22 participation. But it was, the design at that
23 point was specifically to capture populations
24 without exception for enrolling individuals.
25 These changes were made in response to the

1 reluctance of institutions to test their workers
2 for infections of uncertain significance, combined
3 with requests for testing from specific individuals
4 who had a history of specific high-risk exposures.
5 The current modified protocol identifies infections
6 in exposed individuals rather than defining the
7 prevalence of infection in exposed populations.
8 The strength of this study is its ability
9 to identify persons infected with simian
10 retroviruses. Weaknesses include enrollment biases
11 that may favor enrollment of persons with increased
12 likelihood of infection, thereby limiting the
13 confidence with which prevalence of infection among
14 tested workers can be extrapolated to the greater
15 worker population. Additionally, the retrospective
16 exposure information collection limits our ability
17 to identify specific risk factors that may be
18 associated with infection.
19 We reported the first human SFV infections
20 identified under this protocol in Nature Medicine
21 in 1998. At that time we began to work on two
22 additional protocols that were intended to address
23 other issues raised by evidence of these
24 infections.
25 The second protocol is called the "Long

1 Term Follow-up of Persons Infected with Unusual
2 Retroviruses." It enrolls persons documented to be
3 infected with unusual retroviruses and their close
4 contacts, or it is designed to enroll these persons
5 and their close contacts. You will hear later that
6 we haven't actually succeeded in enrolling any
7 contacts.
8 By "unusual retroviruses" we intend any
9 retrovirus infection that is not recognized to be
10 endemic in human populations. All participants are
11 followed for five years. Contacts, when we enroll
12 them, will be tested annually for evidence of
13 infection. Primary participant infection is
14 reconfirmed at the time of enrollment, and infected
15 participants are questioned about their health
16 status as well as risk factors for acquisition or
17 for secondary transmission of infection. This
18 questioning is done by telephone interview using a
19 standard questionnaire.
20 Standard clinical laboratory testing,
21 including complete blood counts, blood chemistries,
22 liver function tests, characterization of lymph
23 site subsets, including CD4, is performed annually.
24 Blood, saliva, throat swabs, urine, and semen or
25 vaginal fluid specimens are collected annually for

1 study.

2 The strength of this study is that it
3 allows prospective virologic, immunologic, and
4 clinical characterization of unusual retrovirus
5 infections, including determination of virus
6 presence in body fluids relevant to secondary
7 transmission. It allows prospective collection and
8 more complete characterization of the health status
9 of infected persons and the prospective study for
10 evidence of secondary transmission.

11 Weaknesses include incomplete availability
12 of health records and of specimen collection. In
13 particular, we have had difficulty getting people
14 to submit semen specimens. It has potential
15 enrollment biases--you will hear later that only a
16 subsegment of the people eligible for the study
17 have chosen to participate--and incomplete
18 enrollment of contacts.

19 And our last ongoing investigation is the
20 "Investigational Look Back Study for Recipients of
21 Blood Products from Simian Foamy Virus (SFV)
22 Infected Donors." It identifies recipients of
23 blood products from donors confirmed to have been
24 infected with Simian Foamy Virus and tests these
25 recipients for infection.

1 The strength of this study is the
2 provision of specific information on infection
3 status of recipients of blood products from donors
4 who are documented to be SFV infected. Weaknesses
5 include the absence of information on infectivity
6 of the blood products per se, and limited power to
7 define transmission risk due to very small numbers
8 of recipients and an even smaller number of
9 traceable recipients.
10 So I'm going to present sort of composite
11 data from all of these studies, and I'm dividing it
12 by questions it addresses rather than which study
13 it comes out of, but I have sketched for you the
14 protocols under which we are collecting this
15 information. So first let's talk about data in our
16 hands that may address SFV transmissibility,
17 beginning with primate-to-human transmission.
18 Of 279 participants enrolled from 12
19 institutions, 11, or 3.7 percent, are seroreactive
20 for SFV by Western blot. And all the data that I
21 am presenting to you is up to date as of the date
22 in September when we originally expected to present
23 this talk. There may be some small additional data
24 collected in various places. There is nothing that
25 changes the overall picture.

1 So 3.7 percent seroreactive for SFV by
2 Western blot. Due to enrollment bias, this likely
3 overestimates the prevalence of infection in the
4 exposed population, although we can't give you any
5 estimate of to what extent. SFV DNA was identified
6 by PCR and peripheral blood lymphocytes of all 10
7 of the 11 who provided additional samples for
8 genetic testing, for DNA testing.
9 Biogenetic analysis of the integrate
10 sequence indicated that the infecting SFV viruses
11 probably originated from chimpanzees (n = 5), from
12 baboons (n = 4), and from an African green monkey
13 in one instance. These 10 workers confirmed
14 frequent exposures to body fluids of the implicated
15 species, and in some but not all instances,
16 injuries associated with these species. The
17 duration of occupational exposure ranged from 4 to
18 41 years, with a median of 20 years.
19 And the testing of archived serum when it
20 was available--which there was very limited
21 availability--identified durations of documentable
22 seropositivity between 2 and 25 years, with a mean
23 of 19.5 years. And again, the two-year limit is,
24 we could get archived serum two years back. We
25 couldn't get archived serum further back, so that

1 it's an open question as to in fact how long that
2 person has been infected.
3 Five of the 11 SFV seroreactive persons,
4 but no contacts, have enrolled for long-term
5 follow-up. These five represent the extremes of
6 the larger group in terms of exposure, having
7 worked from 4 to 41 years, with a mean of 21.2
8 plus/minus 12.2 years, and having documented
9 durations of seropositivity of 10 to 24 years, with
10 a mean of 17.5 years. Combined, they represent a
11 total of 85 person-years of infection. All five
12 reported histories of both mucocutaneous exposures
13 to non-human primate body fluids and of
14 occupational injuries with skin penetration.
15 Now, this slide, I attempted to capsulize
16 our data that may speak to human-to-human
17 transmission, beginning with evidence of virus
18 presence in body fluids.
19 So SFV DNA was identified by PCR in
20 peripheral blood lymphocytes from all 10 infected
21 persons on at least two separate occasions. In
22 other words, each person had blood collected and on
23 at least two separate occasions tested positive by
24 PCR. Virus isolation from peripheral blood
25 lymphocytes was successful in four of the nine SFV-infected

1 persons, but was isolated again on at
2 least two separate occasions from each of these
3 four who were positive.
4 Additional biologic specimens have been
5 received from four enrollees in the long term
6 follow-up study. Throat swabs from two of the four
7 were SFV DNA positive by PCR, but virus was
8 isolated from only one, who we will call Case A.
9 However, virus was isolated from throat swabs from
10 Case A on two separate serial attempts, by which I
11 mean the throat swabs were collected on two
12 separate serial occasions.
13 Saliva samples were PCR positive for DNA
14 from only one of these four persons, again Case A,
15 the only person from whom virus was isolated from
16 throat swab, but virus was not isolated from this
17 saliva sample. A single specimen each of urine and
18 semen were available from only one participant,
19 again Case A, who importantly has a history of
20 hemospermia; which, for the non-medical people in
21 the audience, that is a relatively common but
22 abnormal but completely benign condition in which
23 blood is present in the sperm. It's not that
24 uncommon, actually.
25 SFV DNA was identified in both fluids by

1 PCR, both urine and sperm. But unfortunately, due
2 to this condition of hemospermia, you can reason
3 that if we know viral DNA is present in the blood
4 and we know the blood is present in the sperm, the
5 only reason to not find viral DNA in the semen and
6 the urine would be sampling error. So
7 unfortunately, the only case in which we have to
8 date been able to collect semen can't tell us
9 anything definitive about whether we identify viral
10 PCR there because it's normally present in the
11 semen and the urine, or because in this person
12 blood contaminates the semen and the urine.
13 SFV DNA was identified in both semen and
14 urine, but the volume was insufficient to attempt
15 culture. So we're hoping to get some more semen
16 specimens from Case A and also from other
17 participants, since that's obviously an important
18 exposure route to define.
19 This data suggests that virus can be
20 repeatedly isolated from peripheral blood
21 lymphocytes of only about half of infected persons,
22 despite consistent PCR identification of the
23 presence of viral DNA in PBLs of all infected
24 persons. SFV DNA was present in the throat swab of
25 only about half, two of the four tested people, and

1 the virus was isolated from throat swabs of only
2 one of these two. SFV DNA was identified in saliva
3 of only the throat culture positive person.
4 Now, again I remind you that for the five
5 people in the long term follow-up study, and we're
6 hoping to enroll additional people in that, we will
7 be recollecting and retesting these specimens at
8 periodic intervals for at least five years, so with
9 time we'll have more information on this.
10 In terms of our combined data that may
11 address the question of contact testing or
12 transmissibility between humans, all 10 of the SFV-infected
13 workers are male. The wives of six have
14 been tested and remain uninfected, despite a
15 documented mean of at least 14.5 years of exposure.
16 And by that I mean we're looking at how long the
17 infected husbands have been documented to be
18 seropositive, as opposed to how long they have
19 potentially been exposed and may potentially have
20 been infected.
21 These six wives include the wives of three
22 persons who, again, have enrolled for the long term
23 follow-up study, including Case A. These three
24 remain negative after a combined minimum of 51
25 person-years of intimate exposure. And we have

1 questioned these participants about the nature of
2 their relationships and also use of barrier
3 contraceptives or other things that might minimize
4 exposure, and they all report ongoing sexual
5 intimacy and no significant use of barrier
6 contraceptives, spermicides, anything that you
7 might hypothesize would artificially account for a
8 lack of transmission.
9 Six of the 10 SFV-infected workers report
10 a blood donor history. One of these six had
11 stopped donating prior to the retrospectively
12 identified date of infection. Four of the
13 remaining five, including Case A, were
14 retrospectively confirmed to have been infected
15 prior to the date of the most recent donation.
16 Recipients of blood components donated by one of
17 these four have been traced.
18 Case A, a blood donor, has been
19 characterized more extensively than the other
20 infected cases, and over a two-year period Simian
21 Foamy Virus was isolated from Case A's peripheral
22 blood lymphocytes on two of three serial attempts,
23 and from the throat swab on each of two serial
24 attempts. This is the data you've already heard
25 about. PCR positive cell pellets from throat

1 swabs, saliva, urine, semen, and peripheral blood
2 lymphocytes from Case A argue that SFV-infected
3 cells are present in all of these sites.
4 Case A made six donations between 1992 and
5 1997. Recovered plasma from two donations, 1993
6 and 1994, was sent for manufacturing into plasma
7 derivatives. Samples of one lot of albumin and
8 three lots of plasma protein fraction were
9 available and were tested negative by both Western
10 blot and RT-PCR. Of 11 transfusible components,
11 two were manufactured into non-transfusible
12 reagents and an additional two were not traceable.
13 Recipients of seven components transfused
14 between 3 and 35 days after donation were
15 identified. One recipient of fresh frozen plasma
16 died the day of transfusion, something that was
17 quite obviously not related to the transfusion.
18 One recipient of packed red cells died four years
19 after transfusion, of Crohn's disease and chronic
20 osteomyelitis, bacterial osteomyelitis. One living
21 recipient of platelets was not available for
22 testing. Two recipients of red cells, one
23 recipient of filtered red cells, and one recipient
24 of platelets tested SFV negative 1.5 to 7 years
25 after transfusion.

1 And I should tell you that this look back
2 study was submitted for publication. It's
3 currently under review. We had hoped to be able to
4 report it was in press by now. We hope it will be
5 soon.
6 Now, all of the data we have that may
7 address the question of whether infection equals
8 disease, I have combined here. All 10 SFV-infected
9 workers are male, and report only chronic health
10 problems not suggestive of infectious etiology.
11 You could deduce, if you think about the duration
12 of their occupational exposures, that these are
13 largely men probably between 40 and 60, and they
14 have a variety of expected diseases of aging:
15 degenerative joint disease, adult onset diabetes,
16 things like that. But nothing that we could
17 tentatively associate with an infectious etiology.
18 Five of the 11 SFV seroreactive persons,
19 including Case A, enrolled for long term follow-up.
20 The mean age of these five in enrollment was 51
21 years, with a range from 41 to 65 years. And
22 again, the five who enrolled for long term follow-up, as
23 best we can tell without having comparable
24 data available on the ones who are not yet
25 enrolled, do seem to be relatively representative

1 or at least to represent the extremes of exposure
2 among the affected group.
3 Complete blood counts, blood chemistries,
4 and liver function tests were completely within
5 normal limits for two of these participants. Three
6 persons had occasional values that minimally
7 exceeded the limits of normal. The abnormalities
8 reported all resulted from one-time testing. None
9 have yet been confirmed by repeat testing. And the
10 abnormal values, if they persist on repeat testing,
11 are likely, in our judgment, unrelated to SFV
12 infection, although of course the data is too
13 preliminary to say anything definitive about that.
14 Among these abnormal tests, one
15 participant had a low number of eosinophils. A
16 second had a mildly elevated ALT, which is a liver
17 function test, for the non-clinical people. A
18 third had mildly elevated hemoglobin, hematocrit,
19 and red cells, combined with a mild
20 thrombocytopenia and a CD4 count just below the
21 lower limits of normal.
22 This last participant also reports
23 congestive heart failure associated with congenital
24 heart disease, and his current primary care
25 physician is a cardiologist, although he is a

1 relatively young man. So he's not able to give a
2 lot of details without accessing his medical
3 records for review, but I wondered about some
4 things such as Down's syndrome associated with a
5 marrow dysplasia and heart disease, but that's
6 speculation on my part.
7 So I have summarized the data we have to
8 date. These are ongoing studies. The last three
9 are ongoing studies. On this slide we tried to put
10 some thought into what the major questions are for
11 future study.
12 We, and when I say "we" I mean CDC and in
13 particular the HAR Branch, Dr. Folks' branch, plan
14 to continue extensive research programs that I've
15 just outlined, including continuing to characterize
16 human SFV infections, to document stability or
17 change in those infections over time, and to search
18 for evidence of secondary human transmissibility
19 including conducting trace-back studies on
20 recipients of blood products from infected donors
21 when possible. Our resources are fully committed
22 to this rather extensive program at present.
23 We will be also expanding our surveillance
24 to include--not only to continue to try to enroll
25 more populations of occupationally exposed humans

1 in the U.S., but to also include monkey hunters
2 from Cameroon in order to investigate transmission
3 of SFV from feral non-human primates to humans.
4 Additional research specifically targeted to
5 characterize the infectivity of specific blood
6 components can be envisioned that is outside the
7 range of both our current commitments and our
8 available resources.
9 Such investigations would include studies
10 or could include studies designed to test the
11 ability to transfer infection from an SFV-infected
12 non-human primate into an SFV-negative non-human
13 primate of the same species via blood components
14 collected and processed similarly to current blood
15 banking standards. A parallel experiment could be
16 to process blood donated by an SFV-infected human
17 donor, and to attempt infection of SFV-negative
18 non-human primates by transfusion of various blood
19 components from the human donor. This would
20 require the use of non-human primates; probably you
21 could consider whether this would need to use non-human
22 primates of the same species as the SFV virus
23 infecting the human, and if that is the case, then
24 most likely it would require the use of
25 chimpanzees, which is difficult.

1 Again, we raise, outline these as issues
2 for further study, but I reiterate that they are
3 outside the range of both our current commitments,
4 our direct agency mandate, and our available
5 resources.
6 Thank you. Are there any questions?
7 CHAIRMAN NELSON: Questions for Dr.
8 Chapman? Yes?
9 DR. STUVER: Was there any difference in
10 the exposure histories of the workers who were SFV
11 positive compared to the workers that weren't?
12 Like were they more likely to have been bitten or
13 to have had a saliva exposure, any differences
14 there?
15 DR. CHAPMAN: Yes. We have some
16 incomplete analysis on that, and we have a--unfortunately,
17 our best place to collect that
18 information well is in the long term follow-up
19 study where we only enroll infected people, so we
20 don't have the complete comparisons. In the 1,200,
21 the surveillance study, we have a long--first of
22 all, we are asking people about exposure histories
23 that date back sometimes 20 years, and we're doing
24 it with a self-administered questionnaire. And
25 this is a population that ranges from Ph.D. level,

1 a veterinarian research scientist, to semi-literate
2 or illiterate monkey handlers.
3 So I'm saying these are the caveats behind
4 our ability to look at this data, but if you look
5 at--there is a published analysis of exposure
6 history from the original surveillance study which
7 was designed to look at SFV workers. I believe the
8 first author on that is Mark Sotir, S-O-T-I-R.
9 Bill Switzer is an author. Rema Kabaz is a co-author. And
10 it was published, I think, in the
11 Journal of Primatology. Tom, do you remember?
12 It's somewhere in the primate worker literature.
13 It tried to--this is background--tried to
14 look at overall exposure histories in this group,
15 and in that group, in all the people who
16 participated, and while there was again not
17 complete capture of the exposed populations at
18 these institutions, it was a pretty close to
19 complete capture because they were looking for SFV,
20 which can be presumed to act like HIV, therefore
21 could be a treatable disease if you identify it,
22 and so forth. At least a third of infected workers
23 reported injuries with percutaneous exposure.
24 When we tried to do a subset analysis of
25 the 300 that we tested for SFV, my memory is that

1 we found a higher, a somewhat higher proportion
2 that were infected. But more to the point, if you
3 cut to the comparable worker population--and these
4 infected workers tend to be people who have been in
5 the field for over 20 year, which importantly means
6 they predate 1988 or so when universal precautions
7 became more standard in human medicine and also in
8 working with non-human primates. They also tend to
9 be people who have very intimate contact with non-human
10 primates. They--well, they have very
11 intimate contact with them.
12 It's not clear--and again they are
13 limited. It's difficult to make these comparisons.
14 The data is imperfect. It's not clear that there
15 is a substantially higher proportion. If you look
16 at, with our attempt to look at that proportion of
17 people on this questionnaire, about 75 percent
18 reported these kinds of injuries as opposed to a
19 third of the overall workers.
20 Looking at the first four humans that we
21 reported in Nature Medicine who were infected,
22 three of them could report an exposure history like
23 a bite from the species whose virus infects them.
24 You know, a guy is infected with what appears to be
25 a chimpanzee origin SFV. He was bitten by a

1 chimpanzee. One of them could give no history of
2 that sort. That's the 75 percent exposure rate.
3 I'm not sure exactly how that stacks up
4 with our larger group, but the answer is, this
5 group may have a slightly larger prevalence of
6 those kinds of exposures. It's hard to know how to
7 interpret that because it's not clear that it's
8 statistically larger than a group within that total
9 group with comparable exposures. There is at least
10 one person whose infection can't be explained by
11 that route. And what they all have is close
12 interactions over many years with these primates
13 and their body fluids, and copious opportunity for
14 splash exposures and so on.
15 CHAIRMAN NELSON: I am told to announce
16 that Dr. Jonathan Allan, who is an expert in this
17 area from the Southwest Foundation for Biomedical
18 Research, is hooked up with a phone connection--he
19 couldn't be at the meeting--in case there's any
20 questions that could be addressed to him. Or, Dr.
21 Allan, did you want to make any comments?
22 DR. ALLAN: Yes. I apologize for not
23 being there, first of all. I really wanted to be
24 there, but circumstances didn't allow me.
25 I had a question for Louisa, even though I

1 only got to hear the end of your talk. Wally
2 Hiane's group at the CDC there published a paper
3 recently on infection of two primate workers with
4 simian retrovirus, and so my first question would
5 be, has there been any follow-up in terms of these
6 SRV-infected people?
7 And, second of all, since primates are
8 known to be infected with STLV, did the serosurvey
9 also include HTLV seroscreening of these primate
10 workers and whether or not any of them were HTLV
11 positive?
12 DR. CHAPMAN: To answer your last question
13 first, yes, the expanded surveillance tests for
14 SIV; Simian Foamy virus, the results of which you
15 have heard reported; also simian Type D virus and
16 STLV. We have identified no workers who appear to
17 be infected with STLV. We have identified no
18 additional workers who appear to be infected with
19 SIV, beyond the one that was reported in the New
20 England Journal of Medicine, the first author, Dr.
21 Kabaz, also out of Folks' branch, and I think that
22 was 1995 when that report came out, or so. Tom may
23 have a comment on that later.
24 You have seen the data we have gotten on
25 Simian Foamy Virus. The simian Type D retrovirus

1 paper that Dr. Allan referred to is two people
2 identified under the surveillance who had
3 seroreactivity or seropositivity to serologic
4 testing for simian Type D retrovirus. One of them
5 was seropositive and then later reverted to
6 seronegative. The second one was persistently
7 seropositive on two serial tests.
8 We were not able to identify evidence of
9 simian Type D retrovirus by PCR or by viral
10 culture, and were not able to transfer infection by
11 injecting blood from the infected human into
12 uninfected macaques. The interpretation of that
13 data by the majority of authors was that it was
14 still appropriate to call it infection.
15 Personally, I think you have to make allowances for
16 that persistent seropositivity. But there has been
17 no further follow-upon on either of those beyond
18 what I just reported here, which was also in the
19 paper, Jon, that one of the initially seropositive
20 ones reverted to seronegative.
21 CHAIRMAN NELSON: One issue, that one can
22 look at particularly retroviruses by looking at the
23 degree of genetic diversity over time, and I would
24 think that in order to induce pathology there has
25 to be replication, and the replication could be

1 inferred into time points, how much genetic
2 diversity there is because of the reverse
3 transcriptase error rate. Have those kinds of
4 studies been done with Simian Foamy Viruses, either
5 in primates or in humans, to see in comparison,
6 let's say, to HIV or other pathogenic viruses, how
7 much genetic diversity there is over time?
8 DR. CHAPMAN: I'm going to defer that
9 question to Tom Folks, who is the branch chief.
10 DR. FOLKS: Yes, I'll just make a quick
11 comment about that. Actually Dr. Sandstrom has a
12 paper in JV that has shown significant homology
13 between an early-infecting virus and a later, the
14 later-infecting virus, as well as looking at the
15 individual that has been infected the longest with
16 SIV chimpanzee strain of virus. And there is
17 nearly 97 percent homology between the virus that
18 was isolated from the chimpanzee, that putatively
19 infected the individual 25 years ago, and the virus
20 that we isolated from the human, so there is very
21 little replication. It's very stable over time.
22 CHAIRMAN NELSON: Thank you. Dr. Epstein,
23 did you have a comment?
24 DR. EPSTEIN: Yes, a question for Dr.
25 Chapman. Did I hear you correctly state that one

1 of the laboratory abnormalities in one of the three
2 long term follow-up individuals was an abnormal CD4
3 count?
4 DR. CHAPMAN: No, I think it was a CD8.
5 Let me--
6 DR. EPSTEIN: But the question more
7 broadly is, you know, clearly if there is a
8 lymphocytotropic virus, it raises the question
9 whether there are any immunological abnormalities,
10 and so the broader question is, how extensive have
11 the immunological studies been in the persons
12 infected with Simian Foamy Virus? And related to
13 that, how carefully did we look for Simian Foamy
14 Virus when there were studies about a decade ago
15 regarding idiopathic CD4 T lymphocytopenia? I know
16 that some of that was done actually by Dr. Hewlett
17 at FDA, but the question is, how broad was that
18 survey in people with abnormalities of CD4?
19 DR. CHAPMAN: I'll address that, and then
20 Tom may want to add something, depending.
21 The specific report I reported was a CD8
22 count that was just below the lower limits of
23 normal, and it was literally like, you know, if the
24 cut-off was 2, it was 1.5 or something like that,
25 in an investigational laboratory. That is also the

1 same individual that had the mildly elevated
2 hemoglobin, you know, red cell indices, and the
3 mild thrombocytopenia, so there's something funny
4 going on, and the congenital heart disease.
5 In terms of how extensive the immunologic
6 studies are, at present again we've got five people
7 enrolled and we have, I think, one-time testing.
8 Possibly at this point we're moving up to two-time
9 testing on a subset of them. So everything we have
10 is very preliminary.
11 The design of the study, for simplicity I
12 said we test annually, the design of the study
13 actually is that we enroll people and get samples
14 at enrollment and question them. We get samples
15 and question them again at six months, and then
16 thereafter it's annual from enrollment for five
17 years. And the intent is at the end of five years,
18 if this still seems valuable enough to commit the
19 resources, to ask both the IRB and the participants
20 to allow us to re-enroll for another five years and
21 perhaps beyond that. So at most we have one-time
22 testing on most of these people.
23 In terms of what immunologic studies are
24 being done, James Cummings came to CDC as a post-doc, to
25 Tom's group, recruited by Dr. Sandstrom

1 when he used to be part of us, specifically to try
2 to look at mucosal immunology studies in this
3 population, and is beginning to do some of that
4 work.
5 The CD4 count that I reported was done in
6 Tom Spira's lab. He's a collaborator on the long
7 term follow-up study. He was in fact one of the
8 early people involved in helping me design it. And
9 he is doing lymphocyte phenotyping and other
10 studies in his laboratory with the intention of
11 doing more intensive investigations to follow up
12 any abnormalities identified. He is also the
13 person who is the point person at CDC for the
14 idiopathic low CD4 studies that you're referring
15 to. I don't recall if he looked at Simian Foamy
16 Virus and other retroviruses then, but certainly
17 he's looking at this in light of that now.
18 Do you want to add anything, Tom? Okay.
19 CHAIRMAN NELSON: Is it known that CD4 is
20 the receptor for Simian Foamy Virus? I saw in some
21 of the papers that I was sent that somebody has
22 postulated that CD8 may be, the CD8 receptor may be
23 important for SFV. Is
24 that--
25 DR. NEUMANN-HAEFELIN: At least it is the

1 population of CD8 positive cells that harbors
2 Simian Foamy Virus, and I wanted to answer the
3 question concerning the HIV negative CD4 T cell
4 deficient people. We looked into about 10 of them,
5 9 or 10, and there were no markers, no serological
6 markers nor PCR, so no hint on foamy virus.
7 CHAIRMAN NELSON: This is Dr. Dieter
8 Neumann-Haefelin from the University of Freiburg in
9 Germany that just made the last comment.
10 DR. CHAPMAN: And let me just add to my
11 response to Dr. Epstein that in addition to the
12 studies I outlined, James Cummings came to us from
13 the University of Alabama, and there are a group of
14 collaborators at the University of Alabama who are
15 also looking at immunology, interested in doing
16 studies with immunologic characterization of these
17 folks.
18 DR. HEWLETT: Indira Hewlett from the FDA.
19 We actually did look at SFV in the PBLs of our ICL
20 patients back at that time, and they were all
21 negative. I just wanted to mention that.
22 CHAIRMAN NELSON: I take it that there are
23 no data yet from Africa, and I know that there are
24 populations there that have really extensive
25 exposure to feral animals. They could be more

1 exposed than even the zookeepers.
2 DR. FOLKS: Yes, that's a good point, and
3 that has come up actually with a lot of the
4 discussions, and we have a field site laboratory in
5 Yaounde, Cameroon, and we are currently involved
6 with Johns Hopkins and Don Burke, who has a very
7 big program looking at the interface between humans
8 and animals in these types of viruses that
9 transmit. So we're hoping that we'll get some
10 information out of that.
11 Generally the animals in the wild have a
12 much lower prevalence, so that the odds of a hit
13 are going to be low, so we have to look for a
14 fairly high population, large population.
15 CHAIRMAN NELSON: Any other questions?
16 Thank you very much, doctor. Oh, another comment.
17 DR. NEUMANN-HAEFELIN: Dieter Neumann-Haefelin.
18 May I also comment on that? We had a
19 cooperation with the Pasteur Institute and
20 investigated more than 400 people who had close
21 contact with feral foamy virus--this is feral foamy
22 virus, but feral non-human primates--and were
23 exposed to them. We did not really find
24 seropositivity. There were some weakly positive
25 that could not be confirmed, and using PCR we did

1 not find positivity by PCR, so no genomes.
2 CHAIRMAN NELSON: Dr. Allan, did you have
3 any more comments?
4 DR. ALLAN: No.
5 CHAIRMAN NELSON: Okay. Thank you very
6 much.
7 Dr. Sandstrom from Health Canada.
8 DR. SANDSTROM: I would like to thank the
9 organizers of the meeting for giving me the
10 opportunity to come down here and present some of
11 the work which we are currently doing up in Ottawa.
12 I think probably most people have guessed that I
13 have a past life at the CDC. I have I think the
14 unique advantage of being the only Canadian who was
15 hired by the U.S. Government that's currently
16 working for the Canadian Government, so I have all
17 the right privileges of working for two big
18 bureaucracies.
19 The work that I'm going to present here
20 was done within the Bureau of HIV/AIDS, STD, and TB
21 in the Centers for Infectious Disease Prevention
22 and Control in Health Canada, as part of Health
23 Canada's blood safety program, which is a program
24 which was set up in the wake of the contaminated
25 blood tragedies in the 1980s to ensure that the

1 Canadian blood system had advance surveillance for
2 any potential emerging threats, and the work is
3 done in very close collaboration with scientists in
4 Tom Folks' group down at CDC.
5 The study itself was really focused on
6 trying to gain some information on one specific
7 question that emerged from the work that came out
8 of CDC, and that is that in all the surveillance
9 programs that have been run to date, the infecting
10 species were what we would term maybe perhaps the
11 "boutique" animals that were used in research.
12 These are baboons and African greens and
13 chimpanzees. Whereas the commonly used animals,
14 which are the macaques, to date there have been on
15 documented infections, and there is a range of
16 reasons for this.
17 It could be a barrier, some type of
18 natural barrier in terms of primates out of Africa
19 can transmit, whereas Old World primates out of
20 Asia can't. It could be because of under-representation.
21 That's not to say there was under-representation in previous
22 studies, but it could
23 be because of under-representation of macaque
24 workers within those groups. Or alternatively it
25 could be that people just handle macaques

1 differently, and one of the reasons is, is because
2 they carry some other rather nasty viruses which
3 can be lethal if an individual becomes infected.
4 So what I'm going to outline here is to
5 start out with the trends in primate importation
6 and utilization, and this is really just to give
7 people a snapshot of what I was saying about the
8 predominance of macaques being used in research; a
9 description of Health Canada's animal research
10 division, and the reason this was--it's like one of
11 those opportunities that you have, as we had up in
12 Ottawa a primate facility which housed exclusively
13 macaques; and as well as the results of our current
14 ongoing investigations.
15 So, as I was saying, macaques have
16 historically been among the most common non-human
17 primate used in research. Most primates that are
18 currently used in research are of the cynomolgus
19 macaques, although rhesus macaques are used in
20 certain circumstances.
21 And, as I said, despite frequent, what we
22 would anticipate as frequent occupational
23 exposures, to date there had not been a documented
24 case of human SFV infection originating from
25 macaques. And we felt this was important because

1 it suggests whether or not animal workers as a
2 whole were being exposed, or whether it was justa
3 subset of animal workers who were dealing with
4 these African primates that presented a risk of
5 being infected.
6 This is some data that was provided to use
7 from Tom DeMarcus, who is from the Division of
8 Quarantine down at CDC, and this shows importation
9 of non-human primates into the United States. The
10 point of this is really just to say that if you see
11 the large green bar here on the left of each year,
12 that represents the number of cynomolgus macaques
13 which are imported into the United States. Next to
14 that is rhesus. And so by and large, the majority
15 of animals which are being imported into the U.S.
16 are from the macaque species. Just another way of
17 putting it, out of the 15,000 animals or 15,000-plus animals
18 that were imported, about 14,000 of
19 them are macaques.
20 This is sort of another way of slicing it
21 out of Canada. We don't have the importation data
22 but we do have animal use data, and what this
23 represents is the number of times macaques are
24 being applied in a research study. It's not to say
25 that these are different animals. One animal might

1 be represented a number of times on applications,
2 but it does give us a measure of possible
3 exposures. And again, the green bar on the left of
4 each year represents cynomolgus macaques, and then
5 right next to that is rhesus. So, again, the use
6 of cynomolgus macaques and rhesus macaques is
7 extensive in research.
8 So the study objective was to screen for
9 human SFV infection of macaque origin in a cohort
10 with high levels of exposure to macaque species,
11 and for this we took advantage of the primate
12 facility which is located just down the road from
13 our labs. This is a primate facility which I don't
14 know how early on it was established, but prior to
15 1983 housed both rhesus and cynomolgus macaques,
16 and in 1983 they brought in a number of wild or
17 quite a few wild-caught cynomolgus macaques from
18 the Philippines and initiated a breeding program.
19 Currently there is about 240 animals in
20 the colony. They have temporarily suspended the
21 breeding program, but at the height of the breeding
22 program there could be up to as many as 1,200,
23 1,200 animals. They were used primarily early on
24 for vaccine safety studies.
25 The colony is a specific pathogen-free

1 colony, which means that it's herpes B virus free,
2 and depending--we don't have any solid data on
3 this, but depending on how you want to look at or
4 consider what I said earlier about the presence of
5 other pathogens possibly meaning that people were
6 handling or would handle the animals differently,
7 this could be partially responsible for what we
8 have seen. In addition, when we took a look at the
9 seroprevalence of foamy virus in this colony,
10 although the colony had been bred free of a number
11 of other pathogens, foamy virus persisted, so we
12 still have an 80 percent foamy virus prevalence
13 within the colony. This is just what I was saying
14 earlier about the year-by-year, how many animals
15 were present in the colony.
16 Okay, so the study was an anonymous,
17 unlinked convenience sample of workers having
18 contact with non-human primates or their bloods and
19 tissues, so really this is very, very similar to
20 what Louisa had presented earlier with regard to
21 their earlier studies that were performed by the
22 CDC.
23 The workers were screened using an
24 immunoblot, and one of the observations that we've
25 made is that there tends to be a fairly wide

1 difference in terms of seroreactivities depending
2 on the species. And so the way we did this was to
3 go with a cocktail of antigens which represent SFV-1, which
4 is macaque; SFV-3, which is African Green;
5 SFV-6, which is chimpanzee. And then in addition
6 to that we also cultured virus right out of the
7 monkeys that we had in the colony and used that in
8 the Western blot as well. Any specimens which we
9 found from individuals who are found to be Western
10 blot positive would then go on for PCR
11 confirmation, looking for the presence of 153 base
12 pair foamy-specific fragment in the pool gene
13 located in the PBLs from these individuals.
14 So this just gives you a breakdown of sort
15 of the occupations that people describe themselves
16 at. Thirty-three percent were laboratory animal
17 technicians, and these would be individuals that
18 would go in and clean cages. The animal health
19 technicians would do everything that laboratory
20 animal technicians would do, in addition to
21 assisting in surgical manipulations of the animals.
22 And there is a smaller subset of laboratory
23 scientists and veterinarians who similarly worked
24 with primates or primate tissues.
25 The average age is 45 years. Fifty-six

1 percent male, 44 percent female. They reported an
2 average of 13 years exposure to cynomolgus macaques
3 and 10 years exposure to rhesus macaques. This is
4 to give you an example of the person-year exposure.
5 If you take the green part of the circle, that's
6 cynomolgus and rhesus macaques, and it translates
7 into about 85, 86 percent of the exposure, person-years
8 exposure, was to macaques in this group.
9 If we looked at individuals, and part of
10 the research protocol involved filling out a
11 questionnaire, we found that 90 percent of them
12 reported having some form of occupational exposure
13 to fluids from animals, and if you took that 90
14 percent, you would find that 71 percent of those
15 that had reported exposure, 71 percent had been
16 bitten, 79 percent scratched. Again, this is just
17 sort of a different way of slicing that. This is a
18 report of the total number of bites. Over 90
19 percent of the bites which occurred within this
20 group were from macaque species.
21 So 2 out of the 46 participants--the group
22 that we advertised to was 82, 46 enrolled--2 out of
23 those individuals had positive serologic results to
24 foamy virus using the Western blot assay which I
25 described earlier. One of these individuals

