UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,

JUNE 2, 1999

The meeting was held in the Ballroom, Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland 20879 at 8:30 a.m., PAUL W. BROWN, M.D., Chairman, presiding.

MEMBERS PRESENT:

PAUL W. BROWN, M.D., Chairman
~~RANDOLPH WYKOFF, M.D., Associate Commissioner~~
ERMIAS D. BELAY, M.D.
DAVID C. BOLTON, Ph.D.
DONALD S. BURKE, M.D.
DEAN O. CLIVER, Ph.D.
LINDA D. DETWILER, D.V.M.
BRUCE W. EWENSTEIN, M.D., Ph.D.
BARBARA W. HARRELL, M.P.A.
DAVID G. HOEL, Ph.D.
PETER G. LURIE, M.D.
J. JEFFREY McCULLOUGH, M.D.
PEDRO PICCARDO, M.D.
STANLEY B. PRUSINER, M.D.
RAYMOND P. ROOS, M.D.
ELIZABETH S. WILLIAMS, D.V.M., Ph.D.
WILLIAM FREAS, Ph.D., Executive Secretary

TEMPORARY VOTING MEMBERS PRESENT:

WILLIAM D. HUESTON, Ph.D.
LAWRENCE B. SCHONBERGER, M.D.
EDMUND C. TRAMONT, M.D.
F. BLAINE HOLLINGER, M.D.
SUSAN F. LEITMAN, M.D.
KENRAD E. NELSON, M.D.

GUESTS PRESENT:

LOUIS KATZ, M.D.
MERLIN SAYERS, M.D., Ph.D.
RONALD O. GILCHER, M.D., FACP

CONSULTANT PRESENT:

ROBERT G. ROHWER, Ph.D.

SPEAKERS PRESENT:

STEPHEN D. NIGHTINGALE, M.D.
ALAN E. WILLIAMS, Ph.D.
CHRISTL A. DONNELLY, Sc.D.
PENNY CHAN, Ph.D., MHSc.
PHILIP COMER
MARY ELIZABETH JACOBS, Ph.D.
DOROTHY SCOTT, M.D.

PUBLIC COMMENT:

CAPTAIN BRUCE D. RUTHERFORD
KAY R. GREGORY, MS MT (ASCP) SBB
DAVE CAVENOUGH
DR. MICHAEL P. BUSCH
DR. RICHARD DAVEY
MELISSA McMILLAN
DR. MARIAN SULLIVAN

ALSO PRESENT:

JAY EPSTEIN, M.D.
DR. ED TABOR
JAMES REILLY

I-N-D-E-X

I-N-D-E-X (Continued)

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

(8:30 a.m.)

CHAIRMAN BROWN: My name is Dr. Paul Brown. Welcome to the FDA traveling road show. We are asked yet once more by the FDA to consider a question of theoretical risk in the absence of sufficient knowledge on which to base any firm conclusion.

The issue before us today is that of excluding categories of American blood donors who have either visited or resided for longer periods of time in Great Britain. The issue is sufficiently delicate, as you see that we have been moved outside the Beltway.

(Laughter.)

CHAIRMAN BROWN: And the program has been very nicely designed and very logically designed. We are after a brief discussion of background for this issue by Dr. Mary Elizabeth Jacobs going to hear detailed presentations, the first of which will be by Alan Williams, Dr. Alan Williams, on the effect of any exclusions on the U.S. blood supply.

That will be followed by two presentations, one by Christl Donnelly from the United Kingdom and the other by Philip Comer from the United

Kingdom, in which the question of what exactly would one expect with respect to numbers of new variant cases, new variant of Creutzfeldt Jakob disease cases, in Great Britain because that, of course, is the other term in this risk equation.

Then we're going to hear from Dr. Penny Chan from Health Canada National Blood Safety Council, actually, see what the Canadian response to this issue is, following which we'll have lunch, a public hearing, we'll have extensive committee discussion and a vote at that point. And the end of the afternoon will be devoted to the operational definition of possible cases of new variant CJD as they may occur in this country.

I see that the suggested break for the day is 5:30. I have in mind a substantially earlier termination, if possible before 5:00 o'clock. I think the times allotted to the speakers have been generous, and I would hope that each of them would remain within his or her allotted time.

Now I introduce Dr. William Freas, the Executive Secretary of this Committee.

DR. FREAS: Good morning. I would like to go around and introduce to the audience the members seated at the table who are temporary voting members,

standing Committee members, and our guests. I'll be starting on the right-hand side of the room.

In the first seat is Dr. Lawrence Schonberger, Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, Centers for Disease Control.

Next is Dr. William Hueston. And if the members would raise their hands so that the people in the audience can identify them? Dr. William Hueston, Associate Dean, Virginia-Maryland Regional College of Veterinary Medicine.

Next is Dr. Susan Leitman, Chief of Blood Services, Department of Transfusion Medicine, NIH.

Next is Dr. Stan Prusiner, Professor of Neurology at University of California's School of Medicine.

Next is Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago.

Next is one of our new Advisory Committee members: Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention.

Next is a new Advisory Committee member who is familiar to the table. He has been here many times as a temporary voting member: Dr. Peter Lurie, Public Citizen's Health Research Group, Washington,

D.C.

Next, a standing Committee member, Dr. David Hoel, Professor and Chairman, Department of Biometry and Epidemiology, Medical University of South Carolina.

Around the corner of the table is a new member: Dr. David Bolton, head, Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is a member of the Blood Products Advisory Committee, who will be serving as a temporary voting member at today's meeting. That's Dr. Kenrad Nelson, Professor at Johns Hopkins University.

Next is another new member: Dr. Jeffrey McCullough, Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Hospital.

Next is the Chairman of this Committee, whom you heard from, Dr. Paul Brown, Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke.

Next to me is Dr. Bruce Ewenstein, Clinical Director, Hematology Division, Brigham and Women's Hospital, another new member.

Next, at the corner, is Dr. Linda

Detwiler, Senior Staff Veterinarian, U.S. Department of Agriculture.

Next is Dr. Pedro Piccardo, Assistant Professor, Indiana University Hospital.

Next is Dr. Elizabeth Williams, Professor, Department of Veterinary Sciences, University of Wyoming.