1 demonstrates a very strong serology pattern which
2 should be predictive of infection. The second
3 individual, although they have the bands which are
4 definitive of infection, it's much weaker than what
5 we saw in the first individual.
6 One of the individuals, the one with the
7 strong serology, has been confirmed to be infected
8 with SFV by doing PCR on the PBLs. And this just
9 gives you an example of the Western blot here. I
10 don't know if I can actually point with anything
11 down here. No, I guess I can't, and I don't want
12 to walk away from the mike because you'll never
13 hear me.
14 But along the top we have a variety of
15 species of primates, chimp, baboon, and right next
16 to each of those--oh, great. Thanks. Okay, so we
17 have a couple of different species that we used as
18 control animals. We have chimp and then a negative
19 chimp, which shows this clear pattern of
20 reactivity. This is a gag doublet which we
21 somewhat use as a diagnostic, to call diagnostic
22 positives. This is a baboon, followed by negative
23 baboon. And this is the human, the first human
24 that we saw, which is positive, which clearly has
25 the same pattern. Here is a cynomolgus macaque

1 down here from the colony itself, which was
2 positive. So you see there's similarities in the
3 patterns between these.
4 And this is that second individual I had
5 referred to, which has this much weaker pattern,
6 although it does have--it doesn't show up well on
7 this one, but it has three different bands. And
8 what I have shown down here was, these are made out
9 of crude lysates from foamy virus infected cells.
10 This is just basically the crude lysate, which
11 shows that the reactivity we are seeing is only in
12 the presence of cells which have virus in them, so
13 it doesn't appear to be some type of background
14 reactivity.
15 The question was asked earlier, whether or
16 not individuals who were infected showed anything
17 different in terms of their exposures. What we
18 found was, you know, and again we're looking at
19 quite a small sample size here, but nothing really
20 stood out. The group as a whole was highly
21 exposed, and these individuals just look normal in
22 terms of being highly exposed individuals. They
23 both reported prolonged and ongoing exposure to
24 cynomolgus macaques, and that's because this is
25 predominantly the species which is in the colony

1 now, as well as previous exposure to rhesus
2 macaques, and all of them have reported--the two
3 individuals have both reported some form of
4 occupational accident which may have resulted in
5 infection.
6 This is the genome of SFV, and basically
7 what I'm showing here is that we used this region
8 down here, which was identified from the work out
9 of CDC as a relatively reasonable area to be going
10 after because the sequence stability within this
11 area allows you to use primers that can pick up a
12 number of different species. So we amplified a 153
13 base pair fragment from the infected individual.
14 That's shown right here, and then this was then put
15 into sequencing so that we could see what form of
16 virus was affecting the individual. This was work
17 that was done by Bill Switzer, who works in Tom
18 Folks' group at CDC.
19 And what we found is that in the one
20 individual that we were able to amplify from, Case
21 1 right here, that he clusters quite tightly in
22 here with this group of infections that come from
23 rhesus or cynomolgus macaques. And one thing I
24 guess to mark here is that although he clusters
25 most tightly to this rhesus, on this branch here

1 with rhesus, rhesus is actually represented over
2 here as well, so as best we can say right now is
3 he's just clustering in with the macaque
4 infections, which is different from what the CDC
5 has reported previously, where the infections are
6 down here with baboons, African greens, or
7 chimpanzees down here.
8 Okay, this is just--one of the questions
9 that we had asked on the questionnaire was blood
10 donation patterns of the individuals. And without
11 going into specifics about the two individuals that
12 we looked at, but looking at the group as a whole,
13 the Canadian Blood Services reports that 3 percent
14 of Canadians, eligible Canadians, donate blood on a
15 regular basis.
16 What we found was that 54 percent of study
17 participants reported at least one donation of
18 blood or blood products, and again we're looking at
19 a small sample size here. But out of individuals
20 that reported--the 88 percent of animal workers
21 that reported blood donations also reported bites
22 from non-human primates.
23 So this work was done by--he's the who
24 prepared the slides for me, so he actually left his
25 name off the list here, but it was done by a very

1 talented infectious disease fellow that I have
2 working in my group, Dr. James Brooks. Rick Pilon
3 did a lot of the molecular biology, in
4 collaboration with Bill Switzer at the CDC. And
5 this is just generally a collection of the other
6 people that have provided input into the study.
7 CHAIRMAN NELSON: Thank you very much.
8 Are there questions or comments for Dr. Sandstrom?
9 DR. NAKHASI: Paul, I think I had asked
10 you earlier that question also, whether these two
11 positives which you reported here were from the 22
12 out of 25 animal workers in your last slide?
13 DR. SANDSTROM: Twenty-two of 25? Oh, in
14 other words, were they part of the blood donation--
15 DR. NAKHASI: Yes, yes.
16 DR. SANDSTROM: One of the individuals was
17 within that group. In other words, in fact--well,
18 to the best of our knowledge, he is displaying some
19 evidence of infection. He also reported blood
20 donations. We have no idea at this point--unfortunately, we
21 haven't been able to do the real
22 eloquent look back studies that the CDC has done on
23 archival serum specimens to date, so we can't say
24 whether or not the individual was even infected at
25 the period in which he was donating blood. We hope

1 to get to that. I mean, there's sort of a range of
2 experiments that we're doing on the individuals
3 that are either infected or on the group as a
4 whole, but we're just on sort of the cusp of
5 getting those started right now.
6 DR. FITZPATRICK: Do you have planned a
7 study to follow up those donors and see, look at
8 the transfusion recipients?
9 DR. SANDSTROM: That would be one of the
10 studies that's proposed. At this point here, right
11 now we're just in the process of trying to enroll
12 the individuals in a follow-up research study. The
13 individual who reported the strong positive is--well, the
14 group as a whole has been offered
15 enrollment in a follow-up study, so we're hoping
16 that that will allow us to capture the individual
17 that is reported--that we found to be positive.
18 DR. NEUMANN-HAEFELIN: Neumann-Haefelin,
19 Freiburg. Dr. Sandstrom, have you done repeated
20 PCR on the PBL of the weakly positive or weakly
21 reactive worker?
22 DR. SANDSTROM: Yes, we've done it a
23 number of times, and we're not pulling anything out
24 of it right now. One of the problems that we had
25 is that it was, this was sort of like a one-shot

1 surveillance study. It was unlinked, so we weren't
2 able to go back to the individual and actually get
3 more blood. But in the attempts that we have used
4 either on--you know, we expended some of the sample
5 on virus culture, and on the remaining material
6 we've tried on a number of occasions with a couple
7 of different primer sets and have failed.
8 DR. NEUMANN-HAEFELIN: I should say that
9 in the African populations that we studied, we had
10 several individuals that reacted with proteins in
11 the suspicious position, and you can't really rely
12 on that. If it is not confirmed by PCR, it's only
13 a guess.
14 DR. SANDSTROM: Yes, I agree 100 percent.
15 I only fall short of actually saying the second
16 individual shows--the line is "serologically shows
17 evidence of infection," but I wouldn't ever say
18 that he's infected until we have some other
19 measure.
20 DR. NAKHASI: I must add at this point, I
21 think that this study prompted Health Canada to
22 approach us in CDC, and I would like to ask Paul,
23 what is Health Canada doing? I remember you had
24 some advisory committee meeting, and what have you
25 now as a policy-wise tried to do about these donors

1 and whether they should donate, or what's happening
2 with that?
3 DR. SANDSTROM: Let me preface that by
4 saying, number one, I don't speak for the
5 regulatory branch of Health Canada, the blood
6 regulators, nor do I speak for the Canadian Blood
7 Services, so I'm just speaking from the
8 surveillance. And what I would say is that the
9 discussions at this point--and it's discussions and
10 not decision--that the discussions at this point
11 are that, primarily that at this point there isn't
12 enough evidence to say one way or another. What
13 the final decision is, I can't say.
14 CHAIRMAN NELSON: I guess that there have
15 been a relatively small number of people who have
16 been clearly identified as being infected with SFV
17 who have been evaluated, and I wonder if any of
18 them have been immunosuppressed? Or have they all
19 been healthy?
20 DR. SANDSTROM: I think Tom or Louisa
21 could speak for the CDC. We don't have any
22 information on anything out of Canada.
23 DR. CHAPMAN: I'm sorry. Was the question
24 whether any of the exposed people were
25 immunosuppressed, or--

1 CHAIRMAN NELSON: No, I mean any of the
2 infected people were immunosuppressed. You had
3 some people that received blood donations who died,
4 you know, shortly thereafter, but obviously people
5 receiving blood donations could be
6 immunosuppressed. But also in terms of that
7 there's still an issue of is there any
8 pathogenicity in people who are infected, and both
9 the animals I guess and the humans so far don't--there is no
10 convincing evidence, but I just
11 wondered, have there been people who might be more
12 susceptible to some type of pathology?
13 DR. CHAPMAN: Among the identified SFV-infected
14 people that are reported out of our
15 laboratory, or that we know about that we haven't
16 reported yet--and Dr. Neumann-Haefelin may want to
17 speak to this because he has previously published,
18 at least he published jointly with us which are
19 part of this data, but previously published at
20 least two infected humans that are not part of the
21 data I am presenting, so he may want to address
22 this also.
23 But out of the ones that we have
24 identified, infected workers, there are none that
25 are known to be immunosuppressed. Now, what we

1 know about their medical history, we know by their
2 report, and again there are varying degrees of
3 sophistication. Some of these are veterinarians,
4 and quite obviously we've got a very thorough
5 medical history. Some of them are relatively
6 uneducated and in some cases perhaps semi-literate,
7 although quite intelligent people, but with a more
8 limited history.
9 There are some underlying health
10 conditions we know about that are associated with
11 some degrees of relative immunosuppression. For
12 example, one of the people who has been infected
13 for over 20 years has adult onset diabetes, which
14 runs in his family. That person has had adult
15 onset diabetes for many years. I don't trust my
16 memory, but I think probably at least 10, maybe
17 more. It has progressed to the point where, in
18 addition to oral medicines, he uses insulin. We
19 know there is some degree of decreased immune
20 competence in diabetics. They are more prone to
21 certain infections. But it's not, that's not a
22 condition we would call immunocompromised per se.
23 There is the one person we reported who is
24 an animal handler, who has an undefined sort of
25 congenital heart condition that has involved a

1 cardiologist, with these mild unexplained
2 abnormalities on the bone marrow, with mildly
3 elevated hemoglobin and red cells and mildly
4 depressed platelets and a CD4 count that was just
5 below normal, again on one-time testing. We don't
6 even know if those results will be there again, on
7 one-time testing. It may disappear when we repeat
8 test.
9 And again, when I see a congenital heart
10 disease in association with mild bone marrow
11 dysplasias in a person in middle age, I wonder
12 about Down's syndrome, and if that's in fact what's
13 going on here and he is progressing to bone marrow
14 dysplasia, he may have some degree of undefined
15 immunocompromise, but nothing that is defined or
16 that we can identify.
17 We will get more information about that as
18 we follow up, and one of the things that we will
19 attempt to do if we have--you know, when we have
20 repeat samples, if we have persistent clinical
21 abnormalities, is we'll probably try to get access
22 to medical records on those people, but we don't
23 have that now. And we don't even know if these are
24 going to be there on repeat testing.
25 Among the recipients of the infected blood

1 products, the person who died rapidly I think was a
2 trauma victim. I don't recall. The person who
3 died before we could test them, after four years,
4 died of Crohn's disease with chronic bacterial
5 osteomyelitis. People with Crohn's disease have
6 some degree of immunocompromise. We don't have
7 testing on that person.
8 The other people that we tested, one was a
9 child who had a congenital hematologic abnormality
10 that was treated with a bone marrow
11 transplantation. We were able to test on specimens
12 received after the transplantation. We were not
13 able to identify any stored specimens from before
14 the transplantation. So, again, the hematologic
15 abnormality is not one that is classically
16 associated with immunocompromise, although it's one
17 that's associated with increased rates of bacterial
18 infections. We found no evidence of infection in
19 that child.
20 CHAIRMAN NELSON: Blaine?
21 DR. HOLLINGER: I wasn't sure if I have
22 heard anyone say anything, whether they have looked
23 at any multipally transfused recipients such as
24 sickle cell patients, thalassemics, earlier
25 transplant patients like liver transplant patients

1 who used to get 100, 120 blood products during the
2 time, not currently that way. But has anyone
3 looked at any of these patients? Is there any data
4 on these?
5 DR. SANDSTROM: The question for that is
6 whether or not there's evidence of foamy virus?
7 DR. HOLLINGER: Pardon?
8 DR. SANDSTROM: Whether there's evidence
9 of foamy virus serology within those patients?
10 DR. HOLLINGER: Yes, whether there's any
11 Simian Foamy Virus in patients. I mean, that's
12 really what we're supposed to be addressing here.
13 CHAIRMAN NELSON: I think we've got
14 multiple levels of uncertainty. One is, we don't
15 know whether this virus causes or under what
16 circumstances it can cause any pathogenicity. And
17 then even if it can, we don't know whether it can
18 be--how readily or if it is transmissible by
19 transfusion. Given those two levels of
20 uncertainty, the decision should be at this point
21 fairly straightforward.
22 DR. SANDSTROM: Just one thing I'd like to
23 add to what Tom had said earlier, too, about the
24 stability of the virus, and I think Dieter could
25 add to it as well because I know he has done a

1 really nice study a couple of years back on it, but
2 as Tom said, the virus appears to be very stable
3 and if you look, it's 97 percent holding firm. But
4 even beyond that, a trick of molecular biology, you
5 can look at mutation rates at silent and non-silent
6 sites, so you can get a rough measure of whether or
7 not a specific genetic region is under pressure to
8 change, whether it's sort of randomly changing, or
9 whether it's actually under pressure to stay
10 unchanged.
11 And what we published in that paper was
12 that, at least in the human infection, that area,
13 and we were looking at an area that we thought
14 would be under type of pressure to change, it was
15 actually under a selective pressure not to change.
16 So in human infections, not only is the virus not
17 changing but there's some evidence that suggests
18 that there's a reason why that's the case. And I
19 don't know, you had done--
20 DR. NEUMANN-HAEFELIN: Neumann-Haefelin.
21 I still wanted to comment on the health of the
22 primarily Freiburg-based foamy virus positive
23 individuals. The living, the two living ones are
24 perfectly healthy and there is no hint on
25 immunosuppression, immunodeficiency. The oldest

1 one of them died due to alcohol abuse, so there is
2 no comment on that. We can't follow his history
3 back.
4 We did some work the other way around. We
5 investigated Africans harboring HIV, HIV
6 seropositive individuals, and we did not trace any
7 foamy virus infections person among them. The
8 number was 38, I think.
9 CHAIRMAN NELSON: Dr. Folks?
10 DR. FOLKS: Yes, let me just make a
11 comment about some anecdotal data that I think
12 would b very relevant regarding immunosuppression.
13 Is Jon Allan still on the line?
14 DR. ALLAN: Yes.
15 DR. FOLKS: You can hear me, Jon?
16 DR. ALLAN: Yes.
17 DR. FOLKS: Paul Sandstrom showed some
18 data about prevalence of captive animals, that
19 nearly 80 percent of them have foamy virus, and I
20 think that's probably similar in your colony as
21 well. Am I right?
22 DR. ALLAN: Yes. It depends on the age
23 group, and we actually did--and I actually sent
24 some information to Arifa Kahn yesterday--we
25 actually looked at--we have 3,600 baboons in our

1 colony. It's a large breeding facility, so there's
2 a lot of interaction between baboons. We don't
3 screen out viruses, so that the baboons have
4 several infections including Simian Foamy Virus.
5 What we find it that the adult animals are
6 virtually 100 percent infected, but what we were
7 interested in early on was to see at what point do
8 they get infected. I mean, how is this virus
9 transmitted? And the only way we could look at it
10 was epidemiological.
11 So we looked at different age groups, and
12 we had--fortunately, when they breed these animals,
13 they take them away from their mothers at six
14 months of age and then house the infants and
15 juveniles together. And so what we did was, we did
16 a cross-section of these different group-housed
17 animals, and we looked at animals that were 8
18 months to 14 months, we looked at a group that was
19 11 months to one and a half years, and we looked at
20 a little bit older age group.
21 And we find with Simian Foamy Viruses that
22 it doesn't appear to be transmitted from mother to
23 infant. We have less data on that, but we have
24 looked at milk, mothers, the milk, and the infants,
25 and we don't find any infection in the newborns or

1 within the first six months of their lives.
2 But what happens is, is the rates go up
3 tremendously within the first year and a half,
4 after about eight months of age, so to as high as
5 35 to 40 percent of these infants become both
6 seropositive and PCR positive. So by, let's say by
7 two years of age, almost 40 percent of them are
8 infected. So that would suggest that what you're
9 seeing is a non-sexual route of transmission,
10 probably saliva, as has been suggested by others,
11 and probably not mother-to-infant transmission.
12 So that's the data that we have here in
13 terms of natural transmission studies on Simian
14 Foamy Virus. I don't know if that's helpful or
15 not.
16 DR. FOLKS: Okay, thanks. Well, the point
17 I was going to make regarding immunosuppression,
18 and I think Arifa can probably speak to this, and
19 others who work with primates, is that clearly the
20 rhesus macaque, which is the primary animal that's
21 used in SIV research, when you see those animals
22 dying of extreme immunosuppression caused by SIV,
23 to my knowledge there is no reports of
24 opportunistic complications from foamy virus that
25 those animals clearly are co-infected with, which I

1 think really speaks to the benign nature of foamy
2 viruses, at least in their natural host.
3 DR. ALLAN: I would be a little more
4 cautious, because I don't know that there's any
5 studies that have actually looked at the relative
6 levels of expression of Simian Foamy Virus in an
7 AIDS-infected monkey. Maybe you know of some
8 studies. So I wouldn't want to say, unless we had--I mean,
9 what I haven't been able to see is, and I
10 don't know if anyone has this data, is to actually
11 look in the tissues for evidence of expression of
12 Simian Foamy Virus, either by in situ hybridization
13 or by immunohistochemistry. I think that's
14 something that really needs some attention.
15 DR. SANDSTROM: Yes, I think there is one
16 study. It's not in primates, though, but it's in
17 cats, that they looked at co-infections. And I'm
18 sorry, I can't remember if it was FELV or FIV, but
19 co-infection with foamy virus. And I'm trying to
20 pull this out of the cobwebs of my mind here, but I
21 don't believe that co-infection with foamy virus
22 made any difference on the course of infection with
23 FIV. In other words, the animals would die just as
24 fast.
25 CHAIRMAN NELSON: But the data that you

1 mentioned in the animal colony suggests that
2 whatever these monkeys are doing with each other,
3 they are able to transmit a lot more effectively
4 than what we know about in the little data from
5 humans, and I just wonder what the correlates of
6 that are. Is there more infectious virus, more RNA
7 in the monkeys than you see in a human that's
8 infected, or is it their behavior or their intimacy
9 or their whatever sharing of, etcetera, is
10 different than humans?
11 DR. ALLAN: Well, we don't know, but the
12 fact that people have shown that saliva and tissues
13 in the throat are a prime area for virus
14 expression, you have to suggest that it's salivary
15 transmission.
16 Now, the interesting thing about these
17 infants that were housed together is, they were
18 housed with a surrogate adult female, and
19 invariably those were seropositive. So what we
20 think is happening is that this female adult
21 transmits it to these infants, one or more, and
22 then they transmit it amongst each other. So
23 whatever it is, the Simian Foamy Virus is highly
24 transmissible, probably orally, and that may have
25 behavioral implications in terms of transmission

1 between people.

2 DR. KAHN: Actually I wanted to share some
3 data regarding immunosuppression studies with
4 another retrovirus, a murine retrovirus, in which
5 it has been shown that infection of rhesus macaques
6 can occur with this retrovirus but there is no
7 disease in either normal immunocompetent animals or
8 even moderately immunosuppressed animals, using
9 hydrocortisone. This is French Anderson's data,
10 and others.

11 However, our in-house showed that when
12 rhesus monkeys were severely immunosuppressed using
13 whole body gamma radiation, they had very rapid
14 lymphomas in six months. So I think, you know, the
15 immunosuppressive state, you know, needs to be, you
16 know, evaluated in the case of other retroviruses
17 as well.

18 CHAIRMAN NELSON: So we do need more data
19 on whether this is transfusion transmitted, I
20 guess, as Blaine suggested.

21 DR. HOLLINGER: No, it seems to me that
22 the real risk to the blood banking community is if
23 a donor licks or bites the phlebotomist.

24 [Laughter.]

25 CHAIRMAN NELSON: Or if a rhesus macaque

1 takes the blood specimen, yes.

2 [Laughter.]

3 CHAIRMAN NELSON: Further questions or

4 comments?

5 Okay. Dr. Kahn?

6 DR. KAHN: While this is turning on, I

7 just wanted to say that to investigate the

8 potential risk of Simian Foamy Virus transmission

9 by blood, the FDA has developed a study proposal

10 using rhesus macaques which I will be presenting

11 for your comments.

12 While we're waiting, I just wanted to make

13 a couple of more comments about the latency. These

14 are I guess my own personal scientific comments

15 related to foamy viruses.

16 You know, I think the latency question

17 about foamy virus is an enigma, and it's very

18 important I guess to consider what factors may be

19 involved in that. It is quite interesting that in

20 the case of foamy virus infection in the monkeys,

21 the neutralizing antibody titers are extremely

22 high. I don't know what they are in humans, but

23 earlier this year, before I guess we started

24 considering the question of foamy blood

25 transfusion, I did initiate some studies using a

1 naturally occurring isolate in rhesus macaques by
2 doing IV injection, and extremely high titer
3 neutralizing antibody is generated.
4 And so it's possible that that could be a
5 contributing factor in the latency or, you know,
6 there could be other cellular factors. But I think
7 I will sort of bring this into consideration in our
8 proposed studies, as well, when we're using blood
9 for transfer.
10 So I'm going to just present a general
11 overview first and then go into some of the details
12 for comment. Okay. The overall summary is
13 indicated here, in which whole blood will be
14 transferred from an SFV-infected rhesus macaque
15 into an SFV-negative monkey, and this strategy has
16 been proven to be successful in getting retrovirus
17 infection in the case of SIV. Blood recipients
18 will be monitored for SFV infection by sensitive
19 virological, serological, and molecular assays that
20 we have established in my lab, as well as the
21 animals will be monitored carefully for any
22 clinical changes.
23 And the proposal is to follow the
24 inoculated animals for one year to evaluate SFV
25 infection. I think this period should, I guess in

1 my mind, be sufficient even if there is a very low
2 level or if there is a very small amount of
3 infectious virus present in the inoculum. I think
4 in this period we should have some signs of
5 infection.
6 The donor animal that we will identify is
7 from currently existing rhesus macaques that I have
8 in an ongoing long-term, just longitudinal studies
9 for foamy virus. I have maintained them in single
10 housing for over eight years, and they have been
11 carefully monitored. They were originally obtained
12 from the FDA colony and were free of other
13 retroviruses.
14 And also I have isolated foamy viruses in
15 tissue culture from some of the animals, and we
16 have virus stock, and we have characterized the
17 biological properties of these viruses, and we have
18 specific reagents that we can go back and identify
19 the virus in infected animals. The best fit animal
20 would be one--and I guess we can have further
21 discussions on this--but initially one that would
22 have high viral load in the plasma and/or PBMCs,
23 and this would be determined by TaqMan PCR that we
24 need to establish for the analysis.
25 I should mention that in general the

1 plasma viral load is probably low. I don't think
2 enough studies have been done to know what the load
3 should be or what the load is, but mainly this
4 virus is cell-associated, so we can evaluate the
5 viral load based upon the PBMCs, but we will look
6 at both to make the analysis.
7 Also, we would like to, you know, to
8 possibly create the worst case scenario and go with
9 a monkey that harbors a virus that has high
10 replication efficiency also, and this goes back to
11 the earlier data that I have presented from our
12 studies, that there is a range in the replication
13 efficiency of the different naturally occurring
14 viruses.
15 So the SFV-negative recipient animals will
16 be identified from the FDA rhesus colony. They
17 come to us as juvenile animals, and they are
18 retrovirus free for the known SRV, STLV, and SIV,
19 and in addition they will be negative for SFV, of
20 course. The negative animals initially will be
21 identified by serology, and we will then confirm
22 the negativity of the animals by PCR as well as
23 culture. And the animals will be individually
24 housed at the time of the initial serology, and
25 then maintained as such throughout the entire

1 study.

2 At this time what we are proposing is to
3 use a total of eight SFV-negative animals, and I
4 will come back to this point later, because it is
5 very difficult to get enough numbers for SFV-negative
6 animals, so we feel that this is something
7 we can aim for, at least a realistic number to
8 start the study relatively in the near future. Six
9 will be transfused with SFV-positive blood and two
10 will be with negative blood as controls.

11 The inoculum will be, at least we hope,
12 two doses, two different volumes of blood by
13 intravenous transfusion, according to the body
14 weight of the animal. This is an attempt to
15 administer blood in the animals that may be in the
16 high and low range of what is equivalent in terms
17 of a human donation. We will use CPD-adenine as a
18 preservative, which is currently used in human
19 blood transfusions. Plasma and PBMCs will be
20 prepared and stored from every blood collection.

21 In order to monitor the acute phase of the
22 infection as well as the chronic phase of the
23 infection, the plan is to collect material every
24 week for the first six weeks and then every other
25 week for the next six months, and monthly

1 thereafter for a period of one year. At the end of
2 the one year, if the animal remains negative, then
3 we will challenge the animal with the laboratory
4 stock of foamy virus, our naturally occurring foamy
5 virus, to demonstrate that the negative animals are
6 not in any way resistant to the infection.
7 In terms of a positive control, what we
8 could use, again if we can get a couple of more
9 animals added to this group, would be possibly
10 negative blood spiked with foamy virus that has
11 been isolated from the donor animal.
12 The inoculated animals will be monitored
13 neutralizing antibody titer as well as by Western
14 blot in order to assess infection, and also the
15 PBMCs will be tested by PCR, again to look for any
16 low-level infection. We have highly sensitive PCR
17 assays developed that can detect the naturally
18 occurring macaque isolates, both in pigtails and in
19 rhesus. And I should mention that when we
20 originally tried to use primers based on the Simian
21 Foamy Virus-1 prototype, we missed several infected
22 animals, so we went back and developed primers
23 based on the naturally occurring viruses and then
24 were able to get 100 percent positivity in the
25 positive animals.

1 To investigate whether there is
2 replicating virus, we will do co-culture studies by
3 using monkey PBMCs and cells which are highly
4 susceptible to the virus. Additional analysis will
5 be done to look for any clinical changes by
6 monitoring the hematology, serum chemistry,
7 physical exam. Also, we plan to include
8 immunophenotyping to look at any changes in
9 lymphocytes of populations. Again, we're trying to
10 encompass everything, not knowing what we should
11 see, so we're trying to make it very inclusive or
12 encompassing.
13 At the end of the study, there is a plan
14 to evaluate for histology and toxicology. During
15 the study, we will obtain lymph node samples at
16 various time points to also be able to investigate
17 any ongoing changes that might occur early in the
18 infection.
19 We hope the results of this study will
20 provide a scientific basis for evaluating the
21 potential risk of SFV transmission by blood
22 transfusion, and help formulate criteria for
23 acceptance or exclusion of potential blood donors
24 who are at risk for SFV infection.
25 Before I conclude, I should just mention

1 that there are a couple of challenges to this
2 study, and not just finding whether the virus does
3 anything. One obvious one is identifying funding
4 to do the study. We are in the process, or I
5 should say Dr. Epstein is in the process of trying
6 to identify funding to support this study, and of
7 course your comments will be very valuable towards
8 that.
9 And also a more challenging, I guess,
10 aspect is to get enough negative animals to do a
11 study that can be interpreted in a good scientific
12 manner. At this time we have 50 animals that were
13 tested serologically last week and got the results
14 in this week. Three animals out of the 50 have
15 been identified as negative serologically. The
16 source of the animals were indicated to maintain
17 the animals in single housing, and we're hoping we
18 are able to obtain these animals, you know, in the
19 same way and keep them housed singly. Of course,
20 once we get these negative animals, we would
21 confirm that by PCR and see whether we can add them
22 to the study.
23 Thank you.
24 CHAIRMAN NELSON: Any comments or
25 questions? Yes, Sherri?

1 DR. STUVER: Yes. I guess that would be
2 an issue, the small number of animals, because say
3 you don't see any transmission. Then the upper
4 bound on the zero percent incidence, you know, I
5 think it will be hard to say that there isn't any
6 transmission if you're just looking at six.
7 DR. KAHN: I agree. Yes, the numbers are
8 small. I think that's a limitation of the foamy
9 virus study being done in non-human primates. You
10 know, I think whatever the result is, we'll have
11 to, you know, indicate is based on the small
12 numbers.
13 CHAIRMAN NELSON: But that's always a
14 limitation if you get a negative result, but if you
15 get a positive result, then--
16 DR. STUVER: Yes, but I guess if you had
17 more numbers, then that upper bound, you could pull
18 it down so that you could have some confidence that
19 it wasn't more than this, as opposed to--
20 CHAIRMAN NELSON: But this is, every
21 primate study you look at is--
22 DR. STUVER: I understand.
23 CHAIRMAN NELSON: You know, I've seen so
24 many papers based on one chimp or something like
25 this, that that's a limitation that's sort of built

1 into the--
2 DR. KAHN: I guess again, you know, if
3 it's a positive then it's clear-cut. If it's a
4 negative, then we need to consider how further to
5 confirm that. But I think right now there is no
6 result, so--
7 DR. ALLAN: Can I make a comment?
8 CHAIRMAN NELSON: Sure.
9 DR. ALLAN: Yes, when you're dealing with
10 transfusing blood from one animal, the dose could
11 be important. We know from primary infections, if
12 you took an animal during the primary phase of
13 infection, before the immune system kicked in, it's
14 possible that the viral loads might be much
15 greater.
16 So if you translate that into, let's say
17 Simian Foamy Virus infected people, it may be that
18 the ones that have been infected for a long period
19 of time won't transmit it, but if you find someone
20 who has been recently infected, maybe even within
21 two or three weeks, they may transmit it. So it's
22 hard to sort of like make across-the-board
23 conclusions based on viral load in one particular
24 animal.
25 CHAIRMAN NELSON: I guess you could modify

1 this by, if at the end you find no transmission,
2 and the animals are then challenged not by
3 transfusion but challenged with SFV, take blood
4 shortly after this infection and then use that to
5 re-challenge another animal.
6 DR. ALLAN: I like that.
7 DR. KAHN: Yes, these questions are the
8 discussions, you know, in terms of longer study.
9 CHAIRMAN NELSON: I have looked through
10 this also, as well as all the other data here, and
11 I would say I am not in favor of funding this
12 study. I don't see the relevance of the study.
13 I think you're dealing first of all with a
14 virus that has shown no pathogenicity in its host.
15 While it has efficient transmission, at least
16 through possibly saliva or other things, the
17 transmission through other routes has been
18 extremely low or negligible. There is longevity in
19 the host that's infected, without any evidence of
20 pathogenicity whatsoever. The same thing seems to
21 be true in the humans that have been studied at the
22 present time.
23 Trying to take an animal, a product, and
24 making--first of all, the issue had to do, I think
25 it was brought up that this is maybe like HIV, but

1 in HIV we knew initially that it was transmitted
2 through blood products, and then the studies went
3 into the animals to look at an animal host or a
4 model, to look for various ways in which it might
5 be transmitted and so on.
6 But a selection is being made here in
7 something that may not even be natural in humans.
8 For example, they're going to look for a high viral
9 load in plasma. Well, in most plasma the levels
10 have been negative. Even in humans the plasma
11 loads have been negative. They found it in the
12 PBLs but not in plasma.
13 So finding a sample of blood from a
14 macaque and making a highly choiced selection of
15 whether that sample has a high viral load in plasma
16 and in PBMCs may not be what is even found in the
17 human population in general. Looking for a sample
18 that has good replication efficiency and taking
19 analysis in vitro may not be translatable to the in
20 vivo situation. I think we mentioned that a little
21 earlier in one of the talks.
22 Even when we come down to the issue at the
23 end of the study outcome, if there is no disease,
24 if there is no disease in humans or there is no
25 disease in the animals, so what difference does it

1 make if this disease is transmitted through blood?
2 We already have several other viruses which are
3 being transmitted in blood every day, and that's
4 the GBBC virus, it is the TT super family viruses,
5 and so on, which are much more likely to be
6 transmitted from one host to another through blood
7 transfusions.
8 So until at least I see some evidence in
9 any study that there is transfusion--that, first of
10 all, it is transfused, and there is a good study.
11 I think the CDC study was a good study, in which
12 blood seemed to be infectious and then they
13 followed some of the recipients but didn't see
14 anything and no infection in those recipients. But
15 also whether you see any pathogenicity in humans,
16 and so far none has been demonstrated. I don't see
17 any relevance to the SFV problem right now.
18 DR. ALLAN: Could I make a comment?
19 CHAIRMAN NELSON: Sure.
20 DR. ALLAN: I don't have the same
21 perspective, coming from the simian field. I mean,
22 there are several--there's many examples one can
23 give. I mean, SIV doesn't cause disease in monkeys
24 and it causes HIV in humans in some cases.
25 You also have different strains of Simian

1 Foamy Virus circulating through monkeys, and it's
2 possible that one particular strain could be
3 pathogenic in humans. We just don't know. There's
4 too few people infected at this point to really
5 make any conclusions in regard to its potential
6 pathogenicity, although it looks like it's non-pathogenic, I
7 would agree. The virus is highly
8 cytopathic, which makes me a little cautious as
9 well.
10 And the other point is that since it's a
11 retrovirus, it's a persistent, lifelong infection,
12 and it's going to integrate itself into the host
13 chromosome. That's what retroviruses do. So
14 there's always the potential that one could get
15 cancers. I mean, there's a very small probability
16 of that, but I think that if you have a choice, why
17 allow something that could have the potential to be
18 pathogenic into the human population through blood
19 donation, when there may be an easy way to prevent
20 it? I always go on the side of caution, and so I
21 would think that if there is a simple way to
22 preclude transmission of Simian Foamy Virus in the
23 blood situation, I would certainly attempt to do
24 that.
25 CHAIRMAN NELSON: Dr. Nakhasi?

1 DR. NAKHASI: I just wanted to reiterate
2 what Dr. Allan said there, because I think first of
3 all the number of people who have been studied are
4 very limited. Second of all, as he said, that it's
5 a retrovirus. It gets integrated into the genome.
6 And third of all, we do not have any studies on
7 immunocompromised people. What if during that
8 stage it just flares up and starts doing nasty
9 things which we do not know?
10 That's why I think the purpose is to
11 really see, first of all, whether it is
12 transmitted, whether it is persistent there, and if
13 we can see in long range, in older animals which
14 then become in case "immunocompromised," will that
15 in fact become infectious or not? So I think that
16 was the purpose of the study.
17 CHAIRMAN NELSON: And the other issue I
18 think is that there may be certain circumstances in
19 which transfusion transmission can occur, and if
20 it's only during the small time in infection when
21 they are prior to an immune response, then that
22 would mitigate against a very focused prevention
23 and not worry about even most donors that were
24 infected. Maybe it's only the very recently
25 infected donors that have any risk at all. The

1 animal experiments might help answer some of that.
2 And in the other regard, you didn't show
3 in your protocol whether or not you were going to
4 measure not the neutralizing antibody in the donor
5 but the neutralizing antibody in the recipient
6 animal, but that in the donor animal.
7 DR. KAHN: Yes.
8 CHAIRMAN NELSON: Do you plan to look at
9 neutralizing in cell-mediated or whatever, as well
10 as viral load and so on in the donor?
11 DR. KAHN: Right, yes. And again I think
12 the reason for including the plasma viral load
13 actually was because we don't know--I am not aware
14 of information or data that has mentioned plasma
15 viral loads in monkeys infected with foamy, and so
16 I think that information, that will be important in
17 terms of consideration for, you know, the donor.
18 Like I said, a low plasma viral load may be better
19 but it may have less neutralizing antibodies,
20 whereas if you have a high viral load, like I said,
21 this is a very potent neutralizing antibody
22 generating virus. You know, you can get 1 to
23 10,000 titers, so--
24 CHAIRMAN NELSON: Yes. I mean, it's kind
25 of a black box now. There are so many unanswered

1 questions, that I think that it's probably
2 worthwhile to get some more data if we can, even
3 though monkey experiments are expensive.
4 DR. FOLKS: I'm kind of on the fence on
5 this myself, and Arifa and I have talked about it.
6 I have to say, though, that in the end I think that
7 the animal model is not showing us what we probably
8 need to know and how we would glean important
9 information from a blood transfusion study.
10 And I say that because clearly there is
11 something major different between humans and all of
12 these monkeys. The millions of years of evolution,
13 we would have a species of foamy virus in us, an
14 endogenous foamy, in some way, with our own
15 particular human foamy group, if we weren't really
16 different from the rest of these animals. And Jon
17 may want to comment on this.
18 And also Dr. Chapman's data, that although
19 we haven't followed a lot of the spouses that have
20 been in an unprotected sex scenario with their
21 infected spouse for about 100 person-years, just
22 licking the phlebotomist may not do it. I mean, I
23 have real trouble trying to figure out how this
24 virus is going to move from human to human, and I
25 don't know that the monkeys are showing us the same

1 thing that's going on in the human.
2 DR. KAHN: Again, I think there are many
3 examples of retroviruses that do not cause disease
4 in the natural host, however, on cross-species
5 transmission they behave differently. And that's
6 one of the reasons for, you know, focusing more on
7 looking at the naturally occurring isolates and
8 understanding their biology.
9 DR. HOLLINGER: Could you give me examples
10 of that?
11 DR. KAHN: Well, even in case of SIV, the
12 natural host is African green monkeys and sooty
13 mangabies. You can have high viral loads in those
14 animals, high plasma viremia, but you do not get
15 disease, and that's an enigma. Whereas when the
16 animals go into rhesus macaques or other macaques,
17 Asian macaques, which is not the natural host of
18 SIV, that's where you see disease. And this is
19 also in the case of murine retroviruses.
20 CHAIRMAN NELSON: Well, and there's HIV,
21 human HIV, derived from a human, transfused into a
22 chimp.
23 DR. HOLLINGER: Right, but there is human
24 HIV.
25 CHAIRMAN NELSON: Yes.

1 DR. HOLLINGER: There is not a
2 human/simian virus.
3 CHAIRMAN NELSON: Right.
4 DR. HOLLINGER: And these are big
5 differences, so you have to keep these things in
6 perspective, I think. You can't just jump from one
7 and move to another without looking at the
8 relevance of this.
9 DR. ALLAN: This is Jon Allan again. I
10 mean, I agree with Tom that it's sort of
11 fascinating that humans don't have a Simian Foamy
12 Virus, when these viruses are present in all these
13 other species. So, I mean, we really don't know
14 why that is so, but there's a couple--you can come
15 up with all kinds of scenarios.
16 One is that the way the virus is
17 transmitted, humans don't have the same behavioral
18 contacts to allow person-to-person transmission. A
19 second thing could be that there's something
20 different about the receptors, there's something
21 different about cellular transcriptional factors.
22 I mean, there's a whole range of possibilities as
23 to why the virus doesn't--isn't found in humans.
24 But I think Tom is correct, too, that
25 maybe humans, as they evolved, they have evolved

1 some sort of natural resistance to either--either
2 behaviorally or genetically, to prevent Simian
3 Foamy Virus in people. Now, how does that
4 influence in the blood transfusion situation, I
5 really don't know. I think that, you know, the
6 fact that the virus has been present in humans
7 makes me concerned about the transfusion situation.
8 DR. FITZPATRICK: It seems to me that if
9 the purpose of the study is to determine whether or
10 not FDA should provide deferral criteria for
11 handlers of non-human primates, I mean, that's a
12 very small group of donors, and that seems to be
13 the focus of the study. From a practical
14 perspective, I'm not sure whether that's cost-effective or
15 not. Because that's such a small
16 group, it might be easier to just defer them based
17 upon all the other non-human primate viruses that
18 they might be exposed to that we don't know
19 anything about.
20 The other thing would be that the study
21 should, I think, reflect what is going to become
22 current practice in blood banking, and if we're
23 moving toward leukoreduction and this is a cell-mediated
24 virus, then your study should have an arm
25 that allows for leukoreduction, and there may be

1 protection from transmission just by what is going
2 to become standard of practice in transfusion.
3 And the other would be, if the goal is to
4 see if it's transmitted by a blood product, then,
5 as has been done with variant CJD, you might
6 increase the dosage in order to make up for the
7 lack of numbers of negative animals that you have.
8 So you could harbor buffy coat on numerous
9 occasions from the donor, give a larger dose than
10 you would ever expect to give, but at least you
11 would see if it's transmitted by blood, at least in
12 that respect, and then have the leukoreduction arm
13 with at least similar dosages of red cell products
14 to try and mediate that factor, although that
15 wouldn't be very easy.
16 But I'm not sure if it should be studied--I mean,
17 from an esoteric and scientific standpoint,
18 I think you have a question that is very
19 interesting, and from the primate side of the
20 house, probably worthwhile to study. I'm not sure
21 it's that significant a blood problem.
22 And I'm not sure how respected or where
23 Dr. Mineo is in primate studies, but her review
24 article on "Why Aren't Foamy Viruses Pathogenic?" I
25 thought was pretty convincing that this is a

1 different retrovirus from other retroviruses, and
2 that neutralizing antibodies might or might not be
3 significant.
4 And when I combined that with the study on
5 evidence in the human population, where they did
6 5,000 human sera and were not able to confirm foamy
7 virus in any of those 5,000 sera, in the hierarchy
8 of viruses to be concerned about in blood
9 transmission, I'm not sure this is at the top of
10 the list. So when it comes to determining what to
11 fund or not to fund, I think there ought to be a
12 hierarchy of which ones we are most concerned
13 about, to fund it in regards to blood transmission
14 as opposed to being a scientific question that
15 needs to be answered.
16 CHAIRMAN NELSON: Yes, Lianna?
17 DR. HARVATH: I just had a pragmatic
18 question about the level of funding. You didn't
19 mention how much the budget would be to cost a
20 project like this, given the sample size and what
21 your intended approaches would be in terms of
22 outreach for funding. Would this be written up as
23 an application to be sent to a government funding
24 agency or outside the agency?
25 DR. KAHN: Well, so far actually I've

1 written up sort of proposals internally in the FDA.
2 We had two possibilities, and I think again it
3 depends on, you know, what is being funded through
4 that mechanism, as you might know. So in those two
5 cases, you know, I was not successful. In one case
6 the proposals that were funded were mainly for
7 development of assays, and in the other case it was
8 more along the lines of continuing people's current
9 research projects. So again this was I think, you
10 know, just trying to figure out, you know,
11 different sources.
12 In terms of the actual cost, I guess we're
13 in a fortunate situation that the FDA has its own
14 colony. So, you know, we don't have to pay $5,000
15 a rhesus. However, you know, most of my monkey
16 studies are using a small number of animals but
17 doing extensive analysis so we can look at all the
18 various parameters of infection and clinical
19 changes, which clearly in this particular case the
20 information is not there, so we're really starting
21 from scratch.
22 Whereas in the HIV I think, you know,
23 you're at the other extreme of retroviruses in
24 which, because of the AIDS epidemic, there was such
25 a great surge of resources and push for research

1 efforts that very quickly, you know, a lot of
2 information was generated and things could be
3 followed up. But this is sort of a neglected
4 virus. However, because it's a retrovirus, you
5 know, I think as Jon mentioned, once it gets in,
6 it's going to say with you, and what the
7 consequences might be, whether in an
8 immunosuppressed situation or with aging, then you
9 know one has to look at other retrovirus models.
10 In terms of the actual amount, based upon,
11 you know, the number of animals, but I would
12 probably--the request would be one person that's
13 committed to the study to get it done in a timely
14 manner and, you know, and laboratory resources for
15 that.
16 DR. HARVATH: But you don't know the cost?
17 DR. KAHN: Well, I guess the cost, we're
18 talking about maybe--well, it depends on the
19 person, if it's a technician or a post-doc. I
20 would say possibly $60,000 or, you know, $65,000 or
21 something.
22 DR. HARVATH: Yes, I think that's an
23 important point. I know this is mostly focused on
24 the scientific discussion, but in terms of looking
25 at asking a question to gather proof of concept or

1 lack of proof of concept in a study, even though it
2 may or may not--you know, there will be debate
3 about its ultimate utility, I think it's important
4 to bring out the cost of it, given the resources
5 FDA has on hand.
6 And so then the next question would be, if
7 it's only going to be $60,000 to complete these
8 studies, would there be a mechanism within FDA, or
9 would you then need to ask some other funding
10 agency for that? So that's why I'm raising it.
11 DR. KAHN: Yes. Well, I can tell you in
12 terms of asking outside funding or trying to find
13 outside funding agencies, even for other research
14 projects that we do in the FDA, you know, a lot of
15 the research is mission-relevant, regulatory
16 related, so a lot of the comparative funding is
17 difficult to apply for. You know, some of my
18 vaccine studies we get funded through the NVPO, but
19 this would not qualify for that.
20 So I think being in the FDA, as you know,
21 we are very limited in terms of what's out there
22 for us to apply for, you know, so it will be--I
23 guess we will probably have to somehow search in-house. And
24 I think, you know, again the priority
25 for this project I guess needs to be established,

1 and then hopefully somehow there will be funding
2 identified.
3 CHAIRMAN NELSON: Hira?
4 DR. NAKHASI: Lianna, is there a
5 possibility that it could be funded, if we submit
6 to NHLBI and it can be funded through that part?
7 DR. HARVATH: I can't address that
8 directly. I mean, there are mechanisms where there
9 have been interagency agreements and so on, but
10 it's very much justification of why the study
11 should be done, its relevance, and the bottom line
12 really is the cost-effectiveness of doing such a
13 study. So, you know, those are all of the
14 variables.
15 And if a study is under $100,000 and it
16 could possibly address an interesting proof of
17 concept or a lack thereof, that isn't considered to
18 be a tremendous amount of money in many RO-1
19 situations, which are far more expensive than that.
20 So I don't know what NHLBI's reaction would be,
21 because we have to not only review it in-house but
22 send it out for expert opinion, and it would be
23 reviewed on its scientific merit as well as the
24 amount of money that you would be requesting.
25 CHAIRMAN NELSON: Well, I think we have

1 succeeded in reversing our original sin of being
2 ahead of time. We're now behind time. Jay, did
3 you have a quick comment?
4 DR. EPSTEIN: Well, just that we shouldn't
5 get too hung up on the issue of finding the money.
6 What we're here to ask the committee is whether we
7 should be doing this kind of study. Is the problem
8 important enough? And that's what will guide, you
9 know, the downstream debate over dollars.
10 CHAIRMAN NELSON: Right. I would like, if
11 there are no more comment, to open the open public
12 hearing, and the first person is Kay Gregory from
13 the American Association of Blood Banks.
14 MS. GREGORY: Thank you. Once again, Dr.
15 Louie Katz, who is the Chair of our Transfusion
16 Transmitted Diseases Committee, sends his regrets
17 and me in his place.
18 The American Association of Blood Banks is
19 the professional society for over 8,000 individuals
20 involved in blood banking and transfusion medicine,
21 and represents approximately 2,000 institutional
22 members, including blood collection centers,
23 hospital-based blood banks, and transfusion
24 services, as they collect, process, distribute, and
25 transfuse blood and blood components and

1 hematopoietic stem cells. Our members are
2 responsible for virtually all blood collected and
3 more than 80 percent of the blood transfused in
4 this country. For over years, the AABB's highest
5 priority has been to maintain and enhance the
6 safety and availability of the nation's blood
7 supply.
8 We would like to thank you for your
9 attention to this interesting matter today. Human
10 infection with foamy viruses is not new, and was
11 first described in a nasopharyngeal cancer derived
12 cell line 30 years ago. Although there is no
13 convincing evidence of any disease association with
14 human infection, the number of infected persons
15 studied and the average duration of follow-up are
16 inadequate to prove they are not pathogenic under
17 some circumstances. We would like to note that
18 Simian Foamy Virus is being studied as "a safe,
19 efficient alternative to current Onco- and
20 Lentiviral vectors for gene transfer in cells from
21 a broad spectrum of lineages across species
22 boundaries."
23 Foamy viruses are ubiquitous in captive
24 primate populations, and present in many other
25 animal genera. Infections in man appear to

1 represent rare zoonotic events. SFV does not
2 appear to be pathogenic. Of interest in this
3 regard is the evidence that the putative hepatitis
4 viruses, TT, GBV, and SEN, are either non-pathogenic or
5 uncommonly so. Actually, GBV
6 infection seems to have a beneficial impact on the
7 course of HIV infection. reminding us that not all
8 viral infections are dangerous.
9 The AABB supports careful and expeditious
10 inquiry into the prevalence of Simian Foamy Virus
11 infection in selected populations, including blood
12 donors, and longitudinal analysis of the impact of
13 such infections where identified. Epidemiological
14 and laboratory studies of primate workers in
15 comparison with appropriately matched controls for
16 unique patterns of illness will provide useful
17 information.
18 Newer technologies allow us to detect,
19 with greater and greater sensitivity, more and more
20 infectious agents. Concerns about the potential
21 pathogenicity of these agents will challenge us
22 repeatedly. We are ready to join the public health
23 authorities in studies that may help clarify
24 whether the less well-known agents represent a risk
25 for transfusion recipients, and we applaud the

1 monitoring activities that are taking place. At
2 the same time, we would like to emphasize that
3 available data on Simian Foamy Virus suggest action
4 regarding blood donors is not currently
5 appropriate.
6 Thank you.
7 CHAIRMAN NELSON: Questions or comments?
8 Okay, the second speaker, Dr. Celso Bianco
9 from America's Blood Centers.
10 DR. BIANCO: I am Celso Bianco. I am from
11 America's Blood Centers. We completely support the
12 statement that has been made by AABB in terms of
13 the relative importance or limited importance of
14 Simian Foamy Viruses.
15 I just would like to make a very quick
16 comment about some of the discussion here about
17 these studies. I think all the questions on both
18 sides are very appropriate. I am very in defense
19 in this study, like some of the people here, but I
20 would like to add another aspect.
21 There are many questions that we are
22 asking at the current time in terms of
23 transmissibility or increasing the safety of the
24 blood supply or preserving the safety of the blood
25 supply, and there are limited resources, so I would

1 like the committee also to consider that in the
2 hierarchy of resources that are available.
3 For instance, there has been an attempt
4 for the last year and a half to obtain funding and
5 a substantial need for understanding medical
6 history and medical history questions. That has
7 been very, very difficult, and we are still
8 confronting deferrals of hundreds of thousands of
9 donors, and adding more and more questions to our
10 questionnaire without having a real measure of the
11 impact that those have.
12 I think that those have a higher relative
13 importance than the investment of a tremendous
14 amount of resources in terms of asking questions
15 that we should certainly be monitoring, but not
16 necessarily rushing into it. Thank you.
17 CHAIRMAN NELSON: Questions?
18 Are there any other people who wanted to
19 make a comment or statement in the open public
20 hearing? Jonathan Goldsmith from the Immune
21 Deficiency Foundation wanted to make a statement.
22 I think it's on a different issue. So feel free,
23 but I hope that the discussion doesn't divert
24 completely from where we are right now.
25 MR. GOLDSMITH: Thank you for the

1 indulgence. My name is Jonathan Goldsmith, and I'm
2 the Vice President of Medical Affairs for the
3 Immune Deficiency Foundation. The IDF is the
4 national organization that is dedicated to
5 improving the lives of primary immune deficient
6 patients through research and education.
7 I would like to address an issue that has
8 become extremely important to our--
9 [Fire alarm.]
10 CHAIRMAN NELSON: The issue is more
11 important than I thought it was. I don't know
12 what's going on here.
13 [Recess.]
14 DR. SMALLWOOD: Now that the pseudo fire
15 is out, maybe we could resume with the comments
16 from Mr. Goldsmith.
17 DR. SMALLWOOD: May we have your
18 attention? We are resuming now. We are still in
19 the open public hearing session.
20 MR. GOLDSMITH: Should I just start from
21 the beginning? It's a very short presentation.
22 CHAIRMAN NELSON: Actually, you weren't
23 very far from the beginning.
24 MR. GOLDSMITH: Thank you. Again, good
25 afternoon. My name is Jonathan Goldsmith, and I'm

1 the Vice President of Medical Affairs of the Immune
2 Deficiency Foundation. The IDF is the national
3 organization dedicated to improving the lives of
4 primary immune deficient patients through research
5 and education.
6 I would like to address an issue that has
7 become extremely important to our community as a
8 result of the increased threat of biologic
9 terrorism. I am speaking of the potential adverse
10 impact upon our community that could result from a
11 broad scale, preemptive smallpox vaccination
12 program, should one become necessary.
13 I would like to point out that the risk we
14 are currently focusing on is the impact on our
15 patient group from the vaccination program itself.
16 Because the vaccine contains a live virus, it is
17 highly probable that many immune compromised
18 individuals may be vaccinated or unintentionally
19 exposed to the virus through household and casual
20 contact, and may suffer significant morbidity and
21 mortality. Additionally, the persistence of the
22 virus in some individuals with immune deficiency
23 and its ability to spread to others could pose
24 further risks to our patient group.
25 In an effort to understand this potential

1 impact and to develop strategies to maximize the
2 protection of at-risk populations such as primary
3 immune deficient patients, IDF has assembled an
4 expert working group. Our intention, given
5 different vaccination scenarios, is to recommend
6 strategies to reduce the risk of adverse effects
7 should a public vaccination program become
8 necessary.
9 One such strategy may involve the use of
10 an immune globulin containing vaccinia antibodies
11 to provide transient passive immunity against the
12 vaccine virus. We are also conducting a series of
13 meetings with government officials involved in
14 developing the national strategy for dealing with
15 bioterrorism, including individuals from the Food
16 and Drug Administration, in an effort to voice our
17 concerns and provide input from our panel of
18 experts. Our goal is to help develop a policy that
19 provides the maximum protection for U.S.
20 inhabitants while at the same time reducing the
21 adverse impact on at-risk populations.
22 Thank you.
23 CHAIRMAN NELSON: Thank you very much.
24 Toby?
25 DR. SIMON: There also would be a problem

1 for your population in just the shortage that could
2 result if people are deferred?
3 MR. GOLDSMITH: Correct.
4 DR. SIMON: That would be another issue,
5 and that would be very relevant to this committee,
6 I think.
7 MR. GOLDSMITH: Yes. Dr. Simon is saying
8 if there is live virus vaccination, that there will
9 be a loss of donors.
10 CHAIRMAN NELSON: Right. Yes, despite the
11 fact that whatever it is, 150 million doses, were
12 ordered, I hope that only half a dozen of them are
13 ever used. Talk about budget craziness, this is a
14 prime example.
15 Jay?
16 DR. EPSTEIN: Yes, just a comment that we
17 are aware within the FDA of these threats that you
18 describe, both to the immune deficient population
19 if there is a mass vaccination campaign, and also
20 the issue of blood availability if there were
21 urgent vaccination of the population, and we are
22 thinking about ways that those problems can be
23 addressed.
24 CHAIRMAN NELSON: I would say in addition
25 to the Immune Deficiency Foundation which you

1 represent, I am sure we would detect a large number
2 of people who are HIV-positive and don't know it,
3 if widespread smallpox vaccination were--just like
4 the military did when they didn't stop in the early
5 '80s. So, you know, I think this could be a
6 disaster. We would really have to carefully
7 consider how to deal with this thing.
8 DR. HOLLINGER: The other issue I think
9 that was suggested I suppose was the question of
10 whether there is a high availability of vaccinia
11 immune globulin, also, I presume too, the stock and
12 so on.
13 MR. GOLDSMITH: Right, to determine if
14 there is vaccinia antibody titers in current
15 products, and would these be useful, and could
16 there be made available a vaccinia immune globulin
17 of an intravenous type that could be substituted
18 for current products during vaccination programs,
19 so both.
20 CHAIRMAN NELSON: Okay. Well, let's move
21 back to the Simian Foamy Virus. Are there any
22 other people who want to make a comment about the
23 Simian Foamy Virus issue?
24 If not, then we'll close the open public
25 hearing, and maybe we could re-display the issues

1 for the committee.

2 DR. NAKHASI: Thanks again. So now, since
3 we have come to the conclusion, at this point now
4 we would like to come back to the questions which
5 we would like to ask the committee. And the
6 important thing is, the first question is, "Does
7 the committee agree that the currently available
8 data are insufficient to determine whether SFV can
9 cause adverse health effects in humans?"

10 CHAIRMAN NELSON: Discussion? Yes?

11 DR. SCHMIDT: Dr. Hollinger stated my
12 position very eloquently. It's difficult to try to
13 fit it into this question, because it's a little
14 tricky, but your philosophy is the correct one, I
15 think.

16 CHAIRMAN NELSON: Well, I think the data
17 are negative so far, but I don't think Dr.
18 Hollinger would say that the data are sufficient to
19 exclude the possibility that there could be an
20 effect on human health, would you? I don't--

21 DR. HOLLINGER: They are tricky, and I
22 guess the real issue that would be here is, what is
23 sufficient? 50,000 people that have Simian Foamy
24 Virus infections in humans?

25 CHAIRMAN NELSON: Certainly more than 11,

1 right, or 32 or wherever we are now.
2 DR. HOLLINGER: Yes, I think, if I
3 remember, it's something like 20, maybe, or so.
4 DR. FITZPATRICK: Is this question
5 referring specifically to blood transfusion or
6 just--
7 DR. NAKHASI: The first question is
8 regarding first whether it causes disease.
9 CHAIRMAN NELSON: Yes. Is it pathogenic?
10 DR. NAKHASI: Yes, pathogenesis, whether
11 it causes any disease, first, or the data is
12 insufficient. We believe there is insufficient
13 data to determine that SFV can cause adverse--
14 CHAIRMAN NELSON: The thing that concerns
15 me is that we have been told that this virus is
16 highly cytopathic, you know, in cells outside of
17 the--and in a whole variety of cell lines. If it
18 can do that, then maybe there are some conditions
19 in which, in a human, where the immune response or
20 the load of virus or certain conditions that can
21 cause disease, and I'm not impressed that the data
22 are clear enough now that we can answer that
23 question.
24 DR. HOLLINGER: Maybe someone could
25 explain again cytopathic. The person who said that

1 this is cytopathic, can you explain to me what you
2 mean by cytopathic. I know what I mean by
3 cytopathic. I mean, it gets in a cell and it
4 ruptures the cell and they are destroyed. So I
5 would like to know what cytopathic means to--
6 CHAIRMAN NELSON: Dr. Kahn?
7 DR. KAHN: Yes. Again, if you have
8 infected the cells, initially after infection the
9 first visibility of a cytopathic effect is
10 multinucleated cells. Depending on the species and
11 the cell type, you would have that develop very
12 quickly into a viviculture. It eats away the
13 culture.
14 Actually it's sort of a fun virus. You
15 know, you could use it and monitor. Once you see
16 the initial CPE, it can either progress very
17 quickly to seeing visible cell debris by the eye,
18 and depending on the virus; or in certain cells it
19 develops very slowly but eventually--it may not
20 reach the same degree of lysis, if you want to call
21 it, but clearly the culture slowly progresses to,
22 you know, having a high amount of cell debris. So
23 the cells are totally destroyed.
24 DR. HOLLINGER: I guess the real question
25 that comes up is, because that virus is cytopathic,

1 it doesn't necessarily mean it's pathogenic, as
2 perhaps in this state as we see it. And also
3 there's a lot of non-cytopathic agents that are
4 very pathogenic. So I'm not sure how that helps us
5 one way or the other, basically, in this.
6 And the question is, even if you say that
7 it's insufficient to determine, yes, certainly I
8 would much rather have 5,000 people to look at than
9 a small number. But the question is, are you ever
10 going to get that? Where is that information going
11 to come from, and how long will it take to acquire
12 that kind of information?
13 CHAIRMAN NELSON: Well, I think the FDA
14 has asked us to answer that question, and we can,
15 and we can put more questions. Yes, Toby?
16 DR. SIMON: I guess, based on what I
17 heard, and we had a little bit of discussion during
18 the break for the drill, but it would appear that--I guess I
19 would say "Yes, but." I mean, yes, they
20 are insufficient, but it was certainly appear that
21 there is not a disease problem, based on everything
22 we know. People point out it has been around a
23 long time. You know, handling this type of animal
24 has been around a long time, and a significant
25 disease hasn't occurred. So that's the way I would

1 answer it, "Yes, but."

2 DR. HOLLINGER: Do we have a "Yes, but" or

3 do we just have a "yes" or "no"?

4 DR. NAKHASI: The "Yes, but" is the study,

5 then, obviously.

6 CHAIRMAN NELSON: Yes. I mean, there are

7 diseases that have been there that we haven't--I

8 mean, there have been associations that--I don't

9 think it has been very well studied until recently,

10 and not well studied even now.

11 DR. FITZPATRICK: My problem with the

12 question, I guess, is that "does it cause adverse

13 health effects in humans," I interpret that as the

14 general population, and you're asking about a very

15 specific population. So I would have to say no. I

16 mean, decades of experience with non-human primate

17 handlers in the general population, and evidence in

18 the literature you provide, indicates that it's not

19 a pathogen and a problem in the general population.

20 If you want to look specifically at

21 immunocompromised patients, and is this a problem

22 for a very specific patient population, then that's

23 a different question to me.

24 CHAIRMAN NELSON: Yes. And the way that

25 relates to this committee, I guess, is that people

1 who are transfused are often--you know, sometimes
2 could not get a job as animal handlers, you know,
3 are ill or etcetera. But that relates to the next
4 question, as to how readily or is it transfusion
5 transmitted, and in that setting, could it lead to
6 anything?
7 So, you know, my view is that we don't
8 have enough data, but the next issue is, you know,
9 how hard should we look or what should we do to get
10 more data? And I personally think that it would be
11 worthwhile to pursue the question. The point has
12 been made that this is an integrated virus and, you
13 know, there are special circumstances.
14 So do you want to vote on this question?
15 Okay, let's vote on it. You want to do it? Just
16 go ahead.
17 DR. SMALLWOOD: The procedures for voting
18 will be a little different than we have been
19 accustomed to. I will call the roll of the members
20 of the advisory committee, and I have to tally
21 their vote, so I will be calling names at this
22 time.
23 CHAIRMAN NELSON: And a "yes" vote means
24 yes, the data are insufficient; a "no" vote means
25 the opposite, that it is sufficient.

1 DR. SMALLWOOD: Would you just state the
2 question again?
3 DR. NAKHASI: Okay. Linda asked me to
4 repeat the question again. "Does the committee
5 agree that the currently available data are
6 insufficient to determine whether SFV can cause
7 adverse health effects in humans?"
8 DR. SMALLWOOD: Dr. Fitzpatrick?
9 DR. FITZPATRICK: I'm going to vote no,
10 based on--my interpretation is that's in the
11 general population.
12 DR. SMALLWOOD: Dr. Macik?
13 DR. MACIK: I also vote no.
14 DR. SMALLWOOD: Dr. Schmidt?
15 DR. SCHMIDT: No.
16 DR. SMALLWOOD: Dr. Stroncek?
17 DR. STRONCEK: Yes.
18 DR. SMALLWOOD: Dr. Mitchell?
19 DR. MITCHELL: No.
20 DR. SMALLWOOD: Dr. Stuver?
21 DR. STUVER: No.
22 DR. SMALLWOOD: Dr. Linden?
23 DR. LINDEN: Yes, but.
24 [Laughter.]
25 DR. SMALLWOOD: I'm recording that as a

1 yes.

2 Dr. McGee?

3 DR. McGEE: No.

4 DR. SMALLWOOD: Mr. Rice?

5 MR. RICE: Yes, but.

6 DR. SMALLWOOD: Dr. Koff?

7 DR. KOFF: No.

8 DR. SMALLWOOD: Dr. Hollinger?

9 DR. HOLLINGER: No.

10 DR. SMALLWOOD: Dr. Harvath?

11 DR. HARVATH: Yes, but.

12 DR. SMALLWOOD: Dr. Nelson?

13 CHAIRMAN NELSON: Yes.

14 DR. SMALLWOOD: And, Dr. Allan, are you

15 prepared to vote?

16 DR. ALLAN: If you'd like me to vote.

17 DR. SMALLWOOD: You have been cleared to

18 vote.

19 DR. ALLAN: Okay. Yes.

20 DR. SMALLWOOD: And now I would ask the

21 non-voting consumer and industry reps to give

22 their--

23 MS. KNOWLES: Yes, but.

24 DR. SIMON: Well, I guess I should stick

25 with the "Yes, but," but you're not recording the

1 "buts," right?
2 [Laughter.]
3 DR. SMALLWOOD: For the record, I have
4 polled the committee for this question, and I have
5 asked the consumer and the industry rep where they
6 would agree with the voting. The results of voting
7 are, there are four "yes" votes, there are 10 "no"
8 votes, and the industry and consumer--excuse me?
9 SEVERAL VOICES: Eight no, six yes.
10 DR. SMALLWOOD: Okay. I'm sorry if I'm
11 incorrect. Could I just ask you quickly again.
12 Let me start with the list that I have here. I
13 have to make sure that I have the correct votes for
14 the individuals. All in favor? All yes? Okay,
15 Linden, Stroncek, Nelson, Rice, Allan, Harvath.
16 CHAIRMAN NELSON: Yes, that's six.
17 DR. SMALLWOOD: Okay. Sorry. Okay, and
18 "no" votes? Eight. Okay. Thank you for the
19 correction.
20 Okay, the results of voting, as corrected,
21 there are six "yes" votes, eight "no" votes, and
22 the consumer and industry rep agreed with the "yes"
23 vote.
24 DR. NAKHASI: Should we move to the next
25 question?

1 CHAIRMAN NELSON: Yes.
2 DR. NAKHASI: Okay, the next question is
3 basically to say, readdress the similar sentiment:
4 "Does the committee agree that currently available
5 data are insufficient to determine whether SFV can
6 be transmitted by blood transfusion?"
7 CHAIRMAN NELSON: Discussion? Yes, Toby?
8 DR. SIMON: Well, again I guess I put
9 forward the "Yes, but," but in this case I think
10 the "but" is stronger. It seems to me that there
11 is such a paucity of data to suggest any
12 transfusion effect that this one I would think we
13 have crossed the line on in terms of priority or
14 issues for this committee.
15 CHAIRMAN NELSON: Yes. I'm trying to turn
16 the question around, which if you say that it's
17 sufficient to determine whether SFV cannot be
18 transmitted by transfusion, you certainly wouldn't
19 answer that "yes."
20 DR. SIMON: Well, I think it's just the
21 old proof of absence, or absence of proof is not
22 proof of absence.
23 CHAIRMAN NELSON: Yes, yes. Right.
24 DR. SIMON: You can go round and round
25 and, I mean, I guess we could ask this about any

1 huge number of things for which there is not
2 sufficient data to show it doesn't impact
3 transfusion. But there is such a paucity of data
4 here, it would seem to be highly unlikely that it's
5 significant in transfusion.
6 CHAIRMAN NELSON: Yes. These are
7 different but sort of related questions. I mean,
8 since it's not identified with a disease or
9 condition, it reverts to how many people have been
10 screened who have been exposed to large numbers of
11 units of blood. When I looked at the literature
12 and heard Blaine's comments, I don't see any data
13 on hemophilia patients, thalassemics, or people who
14 have cardiac surgery, any--I mean, the data here
15 are even weaker than the first question. You know,
16 does this mean that we should screen large numbers?
17 Maybe that would be cheaper, if the tests are
18 easier, than to proceed with all the pathogenesis
19 questions. I would think that it might be useful,
20 and I'm not convinced that the data are sufficient
21 to say that there is no risk.
22 DR. HOLLINGER: Well, also I think it
23 seems to me that the question here is not
24 necessarily whether it causes disease in the person
25 who gets it--

1 CHAIRMAN NELSON: Right.
2 DR. HOLLINGER: --just whether it's
3 transmitted or not.
4 CHAIRMAN NELSON: Yes.
5 DR. HOLLINGER: And the only study I think
6 that I saw out there is the one that the CDC
7 presented here--
8 CHAIRMAN NELSON: Right.
9 DR. HOLLINGER: --which essentially showed
10 no transmission.
11 CHAIRMAN NELSON: In six people.
12 DR. HOLLINGER: In six people, from one
13 donor.
14 CHAIRMAN NELSON: Right.
15 DR. HOLLINGER: Well, yes, so I think--
16 CHAIRMAN NELSON: I mean, you could get
17 those same data from HTLV-1, if they all got plasma
18 or something like that. I mean, the data aren't
19 meaningless but they're not alarming, and they are
20 certainly insufficient.
21 DR. FITZPATRICK: Like Blaine, I don't
22 interpret this as it's a pathogen or it's a blood
23 transfusion problem, but is there enough evidence
24 to say it can, or can the virus be transmitted by
25 blood products, whether it's pathogenic or not? So

1 I think that's--

2 CHAIRMAN NELSON: Actually, you know--

3 DR. FITZPATRICK: --that may be too

4 literal, but I think that's what the FDA is asking.

5 CHAIRMAN NELSON: Right. I mean, the

6 other, turning it around, we weren't shown how many

7 of--the people that have been screened have been

8 monkey handlers, but nobody told me how many monkey

9 handlers have been transfused. They said how many

10 have been blood donors. But, I mean, maybe that

11 would be the first thing. We might quadruple the

12 number of data on this by looking at that, but I

13 don't think the data are sufficient here.

14 Any comments? You want to vote on this

15 one?

16 DR. SMALLWOOD: Can you read the question?

17 DR. NAKHASI: The question is, "Does the

18 committee agree that currently available data are

19 insufficient to determine whether SFV can be

20 transmitted by blood transfusion?"

21 DR. SMALLWOOD: Okay. Dr. Schmidt?

22 DR. SCHMIDT: Yes.

23 DR. SMALLWOOD: Dr. Macik?

24 DR. MACIK: Yes.

25 DR. SMALLWOOD: Dr. Fitzpatrick?

1 DR. FITZPATRICK: Yes.

2 DR. SMALLWOOD: Dr. Stroncek?

3 DR. STRONCEK: Yes.

4 DR. SMALLWOOD: Dr. Mitchell?

5 DR. MITCHELL: Yes.

6 DR. SMALLWOOD: Dr. Stuver?

7 DR. STUVER: Yes.

8 DR. SMALLWOOD: Dr. Linden?

9 DR. LINDEN: Yes.

10 DR. SMALLWOOD: Dr. McGee?

11 DR. McGEE: Yes.

12 DR. SMALLWOOD: Mr. Rice?

13 MR. RICE: Yes.

14 DR. SMALLWOOD: Dr. Koff?

15 DR. KOFF: Yes.

16 DR. SMALLWOOD: Dr. Hollinger?

17 DR. HOLLINGER: Yes.

18 DR. SMALLWOOD: Dr. Harvath?

19 DR. HARVATH: Yes.

20 DR. SMALLWOOD: Dr. Nelson?

21 CHAIRMAN NELSON: Yes. I should make this

22 not unanimous, but I'll say yes.