Next is the Chairman of FDA's Blood Products Advisory Committee, who will be serving as a temporary voting member at today's Committee discussions, Dr. Blaine Hollinger, Professor of Medicine, Virology and Epidemiology, Baylor College of Medicine.

Next is our consumer representative: Barbara Harrell from Montgomery, Alabama.

Next is a standing Committee member, Dr. Donald Burke, Director, Center for Immunization Research, Johns Hopkins University.

Next is Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of California.

Then was Dr. Donald Burke, Director, Center for Immunization Research, Johns Hopkins.

Next is Dr. Edmund Tramont, Professor of Medicine, University of Maryland.

At the end of the table is Dr. Robert

Rohwer, who is a consultant to this Committee. He is Director of Molecular and Neuro-virology Unit, VA Medical Center, Baltimore.

We also have three guests that, unfortunately, we could not fit at the table because it is rather crowded up here. The three guests are sitting off to the right-hand side of the room. They are: Ronald Gilcher, President and CEO, Oklahoma Blood Institute.

Next is Dr. Merlin Sayers, Director of the Blood Bank, Carter Blood Care in Bedford, Texas.

And next is Dr. Louis Katz, Vice President for Medical Affairs and Medical Director for Mississippi Valley Regional Blood Center in Iowa.

Welcome to all of you this morning.

Now I would like to read into the public record the conflict of interest statement which is prepared for this meeting. "The following announcement is made part of the public record to preclude even the appearance of conflict of interest at this meeting.

"Pursuant to the authority granted under the Committee charter, the Director, Center for Biologics Evaluation and Research has appointed Drs. Blaine Hollinger, William Hueston, Susan Leitman,

Kenrad Nelson, Lawrence Schonberger, and Edmund Tramont as temporary voting members.

"Based on the agenda made available, it has been determined that the agenda addresses general matters only. General matters waivers have been approved by the agency for all of the TSE Advisory Committee members as well as Dr. Tramont, a consultant.

"In addition, a waiver has been approved for Dr. Robert Rohwer to participate as a nonvoting consultant. The general nature of the matters to be discussed by the Committee will not have a unique and distinct effect on any member's personal or imputed financial interests.

"In regards to FDA's invited guests, the agency has determined that the services of these guests are essential. There are reported interests which are being made in the public record to allow our many participants to be objectively evaluated.

"These statements to be added to the public record are: Dr. Jeffrey Almond is employed by Pasteur Merieux Connaught. Dr. Ronald Gilcher is employed by the Oklahoma Blood Institute. Dr. Louis Katz is employed part-time by the Mississippi Valley Regional Blood Center. Dr. Merlin Sayers is employed

by the Carter Blood Care Community Blood Center.

"Dr. Alan Williams is employed by the American Red Cross, Holland Labs, and is Scientific Adviser for the Florida Blood Services and Canadian Blood Services. In addition, he has financial interests in firms that could be affected by the general discussions.

"Dr. Richard Race has financial interests in firms that could be affected by the general discussions and is a public health science researcher.

"In the event that the discussions involve specific products or specific firms for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement. And their exclusion will be noted for the public record. A copy of the waivers is available by written request under the Freedom of Information Act.

"With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon."

So ends the reading of the conflict of

interest statement. Dr. Brown, I turn the meeting over to you.

CHAIRMAN BROWN: We'll pass directly to Dr. Randolph Wykoff, the Associate Commissioner for Operations in the FDA, for some introductory remarks. Dr. Wykoff?

DR. WYKOFF: Thank you very much.

Mr. Chairman, members of the Committee, invited guests, it is my pleasure and honor to welcome you on behalf of the Commissioner and on behalf of the entire FDA.

Over the next two days, you will be asked to deal with some complex and challenging public health issues. But this is not a situation that is new to this Committee.

Because of the nature of TSEs and because of their potential public health implications, this Committee has dealt with complex and challenging public health issues in the past and will likely do so for many meetings in the future.

The specific issues that you will be asked to advise us on are: the possible deferral of donors based on foodborne exposure in BSE countries, possible revisions in our guidance on processed human dura mater, and issues related to the safe sourcing of

material of sheep and goat origin for use in FDA-regulated products.

The way we will ask you to advise us on these issues is by posing some questions to you. These questions have been developed by FDA's TSE working group. And I would like to take a moment to thank the working group for everything that they have done, not just in keeping up to date with the latest issues related to TSE science but also in putting together an outstanding agenda for this two-day meeting.

As a result of their agenda, you will have the opportunity to hear several distinguished presentations from around the world. You will hear presentations from FDA-regulated industry, from academia, from public health agencies in other countries, and from our sister agencies here in the United States.

It is our sincere hope that based on the information that you hear from those presentations, when combined with the knowledge that you already have and the discussions that you will have here over the next two days, that you will be able to answer and provide us with detailed and specific answers to the questions that we have posed to you.

More realistically, however, you will probably find that several of the questions are more difficult to answer and that you would really like to have additional information and that you don't have complete information upon which to answer the questions.

This, too, is not a situation that is unique to this Committee. Because of the information and lack of information about TSEs, this Committee has found itself having to provide advice to the FDA with less than all of the information than it might otherwise like to have. And I suspect that it will continue to do so for many meetings in the future.

Nonetheless, we have an absolute obligation to try to get these questions answered. And that obligation is our obligation to the American public to make certain that we carefully collect and systematically analyze all of the data that relate to TSEs and based on those data, incomplete though they may be, come up with the recommendations that are fair and balanced and in the best interest of the public health.

And, just as the American public looks to the FDA for advice and recommendations, we look to you for your thoughts, your counsel, and your

recommendations.

The issues that you are dealing with are complex and challenging. And it is true that there is incomplete information upon which to make these recommendations. But I think you understand that we have an absolute obligation to take the information that we do have and based on that information make the best recommendations that we can to promote and protect the public health.

We sincerely appreciate your willingness to be a part of this process. We thank you for being here. We welcome you, and we wish you good luck. Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Wykoff. We'll do our best and start off with some background information provided by Dr. Mary Elizabeth Jacobs.