23 DR. SMALLWOOD: Dr. Allan?

24 DR. ALLAN: Yes.

25 DR. SMALLWOOD: Our consumer and industry

1 representatives?
2 MS. KNOWLES: Yes.
3 DR. SIMON: Yes, but.
4 [Laughter.]
5 DR. SMALLWOOD: The results of voting for
6 question number two are unanimous among the
7 members. There are no abstentions. The industry
8 and the consumer representative both agree with the
9 vote.
10 CHAIRMAN NELSON: Okay. The third
11 question?
12 DR. NAKHASI: All right. The third
13 question is, "Please comment on the adequacy of the
14 proposed studies to validate SFV transmission by
15 blood transfusion."
16 CHAIRMAN NELSON: Here you're talking
17 about the FDA studies or the CDC studies or both?
18 DR. NAKHASI: Both.
19 CHAIRMAN NELSON: Well, there are a number
20 of studies.
21 VOICE: There is no question.
22 CHAIRMAN NELSON: that's true, so the
23 comment is--I mean, I guess they want some advice
24 on study design or--yes, David?
25 DR. STRONCEK: I don't know, because study

1 design, we had some comments about the merit of
2 such studies, and I'd just like to say that with
3 the molecular techniques available today and how
4 rapidly they are improving, this won't be the last
5 time a question comes up about a virus that is
6 either new or one that we have now detected for
7 some reason because of better techniques.
8 It's very difficult to defer donors, just
9 to keep deferring more and more donors based on
10 little data. So even though a virus like this
11 doesn't look like it's pathogenic, I think the
12 studies are worthwhile and I would encourage the
13 FDA and others to move forward with their studies.
14 DR. MITCHELL: Yes. I understand that
15 this is a retrovirus and we don't know a lot about
16 retroviruses, and that we're learning about
17 retroviruses, but the evidence is that it's not
18 pathogenic in animals--I haven't seen any animals
19 where it is pathogenic--and that it's not
20 pathogenic in humans. And like Dr. Stroncek said,
21 I would agree that there are going to be lots and
22 lots of viruses, but my conclusion is the opposite,
23 that we can't study them all.
24 We should be focusing on the ones that are
25 most likely to be causing harm to human health,

1 that are likely to be transmitted through blood and
2 blood products, and this doesn't fit those
3 criteria, so I think that we should leave it to the
4 academics that are going to be doing these kinds of
5 studies anyway, and see whether there becomes
6 evidence at some point. And if at some point there
7 becomes evidence that this virus can be pathogenic,
8 then recommend that there be further studies, but I
9 don't believe that there should be further studies
10 at this time.
11 MS. KNOWLES: I would be interested in Dr.
12 Allan's assessment on this question, too.
13 DR. ALLAN: Sure. Leaving aside
14 pathogenicity, whether or not the virus is
15 pathogenic or not, I still believe that we don't
16 really have enough information on humans.
17 But if you're looking at transmissibility,
18 whether the virus is going to be transmissible in
19 the blood transfusion situation, this is the
20 question that's trying to be asked. It's not about
21 pathogenicity. It's really about if you squirt
22 blood from one monkey into another, does the other
23 monkey get infected, you know? And I think that's
24 an important question to ask, but it's not going to
25 tell you whether or not, you know, in the

1 transfusion situation whether or not humans are
2 going to transmit from human to human, but it will
3 give you a little more information as to the
4 potential transmissibility of Simian Foamy Virus
5 through blood.
6 So I think it's certainly worth doing. I
7 think it's not an exercise for academics, and
8 Simian Foamy Viruses are not well funded. There is
9 almost no funding for virologists to study Simian
10 Foamy Virus, at least through extramural support
11 through NIH, and part of the reason is because no
12 one has been able to demonstrate a disease in
13 humans. So I think that I would like to see a
14 study like this done.
15 CHAIRMAN NELSON: I would, too, but the
16 other side of this question is, what would we do
17 with a positive result? And we're struggling with
18 that now with the variant CJD. We have this one
19 sheep that got infected from a transfusion, and
20 hundreds of thousands of donors are being excluded
21 based on that evidence and some other, you know,
22 theoretical evidence. We still don't know whether,
23 if we find one monkey--of course, it wouldn't have
24 the same impact. It might exclude monkey handlers
25 or something like that, but--

1 DR. ALLAN: Well, see, I don't sit on your
2 committee, so I don't have the same sort of--I'm
3 not in the same situation that you people are in,
4 and the fact that you're being inundated, I'm
5 assuming that you're being inundated at some level
6 about, you know, having to exclude more and more
7 people from blood transfusions. Being a virologist
8 and not being associated with that, I just see it--I mean,
9 to me it's a no-brainer. Well, you know,
10 if people are working with primates and there is
11 evidence of cross-species transmission, then you
12 should restrict blood transfusions from primate
13 workers.
14 I mean, that's a no-brainer for me but,
15 you know, I understand that if you keep doing that
16 you're going to be left with no donors. But I
17 think that in this case, I think you have to worry
18 about, you know, monkey viruses being transmissible
19 to people, and we know from SIV and from STLV we
20 have two human diseases that are coming from
21 monkeys that are both retroviruses. I just across
22 the board would say no monkey retroviruses in
23 humans.
24 CHAIRMAN NELSON: Ray?
25 DR. KOFF: I guess it's a question of

1 perspective, as well. If you're a monkey person or
2 if you're a foamy virus person, this takes great
3 precedence. But I guess from everything I have
4 heard so far today, and everything I have read
5 suggests that any federal agency that's going to be
6 looking at this is going to say this is a low
7 priority; we've got a lot of things that are more
8 important than this. And therefore, good idea,
9 it's interesting to certain people, but I suspect
10 that it's going to have some problems.
11 CHAIRMAN NELSON: You know, there was one
12 issue that was just mentioned as an aside and not
13 discussed very much, but it could have a greater
14 impact, and that is the idea of using a non-pathogenic
15 retrovirus to introduce, you know, as
16 therapeutics to introduce favorable genes or this
17 kind of thing. And if that's being considered, you
18 know, five years from now Simian Foamy Virus may be
19 the most important agent that we need to know more
20 about. And I wonder if somebody could, if there's
21 anybody in the audience today or anybody else who
22 could comment on that and the thinking and what's
23 going on or what's being planned with regard to
24 this. Tom?
25 DR. FOLKS: Let me just say that CDC is

1 always looking for new reagents to turn what we
2 might think are new and emerging agents, I should
3 say, in the human population into prevention tools.
4 Foamy might be that very perfect one. We certainly
5 are looking at that as a possible vector. Dieter
6 certainly has been looking at that, and I think a
7 number of people are beginning to look at live
8 replicating viruses or packaging of defective
9 viruses for gene therapy. That's why the more data
10 we can accumulate about the well-being of
11 individuals infected with this adds to that stack
12 of knowledge in safety issues.
13 CHAIRMAN NELSON: Yes. For that reason, I
14 think that this is perhaps underestimated, that the
15 importance of learning more about this virus is
16 underestimated when we're thinking about a few
17 monkey handlers. And there may also be--I somehow
18 think we get knowledge from places that we hadn't
19 thought about, and if this is a retrovirus that can
20 be transmissible across species and not produce any
21 disease, that there may be some pathogenetic
22 information there that might be very relevant to
23 HIV and all of the retroviruses that we know that
24 cause a hell of a lot of terrible disease. And it
25 may be learning more about the immune response or

1 the biology, the virology, the immunology of this
2 agent could be tremendously important, and I just
3 think of this as very interesting.
4 DR. MACIK: But I think there has to be a
5 difference here, though, between this fascinating
6 topic--you know, if this virus is going to be used
7 for gene therapy, then the gene therapy jocks are
8 going to be studying it out the wahzoo. That's not
9 the question before us. The question before us
10 right now is, in its current form, not as being
11 used for gene therapy, is there evidence or is this
12 a pathologic virus for us?
13 And a very easy thing to do, I mean, this
14 has been around for a long time, we don't have any
15 more monkey handlers here, you already brought up
16 once maybe this should be looked at in Africa,
17 where you're more likely to get a monkey bite than
18 you are in the U.S. Screen, you know, it would not
19 be all that expensive to screen a large number of
20 blood samples at some blood bank and find out how
21 do we find, you know, antibody titer? Is this
22 really in the blood supply now?
23 Because if it's not in the blood supply
24 now, why would it be in the blood supply later,
25 unless it mutates, in which case all the old

1 studies get thrown out and we have to design all
2 new studies. Or all of a sudden monkeys become the
3 hottest new pet, and so we have to know more about
4 this information. Or your final thing, I mean, if
5 it becomes a vector for gene therapy, then
6 obviously more needs to be known about it, but then
7 that throws it into a whole new category.
8 So this point I would see as our purpose,
9 as the Blood Products Advisory Committee, for the
10 questions brought up, I think we've answered the
11 issues in regards to that today.
12 CHAIRMAN NELSON: Well, I think the only
13 think we've answered, that the data is that the
14 virus can be transmitted across species, from a
15 non-human primate to a human, probably by a bite.
16 We still haven't answered the issue of transfusion,
17 and you know, I think that's still a no-no. And
18 therefore, you know, since this is our focus, are
19 the studies that have been proposed worth doing, or
20 are there other studies that we need to do?
21 I would think that, as several people have
22 said, I think that one way to answer this is--and I
23 don't know how easy it is, given the current
24 screening methods, and we've heard about false
25 positive results being reported in the literature

1 and multiple techniques being used to adequately
2 screen and get specific data, and that might limit--I mean,
3 we might not be able to do just an EIA and
4 screen, you know, half of the 10,000 hemophiliacs
5 or something like this.
6 That might not be feasible, but if it were
7 possible to screen a fair number of people who have
8 had multiple exposures--I mean, our cardiac surgery
9 cohort, we have about 12,000 people who have been
10 exposed to 120,000 units, and that's very efficient
11 to detect a low-level risk. But I don't know how
12 these--what the status of the lab is now. Could
13 you screen 12,000 easily? I suspect not. But I
14 think something needs to be done from the focus of
15 this committee, as opposed to the biology. Looking
16 at the transfusion question, that would seem to be
17 a useful approach.
18 DR. STRONCEK: A couple of things. One,
19 you know, just because this--you can't really judge
20 some of the practical things we need to do for
21 research related to blood transfusion on the same
22 level you judge NIH extramural research. It's just
23 different things, and it can't be more practical in
24 nature. So I wouldn't, just because this would
25 never get funded by an extramural NIH grant, I

1 don't think it means that it's not worthwhile
2 doing.
3 And, you know, the second issue is, this
4 may be more like a xenograft situation where, you
5 know, it's probably not naturally--if someone has
6 screened 5,000 donors and not found it, it's not
7 naturally occurring in at least the current human
8 population. Maybe there's good reason. Maybe it's
9 just not pathogenic.
10 On the other hand, if it can be
11 transmitted from monkeys to humans, and if for some
12 reason we end up--you know, there have been very
13 few people that we know of who have been exposed,
14 so there has been very little risk so far of
15 transmitting it through the blood supply. But if
16 for some reason the strain gets more virulent, and
17 it could, or more people are exposed, it could be--we may
18 just not have enough exposures through blood
19 transfusions to know anything.
20 CHAIRMAN NELSON: Do any of the blood
21 banks collect data on the occupation of the donors?
22 I mean, if we could sort on "monkey handler" and
23 trace their recipients--
24 DR. FITZPATRICK: Again, the CDC study and
25 what the Canadian group is doing for the

1 epidemiological aspects seem to be designed to
2 address proactively, if they can increase their
3 numbers, transmission by transfusion.
4 CHAIRMAN NELSON: Right.
5 DR. FITZPATRICK: The problem is the
6 numbers, and there aren't that many monkey
7 handlers.
8 CHAIRMAN NELSON: Right.
9 DR. FITZPATRICK: So maybe they can expand
10 that beyond just those that test positive, and
11 focus in on anyone--they had a very high donation
12 rate in that one group. You know, maybe they could
13 look at recipients of all that group as opposed to
14 just those handlers who tested positive, but I
15 think that would provide some information.
16 The proposed FDA study for--like I said,
17 you know, the question of whether it can be
18 transmitted by blood is a question that may be
19 worth answering. Who funds it is another issue,
20 and in the hierarchy of funding issues before FDA,
21 we don't know how that fits in in all the things
22 that FDA has before it to fund.
23 But it would be nice to have a hierarchy
24 of issues such as viral inactivation, that's very
25 important, the donor history screening

1 questionnaire, that's very important, what things
2 are before FDA to fund that have the most impact on
3 blood supply and safety, and where does this fit in
4 that. And can somebody else fund it if FDA can't,
5 because it doesn't sound like a very, in the scope
6 of things, a huge amount of money for funding of a
7 project.
8 But if it is going to be tied to blood
9 safety and transfusion, then I think the study, not
10 to be redundant, but it needs to reflect
11 transfusion practices, and so increase the viral
12 load is one way to make up for the numbers. And
13 the other is, I really think it should include
14 leukoreduction as an arm of the study, because
15 that's what we're going to be practicing in the
16 future.
17 CHAIRMAN NELSON: With regard to Dr.
18 Allan's suggestion, that just people with non-human
19 primate exposure just be excluded, this is already--
20 xenografts are from non-human primates to humans.
21 They are already excluded, without the large body
22 of data, etcetera, without a lot of research. And
23 so this is already true for the graft situation.
24 It's not true for the human-to-human transfusion of
25 a human who may have had exposure.

1 Any other questions? Comments? Yes?
2 DR. CHAPMAN: If I could, I would just
3 like to comment on a couple of the suggestions that
4 have come up for study. One is, I think it was
5 clear in the presentation, but we are attempting
6 to, our intention is to attempt to trace back
7 recipients of any SFV-positive donors we can
8 identify, but it's not as easy as it may sound. I
9 think I said in the presentation that there were
10 six people we identified who had donated after the
11 documented data of seropositivity. Well, six
12 donors.
13 One had stopped donating before they
14 became seropositive because of other occupation-associated
15 exposures. Specifically, that person
16 had been working with hepatitis studies in
17 primates, and stopped donating blood at that point.
18 Of the other five, one is absolutely not
19 traceable. It was someone who was a paid plasma
20 donor many years in the past, and we cannot even
21 identify the site where they were a donor, and is
22 also off the follow-up with us.
23 One is someone who did only a couple of
24 specific directed donations for his mother, who is
25 not interested in concerning his elderly mother who

1 has had strokes and other health problems, and will
2 not cooperate with further follow-up.
3 One, the most promising one, is the one we
4 have presented here.
5 One is a trace back that we are attempting
6 to do, and we are probably able to do, but the last
7 donation by that donor was over a decade ago, and
8 it is in fact in an inner city hospital with a
9 chaotic population, and it's not very probable
10 we're going to be able to identify recipients but
11 we're still trying to do it.
12 So with time, if we identify more
13 traceable, the intention is to continue to try to
14 trace them, but I don't think you should expect
15 that we're going to rapidly expand our numbers.
16 The suggestion that was brought up about--and I'm
17 really going into Dr. Folks' arena here,
18 but I'll go ahead and say this anyway--about
19 screening samples from blood donors, you know,
20 going from the other direction to see if we can
21 identify seropositivity among blood donors.
22 That had been discussed internally, and
23 our internal decision was that that was actually--you know,
24 what do we know without firm numbers? We
25 know that a very small proportion of people who are

1 occupationally exposed to non-human primates are
2 seropositive, most optimistically about 3 percent,
3 and because of the bias I talked about in
4 enrollment biases, that likely overestimates. The
5 true prevalence among all exposed people is
6 probably lower.
7 What proportion of blood donors are
8 occupationally exposed to non-human primates? I
9 don't know. A very low percentage. If you try to
10 screen a large population of blood donors, it's
11 going to be actually quite labor-intensive because
12 all the serologic assays are investigational and
13 they are Western blots. They are not ELISAs.
14 So it's going to be a very large
15 investment of time and money, and in the end, what
16 is it going to tell us? Well, it may allow us to
17 put a number, you know, that the number of blood
18 donors who are SFV-positive is 1 per 200,000 or
19 something like that. But our decision, at least in
20 terms of internal resources, was that the cost was
21 going to be much greater than the feedback in terms
22 of being able to quantify what we already sort of
23 know in terms of the level.
24 CHAIRMAN NELSON: Is there anybody else
25 with a burning comment on this issue, because we're

1 now pretty far behind. Since we have another--and
2 has our discussion satisfied the need for comments
3 on these proposals, as far as the FDA is concerned?
4 DR. NAKHASI: Yes, it has been very
5 helpful to understand what the--but still obviously
6 the question is, regarding the other questions,
7 what I heard is there is some--there are certain
8 more studies need to be done.
9 CHAIRMAN NELSON: Right.
10 DR. NAKHASI: And I think what we heard,
11 that it is definitely insufficient data on
12 transmission, so whether we can find it, how we can
13 find it, that's a different story, but I think
14 thanks for the input.
15 CHAIRMAN NELSON: Yes.
16 DR. NAKHASI: Jay, you want to say
17 anything?
18 CHAIRMAN NELSON: I think the focused CDC
19 studies seem to be well worthwhile. Blaine?
20 DR. HOLLINGER: Well, I just want to
21 reiterate what Mike said initially because I think
22 it's important. If you do a study like this, you
23 clearly--I think leukocyte reduction would be an
24 interesting additional factor here, since a fair
25 proportion, what, 90 percent of the Red Cross

1 blood--we're going to talk about this anyway later
2 on--
3 CHAIRMAN NELSON: Right, this afternoon.
4 DR. HOLLINGER: But, I mean, that would be
5 another arm that one would want to consider. But
6 on the other hand, if the plasma is also, and I
7 think you sort of selected for that, then that
8 would make a little bit of--some difficulties in
9 that. But I do think that the other course of
10 trying to go to a high-risk population to look for
11 SFV, such as a highly transfused group, should be
12 at the top of the list. That's where I would--
13 CHAIRMAN NELSON: The problem is to find a
14 high-risk group that has not only had a lot of
15 transfusions but also from people who might have
16 been likely to have been infected, and that's not
17 so easy.
18 DR. HOLLINGER: That's true.
19 CHAIRMAN NELSON: Jay?
20 DR. EPSTEIN: I just wanted to say that I
21 think we've heard a lot of very thoughtful comments
22 and that we will consider them in deciding what, if
23 anything, to do next. So I don't feel as if we
24 need to discuss it further. I think we've gotten
25 the feedback that we were seeking.

1 CHAIRMAN NELSON: Okay. Well, I propose
2 that we break for lunch or whatever it is now, not
3 quite dinner, but come back maybe in 45 minutes, at
4 a quarter to 3:00? Well, at least by 3:00.
5 [Whereupon, at 2:00 p.m., the meeting was
6 recessed, to reconvene at 3:00 p.m. this same day.}

1 AFTERNOON SESSION
2 CHAIRMAN NELSON: This session is a
3 discussion on leukocyte reduction, and Dr. Alan
4 Williams from the FDA will give us the introduction
5 and background.
6 DR. WILLIAMS: Thank you, Ken. This
7 session is specifically targeted to discuss product
8 standards and the current draft guidance and
9 potential modifications to the guidance covering
10 pre-storage leukoreduction. That said, there have
11 been several recent publications in the last year
12 regarding the issue of universal leukoreduction,
13 and it was felt it would be timely to have the
14 agency give some indication of what current
15 thinking is in terms of the larger area of
16 universal leukoreduction, so in the first two
17 slides I'm going to do that and then go into
18 discussion of the guidance documents.
19 The value of leukoreduced products for
20 selected patient subpopulations is widely accepted,
21 and I think there isn't too much of an argument
22 over that statement. There may be benefits of
23 universal leukoreduction to the overall recipient
24 population, but at the present time these are not
25 proven.

1 Observational studies at single
2 institutions and limited randomized trials show
3 unexplained conflicting results. The possibility
4 exists that unidentified patient subsets may not
5 benefit from the leukoreduction process, and the
6 possibility exists that there are other undefined
7 variables--for example, something like a site-specific
8 factor--that could play a role in the
9 current observations and the fact that some of
10 these study conclusions don't agree.
11 The agency's thinking currently is that
12 careful reevaluation of all available scientific
13 data regarding the value of universal
14 leukoreduction is indicated. Such an exercise may
15 provide leads to new hypotheses that can then best
16 be tested in a multi-center trial of the
17 appropriate size. Additional public discussion of
18 the available data is appropriate before pursuing
19 rule-making to require universal leukoreduction
20 implementation, and we have been discussing the
21 potential of a public workshop to discuss these
22 issues during 2002.
23 With that, let's move on to the topic at
24 hand, which is the draft guidance for industry
25 concerning pre-storage leukocyte reduction of blood

1 and blood components intended for transfusion and
2 proposed modifications to that guidance,
3 specifically discussions regarding the quality
4 control aspects of it.
5 The session will start with my listing of
6 the proposed modifications and a little bit of
7 context as background. Then the second speaker
8 will be Betsy Poindexter from our Division of
9 Hematology in the Office of Blood, providing an
10 update on filter performance specific to some of
11 the temperature and physical and other factors that
12 affect the efficacy of filter performance.
13 Third, we are very fortunate to have Dr.
14 Edward Snyder with us from Yale-New Haven Hospital,
15 who will discuss the very relevant topic of
16 establishing the appropriate quality control cut-off for
17 contaminating leukocytes and the value
18 relationship to the potential benefits from the
19 leukoreduction process. Fourth, we are also very
20 fortunate to have Linda Kline from the American Red
21 Cross, Holland Laboratory. She has been working in
22 this field for many years, and will discuss the
23 nitty-gritty of current methods to count
24 contaminating leukocytes and just what are the
25 workloads involved in producing data for quality

1 control.

2 Finally, I am going to end the session by
3 introducing specifically the options for quality
4 control and the committee questions.

5 Just a brief review. The current memo
6 which guides the leukoreduction process is a 1996
7 FDA memo which calls for quality control as an
8 evaluation of 1 percent of representative products
9 with a minimum of four products per month. The
10 cut-off for residual white cells is 5 million, and
11 there is a requirement for 85 percent retention of
12 the therapeutic product.

13 For platelet preparations it's a little
14 different. I think that's 3.3, is it, times 10 to
15 the 5th residual white cells and 85 percent
16 retention of platelets--sorry, 8.3, yes. And the
17 figure is different for pheresis. Apheresis
18 platelets, 5 million residual white cells for
19 apheresis platelets.

20 All evaluated products must meet specs,
21 and if failure is observed, the label must be
22 revised and the process investigated. And the
23 methods at that time available are similar to the
24 methods available now, which is manual Nageotte
25 hemocytomer counts, flow cytometry, and option for

1 other validated methods.

2 Draft guidance was issued in January of
3 2001, proposing revisions to these product
4 standards, and the elements of this draft guidance
5 include a product specification change from 5 times
6 10 to the 6th to 1 times 10 to the 6th residual
7 white cells, and 1.6 times 10 to the 5th for
8 apheresis platelets. Validation of the process to
9 be conducted by 60 consecutive counts.

10 Now, this is actually one of the first
11 introductions of a statistical based quality
12 control process, and there is a statistical basis
13 behind this number which we'll get into a little
14 bit later in the session. But the overall theme
15 here is that the process would use statistical
16 quality control to assure that 95 percent of
17 products met the product standard of 1 million with
18 95 percent confidence to be assessed at intervals
19 of every three months, and in terms of actual
20 counts, that would boil down to five per week, 20
21 per month, or 60 per quarter, and it would cycle
22 every quarter.

23 Additionally, as you heard, there was a
24 proposal for testing of all donors for sickle cell
25 trait, because it was well known by that time that

1 sickle cell trait in a donor would result in
2 approximately 50 percent unsuccessful filtration,
3 i.e., the filter would clog, and those filters
4 which did successfully provide filtration, the
5 resulting product would have excess contaminating
6 white cells in about half the instances.
7 And then, finally, there was a proposal,
8 because of the specific importance for CMV, for
9 CMV-susceptible patients, it was built into the
10 guidance, 100 percent quality control of components
11 to be used in lieu of CMV seronegative units.
12 We received a number of comments from
13 industry, 27 comments, to be exact. And there was
14 a discussion at the June 2001 BPAC which began to
15 explore some of the preliminary data regarding
16 filtration failures; some data from Canadian Blood
17 Services and some other sites about the value of
18 validated mixing procedures during collection; an
19 intense discussion of sickle cell hemoglobin S
20 screening of the donor base, and a unanimous lack
21 of support for that policy; and some discussion
22 about potentially labeling filters for optimal
23 conditions for filtration.
24 A couple of contextual things I wanted to
25 mention that I found in getting into this field

1 have sort of been a nagging source of confusion.
2 One is how to define a process failure, and I would
3 propose that the definition is really dependent
4 upon the selection of appropriate and distinct
5 control points. And one thing that's commonly done
6 is, incomplete filtration, i.e. a clogged filter,
7 is often counted as a failure together with white
8 cell contamination of the final product. These
9 really, I would propose, need to be two distinct
10 control points. And then, finally, therapeutic
11 content of final product, over which there really
12 has not been confusion.
13 Another is an observation that the current
14 leukoreduction process has relatively frequent
15 failures, some of which are poorly understood at
16 this time, and additionally the data regarding
17 failures, not only is the definition relatively
18 loose, but the reported failure rates really
19 covering a very broad range. And from data
20 involving a survey conducted by America's Blood
21 Centers, also data reported by the VAT study in
22 recent history of transfusion and some other data
23 reports, the range are from a low of .3 percent to
24 a high of 13 percent cumulative failure, total
25 failure, and this actually compares with another

1 low, which is the data reported by a filter
2 manufacturer at the last BPAC, 3 per million. So
3 what is really going on in terms of failure remains
4 fairly poorly defined.
5 It is known that slow filtration
6 correlates with poor white cell removal, and that
7 in the presence of hemoglobin S, about half of the
8 blood from a sickle cell trait donor will clog the
9 filter. Of the 50 percent that goes through, about
10 half of that has insufficient white cells removal,
11 which is about 25 percent overall. So if you have
12 a 10 percent sickle cell rate in your donor
13 population, it's a fair amount of potential white
14 cell contamination.
15 Other poorly understood donor factors do
16 exist. Donor-related failures appear to be serial,
17 that a donor who fails to filter at one point may
18 also fail to filter at a subsequent visit. There
19 have been lot-specific failures observed for the
20 same filter, different lots, higher rates of
21 failure. And it's fairly well established now with
22 emerging data that a validated mixing procedure
23 during collection does appear to reduce clogged
24 filters, and I think you'll hear more data about
25 that today.

1 Now, what are the implications of
2 failures? Obviously the driving force is safety.
3 If the product is labeled as "leukocytes reduced"
4 and it has high levels of contaminating white
5 cells, patients who really need a leukoreduced
6 product can be harmed. And I think the clear
7 example here would be cytomegalovirus. It's
8 clearly known to be transfusion-transmitted. It's
9 clearly known to cause morbidity and even mortality
10 in a patient who is highly susceptible to CMV
11 infection.
12 Another implication of process failure is
13 loss of efficacy of the process. It could result
14 in undue loss of a therapeutic product and
15 reduction of potency in the final product. And
16 incomplete filtration, at whatever rate, simply
17 constitutes a waste of a valuable blood resource.
18 I will end just by specifying some of the
19 changes being considered to the draft guidance on
20 leukoreduction. We are considering bringing the
21 product specification back to 5 million residual
22 white cells, the reasons for this being not that a
23 1 million cut-off is not justified. It's felt to
24 be a contaminant, that most likely removing it to
25 the greatest extent possible is the right thing to

1 do, but given current technology both in counting
2 and leukocyte removal and failures in trying to
3 meet that 1 million count, 5 million appears to be
4 a more achievable goal at this time.
5 Another proposal is that as a separate
6 process point, incompletion should not exceed 0.5
7 percent, and we're considering a recommendation for
8 use of a validated mixing procedure during
9 collection. In data that was presented at the last
10 advisory committee meeting from the Canadian side,
11 with validated procedures they were routinely
12 achieving 0.3 percent.
13 Diversion of units whose donors do not
14 filter or do not properly leukoreduce on two
15 separate occasions, unless some corrective action
16 is put into place, it really doesn't make a lot of
17 sense to keep putting the donor through the process
18 when they failed to filter properly on two
19 occasions.
20 We are considering not making a specific
21 recommendation for test donors for sickle trait.
22 Admittedly this is one way in which one can
23 prequalify a donor to not have as many clogged
24 filters, but we're considering not putting this
25 recommendation in the guidance.

1 And as of this point, we intend to remain
2 silent on the use of leukocyte reduced components
3 in lieu of CMV antibody negative units. This is a
4 question of medical practice. In fact, many
5 physicians who are taking care of highly
6 immunocompromized patients are now insisting on
7 both seronegative and leukoreduced products, so
8 this is a matter of medical judgment.
9 There are options for statistical quality
10 control, and this I'm going to present just before
11 we discuss the questions because I think it's
12 valuable to hear the other data in advance.
13 In terms of timing, the proposed schedule
14 for leukoreduction guidance, it's a topic obviously
15 today. We hope to have the revised guidance, which
16 will be reissued in draft because of the changes in
17 early 2002, and looking toward final guidance
18 approximately mid-2002.
19 With that, I will welcome the next
20 speaker. I would like to comment that, for those
21 of you who looked at the materials that were shared
22 with the committee and have statistical questions,
23 FDS's Dr. Peter Lachenbrach is in the audience.
24 Unfortunately, he won't be able to stay for the
25 whole discussion, so if you have a specific

1 statistical question, you might like to raise it
2 early in the session while he is still here.
3 Thank you.
4 CHAIRMAN NELSON: Questions? Alan, in
5 regard to the one issue on which the FDA was
6 planning to be silent, I am concerned about the
7 fact that--and I think it impinges on rates of
8 failure, and also I'm not sure I'm convinced how
9 efficacious leukoreduction is to prevent CMV, when
10 you're giving people 5 million cells. And are we
11 not going to discuss that? Is that not part of
12 the--
13 DR. WILLIAMS: It is part of the session.
14 Ed Snyder will be discussing cut-off values in
15 terms of medical benefits. And in a discussion of
16 whether leukoreduction reduces CMV, I think it's
17 pretty clear it reduces CMV.
18 CHAIRMAN NELSON: Right.
19 DR. WILLIAMS: Whether it's completely
20 protective is arguable.
21 CHAIRMAN NELSON: Is it adequate, and
22 should that issue be up to the individual
23 physician, who may not have as much information as
24 the FDA does?
25 DR. WILLIAMS: I think also keep in mind

1 that serological tests for CMV antibody also are
2 not 100 percent effective, so you kind of have to
3 balance the two.
4 CHAIRMAN NELSON: Sure.
5 DR. SIMON: Yes, I was just going to say I
6 thought that the FDA was correct to be silent on
7 that because of these issues of medical practice
8 that relate to it, and what you're looking at is a
9 continuum of reduced risk rather than no end point
10 at which risk disappears. So I thought it was a
11 very pragmatic approach to the subject.
12 CHAIRMAN NELSON: Next speaker is Betsy
13 Poindexter.
14 MS. POINDEXTER: Good afternoon. My topic
15 is leukocyte reduction and reported performance in
16 the literature, not necessarily first-hand from my
17 own experience. The topics that I will attempt to
18 cover are the types of leukocyte reduction by
19 filtration: whole blood, red blood cells, red
20 blood cells apheresis, and platelet pheresis, and
21 then leukocyte reduction by in-process procedures,
22 as with the COBE Trima and with the Baxter Amicus
23 device.
24 Filtration conditions affect the quality
25 of the product as it goes through the filter: the

1 volume of blood that is drawn, and I have listed
2 out the amounts, the minimums and the maximums that
3 might be drawn, depending on whether you are
4 drawing into a 450 mL or a 500 mL collection bag,
5 the hold times prior to filtration, and the
6 temperatures at the time of filtration, whether
7 they are ambient or refrigerated for extended
8 periods of time.
9 Whole blood processing involves collecting
10 the unit, obviously, and processing it into red
11 blood cells from either the 450 or the 500 mL draw;
12 separating it by a hard spin when you're preparing
13 red blood cells for preparation of plasmas or an
14 FFP byproduct, and a soft spin for platelet
15 concentrate and an FFP or plasma byproduct. And
16 the additive solution frequently is added at the
17 end of these spins to the red blood cell product,
18 which is then sent through the leukocyte reduction
19 filters.
20 What I have done is gone through the
21 literature, and this is by no means a complete
22 search. This is abstract presentations from the
23 year 2000 AABB meeting, where various reports from
24 leukocyte reduction filters were in the abstracts
25 and were either oral or poster presentations. I

1 have tried systematically through the slides to
2 include whatever information was available in the
3 abstract for the filtration temperature; the units
4 tested; the hold time prior to filtration; the
5 white cell counts, I have converted all of them to
6 10 to the 5th leukocytes per transfusion dose; and
7 the filtration time.
8 This one example is the only one in the
9 group that I'll be reporting that had a median
10 white blood cell count rather than a mean white
11 blood cell count of 10 to the 5th cells. As you
12 can see, they held products at room temperature for
13 either zero or eight hours. So they filtered some
14 of them as soon as the red cells were processed and
15 delivered into the additive solution, mixed and
16 then immediately sent through the filter; and
17 others were held 24 hours or as much as five days
18 at 4 degrees C prior to filtration. As you see,
19 the white blood cell counts were very acceptable
20 and the filtration times were very acceptable.
21 This is a whole blood filter. This was an
22 RZ-2000. As you can see, the temperatures for
23 filtration are there. The numbers of units tested
24 are rather large. This was their intent, to show
25 that if you take many units over the temperatures

1 that are usually used to store and prepare filtered
2 red cells, that you can repeat the performance over
3 and over again.
4 So out of a total of 4,544 units from six
5 countries--there is one question, Germany was
6 listed twice in this abstract, so I'm not sure
7 whether there was another country represented--all
8 of them had acceptable white blood cell counts.
9 All of them were filtered, either at less than
10 eight hours at 20 to 24 C, or greater than eight
11 hours at 4 C, and they all had acceptable white
12 blood cell counts.
13 The 802 units in the middle were all
14 processed by European method, where they were
15 probably buffy coat preparations, where they were
16 spun, the buffy coat was then pulled off, and so
17 the filter would not have seen as many leukocytes,
18 and that may account for the slightly lower white
19 blood cell counts. Again, all of the white blood
20 cell counts are well within the acceptable
21 criteria. What you will notice missing is red cell
22 recovery data and filtration time data, how long it
23 took those products to go through the filter.
24 This is another with that same filter but
25 with 500 mL draws. Again, some of the numbers are

1 falling off the screen. You can notice the n is
2 rather small. This is actually Linda Kline's work
3 from the Holland Labs at Red Cross. The
4 temperatures at the bottom are 4 to 6 degrees; the
5 other three are 20 to 24.
6 Again, all of the white blood cell counts
7 are well within acceptable means, and the
8 filtration times are listed with the standard
9 deviations there, and the red cell recovery is
10 listed on these. Frequently the red cell recovery
11 data is missing, and when we're looking for 85
12 percent recovery of the product that you started
13 with, if we don't have that information in the form
14 of papers or from the manufacturer, it does give us
15 pause.
16 This is a red cell filter by the Pall
17 Corporation, and let's see, these were 500 mL units
18 collected in AS-3 solution, filtered through the
19 RC2D. And this is showing the variability in the
20 spin speeds. The hard spin and the soft spin were
21 performed within about 30 minutes after the
22 collection of the product.
23 Again, the white blood cell counts are
24 very acceptable. The filtration time and the
25 standard deviation, the mean and standard

1 deviations, are there. The red cell recovery is
2 excellent, and the volumes that were filtered
3 through those units are represented.
4 This is a Baxter soft-sided filter that
5 was unidentified by anything other than that. The
6 numbers tested are about average for what we
7 usually see.
8 The hold times did vary considerably, in
9 that they tested some that had been less than an
10 hour from the donor, so that they were probably
11 still physically warm to the touch. And then they
12 had some that they stored for seven to eight hours,
13 that probably would have completed filtration prior
14 to those units being put into the refrigerator.
15 Then they stored some in the refrigerator for as
16 little as one to two hours, so that the core
17 temperature of the blood may not have been 4 to 6
18 degrees even though that was the refrigerator that
19 they were being stored in. And the other 4 to 6
20 degree measurements were after three days of
21 storage in the refrigerated temperatures.
22 They did report their mean and they did
23 report their range on their mean for the red cell
24 recoveries, and again the white cell removal. All
25 appeared to be very satisfactory in the filtration

1 times within expected limits.