DR. JACOBS: Thank you, Dr. Brown, and welcome to members of the Committee.

Today we are again bringing the question of deferral from blood donation of persons with possible foodborne exposure to bovine spongiform encephalopathy, BSE, as a precautionary measure to reduce the risk of blood transmission of new variant

Creutzfeldt Jakob disease. And we are asking the Committee at this time, as we did in December, to consider this in the light of possible shortages.

Next, the current status. So far there have been no cases of either BSE or new variant CJD reported in the U.S. We're aware and we discussed in December the precautionary measures which have been taken in the U.K. First, they are not using U.K.-sourced plasma; and, secondly, they are implementing universal leukoreduction.

We took the question to our advisory committee in December. And that entire transcript is available on our Web site. I want to mention that in December and again today, in order to have continuity with the Blood Products Advisory Committee, which is also a scientific advisory committee to us, we have invited Dr. Hollinger, who is chair of that committee; Dr. Leitman; and Dr. Nelson.

In order to have continuity with the BSE Committee, which is advisory on the PHS level to Dr. Satcher, we have invited as a guest Dr. Gilcher. We also have guests: Dr. Katz and Dr. Sayers from the blood banking community, and we have also included Drs. Hueston, Schonberger, and Tramont, who served in December as temporary voting members.

Next. In December, we asked the Committee to vote on two votes. I'm going to go through what those votes were. The first one is: Should FDA recommend new deferral criteria for blood donors to attempt to reduce a theoretical risk for transmitting new variant Creutzfeldt Jakob disease be excluding donors potentially exposed to the agent of bovine spongiform encephalopathy? The Committee voted nine yes and six no.

Next overhead. Should FDA recommend excluding donors who have resided in the United Kingdom or other BSE countries? The Committee voted 15 yes, unanimous, to remove "or other BSE countries."

Dr. Williams, who will also speak today, presented data from the REDS donor survey which showed that 11 percent of the current donor base in the United States was in the U.K. between 1984 and 1990. And, thus, the Committee voted 12 in favor of a survey of blood donors addressing residence or travel in the U.K., including the duration and time period.

These survey results will also be used for the questions: Should FDA recommend distinguishing between donors who were resident in BSE countries during periods of higher versus lower risk of exposure to the BSE agent? And should FDA recommend exclusion

of donors who had less intense exposure to beef products based on limited travel to a BSE country? Those questions will all be revisited today.

I want to just put on the record and mention the other votes which were taken in December. Should FDA recommend withdrawal for blood components based on these donor deferral criteria? The vote was seven yes, five no.

And should FDA recommend withdrawal for plasma derivatives based on these donor deferral criteria? Voted eleven no, one yes.

Next one, please. In addition to these questions on deferral of donors, in December we also asked the Committee to consider the actions that FDA would take if there were a report of a possible case of new variant CJD.

We're going to refer those to CDC, but considering our precautionary withdrawal policy for new variant CJD, we asked: Should FDA recommend precautionary quarantine or withdrawal for plasma derivatives to which a possible new variant CJD donor contributed pending confirmation of the clinical diagnosis?

The Committee voted eight yes, one no, one abstained, but they asked us to revisit this question

of our operational definition of a possible new variant CJD case. And in the second part of today's deliberations, after the vote on deferral, we will go back to that question.

The Committee also voted that a tonsil biopsy negative for protease-resistant prion would not be sufficient to make product withdrawals unnecessary.

Next overhead, please. For today's agenda, we have scheduled talks by Dr. Alan Williams on the survey of U.S. blood donors; secondly, on the demographics of BSE and what it can tell us about new variant CJD by Dr., that should be, Christl Donnelly, who is head of the Statistical Unit at the Welcome Trust at University of Oxford in England.

You may remember in December we mentioned that the Department of Health in England had commissioned a risk assessment. That is now publicly available. It was peer-reviewed. It was done by Det Norsk Veritas. Philip Comer, who was in charge of that risk assessment, will discuss it.

We, unfortunately, omitted on this one of our colleagues who is speaking. That is Dr. Nightingale. He is the Executive Secretary of the Committee on Blood Safety and Availability. That's

the committee I mentioned that reports to Dr. Satcher. And he will talk about the reserve capacity of the U.S. blood supply.

And, finally, because Canada is going through a similar process, we asked Dr. Penny Chan, who is the Executive Secretary of the Canadian National Blood Safety Council, to tell us about their recent open forum.

In addition, we have available for comparative purposes results of the two Canadian travel surveys that were done. And Dr. Marc Germain can answer any questions during the open hearing part or the Committee discussion part.

Finally, I want to mention on the agenda that we are having a second part to today's discussion. Dr. Dorothy Scott will talk about the operational definition of possible new variant CJD for use in making decisions about quarantining blood or blood products.

Now, what are the questions that we are taking to the Committee today? In light of the additional information brought forward since the December 18th, 1998 meeting of the Committee, next overhead, should FDA recommend new deferral criteria for whole blood donors to attempt to reduce the

theoretical risk of transmitting new variant CJD from transfusions based on foodborne exposure to BSE in the U.K., 1B) If so, what deferral criteria should FDA recommend, including time period, nature, and length of exposure?

And a second question -- I want to note that for the questions today, we have separated out the questions for whole blood donors, which were addressed in Question 1.

Question 2 has the same approach to plasma donors. Should FDA recommend new deferral criteria for donors of source plasma and recovered plasma for fractionation to attempt to reduce the theoretical risk of transmitting new variant CJD from plasma derivatives based on foodborne exposure to BSE in the U.K.? And 2B) If so, what deferral criteria should FDA recommend?

Now, in addition to giving these formal questions to the Committee, on which we ask them to vote, we also give them an issues summary. That includes some questions, and I want to just read those into the record.

For the decisional issues directly related to the vote, based on the survey results and scientific knowledge, will additional donor deferral

criteria reduce the possible risk of new variant CJD? Secondly, what would be the estimated impact on the supply of blood and blood products in the U.S. of additional donor criteria? And, third, should the donor deferral criteria be the same for whole blood and for source or recovered plasma?

Then we listed also related issues. Can the time course of the BSE epidemic be described? Is the impact of the feeding ban and other restrictions known? Can the time course of the BSE epidemic be related to the risk of foodborne exposure to the BSE agent?

Is the risk of foodborne exposure well-characterized? Can the risk be quantified with factors such as amount, length of time, or type of food consumed? Is dietary history, for example, eating meat, useful to identify individuals at increased risk?

Can the risk of developing new variant CJD be related to the time course of the BSE epidemic? Can individuals at risk for new variant CJD be identified? Is there a genetic or physical predisposition? And, finally, can the potential risk of transmission of new variant CJD be a blood product, be estimated upon currently available data?

And, last, I'd like to mention what our plans are for follow-up. First, today is the day at which the survey results are being presented for a vote for the Committee. Next, these recommendations are considered within FDA. We consult with other PHS agencies, which include NIH and CDC and the Department.

There is a possibility of discussing recommendations at the next PHS Advisory Committee on Blood Safety and Availability; and then, finally, announcement of a revised guidance, which would include the recommendations.

Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Jacobs.

It may have struck members of the audience, as it has me from time to time, that the issue of blood safety and CJD is grist for the mill of three different committees: this one, Blood Product Advisory Committee; and the Blood Safety and Availability Committee.

And, for the record, I think it would be very nice if -- in view of the fact that the FDA has quite justifiably invited one or more members of the

other committees to our meetings for the same continuity -- it would be very nice if one or more members of this Committee occasionally were invited to the other committees.

It's somewhat disappointing to render decisions or advice from the Chair and this Committee only to have it totally reversed within two months on the basis of recommendations by other committees.

So, having got that off my chest, we'll continue now with a detailed presentation by Dr. Williams.

DR. WILLIAMS: Thank you, Dr. Brown. Good morning. May I have the first slide, please? As mentioned by Dr. Jacobs, those of us in the blood collection community left the December meeting of this group with a mandate to conduct additional survey research to try to fine-tune the data with respect to donors who have traveled to the United Kingdom and make use of those data to estimate both the impact on supply as well as the potential impact on a theoretical variant CJD risk to support the deliberations of the Committee at this meeting. So we have, in fact, done that.

The survey that I'm going to describe to you today was supported by numerous organizations. In

fact, most of the data collection activities were supported by the American Red Cross research and surveillance program known as ARCNET. And the analysis activities were supported by the REDS Coordinating Center under the sponsorship of the National Heart, Lung, and Blood Institute. And this took place after the data was in hand at the Red Cross to meet OMB requirements.

In addition, in the planning phase and throughout, we worked in association with the American Association of Blood Banks and membership of American's blood centers to try to provide a coordinate effort. And I think you'll see that evidence throughout the course of the discussion.

So, first of all, the objectives of the survey, as stated, are to estimate U.S. donor travel and residence in the United Kingdom for defined time periods relevant to the BSE epidemic; secondly, to correlate travel and residence in the U.K. with other donation variables to estimate the impact of deferral on blood safety and availability.

Next, please. In conducting this survey, we enlisted the help of numerous blood centers. And a survey was conducted in whole blood community donors in 12 sites. And, in addition, we also had data

collection from the military and a one-center collection specifically from apheresis donors.

To summarize the geographic areas where the study took place, I'll mention these 12 sites by their general metropolitan area. First is American Red Cross in Baltimore-Washington area; Detroit area; Los Angeles; Boston; Connecticut; Atlanta; San Francisco; Oklahoma City; New York Blood Center; Blood Bank of San Bernadino, California; Memphis; and Miami.

Next slide, please. Because time was limited, as were resources, we had to conduct the survey on a fairly simple basis and in discussions of our initial planning committee reviewed several different techniques for potentially collecting the data and after this discussion came to the conclusion that clearly the best way for us to collect the data was through the anonymous mail survey mechanism that had been in use in the REDS study for several years now.

I won't go into the reason for this decision unless someone wants to discuss them, but we did end up concluding that a mail survey would be both the fastest and most representative and economical for us.

We chose random samples representing one

month, about ten percent of the collections, for one month at each of the participating blood centers. This in most cases came from the January '99 donations at the blood centers, in one or two cases came from the December '98 donations because the blood center was in the midst of changing their computer system and couldn't get the '99 sample.

We designed a one-page front-and-back anonymous mail survey to be read by optical scanning. This was sent out in a single mailing with a compelling cover letter explaining without graphic detail the purposes of the study and asking if donors would please respond.

And this was sent out just about five weeks ago. It was the last week in April that this was sent out. As of yesterday, our responses were 9,346 out of 19,000 mailed, for about 49 percent. And I suspect by the end of the week -- we still have surveys coming in -- we will probably hit the 50 percent range.

For a single mailing of a mail survey, that isn't a bad response rate at all. That's really pretty good. And we know that donors typically are pretty good responders to this type of data collection.

The presented data, we had to cut it off at some point to do the analysis we wanted to do. The analysis covers 8,666 donors as of May 24th. And we actually did three different runs of analysis: from early, midpoint, and end of the available data. The results were quite consistent. We really didn't see changes in the data over the course of time receipt of the surveys.

Next slide, please. The question categories included demographics of the donors. These were quite simple: age, gender, first time versus repeat donor, and educational level. We gathered a donation history for the donor, how frequently, how many times they donated in the past ten years.

We asked the primary question about travel or residence in the United Kingdom. And we added into this the Republic of Ireland. For a couple of reasons, that decision was made. One is because most people, blood donors, as an example, really do not understand the details of the split between Northern Ireland and the Republic of Ireland, and we didn't want to confuse the issue. Secondly, there is certainly geographic proximity to the U.K. And, thirdly, after the U.K., it is one of the highest countries with reported BSE.

It's arguable whether we could have done that, whether we should have made that addition or not, but I think the change in the overall travel figures are probably quite minor.

We split the travel into two different periods. This was at FDA request. We separated into intervals between 1980 and 1989 and separately between 1990 and 1996.

We also asked questions about beef ingestion during the period of travel in the U.K. And because historical questions about food ingestion are typically suspect, we asked about beef ingestion in the past year just to get a prevalence value for beef eaters.