2 This is an example of apheresis red blood
3 cells. It was the only one that I was able to find
4 on short notice. These are Gambro Trima red cells
5 filtered with a Pall filter that was only
6 identified by a part number, so that that was all I
7 could go on.

8 This is a different anticoagulant additive
9 solution. Trima collects the red blood cells in
10 ACD-A, so that they can co-collect plasma
11 byproducts or platelet pheresis products in
12 addition to the red cell unit, so this is an
13 unusual circumstance. They filtered them all
14 within eight hours of collection at room
15 temperature.

16 Where I was able to find the notations, I
17 did include how the white blood cell counts were
18 performed. These were done on Nageotte. The mean
19 filter time was 14 minutes, but you will note there
20 are no ranges so we have no idea whether some were
21 6 and some were 60 minutes. The mean residual
22 white count is there. Again we have a very
23 acceptable count, but we have no idea what the
24 range of those counts might have been. And they
25 report a mean red cell recovery of 88 percent,

1 which is certainly within what we would be
2 expecting.
3 This is just one example of three
4 different technologies that are used to collect
5 apheresis platelets. The platelets were separated
6 during the collection process in the Trima. Both
7 the Amicus and the Trima are in-process leukocyte
8 reduced. They do not see a filter. Just the
9 centrifugation process itself leads to quite a pure
10 platelet product.
11 The main note here is, they do give the
12 white cell counts with their means and their
13 standard deviations. They also give the range, but
14 you will note that I have put red for the zeros,
15 depending on how many zeros were represented in
16 that data, and we don't consider zero a number. We
17 would rather them report the lowest count that is
18 able to be achieved by that particular counting
19 method. And I believe on the Nageotte, this is a
20 fact scan, I think they can go down to about a half
21 cell per count, but zero throws those numbers off,
22 so we really don't know where that would lead us.
23 So to summarize just those reports, and
24 what we frequently see in the data is, we see
25 varied exponents. I changed all these exponents

1 and recalculated the data so that they were all
2 being reported at 10 to the 5. The exponents
3 ranged from 10 to the 3 to 10 to the 6, and some of
4 the standard deviations ranged from 10 to the 3, 10
5 to the 6, so you really had to be careful. If you
6 were just looking at the bulk number and not
7 looking at the standard deviations, you might be
8 misled into thinking that the filter was performing
9 better than or worse than what you were used to.
10 The representation of zeros in the white
11 blood cell data, if you have 20 counts and 10 of
12 them are zeros, obviously your mean is going to be
13 much different than what you had anticipated.
14 Sample size are generally very small. If our
15 statisticians were to look at it, they would
16 probably say you couldn't draw great conclusions
17 from ends of 6 and 10. And the data are generally,
18 data in print are generally favorable data. They
19 don't generally report their failures.
20 The varied reporting, we didn't see a lot
21 of collection volumes, whether they were 450 mL
22 collections or 500 mL collections. That's
23 important, because the numbers of white cells and
24 the hematocrits of the donors will then influence
25 how that particular filter might behave, both at

1 room temperature and 4 degrees C.
2 We do have novel anticoagulant
3 combinations coming on line, and those
4 anticoagulant combinations may or may not affect
5 the filter performance, but that is yet to be
6 shown. Frequently the red cell recovery data is
7 not reported, so that when blood centers go back to
8 look at this data and they see that the white cell
9 counts look terrific but they don't know that the
10 red cell recovery may have been 65 or 70 percent,
11 and that would be contrary to what we're expecting
12 the filter performance would be.
13 Frequently the ranges of the residual
14 white cell count and the filtration times are not
15 there, so a mean can be just that. It's just a
16 number unless you know what the point spread, so to
17 speak, was. And the sample sizes vary from 6 to
18 10, and maybe 20 in some circumstances, but that's
19 more of a rare event.
20 The under-reporting that's probably there,
21 filtration problems are rarely addressed. In June
22 we addressed the reports of lack of filtration on
23 sickle cell trait donor products. These were
24 reported in the 1999 Transfusion--the 2000
25 Transfusion--only because in the 1999 AABB meeting

1 there were two reports, one out of Emory and one
2 out of the U.K., of consistent problems with sickle
3 cell trait donor blood.
4 So we don't know what all the donor
5 variables might be that would affect leukocyte
6 reduction from any of the filters that are
7 currently available or might be in the pipeline.
8 Extended filtration times will frequently lead to
9 either very frustrated processing room people or
10 perhaps to white blood cells creeping on through,
11 and then the product is not truly leukocyte
12 reduced. With the higher white cell levels being
13 there, that's definitely something that we want to
14 steer clear of.
15 We have not yet in print seen reports of
16 clots being visible in the leukocyte reduction
17 filter. We know that they are occurring. We have
18 heard from manufacturers and from blood centers.
19 There may have been one report in this 2001
20 Transfusion by one of the manufacturers.
21 The collection times are quite variable.
22 The time that it takes from when you stick the
23 needle in the donor's arm until you are finally
24 collecting that blood ranges anywhere from 3 to 4
25 minutes at the fastest, to 15 to 18 or 20 minutes,

1 and perhaps even longer in some circumstances. And
2 I believe it was the Canadian group in June who
3 related the fact that those units will frequently
4 clog up the filters, and they find them not
5 acceptable for transfusion products.
6 Centrifugation spins, how you prepare
7 those red blood cells, whether you're doing a hard
8 spin for just plasma collection, where you have the
9 full complement of all the platelets and the white
10 cells there on the buffy coat that are then going
11 to see the filter, or whether you're doing a light
12 spin and preparing a platelet product where the
13 bulk of the platelets have gone into the PRP, but
14 you still have probably 90, 95 percent of the
15 leukocyte load going to see the filter.
16 This was a quote in one of the abstracts
17 that I've reported data from: "The efficacy of
18 leukocyte reduction filters is generally
19 demonstrated under clinical trial conditions that
20 use a relatively small sample, often less than 150
21 units." There were only two reports that I
22 reported here today that were anywhere near 150
23 units. "In order to determine the performance
24 level to be expected from a given filter for
25 routine use, a large number of samples needs to be

1 tested."

2 Right now that burden is on the blood
3 centers to do those large numbers of filtration and
4 those large numbers of white cell counts and red
5 cell recoveries. And we've heard discussion from
6 people in the BEST Committee that perhaps most of
7 that burden belongs back on the manufacturers'
8 shoulders; that the numbers of units that they
9 submit to us, the data that they submit to us,
10 should incorporate large numbers of donors, with
11 all of the permutations, that I've attempted to
12 list at least some of them on the slides this
13 afternoon.

14 And that's it.

15 CHAIRMAN NELSON: Questions? Yes, Toby?

16 DR. SIMON: One of the issues always comes
17 up with validation, is the manufacture in an ideal
18 situation versus how you actually use it in your
19 own setting, so you could get different results.
20 Is it your view there should be larger numbers on
21 both sides?

22 MS. POINDEXTER: Well, I think from the
23 manufacturer's standpoint we have been stressing
24 now that the manufacturers have to do both the soft
25 and the hard spin; they have to do the 450 and 500

1 mL draws; if that's what they're anticipating
2 getting clearance or approval for; that they do
3 them both at room temperature and 4 degrees C, and
4 that if they're doing them at either one or both of
5 those temperatures; that they cover that full range
6 of zero to 2 hours at room temperature, 4 to 6
7 hours, 6 to 8 hours, a few hours in the cold or
8 many, many hours or days in the cold, so that they
9 are reporting to us data that will demonstrate that
10 their filters will or will not work under all of
11 those conditions.
12 Granted, you know, in a perfect world
13 everyone would be operating with the same draw
14 volumes, the same anticoagulants, the same
15 centrifuges, so that if you knew that you set 3,000
16 rpm for 7 minutes, that everybody's were going to
17 spin out the same way. But it is a big problem,
18 and I would--in the recent past, in the last year
19 or so, we have been recommending larger numbers of
20 units be tested by the manufacturers of the filters
21 under all of the conditions. Our statisticians do
22 look at that data and tell us whether the end is
23 large enough for them to actually make the claims
24 that they're making.
25 CHAIRMAN NELSON: Of course a review of

1 the literature could always be subject to
2 publication bias. You know, if you present your
3 data at a meeting, if your data meet certain specs
4 they will be accepted; if it isn't, you won't
5 submit it or it won't be presented, and--
6 MS. POINDEXTER: Yes, and the other thing
7 that might be of interest is, I believe all of the
8 data presented, although some of it was a blood
9 center presenting it, it was in collaboration with
10 the manufacturer, so that one or more of the
11 authors on the abstracts, on the papers, were
12 manufacturers, so that it's not just coming from a
13 particular blood center where they did it in-house.
14 CHAIRMAN NELSON: Yes, but if there was a
15 collaboration that didn't get the result that
16 either the author or the manufacturer wanted, it
17 may not get into the literature and may not be
18 captured. I mean, it could be, I mean. Thank you.
19 Dr. Snyder? Talking about establishing
20 the appropriate QC cut-off for contaminating
21 leukocytes, Dr. Snyder from Yale-New Haven.
22 Dr. Smallwood says that in these down
23 times I'm supposed to have a joke, but I guess it's
24 up now, so next time I'll tell one.
25 DR. SNYDER: Thank you very much. It's a

1 privilege to be here to talk to you about this
2 topic. The title sounded like this was going to be
3 a discussion of the quality assurance issues and so
4 forth. What I intend to cover are the medical
5 indications for a reduction of the level of
6 leukoreduction from 5 times 10 to the 6th down to 1
7 times 10 to the 6th.
8 I think it's important to get conflicts of
9 interest out. Again, I realize Dr. Smallwood had
10 mentioned this earlier, but since my conflicts are
11 so strong, I feel it's critically important to
12 mention them again.
13 Our laboratory at Yale has for the past 24
14 years worked with a variety of companies, getting
15 data into a form that could be submitted to the
16 agency for licensure of their products. That's
17 what I have essentially made my career out of.
18 Currently I am on advisory boards for Baxter, Pall,
19 and Terumo; have research grants for Baxter, Cerus,
20 Terumo, and Vitex.
21 I am on the board of directors of the Pall
22 Corporation, not the medical advisory board but the
23 corporation board. It is a paid position, but I
24 have absolutely no equity, no stocks and no options
25 as listed in the proxy statement. This was done

1 specifically to provide some degree of, perhaps for
2 my own personal desire, distance from the changes
3 in the company's stock and my personal gain. I am
4 trying to maintain an academic distance from that.
5 But the companies have the technologies
6 and that's where my research interests lie. I
7 wanted to make sure this was discussed. As you
8 will see from the data, I think it's important to
9 reiterate this.
10 The guidance for industry, just to
11 reiterate very quickly what Alan said, the agency
12 put in the document in January 2001 that pre-storage
13 leukoreduction blood products contribute to
14 safety, and benefits of leukoreduced products
15 suggest they should be made more widely available.
16 The agency considered increasing the level of
17 product safety by mandating that leukoreduced
18 products contain--not mandating that all products
19 be leukoreduced, but mandating that if you were
20 going to label a product as leukoreduced, that it
21 should have less than or equal to 1 times 10 to the
22 6th white cells per unit instead of 5 time 10 to
23 the 6th.
24 And just as an aside, the reason for the
25 .83 times 10 to the 5th for a single random donor

1 unit of platelets was the assumption of a six-unit
2 pool which, when multiplied by six, comes out to 5
3 times 10 to the 6th, which is what it was for the
4 single donor platelet.
5 In addition, directly test every
6 leukoreduced component used as CMV safe in lieu of
7 serological testing, and consider donor screening
8 for sickle cell--screening donors for sickle cell
9 trait.
10 From my perspective--and I am speaking as
11 Ed Snyder, physician, patient caregiver, and human
12 being, I'm not speaking on behalf of Yale
13 University or any of the companies with which we
14 have relations--from my perspective there are three
15 benefits from leukoreduction. This is one slide
16 the committee doesn't have. I added this this
17 morning, to make it a little clearer. Decreased
18 incidence of febrile transfusion reactions,
19 decreased transmission of CMV, and decreased
20 incidence of HLA alloimmunization. And I don't say
21 eliminate. I talk about decreasing.
22 And what I will show you are data that I
23 believe supports the concept that the bases upon
24 which these statements are made were generated on 5
25 times 10 to the 6th levels of white cells remaining

1 in products, and did not require a greater degree
2 of removal, not down to 1 times 10 to the 6th
3 certainly, as a way of supporting my belief for the
4 bottom line that you do not need to move to a 1
5 times 10 to the 6th, that 5 times 10 to the 6th
6 gives the safety and efficacy and purity that the
7 agency is looking for.
8 The first is febrile reactions. This is a
9 slide I got from Nancy Hettle, and basically what
10 Nancy has done is, she has discussed febrile
11 reactions as being due to, in a large degree in
12 stored products, the plasma component. She did a
13 study which is somewhat represented here, but this
14 is not the actual data slide from that, where she
15 took four- to five-day-old platelet concentrates,
16 separated them into supernatant and cellular
17 component, and randomly infused them, and found
18 that in 64 infusions, 30 of them had no febrile
19 reactions at all, 20 of them reacted to plasma
20 alone, 8 to both plasma and cells, and 6 to cells
21 alone. And the assumption here is that there were
22 cytokinins in the supernatant that really were the
23 cause of the fevers.
24 This slide shows mild and moderate and
25 severe in different colors, so the plasma removal

1 sets a level of reduction which you can't see over
2 here, but this is a degree of, I think it was
3 percent of reactions. Post-leukocyte reduction
4 filtration had a higher level--there are no error
5 bars here, so it's sort of qualitative data--in the
6 severe category. But as you got to pre-storage
7 leukoreduced or pre-storage reduced by apheresis,
8 the number of severe reactions was much lower.
9 Moderate reactions and mild reactions were still
10 present, but there was a lower level certainly of
11 the severe reactions.
12 This has been looked at additionally in
13 other studies. This is data that we submitted,
14 discussed at the ABB this past year, on the
15 incidence of febrile and allergic reactions
16 following introduction of pre-storage universal
17 leukoreduction of random donor platelets and red
18 cells.
19 And what we have here is a graph at Yale
20 from April 1998, when we were at about 30 percent
21 leukoreduction. What you see here in blue is the
22 percent of leukoreduced red blood cells, and in red
23 are the number of transfusion reactions reported.
24 Each tic is a month, starting in April '98, ending
25 in November 2001, and this is a best fit curve that

1 was computer-generated. This is the number of
2 reactions.
3 So, as you can see, when we looked at our
4 data, as we increased--here, when we were about 20
5 to 30 percent leukoreduced, which is on this axis,
6 we were getting ranging anywhere from 4 to 12
7 reactions a month. And then as we increased our
8 leukoreduction to about December of '99, we reached
9 about 100 percent leukoreduction, there was a drop
10 in febrile reactions reported which you can see
11 here.
12 Looking at platelets--and we use only
13 random donor platelets at Yale, we always have, so
14 it was not just instituted as cost-cutting--again
15 looking at the same time frame, we have the onset
16 of leukoreduction. There was a little blip here
17 because of some problems with manufacture. And as
18 you can see that the incidence--this was up to 20
19 febrile reactions in a month, and as we went to
20 full leukoreduction it dropped off to the point, in
21 this period of time, I was wondering whether we
22 were just not reporting them at all and where they
23 were. It was a rather impressive drop-off in
24 febrile reactions due to platelets at our
25 institution.

1 Well, we evaluated this, and what we found
2 was that febrile reactions, the percent of
3 reactions, the total reactions dropped from 2.2
4 percent to .7. This is pre-leukoreduced and
5 ramping up to 100 percent. We included that in the
6 same group. And this is at 100 percent
7 leukoreduction. So the drop was .22 to .7 in
8 febrile--I'm sorry, these are platelets, reactions
9 with platelets. With red cells the drop was from
10 .3 percent to .2.
11 Well, this was statistically significant
12 at .0005, and comes out to be a 33 percent drop,
13 and that is calculated--I don't know a lot of
14 statistics, but I know a little, and the percent
15 change is the difference over the original, if I
16 remember that right. So it's .1 is the difference
17 over the original of .3, is a 33 percent drop. So
18 we reported this was significant.
19 We also saw a fairly substantial drop for
20 febrile reactions to red cells as well. Allergic
21 reactions, there was some drop in the total
22 reactions with platelets, and with red cells there
23 was no change.
24 Well, this was good news, and we felt that
25 there was a significant decrease in the rate of

1 febrile reactions after institution of pre-storage
2 universal leukoreduction, and all of our products
3 are prepared by our local blood center. We do not
4 prepare them ourselves. And this was seen about
5 platelets and red cells.
6 There was no decrease in allergic
7 reactions. However, there was a decrease in
8 allergic reactions to platelets which we noted but
9 didn't have a good explanation for, although this
10 did coincide with the decrease in the pools size,
11 as an aside. And we felt that it provided a
12 substantial improvement in patient care.
13 My philosophy is--and this is at odds with
14 the philosophy of others, that prevention of
15 febrile reactions alone is a worthy activity, and
16 I've stated this multiple times. I don't think
17 patients need to pledge, so to speak, and have two
18 febrile reactions before they earn the right to get
19 a filter. I don't think that children should have
20 to rigor in their bed when they're getting a
21 transfusion in order to earn the right not to have
22 to have it chilled by getting a filter.
23 Some people feel that's not the case.
24 Ofttimes, and I am fond of saying that individuals
25 who allow others to have these chills, if they get

1 a sniffle or a head cold will take two or three
2 days off from work until they feel better, so I
3 don't think people should be in a position of
4 deciding what someone should have to tolerate. I
5 think from my perspective as a physician, a patient
6 should be allowed to have this, realizing there is
7 a cost involved, and we can discuss this later, but
8 that's my approach.
9 So retrospective case review was done
10 because there was a possibility that the nursing
11 staff was just ignoring patients rigoring in their
12 beds. It was unlikely but it needed to be
13 considered. So we are in the process of evaluating
14 about 500 red cell and 500 platelet transfusions
15 that we are following, that were not reported as
16 being reactions. We are reviewing the charts and
17 talking to patients through the IRB approval to see
18 if we're missing any, and for those of you who want
19 instant gratification, we are not. There are not
20 any reports, and we have standard criteria. This
21 will be presented at a future time.
22 So we're comfortable at least, and the
23 nursing staff certainly was not aware of the change
24 in filtration practice, most parts of the hospital.
25 They were still getting a unit of blood or

1 platelets or red cells, and they needed to put it
2 through a standard blood filter. The fact that it
3 was pre-storage filtered, they were not really
4 aware of, because it doesn't look any different
5 than it did previously.
6 We also felt that prospective, randomized,
7 blinded studies should be done. Lots of people say
8 this. In Canada you can't even do this anymore
9 because the Canadian government doesn't have non-
10 leukoreduced blood products. And so while we were
11 giving ourselves high fives, so to speak, about
12 this, a paper was published by Uhlmann, and Tim
13 Goodnough was the senior investigator,
14 retrospectively looking at changes, and they felt
15 that there were no differences when they went to
16 full leukoreduction, so we analyzed their data.
17 I'm sorry this has all shifted to the left
18 here. I don't quite know--that's not the--we
19 already found out that wasn't due to the machine
20 not being pushed over far enough.
21 But this was non-leukoreduced blood
22 products. Our group looked at 91,000 units of red
23 cells, and for the leukoreduction we looked at
24 41,907 units. These are for red cells. Dr.
25 Goodnough's group looked at 36,000 units and 16,000

1 units, fully leukoreduced. This was non-leukoreduced. They
2 found the same 33 percent
3 difference we did, yet theirs was not significant
4 and ours was.
5 So we went to our statisticians and talked
6 to them, and they stated that if you have a high
7 enough population, your numbers will be
8 significant. So I saw Dr. Goodnough at the ASH
9 meetings two days ago, and I went up to him and
10 said, "You should be aware that we are going to be
11 presenting all of this, and we found the same
12 percent change that you did, but ours was
13 statistically significant and you reported no
14 difference." And he said, "Well, if you use large
15 numbers, that's what you're going to find."
16 And I thought about that for a while, and
17 it occurred to me that if you apply this, as the
18 FDA would need to, to the 14 million units of blood
19 products collected, you're dealing with huge
20 numbers, and they're looking at it from a national
21 level. So I think the fact that if we used 90,000
22 and 30,000 or 41,000 units and we found a
23 significant difference at a 33 percent drop, and
24 Dr. Goodnough's group used smaller numbers and
25 didn't, that you can draw your own conclusions, but

1 I'm comfortable that the filtration, even if you
2 have a small degree of febrile reactions to start
3 with, it's an improvement that is obvious.
4 Others have weighed in on this issue, as
5 well. This is from the ABB, as well. This is a
6 paper by Dr. Tanz and Dr. Ness, where they looked
7 at full leukoreductions. And Dr. Ness, for purpose
8 of conflicts of interest, and he's not even here to
9 defend himself, he's on the medical advisory board
10 of the Pall Corporation as well, and other
11 activities that I'm not aware of. I should
12 rephrase that.
13 [Laughter.]
14 DR. SNYDER: Other activities that are
15 perfectly fine, I'm sure. I shouldn't do this if
16 I'm being videotaped by three tape machines over
17 there.
18 From January '98 to July 2000, they
19 transfused 37,000 leukoreduced red cells with a
20 percent--their percent leukoreduction was 39, which
21 is sort of baseline, and they had a 44 percent
22 incidence of febrile non-hemolytic transfusion
23 reactions. Then they switched to full
24 leukoreduction, up to 95 percent, transfused 24,000
25 units, 8/00 to 3/01, and that dropped to 17

1 percent, or .17 percent, rather, which they found
2 statistically significant.
3 So when I looked at this, I said, "Well,
4 that 37,000 and 24,000 is closer to what Dr.
5 Goodnough found, and they didn't find significance.
6 Why are they finding it?" And when I do my simple
7 mathematics again, the difference here is 27 over
8 44, which is close to a 60 percent drop. So the
9 reason that Dr. Tanz and Dr. Ness reported a
10 significant drop with numbers that are similar to
11 Dr. Goodnough's is, they had a higher percentage
12 drop. And yet there was another manuscript that
13 had the same numbers that Dr. Goodnough did, and
14 they found a 33 percent drop, and they found no
15 significance.
16 So I think there is consistency in the
17 literature, that if you look at numbers overall for
18 a long period of time, large numbers, you will find
19 that leukoreduction as done under cGMP does give a
20 benefit to patients, both statistically as well I
21 believe as by sci--statistically.
22 Now. Dr. Walter Zeke has published an
23 abstract at the ABB as well, a prospective
24 randomized clinical trial which he believes shows
25 that you do not need to use full leukoreduction.

1 And what he did is, he randomized everyone who came
2 into the hospital at Mass General to get a
3 leukoreduced filter or not, based on whether or
4 not--assume the only exclusion criteria I believe
5 primarily was that they didn't need a filter for a
6 specific reason. They were looking at the
7 universalization, if you will, of the concept.
8 And they found that in-house mortality,
9 100 and 8.5 percent, 9 percent, no difference.
10 Length of stay after transfusion, no difference.
11 They found no difference in anything. Well, he did
12 1,400 versus 1,300, which is relatively small
13 numbers. Some people that I have talked to felt
14 that this may have been underpowered.
15 He did also find that, I think it was I
16 don't know how many patients, it was like 880
17 patients or something received 13,000 cellular
18 products, and it was reported that there was a non-
19 statistically significant difference in febrile
20 reactions but there was a trend. In other words,
21 the difference in the group that got leukoreduced
22 versus not, it was lower in the leukoreduced group
23 but didn't achieve significance at .05, but the
24 trend was there, had they had larger numbers.
25 So, again, you have to look at the numbers

1 and say, well, 1,400, realize we're talking about
2 how many angels are on the head of your pin and how
3 many angels do you consider important." So that's
4 the literature that I could get on that area.
5 Let's move to the second area, which is
6 the reduction in alloimmunization. The TRAP trial
7 was the major study, New England Journal of
8 Medicine, 1997. This was conducting a prospective
9 randomized, blinded trial to evaluate three
10 approaches to preventing platelet alloimmunization:
11 leukoreduction, UVB irradiation, and single donor
12 apheresis.
13 This was reduction by filtration. This
14 was reduction by not only process leukoreduction,
15 by removing it with the apheresis technology, but
16 it was also filter. And UVB irradiation, and UVB
17 presumably affects, among other things, the binding
18 of accessory molecules, so that the ICAM doesn't
19 bind to LFA-1 very well because of some damage
20 induced by UVB. There's also changes in calcium,
21 so that you don't get a good signal, resulting in
22 the generation of an antibody, and HLA type
23 antibody. So they were looking at different types
24 of mechanisms.
25 One or more of the treatment arms were

1 statistically better. In fact, all the treatment
2 arms were better than the control arm, where
3 patients who have acute myelogenous leukemia were
4 transfused, looking for the presence of antibody,
5 and there are a variety of other aspects, no
6 differences among the treatment arms. And let me
7 show you what the results show.
8 This was for refracturing that's due to
9 allo antibody, and the three control, the three
10 test groups--UVB, filtered platelet concentrate,
11 and filtered apheresis platelets--all had a 3 to 5
12 percent rate, whereas it was 13 percent in the
13 control group, and this was a statistically
14 significant difference under an NIH-sponsored
15 study. And another slide from the same show, just
16 cumulative refractoriness, not specifically due to
17 antibody but including it, and again all the
18 control group, the control group was statistically
19 different from all three of the test groups. And,
20 on the basis of that, it was concluded that
21 alloimmunization was prevented by leukoreduction.
22 Okay, what's the last category? It's CMV.
23 Patients at risk for CMV infections are CMV
24 seronegative pregnant women, premature infants, CMV
25 recipients of allogeneic marrow transplants who are

1 themselves CMV seronegative, and CMV seronegative
2 patients with HIV.
3 The study that looked at this was a
4 randomized study that Dr. Raleigh Bowden did,
5 published in 1995. What she took were individuals
6 at the Hutch, divided 250 patients who received
7 leukoreduced blood that was untested for CMV
8 status, and 250 patients received blood that was
9 CMV seronegative. CMV seronegativity is known to
10 have a 3 percent false negative rate.
11 And what she found, to make a long story
12 short, is that there was no difference in infection
13 but there was a difference in disease, and that
14 whether you received CMV seronegative or filtered,
15 you got infected as shown by anti-CMV antibodies at
16 the same rate. There was somewhat of a higher
17 incidence of disease which was seen in one way of
18 analyzing the study. If you looked at day 21 to
19 day 100, there was no difference in disease. If
20 you looked at day zero to day 100, there was a
21 difference. Some of this was attributable to
22 patients who were infected prior to entry into the
23 study, who didn't really show that they were
24 infected until after 21 days. It was an attempt to
25 treat protocol, and they needed to look at both

1 ways of evaluating it.
2 After this study, the furor died down, so
3 to speak. The country went ahead and was using
4 leukoreduced blood products under cGMP as CMV-safe,
5 and the anecdotal information that I had was that
6 there was not any reporting of major problems with
7 this, that it appeared to be acceptable.
8 Several medical centers moved on to this,
9 and at our institution we have for the past three
10 years, since full leukoreduction, not given CMV
11 seronegative blood products to both our
12 allotransplant recipients as well as the neonates.
13 We just had our transfusion committee meeting
14 yesterday, and we had a report of three patients
15 who the pediatricians felt might have gotten CMV
16 from blood transfusion.
17 It turns out under further analysis one
18 of--these are all premature children, about 25
19 weeks of gestational age--one of them received CMV
20 seronegative blood. It turns out the donors were
21 CMV seronegative, as it turned out, in addition to
22 having leukoreduced blood products, so that was
23 essentially eliminated. All their donors were
24 negative. And the other ones had, one donor was
25 CMV seronegative, one of them was negative on four

1 previous donations but was not tested on the
2 donation that was in that case, and another child
3 had one donor that was CMV seronegative and the
4 other donor was a first-time donor.
5 So out of all of those, the feeling was
6 that there may have been one case possibly, which
7 we can't verify yet unless we get that donor back,
8 for all of the patients that have been tested at
9 our institution, which includes surveillance,
10 antigens, culturing. We don't wait for clinical
11 presentation and then go look and see. There is an
12 active surveillance that goes on. So we are
13 comfortable that the level of leukoreduction we are
14 getting is sufficient to prevent CMV transmission
15 both in allotransplant recipients as well as
16 neonates as well as others.
17 So what are my comments on all of this?
18 Let's pull all this together quickly, so we can get
19 on. I believe that the evidence is that less than
20 5 times 10 to the 6th is acceptable. Why? The
21 Bowden study used 3 log leukoreduction filters,
22 since it was done in 1995. The PL-100 and the PL-50 and the
23 RC-100 are rated at 3 log removal. That
24 would get you down to 5 times 10 to the 6th. So
25 the study that is considered to be the standard was

1 not done with a 1 times 10 to the 6th filter, and
2 showed results that were compatible with good
3 public health and safety.
4 The study also used bedside filters, which
5 often have cGMP issues, and therefore it's possible
6 that they may not have been used properly. You
7 can't QC those. So they may have gotten more white
8 cells than even the 3 log, which would have made it
9 even more likely that this process has a little
10 more robustness, to use the term that's very
11 popular these days, because you certainly didn't
12 get 1 times 10 to the 6th, and many times they may
13 not have even gotten less than 5 times 10 to the
14 6th.
15 Up to six off-protocol infusions were
16 permitted in order to stay on this study. They
17 admitted this in the manuscript. So many people
18 got full leukoreplete products and still did not
19 show the CMV conversion, again implying that the
20 filtration process is quite forgiving.
21 And then a prior "crimson standard" before
22 filtration came along was frozen deglycerolized red
23 cells, which gave you at most probably a 2 log
24 reduction, nowhere near the 1 times 10 to the 6th
25 needed, and that was considered acceptable for

1 neonates, and that's what we all used up until
2 filtration. So I do not recommend CMV serotesting
3 of every unit, and I do believe that 5 times 10 to
4 the 6th is acceptable for maintaining public health
5 in terms of CMV transmission of leukoreduced
6 products done under cGMPs, surely not bedside.
7 What about the TRAP trial? The TRAP trial
8 in 1997, when it was published, also used 3 log
9 leukoreduction filters, the PL-100 and the RC-100.
10 They also used the BPF-4, which is a 4 log filter,
11 but primarily they used the 3 log filter. They
12 used bedside filters which often have cGMP issues,
13 exactly like was mentioned for the CMV. And 3 to 5
14 percent of transfusions were off-protocol, which
15 means when these people came in, they needed to be
16 transfused immediately, there was no time to get
17 the leukoreduced blood products, and they got
18 whatever they had in the blood bank. So off-protocol means
19 they got leukocyte-replete products,
20 and they still had significantly less incidence of
21 HLA alloimmunization than the control group, which
22 got fully leukoreplete blood. So again, 5 times 10
23 to the 6th would appear adequate to ensure this
24 public health benefit and safety benefit.
25 There are guidelines that were published

1 in the Journal of Biology of Blood and Marrow
2 Transplantation, published by ASBMT, a Society of
3 Blood and Marrow Transplantation, "Guidelines for
4 Preventing Opportunistic Infections Among
5 Hematopoietic Stem Cell Transplant Recipients."
6 This is a compilation of recommendations of the
7 CDC, Infectious Disease Society, and the American
8 Society of Blood and Marrow Transplant.
9 And they say in the article, and I quote:
10 "CMV seronegative recipients of allogeneic stem
11 cell transplants from CMV seronegative donors
12 should receive only leukoreduced or CMV
13 seronegative red cells or leukoreduced platelets."
14 And then they have in parentheses, "less than 1
15 times 10 to the 6th to prevent TA CMV infection,"
16 and then they reference Dr. Bowden's paper.
17 Well, Dr. Bowden's paper, as I have just
18 showed you, was nowhere near 1 times 10 to the 6th,
19 so they are in error in referring to that number.
20 But the basis of their statement is an article and
21 a study that most likely used closer to 5 times 10
22 to the 6th, and that actually is not the correct
23 number. They base their conclusion that it's okay
24 to use this as CMV-safe on a number based on a
25 study which actually was closer to 5 times 10 to

1 the 6th.

2 I agree that areas of potential benefit

3 not yet established for leukoreduction include

4 transfusion-ready immunomodulation, bacterial

5 overgrowth, viral reactivation, variant CJD

6 transmission, re-perfusion injury, post-cardiopulmonary

7 bypass, storage lesions, TA-GVHD,

8 length of stay, mortality. Those are issues that

9 people are arguing.

10 I am not addressing whether we should

11 leukoreduce or shouldn't; if you are, at what

12 level. Those issues I don't think enter this

13 situation because no one has shown that

14 leukoreduction is beneficial. I'm talking about

15 the three issues for which there are data and for

16 which there is efficacy shown.

17 The effect of mandating that

18 leukoreduction contain less than 1 instead of less

19 than 5 times 10 to the 6th residual leukocytes

20 would present substantial obstacles to compliance

21 with little public health benefit, I believe, based

22 on the data that I have tried to show. And the

23 hardships imposed could make the blood supply less

24 plentiful, a drum that is often beaten by opponents

25 of leukoreduction, due to the need to discard

1 otherwise useful units of blood because they don't
2 meet the labeling standard.
3 And then, lastly, the reports by the NIH
4 Clinical Center regarding sickle cell, which the
5 agency has already addressed at a prior BPAC, but
6 just letting you know that members of this
7 committee are addressing this, two abstracts
8 presented at ASH, both authored by Dr. Stroncek,
9 first author on the first one and senior author on
10 the second one, where they looked at filtration of
11 sickle trait positive blood.
12 Their conclusions were, it should be
13 possible to avoid filter failure by changing
14 collection methods or optimizing intracellular
15 hemoglobin polymerization in AS red cells, AS not
16 being additive solution but being sickle trait, and
17 collection of apheresis components at the gas
18 permeable bags, and pre-incubation at 4 degrees may
19 allow AS components to be effectively filtered.
20 The point I'm making is that the medical
21 community, the academic transfusion medicine
22 community, is on its own addressing this, so it is
23 not--it is removed from the concern about the
24 public health, because there will be ways to filter
25 these appropriately if they need to labeled as

1 leukoreduced without wasting, and the scientific
2 community is moving in that direction. The agency
3 need not be concerned about that.
4 So the last slide, mandating
5 leukoreduction at less than 5 would preserve
6 benefits--keeping it at this level, not mandating
7 all blood be leukoreduced but mandating the
8 labeling be set at 5 times 10 to the 6th, would
9 preserve the benefits from decreasing the incidence
10 of febrile reactions, CMV transmission, and HLA
11 alloimmunization. It would maintain a plentiful,
12 pure and safe supply. It would provide for an
13 achievable and manageable quality program, as other
14 speakers are addressing, and would promote the
15 public health of pre-storage leukoreduced products,
16 and I believe the American public would be well-served by
17 maintaining a level of 5 times 10 to the
18 6th residual white cells per unit for each blood
19 product.
20 Thank you very much.
21 CHAIRMAN NELSON: Comment or questions?
22 DR. KOFF: Are there any data looking at
23 the 1 million? Is there evidence that's any
24 better? Has it been studied?
25 DR. SNYDER: It has not been studied.