In addition, we included in this analysis a further measurement of deferrable risk estimates from United Kingdom travelers. This didn't come from the traveler survey, which is going to form most of the talk, but this is by subsequent analysis or further analysis of the 1998 REDS survey, which was described at the second meeting. And I'll get into the deferrable risk values that we used near the end of the talk.

It really wasn't practical to try to remeasure these deferrable risk values. It would have

made a much longer, much more extensive survey. and we chose not to do that.

Next slide. The question asked is: Did you travel to or live in the United Kingdom (England, Scotland, Wales, Northern Ireland, Isle of Man, Channel Islands, or the Republic of Ireland) between 1980 and between 1989; and separately, as a separate question, between 1990 and 1996?

Next slide, please. The summary results for this travel question, between the period of 1980 and 1989, 15.5 percent of the donor population reported travel; between 1990 and 1996, 13.4 percent; for the total period of 1980 to 1996, 22.6 percent.

Now, keep in mind that these cover different year intervals. So that probably is the major explanation for the difference in percentages.

The range for this 22.6 percent value, as you remember from December, there was quite a bit of geographic variation in the travel prevalence. For this measurement, it ranged from 11.2 percent all the way up to 30.5 percent for that 17-year period.

Now, just for compatibility with the '98 survey, we did an unadjusted figure for U.K. travel per year given that these are different yearly time periods. For the '80 to '89 time period, it is about

1.6 percent; 1.9 percent for the later period; and 1.3 percent overall given that there was some travel by donors in both time periods.

We compared that with a similar figure from the 1984 to '90 measurement made in the 1990 REDS survey, which is 1.7 percent, really right between those two figures.

So I think to the extent that we can validate the responses that we're getting, there is compatibility between the measurement in the '98 survey, which only asks U.K. travel as an ancillary question, and this survey, which asks it as a primary question.

Next slide. I want to mention briefly we do have breakdowns for the intervals for the two separate time periods, the '80 to '89 and '90 to '96, are included in the handout. And I do have a slide. I wasn't planning to go into it unless the discussion comes up, but it is available if you want to discuss those time periods separately.

Some of the demographic correlations we analyzed by logistic regression analysis just to consider their influence independent of other variables. And you can see that in terms of the age breakdown, setting the 17 to 29 age as a reference

category, clearly travel increases with increasing age. And it's really the seniors that have the highest rate of travel, almost three times the likelihood of travel.

I think you will see an interesting -- next slide, please -- correlation there as well when we look at the gender analysis because, in fact, setting females as a reference category, females travel a little more than males. And this might be to the senior phenomenon again, where females are known to have longer survival and may, in fact, do traveling and produce a higher representation there.

In terms of first-time donors, similar to what we presented in December, those individuals who are first-time donors tend to have less travel, both because they're younger and probably have less financial means to do so.

Next slide, please. In terms of education, again, setting the low value as the reference variable, you can see that college-educated and college graduates have four to five times the likelihood of international travel or travel to the U.K.

Next slide, please. Now, looking at the individual intervals between those time frames, these

are pooled data between the two time frames. We used a rather simple rule supported by midpoints of the intervals. And that is if people traveled during both of the time frames, we added the two values and put them to the next category if the intervals were the same or if one of the intervals was longer, we took that as representative of the total period of travel. And that is supported by looking at the midpoints of the intervals.

So for travel exceeding one day, that matches the overall travel to the U.K. during that time period, 22.6 percent. I mainly wanted to show this slide to show the tightness of the confidence intervals around these estimates, generally within a half to one percentage point all the way down the line.

This difference can be shown better on the next slide, which is a bar graph, same numbers, just shown differently. For the one to three-day period, 22.6 percent of the respondents traveled to the U.K.; four to ten days, 19.7 percent; eleven to thirty days, 11.8 percent; one to four months, 4.9 percent; five to eight months, 2.0 percent; nine to eleven months, 1.3 percent; one to three years, 1.2 percent; three to five years, 0.7 percent; and five years or more, 0.4

percent. Obviously these are cumulative looking at the longest time period first.

The next slide, please. Again, these are the same data but here fitted to a line graph. And what we did is run an equation to match this line. And you see this is a power equation. The r^2 of the formula explains the data well, about 97 percent.

This is the formula that derives from it, and we can use this on the next slide to actually plot percentage of donors who would be affected by specific time periods that might be of interest. I think the obvious ones we chose here would be intervals that might serve as a source of discussion for the Committee for potential deferrals.

These include looking, for instance, at the right-hand side, for two years, that would affect 1.1 percent of the donors. For one year, 1.6 percent of the donors; nine months, 1.9 percent; six months, 2.4 percent; three months, 3.7 percent; one month, 7.0 percent; and one week, 16.3 percent of the donors would be affected. Now, this is not the blood supply. This is individual donors. I am going to have some blood supply calculations a little bit later.

Next slide, please. Now, one of the things we were asked to do as well was to -- let me

make one point before going on to this slide. I do want to make it quite clear that the numbers that I am assigning quantitative values to are a one-year calculation. That's similar to introduction of a laboratory screening test, albeit a very nonspecific laboratory screening test.

These types of deferrals have multi-year effects. It is a very difficult model to build, but this is certainly more than a one-year effect to lose percentages of donors of this type. So please keep that in mind. It's a very complex formula to model, however.

Looking at the prevalence of beef ingestion by donors during the U.K. travel and currently, we asked the question whether they recalled eating beef during their U.K. travel for the two separate time periods.

For the '80 to '89 time period, 74.2 percent reported eating beef in the U.K.; 7.0 percent, no. And, as you might expect, 18 or close to 19.0 percent reported that they didn't know or didn't recall that value.

For the '90 to '96 time frame, the difference is kind of interesting. Seventy-two percent reported they ate beef. Fifteen percent said

clearly they did not eat beef.

So maybe recognition of some of the early phases of the BSE epidemic kept some people away and they knew that, in fact, they had not eaten beef in the U.K.

It could be that or it could be the more recency of the travel and they had better recall. That's difficult to distinguish. And 13 percent didn't know for that time period.

Now, comparing that with -- you remember I mentioned that we wanted to get an overall prevalence for beef eating by asking those who had eaten beef in the last year. We are very surprised to see the figure that came out of there. Ninety-six point six percent of respondents indicate that they had eaten beef in the past year.