1 Those are the only randomized controlled clinical
2 trials that have been undertaken in those areas
3 that I'm aware of, and none of them used filters
4 that could get down to 1 times 10 to the 6th
5 reliably, because they were not available when they
6 were done. So unless there's someone else in the
7 audience who knows different, I do not believe any
8 of those studies have been done.
9 DR. KOFF: I mean, what's your gut
10 feeling? If there is virtually no CMV but the HLA
11 alloimmunization levels are lower, but they are
12 still there, and febrile reactions are reduced by a
13 third, do you think if in fact it was feasible to
14 do it, it would make a difference?
15 DR. SNYDER: Well, I mean, any improvement
16 in public safety and health would be desirable.
17 The question is, how much more is your increment
18 going to be per unit cost? And I know cost is not
19 something that BPAC addresses at all, but I think
20 it comes down to that.
21 It comes down to resources. I think you
22 would probably lose more units in the name of
23 attempting to reach that goal than actually you
24 might help people. And these days, once the
25 September 11th disaster has left people's minds and

1 the degree of blood donation may return back to a
2 pre-September 11th point, blood supplies again
3 become critical, and you have to balance that with
4 the availability of blood in general.
5 It's a very complex question, as you bring
6 up, and I would think it would be difficult to
7 convince someone to do those studies. The
8 companies might be interested, but I don't think
9 federal agencies would be interested in funding it.
10 You couldn't do it in Canada, although you might be
11 able to do a 5 times 10 to the 6th versus 1 times
12 10 to the 6th. You probably could do that in
13 Canada.
14 CHAIRMAN NELSON: You raised the issue of
15 power with regard to febrile reactions, but how
16 does the issue of power in regard to CMV
17 transmission, looking at comparing screening,
18 antibody screening versus leukoreduction, or both?
19 And, you know, why not do both for a high-risk
20 patient?
21 DR. SNYDER: Well, there are people who
22 believe that. As far as my understanding, the
23 reported incidence of failure of CMV seronegative
24 testing is 3 percent. I was under the impression
25 it was similar for filtration, 3 percent. I did

1 hear a rumor that there may be a study that has
2 come out of Seattle, that has shown a slightly
3 higher degree of failure for filtration of maybe 4
4 to 5 percent, although I haven't seen data on that
5 and don't know if that's true.
6 Some places want CMV-seronegative plus
7 leukoreduced. We don't ascribe to that. If we had
8 found any evidence at our institution of a failure,
9 we might consider that. Again, it comes down to a
10 matter of resources, which is not germane to this
11 particular group.
12 CHAIRMAN NELSON: Yes, I heard about the
13 same study but I don't see the data. Toby?
14 DR. SIMON: Yes, I think it's interesting
15 also to look at this from a historical perspective,
16 which I think gives us an insight into the numbers
17 game here and the power game, because there was
18 very good data that the first generation of
19 filters, which originally were developed for
20 microaggregate filtration, actually reduced febrile
21 reactions. And there are some people who thought
22 that we are actually overkill with our current
23 filters in terms of cost, because we can gain
24 reductions in febrile reactions using filters that
25 filter less well than what we're using today. So I

1 think it stands to--you would anticipate that you
2 would have a significant reduction with the kind of
3 filtration that we're now using.
4 And similarly for the CMV, there were many
5 of us who published articles showing that washed
6 and frozen red cells gave you significant reduction
7 in CMV. So it's all sort of a continuum of reduced
8 risk, and it's a question I guess of where to find
9 the most effective point. I think Dr. Snyder has
10 made a very persuasive case for the 5 number right
11 now. I think if we begin to get data in some of
12 these other areas like transfusion-induced
13 immunosuppression, then there may be a reason to
14 try to go for lower numbers, and then you also have
15 to have technology as well.
16 So we tend to want to think of a black-and-white,
17 where we cut off the risk, but I think
18 what we have here is just risk reduction as we
19 bring the white cell numbers down, because we still
20 have lots of white cells there that are being
21 transfused.
22 DR. FITZPATRICK: Dr. Snyder, two
23 questions. Like Toby said, have you seen a
24 comparison of--and I can't remember where we were.
25 When we did the 2 log reduction with frozen

1 deglycerolized cells, there was a reduction in
2 febrile reactions. What do you think it was? Was
3 it comparable to the 3 log reduction, or do you
4 think the 3 log reduction is significantly better?
5 DR. SNYDER: Well, I think a 2 log
6 reduction, I don't have any data on that. There
7 were certainly--we weren't using it for all
8 patients, so we were seeing an improvement. But
9 with the 3 log reductions there were reports--Dr.
10 Chambers, as a matter of fact, had the paper and
11 the abstract on that with her group, looking at
12 filter failures, people who were breaking through
13 with febrile reactions with the 3 log reduction
14 filters, which many of us were surprised about.
15 Turns out she was correct, that there were people
16 who were exquisitely sensitive.
17 I think the more you remove, the more
18 likely you are to decrease febrile reactions in a
19 larger number of people, but the numbers start
20 getting very, very difficult to deal with because
21 you need so many numbers to show a significant
22 benefit. I personally feel that most of the
23 patients who might have a febrile reaction with the
24 filter, if you then either pre-treat them with
25 medication, whether it's a steroid or an N-SADE,

1 you might be able to prevent further reaction. I
2 don't feel strongly the need to continue to try to
3 remove every white cell that there is, but that's
4 just my own personal opinion.
5 CHAIRMAN NELSON: Do you have a second?
6 DR. FITZPATRICK: You didn't say anything
7 about red cell recovery, and I was just wondering
8 what your feelings were on the 85 percent mark for
9 red cell recovery?
10 DR. SNYDER: Oh, I think that's an
11 appropriate standard. I think when you give a
12 transfusion, you want to get the largest amount of
13 product that you can get into someone, so I think
14 that that's an appropriate level.
15 CHAIRMAN NELSON: Thank you. Next is Dr.
16 Linda Kline from the American Red Cross,
17 "Establishing the Appropriate QC Cut-off for
18 Contaminating Leukocytes."
19 DR. KLINE: Good afternoon. What I'm
20 going to talk about really is just the current
21 methodology that is being used for QC of
22 leukoreduced products.
23 As both Alan and Dr. Snyder have talked
24 about earlier, currently we are to QC 1 percent of
25 our whole blood and red cell products per filter

1 type, so if a blood center is using multiple
2 filters, they have to do 1 percent for each filter
3 or four units, which is ever greater, and the
4 guidelines are greater than or equal to 85 percent
5 recovery and less than 5 times 10 to the 6th white
6 cells per unit.
7 For platelets, for whole blood drive
8 platelets, it's the same, 1 percent and less than
9 8.3 times 10 to the 5th white cells per unit, and
10 as Dr. Snyder said, it's based on a pool of six,
11 which would give you less than 5 times 10 to the
12 6th per unit, which is currently what our
13 apheresis.
14 Now, the apheresis requirement is a little
15 bit different. We not only have to do 1 percent of
16 each--we have to do 1 percent of each product, but
17 it's per instrument type, per collection site. So
18 again, if the blood center is using a Cope and an
19 Amicus, and they have four different sites, they
20 have to do 1 percent for each of those apheresis
21 machines per each collection site, so you can see
22 how the numbers start really building up.
23 I guess the gold standard currently is
24 Nageotte. This is just a schematic of a Nageotte
25 chamber. There's two counting areas divided with

1 40 lanes, and the white cells are counted. Each
2 counting chamber has a volume of 50 microliters.
3 This was developed, it's kind of an improvement on
4 the current hemocytometers, so that you could get
5 larger volumes, so that you could get increased
6 sensitivity.
7 It's very, it's pretty labor-intensive. I
8 mean, this is the procedure here, and I won't go
9 into details, but basically there's a lot of
10 pipeting, mixing, adding reagents. If you're doing
11 red cell and whole blood products, you have to lyse
12 the red cells, and you have to make sure they are
13 lysed very well, otherwise they obscure the white
14 cells.
15 And then you use a microscope to count the
16 white cells in the 40 lanes. Some places count one
17 counting area, some places count two. It depends
18 on the sensitivity that you're looking for. Then
19 there is a manual calculation where you just take
20 your white cells, divide it by the volume times the
21 dilution times 1,000--that converts it to
22 milliliters--times your product volume to get your
23 final white cells per unit. And we use, in the Red
24 Cross we use two different dilutions. That's what
25 the bottom is. If the hematocrit is less than 60

1 percent, we dilute 1 to 5. If it's greater, we do
2 1 to 10. And platelets currently are 1 to 5
3 dilution.
4 The second method is microfluorimetry.
5 This is an Imagn 2000, or was. It's currently not
6 available anymore. Hopefully they are reworking it
7 and redoing the assays so that it will be re-released,
8 hopefully maybe in late 2002 or 2003.
9 This is a somewhat semi-automated method. As you
10 can see, everything is pretty incorporated into one
11 instrument, and this is just a schematic of a red
12 cell assay.
13 It has these cartridges and capillaries,
14 and basically you add your reagent to a diluent if
15 it's a red cell. If it's not a red cell, you don't
16 need to do Step 4. You add your sample and it's
17 stained. There is a staining. And then you just
18 pipet your sample into the capillary. You can load
19 up to 10 of these cartridges in the machine at one
20 time, and then walk away. If you enter your volume
21 of your product using the keypad, it will actually
22 print out your total white cells.
23 So it's somewhat semi-automated once you
24 load your cartridges. You put 10 in, you can walk
25 away and do something else. Calculations are much

1 simpler. Again, you just enter the volume of the
2 product, and the results are printed out for each
3 sample as the white cells per unit.
4 There is a review process. There is a
5 review process per run of 10 cartridges, as well as
6 per sample. There's three QC steps that you have
7 to make sure they all fall into the right
8 parameters, and then you can accept or reject your
9 sample results.
10 The last method is flow cytometry. This
11 is a BD FACS Caliber which some of the blood
12 centers have purchased when the Imagn went off the
13 market. A few people have converted to this.
14 Again, this is an example of a BD leukocount
15 procedure, fairly simple, pipeting the sample into
16 reference beads, add your reagent mix, incubate,
17 and then run your sample.
18 Some of the difficulties and some of the
19 subjectivity comes into play for your calculations.
20 Although the data is downloaded into, can be
21 downloaded into a spreadsheet, you still have to
22 review your dot plots to make sure that everything
23 went okay, so you do need some kind of expertise in
24 using this machine. The data is imported into a
25 spreadsheet. You verify the controls and then,

1 again, accept or reject your sample results.
2 This, I was trying to compare the three,
3 and I just tried to pull out some aspects of
4 different parameters. Throughput, I mean, you can
5 see Nageotte. Now, we have gotten reports anywhere
6 from three samples per hour up to some regions say
7 they can do 15. I'm not quite sure how that works.
8 But because you're looking through a microscope,
9 the staff people after one or two hours start
10 getting kind of bug-eyed, and basically you might
11 be able to do 10 in one hour but then that's
12 probably all you can do for your eight-hour shift,
13 until you recover.
14 So overall, over an eight-hour shift,
15 we're probably averaging about three to four
16 samples per hour. The Imagn and the flow, BD says
17 about 10 per hour. You can't see, that's off the
18 slide. That's supposed to be CLIA classification
19 for Nageotte and Imagn. It's classified as a
20 moderate test. The flow is still classified as
21 high complexity, so you do need a higher level
22 person running these machines and doing the
23 interpretations.
24 Again, the next line, that's supposed to
25 say analysis. Nageotte is very subjective, and

1 even when we do studies in our lab, our
2 technologist, if someone is working on a study,
3 they will do that whole study, because even people
4 who are highly trained don't necessarily get the
5 same result counting the same sample. The Imagn is
6 very objective. The machine looks at it, gives you
7 the result. The flow is somewhat subjective, and
8 again that's because of the analysis and final
9 determination of the gates, and that is done by the
10 operator, so it adds some subjectivity.
11 Sensitivity, the Nageotte still is the
12 most sensitive. Flow is reporting one cell per
13 microliter for both assays. The Imagn was .5 for
14 PRP and three cells for red cells, which was a
15 problem, and that was an issue, and I know that
16 they are readdressing that in their new release of
17 the assay, and they hope to bring that down to 0.5
18 also.
19 The last two lines, and I know you're not
20 supposed to look a pricing, but it's just to give
21 you a perspective of the--you know, going up. And
22 again with the Imagn not available, we're kind of
23 left with Nageotte and flow, and just to give you a
24 perspective of what the cost of these instruments
25 and reagents are.

1 Okay, the last thing is red cell recovery.
2 As we mentioned earlier, there's two parts of your
3 QC procedure. One is determining residual white
4 cells. The other is looking at the red cell
5 recovery. And I think a lot of people, especially
6 before now, a lot of people forget to include red
7 cell recovery, but it is an important aspect.
8 Currently, what most places are doing in
9 your component lab, pre- and post-filtration, you
10 have to weigh the unit, record the weight. You
11 have to strip the tubing multiple times while
12 you're mixing, remove a length of tubing, empty it
13 into a tube to be measured for hematocrit, and this
14 is done on pre-filtration and post-filtration.
15 And I have critical steps for that last
16 one, because what we found was happening is, the
17 component lab would take the piece of tubing, stick
18 it in a tube, and then send it to the QC lab, who
19 hours later might cut it open and drain it. What
20 was happening is, the red cells and plasma were
21 separating and they were getting erroneous
22 hematocrits. So we have now implemented and told
23 them they have to immediately cut that tubing out,
24 open and drain it. And then the QC lab, they are
25 the ones that perform the hematocrit test on both

1 samples, calculate the red cell recovery which is
2 here.
3 Now, an alternative procedure which many
4 blood centers are starting to use, since there's no
5 change in hematocrit pre- and post-filtration,
6 there's been many reports in the literature and by
7 the manufacturers stating that filters cannot
8 selectively absorb plasma, so the hematocrit, we
9 have lots of data to indicate that the hematocrit
10 is the same pre and post. It doesn't change.
11 So instead what they're doing is really
12 just weigh the unit pre- and post-filtration and
13 calculate your red cell recovery, so a much simpler
14 method. It takes out a lot of the error that has
15 been incorporated into performing hematocrit
16 determinations.
17 And that's it. Any questions?
18 CHAIRMAN NELSON: Any questions? Yes,
19 Alan?
20 DR. WILLIAMS: Linda, as you will hear in
21 a few minutes, the proposed QC strategy is based on
22 a binomial distribution. And what that means is
23 that instead of actually enumerating residual white
24 cell counts, you can actually have a dichotomous
25 answer: Either it passes criteria or it fails

1 criteria.

2 Can you envision any way in which the
3 manual procedure could be modified so that either
4 one could consider some sort of dilution strategy
5 to basically count a smaller field and make a quick
6 decision as to contamination, and/or consideration
7 of pooling multiple units if your expectation is
8 that most of them will be within a certain range,
9 that you don't have to do each one individually?

10 Certainly a process like this would have
11 to be validated to be put into actual use, but I'm
12 just wondering if there might be some legitimate
13 shortcuts which could be used.

14 DR. KLINE: Well a number of years ago
15 Gary Moroff did develop a procedure for kind of a
16 quick for platelet QC, and that was published, oh,
17 I don't know, about three or four years ago, I
18 guess, which is similar to that simplified method.
19 And basically for platelets, you scan it and if you
20 see, I think it's less than 10 white cells in a
21 field, you can consider it leukoreduced. And I
22 don't remember all of the primers, but he does
23 spell out kind of a simplified, I think he even
24 calls it simplified Nageotte procedure for
25 platelets. It was looked at for red cells, too,

1 but there were just too many problems with doing
2 that for red cells.
3 it just didn't work as reliably as it did
4 for platelets. So I don't know about pooling
5 products. I think that might be difficult. I
6 mean, you would have to be careful and make sure
7 you pooled from the same filter lot, you know,
8 because again you want to think about lot-specific.
9 So I think that one might be difficult. I don't
10 know.
11 DR. HOLLINGER: I'm trying to figure out
12 where the
13 --again, the blood that you're testing, it comes
14 from strips, is that right? The strips, or where
15 does it come from?
16 DR. KLINE: For the QC, it comes from
17 segments, the tubing.
18 DR. HOLLINGER: From a segment?
19 DR. KLINE: Right.
20 DR. HOLLINGER: That already has coagulant
21 in it and everything, or--
22 DR. KLINE: Yes. So basically what you do
23 is, you take--there is a piece of tubing on the end
24 of the product, and you strip that blood that's in
25 the tubing into the whole product, mix it really

1 well, and you do that multiple times to get a
2 representative sample of the product in your
3 tubing. You then heat-seal that piece of tubing
4 off, cut it open, drain it into a test tube, and
5 that's how you get your sample.
6 Now, that's for pre-filtration samples.
7 Post-filtration samples, some of the manufacturers
8 actually have, like on apheresis kits there is a
9 little tube, like on the Gambro kit there is
10 actually a little test tube that's off-line, that
11 you can fill with the product and heat-seal that
12 off. And some of the red cell filters actually
13 have what they call a QC segment, which is a thick
14 segment so you can get a better sample.
15 DR. HOLLINGER: And if it fails, if the
16 process fails, it's more than 5 million or 1
17 million, whatever the number, are you allowed to go
18 back and re-test again, do it again or two, three
19 times, or you just have to take whatever happens
20 there?
21 DR. KLINE: You take whatever happens.
22 DR. HOLLINGER: Okay. Just one other
23 question. Then in terms of if you had to repeat
24 this several times, if you did it in the same bag
25 and you had to repeat it several times, what kind

1 of, again what kind of confidence interval is
2 there? Say you had 1 million in there or 5 million
3 in there, what would you expect over several times
4 doing this, 4 or 5 or 10, 20 times?
5 DR. KLINE: What we have found is, if a
6 product is truly leukoreduced, we see no cells. So
7 when we're looking through the microscope, because
8 we do all Nageotte counts, you're seeing anywhere
9 from zero to two to three cells. You can repeat it
10 multiple times, and you might see zero cells one
11 time, two cells another, three another, but they're
12 all so far below--I mean, the margin is just huge.
13 So what we find is either you see no cells or you
14 see lots of cells. I mean, there doesn't--there's
15 not a big gray zone.
16 DR. HOLLINGER: Okay. Thank you.
17 DR. RUTA: I was wondering if you could
18 tell us what percent of the red blood cells are
19 currently being filtered, where you are with
20 implementation?
21 DR. KLINE: I'm not sure. I would have to
22 ask Dr. Chambers where we are.
23 DR. CHAMBERS: What is the question?
24 DR. RUTA: I was asking if you could give
25 us an update on what percent of units are filtered

1 at this point.

2 DR. CHAMBERS: What percent of the units

3 are filtered?

4 DR. RUTA: Right.

5 DR. CHAMBERS: About 96 percent of red

6 cells.

7 DR. RUTA: Okay, and I'm trying to

8 remember from June, I thought you had data that

9 showed a very low failure rate at the 5 times 10 to

10 the 6th level. I thought it was around 0.3

11 percent--

12 DR. KLINE: Yes.

13 DR. RUTA: --with failure being defined as

14 not leukoreducing properly. So I was trying to

15 keep it aside from, you know, the clots. And I was

16 wondering, because there seems to be a discrepancy

17 or a wide range in failure rates among different

18 folks, and I was wondering if you had any thoughts

19 on why you're able to get to the low end of the

20 failure rate.

21 DR. KLINE: We do good counting. I don't

22 know. I can't answer that. You know, a lot of it

23 is filter-dependent, manufacturer. I mean, we've

24 gone through lots of filters and had problems with

25 manufacturers like everyone else, where we have had

1 quite a number of failures, but overall the filters
2 out there are very good and we really don't see too
3 many problems.
4 DR. RUTA: Okay. I was going to
5 correspondingly ask other folks later on where they
6 are in implementation, if they have an idea whether
7 there has been a learning curve and an improvement
8 in failure rate.
9 CHAIRMAN NELSON: Okay. Alan was going to
10 talk about QC strategy.
11 DR. WILLIAMS: Okay, we'll finish up the
12 presentations with a little more specific outline
13 of the proposed quality control strategy, and this
14 is actually relatively short. But when I start to
15 talk about the options, I think it would be good to
16 pay careful attention, because these options
17 directly feed the questions to the committee, so
18 just to help keep this an efficient process.
19 In providing quality control, and I'm
20 really speaking primarily toward white cell
21 contamination for this discussion, there are two
22 ways to do it. One is to count the whole
23 population, basically 100 percent qualification of
24 the product. That gives you really pretty good
25 assurance that what's going out the door meets a

1 certain standard.

2 The other way is to do a sampling. In the
3 past there have been standards out there saying a
4 certain percentage of products need to meet a
5 standard, and there are many, many ways to approach
6 that goal which give differing levels of
7 confidence. So by introducing statistical
8 boundaries around that approach, it helps to fine-tune what
9 your confidence limits are in terms of
10 the end point that you're determining.

11 And I think what denotes the difference
12 between this 100 percent qualification versus a
13 sampling scheme is, how critical is the final
14 product specification? I think this underlies the
15 decision that we'll be asking you to make with the
16 questions.

17 Once you choose a sampling scheme, you
18 need to determine what the appropriate underlying
19 distribution is on which to base your analysis.
20 There are, as you see in the literature that was
21 distributed to you, two primary ways of determining
22 residual counts. One is dichotomous. It would
23 seem intrinsically relatively easy to achieve, but
24 in fact most of the counting being done is actual
25 white cell counts. And then second is continuous

1 outcome, where the counts are actually enumerated
2 and over time will establish a certain
3 distribution.
4 Now, the literature does address several
5 different techniques for reaching a statistical
6 quality control end point, and they really are
7 distribution-dependent. The binomial distribution
8 with a dichotomous outcome is really fairly
9 simplistic, and it really doesn't depend on the
10 underlying distribution of the actual enumerated
11 white cells, whereas the continuous outcome does.
12 If one chooses to use some of the quality
13 control schemes that are out there, one has to have
14 an underlying data that meets either a normal or a
15 log-normal distribution, so that the analyses based
16 on that distribution are legitimate. And there are
17 tests to do that, but the concern is that in a
18 process like quality control for leukoreduction, at
19 this point there is potentially a large right-hand
20 tail with a blip up, because as Linda mentioned,
21 when units fail, they don't just fail a little bit
22 for the most part, they really fail and let white
23 cells through. So it's questionable whether most
24 of the centers out there at this point really can
25 use a log-normal distribution and the analysis

1 which that underlies.
2 The second is consideration of one tail
3 versus two tail, fairly basic statistics. This is
4 an example from Jed Gorland. If you're looking at
5 white cell counts, you only care about one end.
6 You don't care if they are too low. That really
7 doesn't help or harm. However, if you're providing
8 quality control for an automobile piston, if it's
9 too large it won't fit, if it's too small you won't
10 get compression, so it's a basic assessment as to
11 the number of tails of the distribution to use.
12 And then the third is the frequency of the
13 quality control cycle. This is also important,
14 because if you have an out-of-control process and
15 you don't know about it for a month, you have
16 released a lot of product with a lot of potential
17 implications. So the frequency of that cycle is
18 also a factor to be considered.
19 Now, the FDA-proposed approach to
20 statistical quality control was really first
21 introduced in the January guidance, and it's based
22 on a binomial distribution. Once again, it's that
23 95 percent of the product should meet defined
24 specifications with 95 percent confidence.
25 One can argue that 95 percent conformance

1 is in line with other types of manufactured medical
2 products and reasonably produces a safe and pure
3 product. Ninety-five percent confidence is an
4 accepted scientific norm. Looking at it another
5 way, it's a probability of less than 5 percent that
6 chance nonconformance will exceed 5 percent.
7 Now, the easiest way to get to this
8 statistical definition is by counting an equal 60
9 counts with zero failures, and this is based on an
10 exact binomial distribution. Similarly, using the
11 same distribution, if you predetermine that you're
12 going to count 93 samples, it allows for one
13 failure and you still would meet that criteria, and
14 2 in 124, and so forth.
15 The use of this particular approach does
16 not require log-normal distribution of the data.
17 There was discussion earlier about some of the
18 means of the data that were in the published
19 literature. To legitimately say that something is
20 a mean, it has to have a normal or a log-normal
21 distribution, or else the mean really doesn't mean
22 what it might seem to. With a binomial
23 distribution, white cell counts can be pass/fail
24 with an appropriate technique. That may be an
25 easier way to provide counts.

1 Now one also needs to consider process
2 validation versus ongoing quality control. Process
3 validation is when a new process is introduced or
4 some major change is made to it, or a problem has
5 been found and corrected, one needs to establish
6 that process is behaving as it should. Under this
7 scheme, we are recommending 60 consecutive white
8 cell counts to show that the process is behaving as
9 it should.
10 Subsequent to that, ongoing QC, because we
11 need to allow for very large manufacturers of this
12 product as well as very small manufacturers of this
13 product, we are proposing that ongoing QC remain at
14 1 percent of total production, and that goes back
15 to the earlier memo, but not less than a random 60
16 counts per quarter, so that a facility producing
17 400 leukoreduced products in a day would be
18 counting four in a day. A facility doing 40 in a
19 week would be counting 5 products in a week to meet
20 that minimal standard.
21 Failure in the QC process requires some
22 level of change in approach, and we are
23 recommending that the next step should be to
24 require consecutive counts of the next 60 units
25 being conducted under that process. If no failures

1 are found in those consecutive counts, there is a
2 resumption of normal QC. If one or more failures
3 is found in those 60 counts, it is a reasonable
4 indication that the process is out of control and
5 an investigation is appropriate.
6 Now, as I mentioned, there are some other
7 approaches to providing quality control, and
8 certainly very legitimate as long as some of the
9 underlying assumptions are met, so that alternate
10 equivalent SOPs may be acceptable. Log or log-normal
11 distribution data may be necessary. And at
12 this point we are suggesting that these should be
13 submitted to FDA for prior approval before
14 implementation, to make sure that the distributions
15 and the overall approach is sound.
16 There are several publications which
17 detail these approaches. The one that I find to be
18 the most readable is the Larry Dumont paper, "The
19 BEST Working Group," which was included in the
20 handouts. I think it gives a good explanation of
21 both the binomial and the log-normal approaches.
22 So to get toward the decision that we're
23 going to be asking you to make, option one: FDA
24 should recommend that all products labeled as
25 "leukocytes reduced" need to meet the defined

1 standard as demonstrated by counting residual white
2 cells in all such products prior to distribution.
3 What are the advantages to this? A
4 hundred percent of labeled leukoreduced products
5 will meet the product standard. This approach
6 would reduce inappropriate white cell exposure to
7 at-risk patients, i.e., patients susceptible to
8 cytomegalovirus and other patients subject to
9 febrile or the other reactions. And we feel this
10 approach would help to stimulate new technologies
11 that will facilitate cost-effective white cell
12 enumeration after a certain period of time.
13 Disadvantages: Manual counts are
14 obviously very labor-intensive. There is currently
15 a limited selection of automated devices. And, as
16 stated before, blood centers may ultimately choose
17 to provide fewer leukoreduced products.
18 Option two: FDA should recommend
19 statistical quality control of the leukoreduction
20 process, as described earlier, so as to ensure with
21 a high level of confidence that products labeled as
22 "leukocytes reduced" meet a defined standard.
23 Advantages: This approach assures that 95
24 percent of products labeled as "leukocytes reduced"
25 will meet the product standard with 95 percent

1 confidence. The quality control workload at blood
2 collection centers will be considerably less than
3 would be needed to count all products, and
4 subsequently leukoreduced products may be more
5 readily available.
6 Disadvantages: Leukoreduced products are
7 currently commonly substituted for CMV-negative
8 products. Occasional products with levels of
9 residual white cells that exceed the product
10 standard may unknowingly be transfused to CMV-susceptible or
11 otherwise at-risk patients. The
12 quality control strategy proposed may be complex
13 and contribute to reduced compliance simply due to
14 its complexity.
15 The questions for the committee directly
16 relate to these options.
17 "Does the committee recommend option one,
18 that is, that FDA should recommend to industry that
19 all products labeled as `leukocytes reduced' meet
20 the defined standard as demonstrated by evaluating
21 all such products for residual white cell content?"
22 Question two: "If no to question one,
23 does the committee concur with the modified
24 statistical quality control strategy as outlined?"
25 Question three: "If no to one and two,

1 what elements of the modified statistical quality
2 control strategy proposed by FDA are in need of
3 further consideration?"
4 Thank you.
5 CHAIRMAN NELSON: Questions? Yes?
6 DR. SIMON: I wanted to ask Alan, if an
7 institution under the option two were to be
8 concerned that they might periodically find a
9 defective product, could they establish their
10 protocol from the beginning to count 93?
11 DR. WILLIAMS: Absolutely, as long as that
12 is established in advance.
13 DR. SIMON: Okay, and then the one--
14 DR. WILLIAMS: You can't have a miss and
15 then count the other 33.
16 DR. SIMON: Right, so then under those
17 circumstances, one failure would be acceptable
18 under option two.
19 CHAIRMAN NELSON: So they couldn't do 60
20 and if they get one failure, count 33, is what
21 you're saying. Right, yes.
22 DR. STRONCEK: Alan, do you have data from
23 people? If you count 60, how often will a center
24 go through 60 units and not have a failure? Or the
25 question I'm getting at, is that criteria really

1 going to go from a 1 percent test to a 100 percent
2 testing of products?
3 DR. WILLIAMS: Well, I think one thing
4 that I think Dr. Bianco is going to raise, and I
5 raised although not with a lot of emphasis, is the
6 distinction of the quality control points. When
7 providing this statistical quality control, we're
8 talking about residual white cells. We're not
9 including filter failures, as I think some have
10 assumed in the past, so you eliminate that as a
11 separate control point. The VAT study data showed
12 that at the 5 million cut-off I think the average
13 failure to reduce was something like .8 percent.
14 So I think it's a reasonable approach as long as
15 one doesn't have to consider that up front loss of
16 product due to clogged filters that really does
17 create some serious failures.
18 DR. BIANCO: I had the opportunity to talk
19 to Dr. Lachenbrach before he left--I don't see him
20 here anymore--and asked that exact question. And
21 he made a calculation with his pocket calculator,
22 and what he estimated is that if the basic process
23 failure is 1 percent, you have a chance of
24 completing your 60 count 54 percent of the time.
25 If your basic failure rate is .5 percent, then you

1 have a chance of completing your 60 without failure
2 74 percent of the time. So it's a very good
3 question, because essentially it's not going to be
4 a common event to count these 60 and get to the end
5 without failure.
6 DR. WILLIAMS: But, Celso, would you
7 expect something like a half percent failure rate
8 solely due to white cell contamination?
9 DR. BIANCO: I don't know. I don't know.
10 I think that actually, Alan, you created I think a
11 very smart separation between the several steps in
12 manufacture, but I don't know myself that these
13 elements have been, in any of these studies or at
14 least in our surveys or studies, have been
15 considering in the way you are considering.
16 For instance, the micro clot has not been
17 defined, what is the failure on that side, and how
18 much that interferes with then the actual
19 leukocyte. And these may explain a lot of stuff.
20 DR. LINDEN: Could you elaborate on the
21 donor-specific factors that you mention in here,
22 that if in the 60 there's a failure but it's found
23 to be a donor-specific factor. Now, is that things
24 I presume like sickle cell trait? What else could
25 that include? And how would those be determined,

1 and do you then just kick those out and not count
2 that? How would that work?
3 DR. WILLIAMS: Well, again it's a matter
4 of what information you have available. If it's a
5 failure in one point or another and you don't know
6 what it's due to, if in actuality it's due to a
7 donor factor but you don't know that, you can't
8 rule out that it's a process failure so you need to
9 include it.
10 If, however, on a preliminary
11 investigation or some other means of obtaining the
12 data, you know that that donor either has sickle
13 cell trait or has a prior donation which led to
14 failure, that is a reasonable set of data leading
15 you to conclude that it's not a process failure per
16 se but something that's defined by a different
17 control point, i.e. the starting material. So it's
18 not a failure of the process, it's a different
19 incoming point.
20 So the bottom line is, if a center--and
21 some are doing this, doing 100 percent sickle cell
22 screening. They are having lower failure rates and
23 obviously not including these. But if another site
24 has a donor and with a quick test determines that
25 that failure was due to sickle cell hemoglobin, it

1 would be appropriate not to count that as a process
2 failure, but one would have to have a mechanism for
3 doing that relatively rapidly.
4 DR. HOLLINGER: Alan, what constitutes,
5 again, a filtration failure? I mean a failure, is
6 it the time? Is that it?
7 DR. WILLIAMS: Well, that's another good
8 question, because presumably when you consider a
9 failure to filter, i.e. that the blood doesn't go
10 all the way through the filter, one has certain
11 parameters at which you make a cut-off. In many
12 cases those parameters of time, temperature, time
13 since collection, etcetera, are not spelled out in
14 the product insert, so you don't have
15 manufacturer's information to go to, and basically
16 it reverts I think to the local SOP at the center.
17 Whatever the center is doing now, if it doesn't
18 filter in a period of time that is part of your
19 current SOP, then that would be considered a
20 failure.
21 DR. HOLLINGER: It's not a standard type
22 of thing. I mean, it's at the discretion of the
23 center?
24 DR. WILLIAMS: At this point it would be
25 the center SOP, except where those parameters are

1 included in the product insert, and Betsy may have
2 a comment on that, if I missed anything or stated
3 it wrong. But right now those parameters really
4 are not well elucidated in the product insert, and
5 it's largely left to the blood centers.
6 DR. FITZPATRICK: That's a question I
7 have. In what circumstance of a process would you
8 see a count that exceeds the criteria, that isn't
9 attributable to a filter failure?
10 DR. WILLIAMS: You're saying is there an
11 instance where you have controlled the incoming
12 donor, you have controlled the collection
13 parameters, would you still see any instances where
14 there is a high white cell count?
15 DR. FITZPATRICK: Right.
16 DR. WILLIAMS: We don't know that for
17 sure. Part of the thinking is, that figure ought
18 to be quite low, once you have controlled those
19 elements of the process.
20 DR. FITZPATRICK: I mean, we haven't seen
21 anything presented that would lead us to believe
22 that there would be a result, an out-of-control
23 result that isn't attributable to what we currently
24 know is a filter failure.
25 DR. WILLIAMS: That we know is a cause of

1 filter failure. That would not be an unreasonable
2 outcome.
3 DR. FITZPATRICK: I mean, if you can now
4 exclude defined filter failures from the parameters
5 of computing your statistics, given our current
6 scope of knowledge, one could anticipate that
7 almost 99.9 percent of the out-of-control results
8 could be attributed to filter failure, and the
9 centers would not have to do the additional steps
10 necessary if they had an out-of-control process.
11 DR. WILLIAMS: I think the underlying
12 philosophy here is, once you recognize a step that
13 results in a failure, you take steps to correct it
14 one way or another, so you keep improving the
15 process. Now, once it would reach that stage, you
16 could probably very easily convert from a binomial
17 based quality control strategy to a normal or log-normal
18 strategy, and that would require fewer
19 counts, and you would in fact have a more
20 consistent process over time, but that's the
21 general scheme. I think there are still too many
22 remaining undefined elements now, that we are not
23 there yet, but that is hopefully a stage we should
24 reach.
25 DR. HOLLINGER: Just along this same line,

1 though, could Ms. Kline tell us about, at the Red
2 Cross, what do you determine is a filtration
3 abnormality versus a filter failure and so on? At
4 what point is the filtration process
5 --it's taking too long and so on, there's a problem
6 there, versus--
7 DR. KLINE: Typically, and what I was just
8 talking about back here is we don't really see too
9 many process failures. Most of our failures are
10 due to either a donor issue, maybe sickle cell
11 trait, maybe cold agglutinins, that's a big one
12 also, where it really just doesn't filter. I mean,
13 it just stops filtering.
14 Or they are due to a manufacturer's issue,
15 where for whatever reason there was a bad lot.
16 There was an incident not too long ago with the
17 Amicus, where there was a problem actually with the
18 machine and we were seeing lots of white cell
19 spillover. So we very rarely see process failure.
20 It's really either a donor-related issue or a
21 manufacturer-related issue, or unknown.
22 CHAIRMAN NELSON: Well, isn't a
23 manufacturing issue a filter failure issue? I
24 can't understand the difference between those.
25 DR. KLINE: Well, but it's not due to our

1 process.

2 CHAIRMAN NELSON: Yes.

3 DR. KLINE: It's not due to the blood
4 center's process of filtering. It might be a bad
5 lot of filters or--

6 CHAIRMAN NELSON: Yes, but that's one of
7 the things we're looking for, right?

8 DR. KLINE: Right, but what I'm--I guess
9 there is this fine line between, is it the process
10 that we're going through that's at fault or is it
11 the filter? And again, if we see these
12 manufacturer issues, they are the ones where we see
13 just huge numbers. You know, we'll get, our 1
14 percent QC will just pick those up very quickly.

15 CHAIRMAN NELSON: So would you include
16 manufacturing defects in the process failure
17 category, Alan? I would think so.

18 DR. FITZPATRICK: It wouldn't be the donor
19 center process, though. It would be the
20 manufacturer. It wouldn't be the process of the
21 collection center, it would be the process of the
22 manufacturer, so it would have to go back to them.

23 DR. WILLIAMS: My top-of-the-head answer
24 would be, that would again be a separate control
25 point. Obviously if you have a bad lot, you're

1 probably going to stop using it.
2 CHAIRMAN NELSON: And if they occur more
3 than 1 percent of the time, then something ain't
4 working. David?
5 DR. STRONCEK: You know, the way I
6 interpret this is, you get your unit, and the first
7 part of the leukocyte reduction is you hang your
8 bag up and run it through this plastic unit. Now,
9 if that unit plugs, I'd look, I'd ask my staff,
10 "Okay, go test that donor for sickle cell trait."
11 If it's got sickle cell trait, that's a donor-specific
12 thing. I don't count that as part of a QC
13 failure.
14 I would probably have them look for a
15 clot, which we never see. Well, you might see, and
16 if you saw a clot you would say, "Okay, I can
17 explain it," and you would throw that one out.
18 If you saw--we had a filter upside down
19 once. If you saw something like that, maybe you
20 would throw that one out. But then once you--none
21 of this stuff happens very much--then once you get
22 your 60 that filter completely according to your
23 criteria and start doing white counts, if all 60
24 didn't have the same--meet the standard, then you
25 would be in trouble.

1 Our concern is that most--yes, I agree
2 with Linda Kline that most of these counts are real
3 low, but for some reason, some bounce up for
4 unexplained reason. So I'm not so sure that if I
5 did 100 of them, that I would--I think I would get
6 1 or 2 percent bouncing up for unexplained reasons,
7 and I think I'm not going to be doing 1 percent of
8 my units but probably closer to 25 or 50, even 100
9 percent of the units.
10 So, I mean, I think you have to be real
11 careful about--I don't think anyone has got the
12 data to say how many units we're going to be
13 counting. And maybe we have to count 100 percent,
14 but that could be an implication of the way these
15 rules are set up.
16 MR. HEATON: I'm Andrew Heaton of Chiron.
17 I previously was head of the component subcommittee
18 of the BEST Group, and we looked very carefully at
19 the issue of the statistical profile of failures in
20 leukofiltration. Critical issues which dropped out
21 was that it was very important to have clear
22 manufacturer's instructions which define the time,
23 the temperature, the height of filtration, the
24 speed, in order to provide reproducible criteria
25 under which filtration could be performed.

1 But when we looked at the failure profile
2 of filters, we found that the failure was, as Alan
3 just pointed out, non-linear, so that you had
4 random events that contributed to failure but very
5 rarely did you see systematic events that
6 contributed to filter failure.
7 Our recommendation, which Betsy referred
8 to, was that you not do one but that you do 60, and
9 then continue on the basis of 1 percent per month,
10 and then later monitor on a facility- or
11 instrument-based basis at least six per month.
12 Because if you have 10 centers all making
13 leukoreduced components, 1 percent might all come
14 from one center or a small subset of the centers,
15 and you would miss a non-linear or random failure.
16 So our recommendation, which we published
17 at the end of 2000, is to focus on six units per
18 month, either per facility or per device or per
19 component laboratory. And if you do that, even
20 with a binomial distribution you would have a 90
21 percent chance of picking up a 20 percent failure
22 rate, which if you calibrated it with appropriate
23 validation and you knew the procedure was
24 reproducible, this would give you an acceptable
25 level of quality control.

1 So that's where we came from on the issues
2 that we identified as contributing to filtration
3 failure.
4 DR. McGEE: I just wanted to point out
5 that in statistical quality control you make the
6 assumption that you're going to find this 5 percent
7 of the time, and that's what they are doing, but
8 then you go on, and the probability of finding it
9 in two consecutive ones is extremely trivial. So
10 if you do 60 and you find that 5 percent of the
11 time you've got to go back, it actually turns out
12 to be I think 4.6 percent in this case. And so
13 even if you're in control, and that's if you are in
14 control at 5 percent, which is their assumption; if
15 you're really in control at 1 percent it's going to
16 be much less than that, but occasionally you're
17 going to find this, and then you just have to look
18 at it the second time. But the probability of
19 finding it twice is really trivial.
20 DR. FITZPATRICK: When you're talking
21 about the 1 percent, I have a question on what the
22 intent is with the sentence that says "SOPs used
23 for filtration should be considered individually."
24 What is--
25 DR. WILLIAMS: The intent is that the 1

1 percent--well, let me just start off. Any
2 individual blood center may have a half dozen
3 different protocols running for leukoreduction for
4 a red cell product. The 1 percent refers to the
5 overall leukoreduced product, irrespective of
6 individual SOP, but the 60 count, the 5 per week,
7 refers to each individual SOP in use for that
8 period of time. So if you don't use an SOP for a
9 six-month period, you obviously don't need to
10 provide quality control, but if you're running
11 multiple processes, the 60 counts need to apply to
12 each individual SOP.
13 CHAIRMAN NELSON: Several people have
14 asked to testify at the open public hearing, and
15 first is David Stroncek, I think.
16 DR. STRONCEK: I guess I'm testifying as
17 an employee of the NIH and part of the Department
18 of Transfusion Medicine, and I thought I would just
19 show quickly the data that Ed Snyder mentioned
20 about filter failure with sickle cell trait.
21 The studies I'm going to talk briefly
22 about were initiated after conversations that the
23 FDA initiated with the NIH and my boss, Harvey
24 Klein, and Alan Schechter from NIDDK, who is an
25 expert in sickle cell trait, the AABB, and the Red

1 Cross, just talking about why red cells from donors
2 with sickle cell trait should fail. And after that
3 meeting Harvey suggested we study this, and I have
4 never found it worthwhile to be disagreeable with
5 the boss, so we started studying these, this
6 problem.
7 And when we started I really had no idea,
8 but Alan Schechter had some good ideas on what to
9 do with it. He was right on with what we found
10 out. Let's see. This slide just summarizes what
11 you heard already. About 1 percent of red cells do
12 fail filtration, but when you look at units from
13 donors with sickle cell trait, about half of them
14 will occlude filters, meaning they don't filter
15 completely. Half will filter completely but the
16 white counts are too high. And then a quarter will
17 filter completely and their white counts will be
18 fine.
19 So what we wanted to do was find out the
20 cause of our red cell filtration failures in units
21 drawn from sickle trait donors, and the first thing
22 to remember is, there's a number of things that
23 affect hemoglobin S polymerization, including the
24 hemoglobin S concentration, oxygen saturation, pH,
25 and temperature. Now, sickle trait donors under

1 physiologic conditions don't have hemoglobin S
2 polymerization, but what we have to remember is
3 that when we collect blood we go through a number
4 of different processes and these things change.
5 Hemoglobin S concentration really shouldn't change
6 too much, but oxygen saturation might. pH clearly
7 does, and temperature does.
8 When we collect blood, it's not collected
9 into an empty bag. The 500 mLs or 450 mLs of blood
10 we collect is collected into 60 mLs of
11 anticoagulant, and that anticoagulant is usually
12 citrate-based and it's got a pH of about 5.7 and
13 it's got osmolality of 585. So when Alan Schechter
14 saw this, he speculated that it could be the low pH
15 and high osmolality which causes hemoglobin S
16 concentration, causing the filter failures. So our
17 hypothesis was that the ineffective filtration of
18 sickle cell red cells is due to the collection of
19 blood into the citrate anticoagulant, and the
20 initial low oxygen tension in venous blood, coupled
21 with the low pH and high osmolality of the citrate
22 anticoagulant caused hemoglobin S to polymerize,
23 and that was responsible for the filter failures.
24 So what we did is some very simple
25 studies. We took some donors with sickle cell

1 trait, collected half a unit of blood in a standard
2 red cell anticoagulant, CP2D, citrate phosphate 2
3 dextrose, and then half a unit from the same donor
4 in Heparin. Heparin, we only needed 2.5 mils, so
5 there's much less of a problem with its pH and
6 osmolality affecting the red cells. We then made
7 red cells, filtered them with standard Pall RCM-1
8 leukocyte reduction filters, and then assessed the
9 filtered red cells.
10 And this is what we found. We studied six
11 donors with sickle cell trait. We documented they
12 had hemoglobin S by HPLC. And of the units
13 collected in CP2D, we waited two hours to see if
14 they would filter, and only one of those six units
15 filtered completely, and that one filtered in a
16 little over an hour, in 72 minutes. The other five
17 occluded the filters. Two of them occluded the
18 filters completely, meaning none of the red cells
19 passed through the filter. And other ones, 34
20 percent of the red cells passed through, 26, 40,
21 and then the one that filtered completely, the red
22 cell recovery was only 71 percent.
23 In contrast, when we collected blood in
24 Heparin--this is from the same donors--all of them
25 filtered completely, and the red cell recoveries

1 were remarkably better, 96 percent, 75, 68, 69, 80,
2 and 83, so there was much better red cell recovery.
3 These aren't as high as the 85 percent standard,
4 but you have to remember these are half units, so
5 if we collected whole units, we would probably have
6 the same amount of loss in the filter so these
7 recoveries would be higher.
8 The time of filtration was only, average
9 time was only 26 minutes, so they filtered much
10 faster also. We did do controls, and the control
11 units filtered fine in Heparin and in CP2D. So we
12 thought, well, okay, the citrate units are
13 collected in the very acidic CP2D, and very
14 hyperosmotic CP2D. Let's compare those values
15 between units. And we were surprised that after
16 they filtered, in whole blood we found no
17 difference in pH, in osmolality or mean cellular
18 hemoglobin concentration, or even oxygen
19 saturation.
20 So we speculate this is a collection
21 lesion, meaning that it's just the first portion of
22 the red cells exposed to the citrate that are
23 damaged. And this is an RID about 1956. When
24 citrate was first being used as an anticoagulant,
25 this was described, and it really hasn't been

1 significant until we have started filtering sickle
2 trait blood donors.
3 Now, to test this out, you know, to really
4 prove that this is hemoglobin S polymerization, the
5 most important factor in preventing sickling of
6 these red cells would be oxygenating the red cells,
7 because if hemoglobin is oxygenated, it won't
8 sickle. The problem is with oxygenating the red
9 cells, if we did in the lab, then took it down to
10 filter, the oxygen levels might fall, so we decided
11 to use carbon monoxide. Carbon monoxide binds
12 hemoglobin in the same way, and when carbon
13 monoxide binds hemoglobin, it won't sickle, and
14 really the binding is for all practical purposes
15 irreversible.
16 So what we did in these studies is again
17 took donors with sickle cell trait, collected one
18 full unit in CP2D, split the unit and took half
19 that unit, treated it for one hour with carbon
20 monoxide, and then filtered that unit. As a
21 control, we took half of that same unit, didn't
22 treat it with carbon monoxide, and filtered that
23 unit. And we found that three of the four units
24 that weren't treated with carbon monoxide occluded
25 filters, and all four that were treated with carbon

1 monoxide filtered very well. The overall red cell
2 recovery was 84 percent versus 40 percent.
3 So this was, to us it's quite convincing
4 that hemoglobin S polymerization is responsible for
5 the filter failures, and this is quite encouraging,
6 because it shows that even though there may be a
7 citrate collection lesion, appropriate treatment of
8 the red cells could actually overcome this problem
9 with sickling. It's not appropriate, of course, to
10 treat red cell units with carbon monoxide, and we
11 can't really treat units with--collect units in
12 Heparin, but we might be able to reoxygenate or--well, let's
13 skip ahead here.
14 Let me summarize why I think the units are
15 failing filter. I think when we have the citrate
16 collection lesion, hemoglobin S polymerizes, red
17 cell intracellular viscosity increases. This
18 reduces red cell deformability, and this impairs
19 filterability. The trapping of the red cells with
20 hemoglobin, polymerized hemoglobin S, leads to
21 either complete obstruction of the filters or the
22 channeling of flow which makes filtration
23 ineffective.
24 So what alternatives do we have? Well,
25 one of these alternatives might be collection of

1 red cells by apheresis. We know that apheresis
2 delivers much less citrate to units. As we collect
3 red cells by apheresis, citrate is added at a
4 metered rate, so as blood flows immediately out of
5 a donor's arm, small amounts of citrate are added
6 at a metered rate, and overall only half the
7 citrate is added. So when the process is done we
8 would have one part per eight of whole blood is
9 citrate, or one part of sixteen of an apheresis
10 unit of red cell is citrate.
11 The other issue, too, is that it's added
12 as it goes. The red cells are never exposed to
13 huge quantities of citrate at one time. So we
14 thought that apheresis red cells might filter much
15 more effectively.
16 So what we did is, we collected red cells
17 by apheresis from six donors, and this is the study
18 we performed. We collected, we had, again we had
19 seven donors with sickle cell trait, collected the
20 units by apheresis. Took the unit, we split it in
21 half again, because we wanted to do further studies
22 with this unit, and then filtered half of the unit,
23 half of the apheresis unit.
24 And this time we collected, again, seven
25 units from donors with sickle cell trait, and five

1 of the six filtered effectively. Remember, in the
2 first study, we're using the same filters, five out
3 of six failed to filter, so the results of
4 filtration were much better, and the filtration
5 times on some of these units were very, very fast,
6 12 minutes. Well, not fast, normal is what you
7 would expect, 12 minutes, 8 minutes, 10 minutes and
8 6 minutes. One of them, though, took 100 minutes
9 to filter. The red cell recoveries were
10 reasonable, and the leukocyte reduction was good.
11 So apheresis worked in part, but it wasn't
12 the complete answer. So we asked a question on why
13 would four of the units filter very quickly but
14 three of them, this one, this one, and this one,
15 not filter so well. So we compared those units.
16 We looked at a number of blood chemistries, and we
17 looked at pH, osmolality, MCV, and hemoglobin S
18 concentration.
19 There's no difference in hemoglobin S
20 concentration. The only differences we saw were a
21 little bit difference in potassium, a little higher
22 potassium in the slow filtering units, which could
23 indicate some red cell damage. But the major
24 difference was in oxygen saturation. The oxygen
25 saturation levels were much lower in the slower

1 filtering units than the faster filtering units,
2 and that would make sense. That would indicate
3 that these units had hemoglobin S polymerization
4 and those didn't.
5 And this is just another way to show that
6 data. The red bars show the oxygen saturation in
7 units filtering quickly, and all of those were
8 above about 55 percent saturation, and all the ones
9 that didn't filter well were below 45 percent
10 saturation.
11 The final thing I just want to show is,
12 okay, so we think that the filter failure is due to
13 hemoglobin S polymerization, and that is a
14 multifactorial problem. But I guess the important
15 question is, can we reverse it? Either could we
16 reverse the problem in blood from sickle trait,
17 from apheresis collections or phlebotomy
18 collections?
19 We had a couple units that came through
20 the laboratory that just plugged filters
21 completely. These weren't as part of a study.
22 These were donors that had just walked in off the
23 street, our normal donors. So we took a couple of
24 those units and we split them in two, and the first
25 unit I only had half a unit, and the second one I

1 had the whole unit. And one half we treated with
2 oxygen by putting it in a gas-permeable bag for two
3 hours, and we put it in the refrigerator, and the
4 other half of this unit, we just put it in a
5 standard bag for two hours at room temperature. I
6 chose 4 degrees because I tried this at room
7 temperature and it didn't work, so I think 4
8 degrees is helpful.
9 But anyway, here are the two units. The
10 first unit, even though half of it obstructed the
11 filter, the second half when we filtered it, the
12 oxygen tension went up and it filtered in 12
13 minutes and red cell recovery was 89 percent.
14 The second one, again, when we incubated
15 it in the gas-permeable bag, the oxygen tension
16 went up or oxygen saturation went up to 69 percent,
17 and it filtered in six minutes with 90 percent red
18 cell recovery. And as a control, the unit
19 incubated in a regular bag, a transfer bag, the
20 oxygen tension went up a little bit but it didn't
21 filter. It only filtered partially. So after 120
22 minutes, 39 percent of the red cells passed
23 through.
24 Now, that's just anecdotal, two units, but
25 I think the studies do suggest that we can get

1 around the problem of collecting and filtering
2 blood from donors with sickle cell.
3 Let's just skip the summary and
4 conclusions. I think I covered that. The hour is
5 late. I just want to thank the people in my lab
6 that helped out, including Susan Leitman and Harvey
7 Klein, and of course Alan Schechter and Connie
8 Noguchi from NIDDK.
9 CHAIRMAN NELSON: Thanks, Dr. Stroncek.
10 Any questions?
11 DR. RUTA: I just want to say thank you to
12 David and his colleagues for taking on these
13 studies and for the interesting results.
14 CHAIRMAN NELSON: We have several other
15 people that wanted to comment. Next is Mr. Leonard
16 Buchner from Becton Dickinson. Since there are
17 quite a number of--two, four, seven--if you could
18 keep the comments as crisp as possible, it would be
19 helpful, since we still have to go back and discuss
20 the issues raised by the FDA.
21 MR. BUCHNER: I will try to keep this as
22 brief as possible. As most of you are aware, we
23 are to give an update, it has come up a couple of
24 times, in terms of the status of the Imagn
25 instrument and the Seeker assay, which is the assay

1 for measuring residual white blood cells. And I
2 will, in the interest of being brief, I will skip a
3 number of things.
4 But essentially we have had a development
5 team working on the Imagn system and bringing the
6 Seeker assay back to the market, and they have
7 spent a fair amount of time working on a variety of
8 technical issues as well as understanding the Imagn
9 system and the assay. We have had to do some
10 reverse engineering. One of the issues with the
11 system and for BD was that when they acquired BMI,
12 the design group for that system was no longer with
13 BMI. And so as we have had to go back and create
14 design history files and things like that to plug
15 the holes and gaps that forced us to pull the
16 product off the market, we have had to solve some
17 technical issues as we have gone along.
18 We are continuing to work on that. We are
19 very excited about it. We are making progress for
20 that. We are looking for adding some features in
21 terms of, with the assay, to have a single assay
22 instead of two assays, one for platelets and one
23 for RBCs. Our plan right now is to have a single
24 reagent assay that would run on the system. And we
25 will be bringing the low insensitivity down to one

1 cell per microliter for that.
2 And we have a few other modifications that
3 we are planning on making in the system. The
4 likelihood of those making it in will depend upon
5 their impact for getting into clinical evaluations.
6 If we can add a bar code reader and swap out the
7 thermal printer, we will be making those changes,
8 as long as it doesn't impact our time in terms of
9 bringing the product back to the market for first
10 release.
11 The resolution of technical issues has
12 taken significantly longer than we anticipated, but
13 we do plan and we're working hard to complete that
14 feasibility phase for the project by actually the
15 end of this month. Until we have actually finished
16 that and completed that and had that review, I
17 can't give an accurate estimation for the timing on
18 the clinical evaluations.
19 Our current guess for getting into
20 clinical studies would be mid-year in terms of '02,
21 but we will update you as we make progress on that,
22 and we will have updates coming out now on a
23 monthly basis to keep our customers informed on
24 that. And if anybody is not getting those updates,
25 you can see either myself or Rick Champion after

1 the meeting and we'll make sure that your name is
2 added to the list.
3 So thank you very much for your time.
4 CHAIRMAN NELSON: Thank you. Are there
5 questions or comments? Thank you.
6 Next is Mr. John Sokolowski from
7 Haemanetics.
8 MR. SOKOLOWSKI: Thank you all. I'll be
9 very brief.
10 First of all, I think the idea of the
11 separation of the process validation by control
12 points is a very good idea, and we support that.
13 The current draft document was not clear as to what
14 would constitute a process failure. And I think
15 the separation of the donor-related failures is
16 also good, because that I think will make the
17 process much more controllable.
18 There is one area, though, that I would
19 like to mention, and that is in the current draft
20 guidance, the minimum therapeutic content of red
21 cells is defined as 160 mL, and we believe this is
22 too high. For example, if you have a 450 mL unit
23 of whole blood drawn from a donor with a 38 percent
24 hematocrit, it should yield around 171 mLs of red
25 cells. And we assume an 85 percent recovery, then

1 the leukoreduced red cell volume would be much less
2 than 160. So we think that this needs to be
3 addressed in the guidance document, either set as a
4 lower volume or perhaps as a gram of hemoglobin
5 definition, but we think the current volume is too
6 high.
7 Thank you.
8 CHAIRMAN NELSON: Thank you? Any
9 questions?
10 Next is Mr. Jim Herzfeld from SEBRA.
11 MR. HERZFELD: Thank you for the
12 opportunity to make this presentation. My name is
13 Jim Herzfeld. I'm with SEBRA, a company which has
14 been making mixing scales for approximately 25
15 years. We call them blood shakers.
16 As you know, whole blood is collected by
17 weight, using a scale, in the approximate volume of
18 one pint. As blood leaves the body, it begins to
19 clot. To prevent this occurrence, an anticoagulant
20 solution is pre-added to the blood bags and mixed
21 with blood during collection. The most common type
22 of scale used during collection is mechanical in
23 nature and does not provide any mixing. Rather,
24 manual mixing is required by the phlebotomist
25 during collection.

1 When performed continuously, manual mixing
2 can be a most effective method. However, in
3 practice continuous mixing is rarely done because
4 it is simply not efficient from a labor
5 perspective. Blood centers would require
6 substantial investment in staff to provide adequate
7 manual mixing. In practice, the blood bag is
8 agitated for a few seconds once or twice during the
9 collection. Typically there are no controls in
10 place to ensure proper mixing, and for all intents
11 and purposes the blood is left to mix itself.
12 The resulting problem with the practice of
13 manual mixing is the lack of a standard, consistent
14 mixing process. Unmixed blood will pool in an area
15 of the blood bag and begins to clot. Frequent,
16 vigorous mixing can break apart these clots, but
17 the lack of control results in a certain amount of
18 microclotting. We believe this microclotting is
19 what causes much of the clogging of filters during
20 leukoreduction. Vigorous and continuous agitation
21 of the blood bag will prevent microclotting.
22 Unfortunately, there are no published
23 before-and-after scientific studies to support this
24 contention. We do have, however, substantial
25 anecdotal evidence from long-time users of blood

1 shakers. Canadian Blood Services, the Southern
2 Arizona Chapter of the Red Cross, United Blood
3 Services of Arizona, were all using blood shakers
4 long before they converted to leukoreduction. All
5 of them have reject rates of filtered units of less
6 than one-half of 1 percent.
7 There is currently a study being conducted
8 by the Oklahoma Blood Institute--we were hoping
9 they would be here today, unfortunately, they are
10 not--investigating the use of SEBRA shakers for
11 blood collection. Included in the study is the
12 yield of leukoreduced units. Unfortunately, I do
13 not have any of their data with me today, but
14 preliminary results do indicate the filter clogging
15 has been virtually eliminated. I recommend that
16 you contact Dr. Ron Gilcher concerning the details
17 of their study.
18 I mentioned earlier that manual mixing can
19 be effective. Indeed, a study using whole blood
20 performed by the Montreal Center of Canadian Blood
21 Transfusion in July of 1992 indicated that the most
22 thorough mixing of blood and anticoagulant occurred
23 with continuous manual mixing. There were two
24 automated shakers involved in the study, and they
25 provided mixing at 75 percent and 25 percent of

1 what the continuous manual mixing provided.
2 Left undetermined are the degrees of
3 mixing which would constitute excessive mixing,
4 which could result in cell damage; what is optimal
5 mixing, adequate or insufficient mixing. This
6 would made an interesting study if anybody wants to
7 take it on, someone with a little more resources
8 than SEBRA has.
9 Although not related to leukoreduction, an
10 additional productivity gain of some automated
11 shakers is a flow monitoring feature. This feature
12 provides continuous feedback to the phlebotomist
13 concerning blood flow during the collection. This
14 information lets the phlebotomist know when a
15 donation is not proceeding within the proper time
16 parameters. This will help eliminate underdraws.
17 I mention this additional feature because it
18 demonstrates how automated shakers can help achieve
19 the goal of maximizing the yield of the donor base.
20 I'd like to close by reiterating that
21 mixing whole blood during the collection process
22 improves the economics, quality, and yield of the
23 blood supply, and that automated blood shakers can
24 help provide a consistent, high quality product.
25 Thank you.

1 CHAIRMAN NELSON: Thank you, Mr. Herzfeld.
2 Comments? Questions?
3 Next is Dr. Celso Bianco from America's
4 Blood Centers.
5 DR. BIANCO: Thank you for the opportunity
6 to comment. ABC members thank CBER for the careful
7 consideration of both the comments we presented to
8 this committee at the June meeting and our formal
9 comments to the FDA docket.
10 The modifications proposed by FDA make the
11 guidelines reflect much more accurately what can be
12 achieved in practice with currently marketed
13 filters. There is substantial evidence that we
14 heard today from Dr. Snyder suggesting the clinical
15 benefits of filtration are realized when the 5
16 times 10 to the 6th is applied.
17 We also endorse the elimination of the
18 requirement for sickle cell screening, and we thank
19 Dr. Stroncek effusively for having resolved
20 probably the most painful issue that we had to
21 confront, because genetic screening is complex and
22 requires much more than the solubility test to be
23 resolved.
24 We are also happy that FDA has recognized
25 that counting residual white blood cells will not

1 eliminate CMV transmission. Transfusion medical
2 specialists are aware of the risk of transmission
3 both by leukocyte reduced and serologically
4 screened red blood cells or platelets, and will
5 continue to use their best judgment in the
6 management of patients at risk.
7 Unfortunately, there are still some issues
8 that need to be addressed, and we submit the
9 following for consideration. The term "incomplete
10 filtration" needs to be clearly defined by FDA and
11 the manufacturer. Dr. Williams suggested that this
12 could be defined by a blood center, but that will
13 create a lot of variability, and if I were kind of
14 less than cooperative, I could create a definition
15 where I would never have a filter failure.
16 We would be glad to work with you in order
17 to create appropriate definitions. For instance,
18 it could be defined as a process that did not
19 complete within a certain period of time. We feel
20 that it's premature to establish a recommended rate
21 of incomplete filtration-the document says that it
22 should not exceed .5 percent--before this
23 definition is established. A very strict
24 definition would create an excessive rate of
25 failures, while a loose definition could compromise

1 the quality of the final product.
2 We are also concerned about the cut-off
3 chosen even before we know the definition. For
4 instance, ELISA assays have failure rates that
5 range between 1 and 5 percent, due in general to
6 controls out of range. NAT assays have similar
7 failure rates. Thus, .5 percent appears to be too
8 strict for a biological process like cell adhesion.
9 We are still concerned about the
10 requirement for counting 60 consecutive units.
11 This counting will require 15 to 20 hours of
12 specialized technician time with the tedious
13 Nageotte chamber counting. Since it has to be
14 carried out within a limited period of time,
15 multiple technicians will have to be involved. We
16 are concerned that many of the failures will occur
17 because of staff exhaustion, not because the
18 process is out of control. And when it fails, the
19 clock starts again, and a new set of 60 units needs
20 to be counted.
21 We strongly suggest that FDA delay
22 implementation of this requirement until two
23 automated instruments are validated and approved by
24 FDA for this specific purpose and available in the
25 market. I would like to remind the committee that

1 in the past, the automated instrument most commonly
2 used by blood centers was withdrawn from the
3 market, and we just heard that.
4 In addition, we ask that FDA exclude
5 incomplete filtration from the set of units
6 included in validation, and actually I think that
7 we had a very productive discussion I heard from
8 the members of the committee about that, about the
9 separation of the processes.
10 We need, in addition, we don't have in our
11 staffs experts in mathematics and probability. My
12 statistics got maximum to tossing coins. And we
13 need help from FDA and from filter manufacturers to
14 establish less burdensome methods for statistical
15 process control. Without such help, the
16 flexibility of alternative procedures offered by
17 FDA is meaningless.
18 We recognize that validated shakers reduce
19 the probability of filter failures caused by
20 clotting. We are concerned about the manner in
21 which this requirement will be implemented.
22 Sophisticated shaker platforms require validation,
23 have to be sturdy enough to survive transportation
24 to our mobile collection sites, and have to be
25 battery-operated because many of the sites we use

1 do not have a sufficient number of electric outlets
2 around to have all of them running. In addition,
3 they are expensive and they require a substantial
4 capital investment. We strongly suggest that FDA
5 provide a sufficient time for implementation to
6 allow manufacturers to develop the type of
7 instruments needed in the field, and for centers to
8 amass the resources needed to acquire these
9 instruments.
10 Finally, we do not believe that product
11 withdrawal, consignee notification, and product
12 recalls will benefit the recipients of these
13 products. In case of filter failures, febrile
14 reactions may occur. There is nothing the
15 transfusion physician can do except to medicate the
16 patient with antipyretics. The notification will
17 arrive days or weeks after the event. Nothing else
18 can be done.
19 Moreover, notification does not benefit
20 patients who may become alloimmunized.
21 Alloimmunization occurs after multiple
22 transfusions, and is recognized in subsequent
23 hospital admissions, in a time frame that will not
24 coincide with consignee notification or recall
25 notices. We suggest that the corrective action be

1 limited to bringing the processes into control and
2 submission of deviation reports to FDA.
3 Regarding the questions posed by FDA, we
4 respectfully request that the committee reject
5 option one, that requires all leukocyte-reduced
6 products to be counted. The requirement would be
7 so burdensome that it actually, as noted by Dr.
8 Williams, would prevent further adoption, and may
9 even lead those that leukocyte reduce today to go
10 back to non-leukoreduced products.
11 We also ask the committee, reject option
12 two as burdensome, and suggest option three. This
13 would allow the development of alternative, less
14 burdensome QC approaches by both the FDA and filter
15 manufacturers.
16 Thank you for your response to our earlier
17 concerns. Hopefully you will be able to be as
18 responsive to our current concerns. Thank you.
19 CHAIRMAN NELSON: Thank you. Comments?
20 Yes?
21 DR. HOLLINGER: Celso, and also maybe some
22 of the members of the committee here, too, from a
23 blood banking perspective, what do physicians want
24 for a patient who is a CMV-negative, seronegative
25 patient, who has received a seronegative organ?

1 Are they content with just a leukoreduced,
2 leukocyte-reduced product, or with an antibody
3 negative product, or do they want both? So can we
4 get some feeling for--
5 DR. BIANCO: In recent times there has
6 been a tendency for physicians that deal with
7 patients at extremely high risk to ask for both
8 serological screening and leukocyte reduction, and
9 I would remind you that there was a very, somewhat
10 important for our field in terms of practice,
11 consensus conference in Canada about a year or a
12 year and a half ago, and that was the
13 recommendation, because none of the methods is
14 sufficient to ensure complete prevention of CMV.
15 Both will reduce it, the incidence, and this is so
16 devastating in a patient that receives a bone
17 marrow transplant or other.
18 DR. RUTA: Celso, I was wondering if you
19 could give us an update on the status of where your
20 members are with implementation. Do you know what
21 concerns them?
22 DR. BIANCO: Yes, I know we actually, in
23 preparation for this meeting, we did a survey and
24 we asked both about where they are today and where
25 they are going to be on January 2002, and actually

1 what Dr. Williams has in the preamble of 60 percent
2 is very accurate.
3 DR. RUTA: And also I was wondering, in
4 terms of whether there has been--
5 DR. BIANCO: And that's for red blood
6 cells. The percent for platelets is much higher.
7 DR. RUTA: I was wondering if you had any
8 comments on whether you know if there has been a
9 learning curve in terms of, you know, failure rates
10 that you gave the committee last June, at the 5
11 times 10 to the 6th level, and whether there has
12 been any change?
13 DR. BIANCO: I cannot respond to that
14 question, Martin, because we did not do a
15 longitudinal survey. I have anecdotal information,
16 and I heard a few minutes ago from Ms. Linda Kline,
17 these things happen in spurts. It is not just--I
18 think we will need to do a very good survey over a
19 period of time to have a good idea. Maybe some
20 centers have done that, and the numbers are there
21 to see, so essentially it is just to sit down and
22 go to review and plot that.
23 CHAIRMAN NELSON: Dr. Snyder?
24 DR. SNYDER: In response to the question
25 about what most oncology programs are doing, my

1 understanding is, most oncology programs who are
2 autologous stem cell transplants will accept
3 leukoreduced and do not necessarily require CMV
4 seronegative. There are some centers around the
5 country that will leukoreduce blood products as
6 equivalent to CMV-safe for allotransplant programs,
7 as well. There are some, however, who do want CMV
8 seronegative as well as leukoreduced.
9 Major centers that we checked in before we
10 switched were willing to take leukoreduced if it
11 was done under cGMP. Those are usually centers
12 where the oncologists have a much better
13 relationship with the blood bank director, to have
14 a sense of comfort. I guess if you don't know your
15 jewels, know your jeweler, is the adage. Those
16 centers that the oncologists were much more
17 rigorous in running the program themselves demanded
18 sometimes CMV seronegative in addition to
19 leukoreduced.
20 So it's kind of mixed, but the
21 presentation I showed you from the ASBMT Journal
22 stated that either would be acceptable for their
23 purposes. That was the one where they gave you the
24 1 times 10 to the 6th. It really should have been
25 5 times 10 to the 6th.