So I think it's useful to compare the validity of this type of answer. I think it bears out that it's tough to get a historical dietary question answered.

Next slide. Now, we didn't really set out to measure the impact of a potential deferral on different types of donors, but it did become evident that there would be some interest specific to apheresis donors and specific to the military.

We know in general and supported by REDS data that apheresis donors are significantly older and more educated than whole blood donors, and I'm not going to show the data. And higher travel rates would be expected.

Now, in collaboration with Ron Gilcher and Jim Smith in Oklahoma, we did run a small survey of 200 apheresis donors in Oklahoma and compared those donors' travel histories to the overall blood donor values.

Two hundred were surveyed. And apheresis donors had 20 percent higher 1980 to 1986 U.K. travel rates, at 13.3 percent, than whole blood donors, 11.1 percent.

So it's only one center, but I think it gives a rough estimation that apheresis donors are going to be hit a little bit harder than whole blood donors for some of the demographic reasons.

Next slide, please. We also included military donors in this survey with the collaboration of Lianne Groshel. These actually were all Air Force donors because Lianne felt that it would be the Air Force that would be most likely to have been stationed in the U.K. because of the base locations.

Military donors are more mobile on

average. And, therefore, U.K. travel would be expected to be higher. And certainly if there was a base there, it would impact things.

Unfortunately, we had a fairly low response rate in the military. They sent out I think 300 questionnaires. And we got 25 back. So it was only a 12 percent response rate.

Given that, 8 of 25 indicated that they had lived or traveled in the U.K. or Ireland during the 1980 to '96 time frame, so again a little bit higher but some real broad confidence intervals around that one.

Next slide, please. This is one of the same slides I showed in December, and it serves as a basis for some of the blood supply impact discussions, I think.

The generally accepted figures for the U.S. blood supply, which AABB provides, is that there are 13 million allogeneic units collected, made into 22 million components annually. These derive from eight million donors and are given to four million recipients.

From this total number of donors, we know from the large Red Cross ARCNET database that 32 percent of these donors are first-time donors. Now,

most of you -- well, some of you will recall that the proportion of blood from first-time donors is 20 percent. That's donations versus donors.

If you look at donors, it's actually a little higher. It's 32 percent. So, using that ratio, we can break the donor base down into 2.6 million first-time donors and 5.4 million repeat donors.

Next slide. Extending those calculations a little further, annual loss of units donated by first-time donors can be calculated as percent first-time donor travel loss times 1.3 units per year times 2.6 million first-time donors.

Annual loss of units donated by repeat donors is percent repeat donor travel loss times 1.8 units donated per year -- these two figures also derive from the ARCNET database -- times 5.4 million repeat donors.

Next slide. If you take that math and simply compact it, you can determine or convert a deferral prevalence into an impact on the blood supply and lost units from the blood supply by multiplying deferral prevalence times 11.9 million. And that gives estimated annual lost units.

If you then divide that by 13 million, the

annual supply, it gives the impact on the percent of the U.S. supply. So for five years at a 0.3 percent deferral, 35,700 lost units, 0.3 percent of supply. Those are the basis of the calculations that go into some of the figures that I am going to show you coming up.

May I have the overhead, please, and shut the slides down for a moment?

DR. PRUSINER: Can you tell us why the number, the year number, is 1984 to 1990?

DR. WILLIAMS: That was from the 1998 REDS donor survey. And that figure was taken from the *Lancet* review paper, the two-part review, that mentioned '84 to '90 as the likely period of highest theoretical dietary risk. So that's how we referenced it.

You probably understand the happenings in Britain better than I do to correlate with those dates, but that was related to that *Lancet* review paper.

DR. PRUSINER: I see. Okay. All right.

DR. WILLIAMS: Now, one of the things we did -- and I have to thank Peter Lurie for getting us started on this -- is to not only look at loss of the donor base but the impact on a theoretical variant CJD

risk coming into the U.S. from donors who have traveled in Britain.

What we have done here is calculated the theoretical risk associated with U.S. blood donor travel to the U.K. or Republic of Ireland during 1989 to 1996 as measured by the survey, taking the intervals, computing the midpoint of that interval and the number of persons who traveled as reported from the survey, and using that to calculate person-days, this as a representation of potential dietary exposure to BSE on the assumption that duration of travel can be related to magnitude of theoretical risk. That's a basic assumption in doing that.

So if you run these calculations, for the one to three day period, we have 494 person-days; four to ten day period, 4,600 person-days; and so forth. You can start to notice a larger number here as the time period gets longer. And I think that's going to provide some meaningful discussion.

The last time period here I'll mention, the question that we asked was greater than five years. I calculated the interval as 5 to 17 years because the overall interval that we were measuring was 17 years. So if someone asks more than 5 years, in fact, it could have been, you know, 5, 10, 16, 17

years. So I think it's valid to use the midpoint for that interval as well.

Calculation of the theoretical risk of donors traveling for those intervals was then figured by adding up the person-days and dividing those into the person-days for each of the intervals. So for 252,804 total person-days, we divided that into the interval person-days and got a percent contribution to the total. You can see again that a lot of this is clustered into the higher interval time frames.

Then we just added these cumulative in descending order to support today's discussions. For the greater than five year time period, 49.2 percent of the risk would be related; adding to that the three to five year interval, 67.1 percent; one to two years, 77.8 percent; and so forth. And you will see these graphically in a moment.

One of the graphs actually used residual theoretical risk, as opposed to remaining theoretical risk. And the figures for that are shown here.

Maybe I'll ask: Are there any specific questions to this calculation -- because I think this is fairly basic -- from the Committee?

DR. HUESTON: Did I understand correctly that you used the mid-range of your five to 17 years?

DR. WILLIAMS: That's correct.

DR. HUESTON: Is that pretty surely a skewed segment of your curve?

DR. WILLIAMS: I wouldn't say that inherently. For someone who has been there at least five years, chances are good they equally likely have been there ten years.

I am not sure, you know, I could address whether there is a bias there or not. I think it is a topic for discussion, but I wouldn't inherently assume that there is.