1 DR. MACIK: Blaine, if I may answer that,
2 too, as a hematologist, I asked at my own
3 institution, and what I found is the bone
4 marrow/stem cell transplanters followed a totally
5 different protocol than solid tumor transplanters.
6 One would use leukoreduced; the other one wouldn't.
7 One wanted CMV negative; the other one didn't. And
8 so within one institution the blood bank was faced
9 with two different demands from the clinician. And
10 that's at my institution, so I'm not sure what
11 happens, but I would assume that across the country
12 what you're going to find is just a great variation
13 in what is required.
14 CHAIRMAN NELSON: Our next speaker at the
15 open public hearing is Kay Gregory from the
16 American Association of Blood Banks.
17 MS. GREGORY: I'm going to come up here
18 because I know I can get the microphone adjusted.
19 The one back there probably won't go low enough for
20 me to be able to speak into it.
21 You heard this morning about the American
22 Association of Blood Banks, so I'm going to skip
23 that part for now. And at this time the AABB is
24 not proposing specific quality assurance measures.
25 Instead, we want to highlight some parameters that

1 the AABB believes must be considered by the FDA
2 before arriving at recommendations for
3 leukoreduction.
4 First, terminology must be clearly
5 defined. In discussions between experts in
6 statistical evaluation on the AABB Standards
7 Committee and the FDA, it is clear that the blood
8 banking community did not understand certain
9 terminology in the draft FDA guidance. The FDA
10 guidance discussed the use of tolerance bounds, but
11 the blood banking community generally interpreted
12 this as a confidence interval. There is a great
13 deal of difference between these two parameters,
14 including the number of leukocyte reduced units
15 that would require direct quality control testing.
16 Secondly, requirements should be set based
17 on clinical relevance of requirements, not on
18 process capability alone. FDA must evaluate the
19 available clinical data for the intended users of
20 the product. Three leading benefits for the use of
21 pre-storage leukocyte reduced blood products are
22 the reduction of risk of febrile non-hemolytic
23 transfusion reactions; alloimmunization to
24 platelets; and transfusion-transmitted CMV.
25 There are numerous studies of these

1 indications that may be interpreted to achieve
2 these benefits at a cut-off of 5 times 10 to the
3 6th. There is little clinical evidence that the
4 proposed reduction of the specification limit or
5 standard for white cell residual content in blood
6 products to 1 times 10 to the 6th white cells would
7 have measurable benefits with regard to these end
8 points.
9 Third, technological capabilities for
10 measurement methods must be considered. For
11 example, manual counting methods are widely used
12 for determining the number of residual white cells
13 in a leukocyte-reduced product. Although automated
14 methods are widely available, direct quality
15 control of large numbers of units may not be
16 practical. Even when automated counting methods
17 are available, the additional steps involved in
18 collecting the sample for counting and the
19 necessary record-keeping will introduce additional
20 complexities. Measurement of red cell recovery is
21 even more difficult.
22 Fourth, the technical ability to achieve
23 the proposed end points must be considered. In the
24 recently published VAT study, Figure 22 and Table 2
25 demonstrate that 1 to 22 percent of filters

1 currently used for pre-storage leukoreduction would
2 not have met the proposed standard. In light of
3 the markedly increased number of quality control
4 measures that would be required upon encountering
5 each failure to achieve the 1 times 10 to the 6th
6 cut-off, these data predict the resultant quality
7 control requirement increase could be truly
8 massive.
9 Fifth, requirements should not be set
10 based on requirements for tests that are not tests
11 for CMV, and the true sensitivity and specificity
12 of these assays is not known. The use of various
13 tests across the U.S. is also not known, and is not
14 easily determined. The rate of transfusion-transmitted CMV
15 is reported to be 1 to 4 percent in
16 antibody-screened units. Thus, requiring CMV
17 testing for all leukoreduced units would not
18 eliminate CMV transmission. You should also be
19 aware that the use of leukoreduced units to prevent
20 CMV transmission is already a standard of practice
21 in a number of facilities.
22 The AABB encourages the FDA to continue to
23 evaluate the use of statistical quality control in
24 blood and blood components, and will assist the FDA
25 in any way possible. However, we anticipate that

1 the FDA will consider the impact on both the blood
2 collection facility and the transfusion service,
3 and will set requirements that will not be
4 unnecessarily burdensome, will be technologically
5 feasible, and will contribute to the effectiveness
6 and safety of blood components.
7 We must not lose sight of the ultimate
8 goal: to provide the patient with the needed
9 transfusion component that is safe and effective.
10 Thank you.
11 CHAIRMAN NELSON: Thank you. Any
12 comments?
13 The final person that's listed to testify
14 at the open public hearing is Dr. Linda Chambers
15 from the American Red Cross.
16 DR. CHAMBERS: Thank you. Good evening.
17 I am Linda Chambers. I am one of the senior
18 medical officers at the American Red Cross. Thanks
19 for the opportunity to speak to the committee
20 regarding FDA's draft guidance on leukoreduction.
21 I have brought a fairly extensive testimony to read
22 into the minutes, but I will forego the entire
23 thing if that's okay with the committee, because
24 all of the content and points have been made by
25 other speakers.

1 What I would like to do instead is share
2 some data with you in the vein of the following
3 comment regarding the draft, and that is that Red
4 Cross agrees that the guidance focus on donors with
5 sickle trait as a cause of leukoreduction failure
6 was too strong, since there are many other causes
7 of failure to filter and failure to leukoreduce.
8 We believe that FDA would be providing the best
9 guidance if it allowed blood centers to focus on
10 leukoreduction failures, and required specific
11 systematic evaluations relevant to that portion of
12 the filtration leukoreduction process with
13 evaluation for all possible causes.
14 I have brought data reflecting our
15 experience with leukoreduction filtration that
16 illustrates key differences between what I'm going
17 to call process failures involving failure to
18 filter and process failures involving failure to
19 leukoreduce. This distinction is important, in
20 fact it's key in terms of the required quality
21 control and the corrective actions necessary to
22 protect transfusion recipient safety.
23 Could I have the first overhead, please?
24 Just by way of coding, so you can read the tables,
25 we have three different methods of filtration that

1 we're using. The first is several manufacturers'
2 worth of sterile dock filters that are added to the
3 collection set after collection. We use a set
4 where the filter is in-line and comes with the
5 collection kit for the red cell bag, and another
6 collection kit that is designed with an in-line
7 filter that filters the whole blood before the
8 components are prepared.
9 Now, before we look at the numbers, the
10 terminology I will use is the following. I will
11 refer to the entire process of taking a unit of
12 blood and intending to attach a filter and produce
13 a leukoreduced unit as "manufacturing," and there's
14 two portions of that manufacturing where problems
15 can occur. The first is failure to filter, which I
16 will use to mean that the blood didn't go through
17 the filter and end up in the second bag. The
18 second being failure to leukoreduce, or failure of
19 the intended use of the leukoreduction filter.
20 You've already seen the data in the first
21 column. The first 3.62 million data was shared
22 with you at the June meeting. What I'm bringing is
23 a recent 439,000 for comparison, so that you can
24 see where we have at least made headway on what
25 appear to be at least stable observations with this

1 regard.

2 In the portion of failure to filter, where
3 the blood doesn't go through the filter, and the
4 entire contraption is discarded and does not result
5 in a product that's issued for transfusion, the
6 primary problem appears to still be clots.
7 However, the next biggest category is unknown. We
8 don't in all cases have, as defined, a protocol for
9 investigation of these failure to filter episodes
10 that might disclose less frequent or less well-appreciated
11 causes for failure to filter, but you
12 can see in our experience finding the unit to be
13 sickle positive is a small rate, small contributor
14 to the failure to filter problem in the
15 manufacturing process. I may point out these
16 numbers as well are not percentages. These are per
17 10,000 procedures.

18 The leukoreduction failure rates at 1
19 percent sampling are as represented, and it appears
20 that between the first 3.62 million that we did and
21 a recent 439,000 data set, that our leukoreduction
22 intended use failure rate may be going up. It's
23 approximately evenly distributed at this time
24 between poor red cell recovery and adequate red
25 cell recovery and excessive white cell residual.

1 Next slide, please. When you roll all
2 these together, of total manufacturing failures, by
3 far the majority of them are failure to filter and
4 not failure to leukoreduce. This is an important
5 observation, because the failure to filter units
6 are not transfused, so they do not compromise the
7 safety or efficacy of leukoreduced blood products
8 received by patients. I would also point out that
9 since I gave you the rates of leukoreduction,
10 apparent leukoreduction failures at 1 percent
11 sampling, but I normalized that to 10,000, we are
12 seeing approximately 1 percent leukoreduction
13 failure, we would see approximately 1 percent if we
14 were doing 100 percent QC on all of our units.
15 Next slide. The total manufacturing
16 failure rates are not evenly distributed by
17 manufacturer or by filter within a given
18 manufacturer's repertoire. We had in the initial
19 3.6 million and in the most recent experience, an
20 over-representation of one manufacturer and two
21 different filters in the total manufacturing filter
22 failure rate.
23 Next slide, please. Similarly, the
24 leukoreduction/intended use failures are not evenly
25 distributed. One particular filter, manufacturer

1 one, which is sterile dock for AS1 filters,
2 represented 24 out of 29 red cell recovery QC
3 failures but only 43 percent of all
4 leukoreductions, and manufacturer one's red cell
5 filter, which is an in-line for the red cell
6 component only, was 19 percent of manufacturing but
7 14 out of 19 of white cell residual QC failures in
8 that same 439,000 data set.
9 Next slide. So, in summary, if you look
10 at the entire chain of manufacturing failure, there
11 are multiple causes to not be able to get out the
12 end what you intend to when you take a unit of
13 blood out of the refrigerator or out of the
14 transport pack and intend to do a filtration
15 leukoreduction. Clots in the unit are, in our
16 experience, still accounting for about a quarter of
17 the total failures of manufacturing. Sickle trait
18 units are an uncommon cause and a minor player in
19 this problem.
20 Most manufacturing failures are simply
21 failure to filter, and they are not leukoreduction
22 failures, a ratio of 65 to 1. The total failure to
23 filter rates vary substantially by manufacturer,
24 two- to eight-fold, and the leukoreduction
25 failures, while they are rare, are also not evenly

1 distributed, in our experience, among filter types.
2 Having said this, you see the problems in
3 trying to compare experience between blood centers
4 that are using not only different techniques in
5 terms of flow rates, temperature, hold time before
6 filtration, but a different mix of manufacturers
7 and filter types. It's very difficult to compare
8 between programs.
9 This is what I think is perhaps the
10 contribution that Red Cross could make at this
11 point to the formation of good guidance, and that
12 is that failure to filter is, certainly it's an
13 operational problem, but it's not a leukoreduced
14 transfusion safety or efficacy problem because
15 those units are all discarded. So it would be most
16 helpful to us if the guidance was focused on that
17 leukoreduction failure subset, with some
18 clarification and standardization of the
19 expectations for investigating not the total
20 manufacturing failures but the failure to
21 leukoreduce portion, the 1 out of the 66 that
22 really do produce a product that is going to
23 otherwise be labeled, distributed, and transfused.
24 For example, as far as we know, if we
25 could do something, or at least based on our

1 experience--which I did show you we've got a 30
2 percent decrease in our rate of having clotted
3 units--in our experience, if we got rid of all the
4 clots, we would have a substantial reduction in our
5 manufacturing failure but it would not affect the
6 likelihood of an inadequately leukoreduced red cell
7 being inappropriately released.
8 And that's the data. Are there any
9 questions?
10 CHAIRMAN NELSON: Thank you. Yes?
11 DR. LINDEN: I believe when Dr. Haley
12 spoke in June, she indicated that the sickle
13 positive rate that you have of 1.1 was only donors
14 who were known for some reason to be sickle
15 positive, and that in fact the unknowns of 30.9
16 were not tested, so that a significant proportion
17 of those could in fact be sickle trait and you
18 don't know. I mean, I don't think you can say that
19 it's less than 1 percent if you didn't test all of
20 them to determine that.
21 DR. CHAMBERS: Right. Even if all of
22 those were sickle trait units, though, and you put
23 those in the category with sickle trait, you're
24 still talking 30 in 10,000 failure to filter
25 episodes, as opposed to failure to leukoreduce

1 episodes, which makes it a minor player, puts it in
2 the same category as clots, basically. It still is
3 not the primary cause of failure to filter. It
4 becomes a small player.
5 You're right, Jeanne, that right now the
6 protocols within Red Cross of what to do when the
7 blood won't go through the filter are not
8 standardized. For example, one of the categories I
9 showed you was cold agglutinins. In some regions
10 that may actually be sampling the unit and testing
11 for an NTI that's reactive at room temperature. In
12 another region it may be a visual inspection, at
13 which point I would challenge anybody to tell me
14 the visual distinction between a clot, a bona fide
15 fiber and platelet clot, and a cold agglutinin. I
16 think it's subtle and it's quite subjective.
17 But my bottom line observation at this
18 point would be that all of those are interesting
19 but they're not the manufacturing problem that
20 results in the blood product that's going to be
21 unsuitable for transfusion or unsafe for somebody
22 to receive. In my mind those all add up to a
23 problem akin to a bad conveyor belt. I've been
24 using this example with my colleagues, that if we
25 had a conveyor belt that every 1 in 100 units, it

1 spit it off the end and broke it on the floor,
2 that's a problem. That's an operations problem and
3 it's messing up the manufacturing, but it's not
4 producing a unit that's going to be labeled
5 leukoreduced, that in fact contains more than 5
6 times 10 to the 6th white cells. And that really
7 ought to be our focus and our concern.
8 DR. SIMON: I just wanted to clarify, I
9 may have missed on the statistics, I thought you
10 said that if you did quality control on all of your
11 units, you would have a 1 percent failure, but I
12 saw the 1 in 10,000 number.
13 DR. CHAMBERS: Yes. What I showed you was
14 1 in 10,000 at 1 percent sampling, so if I'm seeing
15 1 in 10,000 at 1 percent sampling, then at 100
16 percent sampling I would be seeing 100 in 10,000,
17 which is 1 percent. I'm just making a quick
18 correction for the fact that we only have 1 percent
19 sampling, and approximating the actual failure rate
20 as 100 times the observed rate.
21 DR. SIMON: Why wouldn't you expect the
22 proportion to change? Am I missing something?
23 DR. CHAMBERS: I'm only doing 1 percent
24 sampling. At 1 percent sampling, every 10,000
25 times I run this manufacturing stuff, I get a QC

1 failure. So presumably if I were QCing everything
2 that came off this manufacturing line, I would see
3 it at a hundred fold, the rate. So instead of 1 in
4 10,000, I would see 100 in 10,000, which is 1
5 percent.
6 CHAIRMAN NELSON: Yes, I'm confused by
7 that. I think a sample is a sample is a sample is
8 a sample. Isn't that right?
9 DR. CHAMBERS: No. The data that I have
10 shown you is the frequency with which, when we take
11 a unit of blood and pop a filter in it and try to
12 get a leukoreduced product out the other end that
13 we can put into inventory, we have some problem and
14 don't end up at the end point where we want. We
15 can have a failure to filter for a whole variety of
16 reasons, or it can filter just fine and it's a unit
17 we happen to select for QC and it fails QC.
18 CHAIRMAN NELSON: It's still a proportion,
19 isn't it?
20 DR. CHAMBERS: That's my point. I've
21 sampled only at the 1 percent rate. I've done a
22 correction, and the correction of course is not
23 perfect. Do you have another way to talk it
24 through that might be clearer?
25 DR. EPSTEIN: If I can get there. If I

1 understand what you're saying, and correct me if
2 I'm wrong, because I didn't do this, what's being
3 said is that for approximately every 10,000 units
4 that go through, only 1 percent were tested, so
5 that means only 100 were tested. Of those 100, 1
6 failed. So what's being said is that the
7 throughput was 1 detection out of every 10,000
8 processed, but that was 1 detection out of every
9 100 samples that were--
10 DR. CHAMBERS: That's correct.
11 DR. EPSTEIN: Right.
12 DR. CHAMBERS: So the reason that that's
13 important is, when you look at a protocol--
14 DR. HOLLINGER: Why put it that way?
15 DR. CHAMBERS: Why put it that way?
16 DR. HOLLINGER: It shouldn't be that way.
17 It's misleading.
18 CHAIRMAN NELSON: The 1 in 10,000 is
19 misleading, yes. 1 in 100, yes.
20 DR. CHAMBERS: I was trying to answer two
21 questions simultaneously, really, with the data,
22 because there's two questions you could ask. One
23 is, when you start with a certain number of red
24 cells that you intend to leukoreduce, how many are
25 you going to get into the refrigerator when you're

1 all done? And that's a combination of a host of
2 things, including those that you sample for QC.
3 You don't QC the entire group that are coming
4 through the filter.
5 So the loss in the manufacturing chain
6 reflects your QC sampling rate, but then having
7 observed what that rate is, you can then estimate
8 what your actual, if you were doing 100 percent QC,
9 what your actual failure rate would be. And our
10 estimate from the most recent experience is that it
11 would be about 1.1 percent.
12 The reason that's important is, when you
13 look at a testing protocol that includes running 60
14 sequential to check a process, a validated process
15 that has had one QC failure, then Dr. Celso's
16 business card and the calculation on the back,
17 about 50 percent of the time you're going to have
18 another failure in that set of 60 and roll to a
19 second set of 60. So it's not 60 units on average
20 that you'll be doing for each QC failure, it's
21 going to be closer to 90 or 100, and that's the
22 number that needs to be used to estimate the
23 increased workload if you go to the 60 revalidation
24 number.
25 DR. STRONCEK: My understanding, a

1 reasonable size Red Cross center would collect
2 about 5,000 units a week, so then you'd be sampling
3 50 units a week, and if there's a 1 percent filter
4 failure once every couple weeks, you're going to
5 have to redo the 60. Is that right?
6 DR. CHAMBERS: It would be even worse than
7 that.
8 DR. STRONCEK: So you would be doing 50
9 one week, 50 the next week, and then see a failure,
10 then do 60, and--
11 DR. CHAMBERS: It's actually many-fold
12 multiplied because we use multiple filter types and
13 methods at each center. We may have a center using
14 one filter that can be used on a room temperature
15 product or a refrigerated product. They may be
16 doing both things, so that's two separate
17 processes, each of which are sampled at 1 percent
18 and subject to approximately a 1 percent failure.
19 A little bit higher with some filters, a little bit
20 lower with others. And then we have a whole
21 different filter set being used in another part of
22 the plant, so we actually--it's many-fold at each
23 location that these QC protocols will be run
24 through.
25 And we've tried to model out. It looks

1 like we could easily get in a continuous QC loop,
2 as well, at the 60. But I know that point has been
3 made and you've talked about it already today.
4 DR. HOLLINGER: Is there a reason that you
5 use different manufacturers in different sites and
6 so on, where you have those?
7 DR. CHAMBERS: Yes, and I think they're
8 valid. The first is that you can't always control
9 when blood comes back to the blood center, so it's
10 important to have, be using a technology that can
11 accommodate something that's been refrigerated as
12 well as something that's at room temperature.
13 Because if you've got to transport blood, for
14 example, overnight from a blood drive into the
15 center, you're not going to keep it at room
16 temperature for that length of time. It's going to
17 be refrigerated. So that's the first requirement,
18 to be doing both cold and room temperature
19 leukoreduction.
20 And then, secondly, we are committed at a
21 95 percent plus rate to be leukoreducing blood. We
22 can't be committed to one manufacturer who could
23 have a fire, a production problem or a QC problem,
24 and have non-availability of filters for any length
25 of time, and so it's actually--it's protective. It

1 obviously complicates everything, quality control,
2 training, procedure maintenance. Not every region
3 uses all the filters, but somewhere in the Red
4 Cross, everything of what I represented to you is
5 being used in fairly hefty volumes.
6 CHAIRMAN NELSON: Okay. Is there anybody
7 else who wanted to make a comment at the open
8 public hearing? Yes?
9 MR. SIVAN: Hello. My name is Yasir
10 Sivan. I represent a French manufacturer called
11 Maco Pharma. We are not in the States, but I
12 thought I would lend a bit of a French, European
13 perspective to some of the things that have been
14 going on here.
15 First of all, I had a comment to Alan
16 Williams concerning the comment of current
17 technology, whether it exists to have under 1 times
18 10 to the 6th on a regular basis. In most of
19 Europe today that are doing 100 percent
20 leukodepletion, and we have quite a few years of
21 experience of that already, we are doing under 1
22 times 10 to the 6th.
23 In France we're doing 95 percent
24 confidence. Ninety-seven percent of the units have
25 to have 95 percent confidence of being under 1

1 times 10 to the 6th. And there are manufacturers
2 that aren't standing up to that, there are
3 manufacturers that are. It isn't the changing, but
4 the technology exists and it is being done all the
5 time. And I believe that even if you talk
6 internally into your labs, you find that most of
7 the readings are in those ranges in the products
8 that are being used in the States.
9 Second of all, we found it from France,
10 using the European Union standards, difficult to
11 understand the rates of recovery at 85 percent. It
12 seems to be very, very influenced from the pre-volume
13 compared to the post-volume. It doesn't
14 seem to represent the final product as a clinical
15 value given to the patient, whereas the standard
16 used in the European Union is a gram of hemoglobin,
17 and the final product seemed to represent more
18 completely the quality of the final product given
19 to the patient.
20 About my first comment, I have no idea or
21 comment concerning whether--I have but I won't
22 state comments concerning the beneficial number of
23 5 times 10 to the 6th or 1 times 10 to the 6th.
24 It's just that I had the comment concerning the
25 technology.

1 Concerning the mixing, we have quite a few
2 years of experience of countries moving over to 100
3 percent leukodepletion, and we have found that it
4 is not only an issue over the filter, it is a very,
5 very large issue of the process as a whole, and
6 without having proper mixing, which is the
7 beginning--stripping, mixing, the whole process--
8 leukoreduction as a universal process will have
9 problems. And it is our experience that you should
10 look at the process as a whole process and not only
11 at the filtration. It is a process.
12 And lastly concerning the learning curve
13 that I don't remember, the question arose twice, we
14 have experienced the fact that over the years the
15 quantity of nonconformities has gone down with the
16 level of experience of people in the field of how
17 to collect properly, the processing, and of course
18 the filtration and the quality of the different
19 filter manufacturers.
20 That's all. Thank you.
21 CHAIRMAN NELSON: Thank you. Alan, you
22 had a--
23 DR. WILLIAMS: Just a couple of brief
24 comments to the last speaker. My understanding is,
25 most of Europe removes the buffy coat prior to

1 using leukoreduction filters. Isn't that correct?
2 MR. SIVAN: Yes, but before moving to
3 buffy coat, there were studies done, and we have
4 not found that the quantity of cells, of white
5 cells in the filter, when you're talking about the
6 one unit of red cells, greatly influences in terms
7 of the standards--I'm not talking about whether
8 it's 0.24 times 10 to the 5 or 0.5 times 10 to the
9 5, you will see differences--but whether concerning
10 the standards doesn't influence a great deal the--
11 DR. WILLIAMS: And you mentioned the
12 technology. Clearly for the leukoreduction filters
13 in most cases the ability to produce counts under 1
14 million is clearly there. What I was referring to
15 primarily was the counting technology, an ability
16 to count accurately to that level, which at least
17 in this country is not currently available in an
18 automated fashion. I believe it's also the case in
19 Europe. In speaking with our colleagues in the
20 Netherlands, we understand that most of the
21 residual white cell counting is done manually, as
22 well.
23 MR. SIVAN: Yes, that's true. And just
24 one more issue. I will forward to whoever, if you
25 want, with all the questions of how the quality

1 control is done. If you want, I can forward you
2 what is done in front. You can tell me if you want
3 that. It may help you.
4 CHAIRMAN NELSON: Okay. Thank you.
5 Alan, should we consider the questions
6 now? Are there any comments?
7 DR. WILLIAMS: The questions are fairly
8 simple. I'm not sure if we need to put them up.
9 That's up to you, and whether or not you want to
10 revisit the options which address the questions is
11 also up to you.
12 The first question for the committee is:
13 "Does the committee recommend option one, that is,
14 that FDA should recommend to industry that all
15 products labeled `leukocytes reduced' meet the
16 defined standard as demonstrated by evaluating all
17 such products for residual white cell content?"
18 CHAIRMAN NELSON: Discussion on this?
19 Toby, yes?
20 DR. SIMON: I think this would be overly
21 onerous. Based on what we've heard, it would
22 basically mean counting every unit, and I think it
23 would be a strong deterrent to increased
24 leukoreduction and a significant increase in cost
25 of the product. And while it's true that every

1 unit would be pulled that didn't represent it, I
2 think as we have seen, all of the studies showing
3 benefit are based on a relative leukoreduction and
4 some breakthrough products being given either
5 inadvertently or intentionally in some cases to
6 some of the patients, so I don't think it's
7 necessary to reach the safety that one desires
8 based on the current data. So I would recommend
9 against option number one, or question number one,
10 voting no.
11 CHAIRMAN NELSON: Yes, I agree. I don't
12 think this is like screening a donor for HIV, for
13 instance, that if one slips through you've got a
14 problem. It's a continuum, and this is a process.
15 But does anybody else have any--if not, can we vote
16 on this? You're in charge of this part.
17 DR. SMALLWOOD: Okay, I'm polling the
18 committee on question number one. Do you want to
19 just read it again for the record, please?
20 DR. WILLIAMS: Question number one is:
21 "Does the committee recommend option one, which is
22 100 percent product qualification?"
23 DR. SMALLWOOD: Dr. Macik?
24 DR. MACIK: No.
25 DR. SMALLWOOD: Dr. Fitzpatrick?

1 DR. FITZPATRICK: No.

2 DR. SMALLWOOD: Dr. Stroncek?

3 DR. STRONCEK: No.

4 DR. SMALLWOOD: Dr. Mitchell?

5 DR. MITCHELL: No.

6 DR. SMALLWOOD: Dr. Stuver?

7 DR. STUVER: No.

8 DR. SMALLWOOD: Dr. Linden?

9 DR. LINDEN: No.

10 DR. SMALLWOOD: Dr. McGee?

11 DR. McGEE: No.

12 DR. SMALLWOOD: Mr. Rice?

13 MR. RICE: No.

14 DR. SMALLWOOD: Dr. Koff?

15 DR. KOFF: No.

16 DR. SMALLWOOD: Dr. Hollinger?

17 DR. HOLLINGER: No.

18 DR. SMALLWOOD: Dr. Harvath?

19 DR. HARVATH: No.

20 DR. SMALLWOOD: Dr. Nelson?

21 CHAIRMAN NELSON: No.

22 DR. SMALLWOOD: Okay, the consumer and

23 industry rep?

24 MS. KNOWLES: No.

25 DR. SIMON: No.

1 DR. SMALLWOOD: Okay, the results of
2 voting on question number one, unanimous no vote.
3 And the consumer and industry representative with
4 the no vote.
5 DR. WILLIAMS: Question number two is:
6 "If no to question one, does the committee concur
7 with the modified statistical quality control
8 strategy as outlined?"
9 CHAIRMAN NELSON: Discussions? Yes?
10 DR. McGEE: I just want to make a comment
11 on this 60 in a row. I hate to show that I'm a
12 statistician, but essentially I think what the 1
13 percent really means is more like Dr. Bianco said,
14 which is a coin toss. It just happens to be a very
15 biased coin with 1 percent. So that what the
16 probability is, is each unit, not the 100 units.
17 So, if that interpretation is correct, then there
18 is much less than a 5 percent probability of
19 finding a bad unit in any particular 60. So that's
20 it.
21 DR. SIMON: My problem with this, and
22 perhaps Dr. McGee could help, is I'm also finding
23 this somewhat onerous. And the comments from the
24 Red Cross and America's Blood Centers and the AABB,
25 if I am interpreting them correctly, would suggest

1 that this is going to be onerous also. But do you
2 have--I don't really have an alternative to offer.
3 What would be an alternative to allow one to assure
4 that the process is valid?
5 DR. McGEE: Quite frankly, I don't think
6 there is one. I think it's a pretty good process.
7 I think there is the misinterpretation I was
8 talking about, that 1 percent means every 100
9 you're going to find that there's one in there, and
10 that's not what it means. I means the toss of a
11 coin, with 5 percent getting a head, and if you
12 toss such a coin 60 times, there is less than a 5
13 percent chance of seeing a head. So I don't think
14 it's as onerous as is being pointed out, you know,
15 in the discussions. I'm not sure that helps.
16 DR. HOLLINGER: Dr. McGee, could you also
17 comment a little about the use of some sort of
18 control charts and so on in this process?
19 DR. McGEE: Yes. As Dr. Williams said,
20 the article is actually pretty good. The problem I
21 had with this approach with this particular
22 segment--and this is pretty standard if you run a
23 lipid lab, you would find these charts on the wall
24 of any reasonable lipid lab--is the assumption of
25 the log-normal distribution just doesn't hold. I

1 mean, both this article--well, our normal is, you
2 would look at Figure 3, but you could see that
3 there is this problem that somebody pointed out
4 with the zeros. It's got too short a tail on one
5 end, too long on the other, and without the
6 assumptions, the probabilities just don't work out
7 right. Whereas with the coin toss example, the
8 probabilities are absolutely correct, as was
9 pointed out. And the other article dealt with a
10 negative binomial, and it also admitted in the
11 article that the data aren't negative binomials.
12 I'm not quite sure--while I think any reasonable
13 lab would have these kind of control charts up, I'm
14 not sure that they should be used for a regulatory
15 process.
16 DR. SIMON: So you think it is a good
17 method? You would support a "yes" vote on this,
18 based on what you heard.
19 DR. McGEE: Yes, I would.
20 DR. FITZPATRICK: Toby, I mean, I think
21 this is a vast improvement over the original
22 recommendation. I would agree with the comments
23 from AABB and Red Cross and others that FDA needs
24 to define better from a manufacturer's standpoint,
25 and with the manufacturers, the parameters used to

1 filter a unit. I think leaving that to the
2 validation of the individual center is onerous;
3 that the process for approving a filtering device
4 should include, in the directions from that device,
5 very specific directions on how to use it, and that
6 if you follow those directions, you should expect
7 the outcome.
8 I'm a little concerned about the
9 difference in failure rates between what the
10 manufacturer says and what we're seeing in
11 practice, but that's a learning curve, and possibly
12 there may be other things with that. But now that
13 we have the opportunity to exclude those non-filtering
14 products and focus on the white cell
15 reduction failures, and that you have stated that
16 you're going to reissue this as draft guidance
17 again, that gives us the opportunity to reply. It
18 gives us the opportunity to work with you to define
19 better what a filter failure is, to focus on those
20 white cell reduction failure pieces, and as ABC
21 asked, number nine gives the alternative for anyone
22 to recommend a different approach to you for their
23 process.
24 So I think it's an improvement, and it
25 allows us and allows the industry to come up with a

1 good process to meet what you've asked for. So I
2 think we're in better shape than we were when it
3 was first proposed.
4 CHAIRMAN NELSON: Your definition of a
5 failure here, to clarify the question, is a failure
6 of leukocyte reduction, but does it all include red
7 cell recovery in the question, or no? That's
8 separate?
9 DR. WILLIAMS: The red cell recovery
10 standard was really not proposed for modification,
11 so I think it's inherent. It would be included,
12 yes.
13 CHAIRMAN NELSON: Only the leukoreduction,
14 you're talking about. Yes?
15 DR. MITCHELL: I also agree this seems to
16 be much improved over the last time we discussed
17 it, and we got more information about the clinical
18 effects of the 5 million versus 1 million, and the
19 reduction to 5 million would in fact improve the
20 clinical outcome, and so I think that I'm very much
21 supportive of adopting that standard.
22 My questions still, again, are about the
23 burdensomeness, and how clear it is about the
24 statistics and the number of failures that would be
25 allowed if this is adopted and whether that would

1 be burdensome, and whether there is an option to,
2 instead of counting the 60 units, count the 93 or
3 94 units. Anyway, so that's sort of my hesitation,
4 but I think that this is an improvement.
5 DR. McGEE: There are two ways, you know,
6 that you could bring down the number. It's based
7 on 95/95. You want 95 percent confidence and 95
8 percent of the units meet it. So you could drop
9 either one of those numbers, and it will reduce the
10 number that are required. If you wanted 80/80--and
11 I didn't work any of this out ahead of time, but
12 you could do that. My assumption, you know, based
13 on what I think, was that 95/95, you would be
14 reasonable people.
15 CHAIRMAN NELSON: Okay, are we ready to
16 vote? Okay, Linda.
17 DR. WILLIAMS: Question two is: "If no to
18 question one, does the committee concur with the
19 modified statistical quality control strategy as
20 outlined?"
21 DR. SMALLWOOD: The committee is being
22 polled on question number two. Dr. Macik?
23 DR. MACIK: Yes.
24 DR. SMALLWOOD: Dr. Fitzpatrick?
25 DR. FITZPATRICK: Yes.

1 DR. SMALLWOOD: Dr. Stroncek?
2 DR. STRONCEK: Yes, but.
3 [Laughter.]
4 DR. SMALLWOOD: Dr. Mitchell?
5 DR. MITCHELL: I abstain.
6 DR. SMALLWOOD: Dr. Stuver?
7 DR. STUVER: Yes.
8 DR. SMALLWOOD: Dr. Linden?
9 DR. LINDEN: No, but.
10 [Laughter.]
11 DR. SMALLWOOD: Dr. McGee?
12 DR. McGEE: Yes.
13 DR. SMALLWOOD: Mr. Rice?
14 MR. RICE: Yes.
15 DR. SMALLWOOD: Dr. Koff?
16 DR. KOFF: No.
17 DR. SMALLWOOD: Dr. Hollinger?
18 DR. HOLLINGER: Yes.
19 DR. SMALLWOOD: Dr. Harvath?
20 DR HARVATH: Yes.
21 DR. SMALLWOOD: Dr. Nelson?
22 CHAIRMAN NELSON: Yes.
23 DR. SMALLWOOD: Consumer and industry
24 representatives?
25 MS. KNOWLES: Yes, but.

1 DR. SIMON: Yes.
2 DR. HOLLINGER: Before you read those in,
3 though, could we have a--I would like to know what
4 the "buts" are about in this. I mean just for
5 comments. Dave, if you wouldn't mind, maybe
6 Jeanne.
7 DR. STRONCEK: Well, I think it's just the
8 same concerns that Dr. Fitzpatrick expressed. I
9 think this is much improved. I do worry that the
10 automated methods aren't great to do this. I
11 suspect, though, as we do more, as the industry has
12 to do more counts, those methods will come around.
13 I think the big centers, I don't think
14 this is going to be that much of a problem, because
15 if you do 50 counts, what's 50 more? Small
16 centers, it's a little more onerous because you're
17 only doing 1 percent, so it could be more.
18 But I think I do have the concern that
19 it's detrimental to the patients to have products
20 going out that don't meet count. So I think this
21 is--the science behind the numbers looks great, so
22 I don't know that there is any way around this.
23 DR. LINDEN: My "but" was because I think
24 generally, you know, it seems statistically valid.
25 It is improved from the previous. But I am

1 concerned that the zero to 60 is going to be
2 particularly onerous, especially for smaller sites.
3 You know, as David had said, the large sites could
4 do that. The small ones are not going to be able
5 to do that, so I think that that could be
6 problematic, and I would prefer to just see a
7 little bit more consideration, evaluation of
8 possible options.
9 MS. KNOWLES: My pieces was that, while I
10 agree it's definitely an improvement, I think that
11 a little bit more thought needs to go into the
12 proposal. And as some of us who have sat here for
13 a while know, there have been other proposals by
14 FDA staff where we have continued to ask for that
15 particular individual to come back with a revised
16 algorithm or whatever, and I think in the end it
17 just makes it a better piece of information,
18 guidance.
19 DR. FITZPATRICK: I actually had a "but",
20 Blaine. If this had been proposed as final
21 guidance, I think I would have considered it
22 differently, but since it's being proposed to be
23 re-sent out as another draft.
24 DR. SMALLWOOD: The results of voting:
25 There were nine "yes" votes, two "no" votes, one

1 abstention. The industry and the consumer
2 representative both agreed with the "yes" vote.
3 CHAIRMAN NELSON: That makes the third
4 question moot, I guess, right? Yes. All right, so
5 we'll see you tomorrow.
6 [Whereupon, at 6:25 p.m., the meeting
7 adjourned, to reconvene at 8:00 a.m. on Friday,
8 December 14, 2001.]