CHAIRMAN BROWN: Dr. Epstein?

DR. EPSTEIN: Alan, is that supposed to be 1980 to '96? It says "'89."

DR. WILLIAMS: I'm sorry. Yes, you're right, Jay. That's 1980 to 1996. It's a computer error.

Next slide, please. Okay. This is the first graphic that I'm going to show utilizing these data. I'm not going to keep this up long because there's a better one to follow.

What this is, this shows residual theoretical risk, shown in the red line, for the full time period of consideration. In other words, for here this is the midpoint of the five to 17 year

interval and then going down plotted against the percent of blood supply lost. You can see that as a figure which goes down slowly until you get near these lower travel intervals, where you start to lose more and more donors. I wanted to show this mainly to give the total picture and sort of the area under the curve out here that really explains a lot of the data here.

So next slide, please. This I think probably would constitute a good working slide for some of the discussions. It's the same graph, but it's really zoomed in on probably the more likely deferral periods that the Committee might want to consider.

For instance, looking at percent of blood supply lost, the figures are labeled here. For a one-year deferral, it would be an impact of loss of 1.5 percent of the blood supply; for six months, 2.2 percent; three months, 3.4 percent; one month, 6.4 percent; and one week, 14.9 percent. And then that can be compared with the values for theoretical remaining variant CJD risk.

We tried to mathematically assign a function to this line, and it just didn't work well enough. So I think you're probably just as well off trying to do a visual comparison where needed.

For the one year time period, that equates to about 22 percent residual. For example, a six month time period, that equates to about 13.0 percent residual; for three months, almost right on the same point, 6.7 percent residual; one month, about three percent; and so forth.

Obviously, as you can see, most of the theoretical risk is accounted for by the time you get to about one year. And then the efficiency declines, and you start to lose more and more donors as you get to a later time period. So I think that is going to be an important consideration.

CHAIRMAN BROWN: Alan, why are the time points different top and bottom?

DR. WILLIAMS: Because the bottom one is based on what we thought would be likely discussion points for deferrals. The top one, in the absence of being able to assign a function to that line, we didn't try to exactly plot those points. And the fact that we didn't, in fact, put them up there and label them simply was an omission. But you can extrapolate to those time points.

Next slide. Now, the request was also made to consider impact of deferral on traditional risk. This is a difficult issue to get a handle on.

We have been working with a quantity known as deferrable risk for several years within the REDS donor surveys. And, really, given the rarity of post-transfusion HIV and hepatitis nowadays, it's almost getting impossible to measure. The studies in which you would actually measure this empirically are getting so expensive that you can't really conduct them anymore.

So we have defined this factor, known as deferrable risk. It was described at the December meeting. There was a copy of the JAMA paper there, which described it in detail.

Deferrable risk by the 1993 measure, as reported in the JAMA report, dealt primarily with the parenteral and sexual behavior risks, most important related to HIV and hepatitis transmission. The figure at that time overall was 1.86 percent prevalence in the accepted donor blood supply.

In the 1998 survey, we added another variable. We wanted to maintain continuity by being able to look at this one over time, but we introduced a deferrable risk '98. This includes an additional ten questions that would serve as a deferrable basis for donors but are perhaps less important in terms of magnitude in relation to transmissible disease than

some of the others but still, nonetheless, are deferral questions and questions that some donors may not answer correctly, things like body piercing, tattoo, whether or not a donor has spent more than 72 hours incarcerated, birth in an HIV Group O endemic country, et cetera. There are about ten questions.

Next slide, please. If you look at donors who traveled to U.K. during the time frame and donors who did not remember, this is from the '98 survey, not the latest travel survey, so it's '84 to '90 period -- deferrable risk by the '93 measure is 2.1 percent, dead even in both groups.

Don't infer from this that deferrable risk is rising in the blood supply. There are other factors involved. For instance, we had different blood centers participating in the survey. So until that analysis is done completely, don't draw any conclusions to the '93 report.

The deferrable risk by the '98 criteria is 7.2 percent in the travelers, 7.7 percent in the non-travelers. And that comparison is not significant at all.

However, if you compare these values to first-time donors, who would need to fill in the gap were you to defer long-term repeat donors, deferrable

risk for '93 in the '98 survey is 4.3 percent. That's highly significant. Deferrable risk for the '98 value, 13.3 percent. In both cases, the odds ratio in repeat donors is about half that of first-time donors. And it's highly significant.

I think it's important to mention that in some of the work done by Mike Busch and others looking at the lower-sensitivity HIV assay, to apply that to incidence of HIV, they, in fact, found a similar ratio, that first-time donors had a twofold higher likelihood of HIV incidence. So I think these data are very compatible with the lab-based findings between first-time and repeat donors.

Next slide. Trying to convert these risk estimates into something meaningful is a difficult job because there are estimates provided for HIV and hepatitis C, hepatitis B transmission. They're now all very rare. We have just started moving into a period of nucleic acid testing for hepatitis C and HIV. So it gets very theoretical to try to measure an impact.

To try to apply these deferrable risk values in that equation, you're figuring if you defer donors and have to replace two of them with first-time donors, you're doubling the risk in 2.0 percent of the

blood supply, which is a 0.4 percent overall increase in risk, which is well within the confidence intervals of the current estimates for HIV and hepatitis C risk factors. So I think trying to quantitate that precisely just really becomes an exercise in numbers.

I'd like to end with mentioning the limitations of survey data collection. These estimates are reproducible and have been remarkably reproducible since the 1990s, but everything is based upon self-report. It's subject to potential differential response rates in the survey and to differential reporting. The accuracy has not been validated by other independent measures, but we know that between surveys, things tend to be very consistent.

Next slide. I want to make some specific acknowledgements here. First of all, the participating blood centers. In many instances, the blood centers cost-shared on this project and did not reflect their costs back to the Red Cross. So we thank them for that the PIs and the staff.

Ron Gilcher and Jim Smith for suggesting and conducting the apheresis survey at the Holland Laboratory. Melinda Tibbals coordinated the survey. Ed Notari and Roger Dodd helped with the analysis. Ed

Westat, Dannie Ameti, and Kevin Watanabe were instrumental in helping with the survey.

We got some specific help from Committee members. I'd like to mention Paul Brown, Peter Lurie, Larry Schonberger, Jay Epstein, and Mary Beth Jacobs and the Planning Committee, made up of AABB and ABC and Red Cross representatives Celso Bianco, Richard Davey, Kay Gregory, and Steve Kleinman. I'll end there and be happy to take any questions.

Thank you.

(Applause.)

CHAIRMAN BROWN: We now have theoretically a half-hour or so to ask questions. Bob?

DR. ROHWER: I just want to make sure that I understood you correctly. Your summary in terms of the replacement of donors lost is that it would be an insignificant increase in risk. Is that what you concluded?

DR. WILLIAMS: On a statistical basis, yes.

CHAIRMAN BROWN: Alan, I had a question. I may have missed a beat. On the slide which is the zoom-in slide, --

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: -- the same one I asked

a previous question about, what precisely do the figures on the top half of the slide represent? That is to say, the legend says, "Theoretical residual risk."

DR. WILLIAMS: Right. If you look at the single sheet that is part of the handout, the calculation that is there, over in the far column, it's the risk associated with each of the periods. And assuming that there is a deferral and that portion of risk removed, that last column represents theoretical risk remaining. And those are those figures.

CHAIRMAN BROWN: Okay. So an alternative legend would be cumulative person-days?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: Larry?

DR. SCHONBERGER: If I had traveled to the U.K. between 1989 and 1992; that is, one year in '89 and three years in the period 1990 to 1996, for a total of four years, how do I appear on the graph?

I would have had checked off one to two years for the earlier period and three to five years in the second period. How would I appear on this table of calculation of theoretical variant CJD risk?

DR. WILLIAMS: You would be in the three

to five-year period.

DR. SCHONBERGER: I would be in the three to five-year period because you just take the longer --

DR. WILLIAMS: Yes.

DR. SCHONBERGER: -- period when there's a --

DR. WILLIAMS: If the periods were the same, we moved it to the interval. If one was shorter, one was longer, we took the longer period. There is a little error in doing that, but, again, --

DR. SCHONBERGER: As you point out, that --

DR. WILLIAMS: -- the way the data was set up, that's really the only way we could do it.

DR. SCHONBERGER: Right. And you pointed out that the number that overlapped was relatively small, as I recall. Is that right?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: I would suggest that the Committee not get too exercised about the distinction between these two time periods. I was in London last week in front of the Transmissible Spongiform Encephalopathy Committee. There really is no basis that can be defended for dividing this period into

two. The consensus is that the earliest years of the 1980s and the latest years covered in this survey, '94, '95, '96, are less risky than, say, something from about 1983 through 1993.

I think we can spin wheels all afternoon or morning if we really worried about these two time periods because of exactly the kind of question you raise.

Suppose you visit for six months in 1984 and revisit three months in 1989. How do you stack it up? The fact is it's probably not important to make this distinction.

DR. SCHONBERGER: No. In response to that, I agree with you. I was really responding, in part, to your recommendation initially to the group to ask the question for the one period and just ask them how long you stayed.

I think that he's given me enough information to satisfy me that that error that has been introduced because of the breakdown of the two periods is not going to be that significant.

I would be more worried, however, about that five to 17 year group given that it seems to account for about half the risk if I'm reading this correctly. I would think it would be extremely

unlikely for somebody to be there the entire 17-year period. And, yet, those 31 individuals are accounting for, as I say, 49 percent of the person-days of risk.

Is that right? Is that the right interpretation?

DR. WILLIAMS: That's right.

CHAIRMAN BROWN: Yes, Dr. Roos?

DR. ROOS: First, I wanted just to congratulate Dr. Williams and his colleagues who carried this out, because we had given you this mandate some months ago. And we do have the data that was requested. So I think we appreciate that information.

DR. WILLIAMS: Thank you.

DR. ROOS: Second, I had some questions about the military donors here. And I don't know whether we're going to pick up later with any speaker about that.

CHAIRMAN BROWN: Yes. There will be a presentation during the public hearing. It's really a separate issue.

DR. ROOS: Well, then maybe I just want to ask you a couple of questions: first, whether there is any information about the breakdown with respect to the time periods that those respondents in the

military spent in U.K., as you did with the nonmilitary; and also whether you could tell us a little bit about the military donors. I mean, is that a separate group? I was a little bit confused here about where those donors go and how they're handled.

DR. WILLIAMS: I'll answer what I can. I think there are probably people in the audience who can answer some of the military-specific questions much better than I can.

Looking at the intervals, I don't have the data with me, but I think what you're getting at is: Of those military donors, were they all up in the one, three, five-year time frames?

And clearly not even a majority were, but I think overall the time periods tend to be somewhat longer than the whole blood donors. And of the 12 who reported travel, I think there were 2 or 3 up in that longer time period. So disproportionately they were up in the longer intervals, but that's an important consideration, yes.

In terms of the characteristics of military donors, I know these were all Air Force donors. The military maintains its own blood supply and has in comparison a relatively small pool of donors that it uses. And I think perhaps Captain

Rutherford or anyone else who would like to add more should do that.

CHAIRMAN BROWN: Dr. Sayers?

DR. SAYERS: Thanks.

Alan, I was interested in that slide you showed on the apheresis donors from OBI. You know, that's certainly a group of individuals who are becoming increasingly important as far as transfusion support for patients is concerned. And they certainly do donate at a frequency much greater than the 1.3 units a year or 1.8 units a year that the other donors that you referred to donate at.

Did you have any separate calculations for what the loss of pheresis platelets might be?

DR. WILLIAMS: We did not take the calculations that far. I'm sorry. I think to produce the data to support that type of analysis, we probably would need to do more than one blood center and get a reasonable geographic distribution. I think what we got is just a window into the likely comparison, but we probably would need more blood centers.

DR. GILCHER: Alan, with reference to the same point on apheresis donors, if you looked at the loss of donors in Oklahoma specifically because the data which you showed was specifically apheresis

donors in Oklahoma, I believe it's somewhere around 4.6 to 6 percent on the whole blood side, which shows, then, that from the apheresis standpoint, it's much, much higher within our center.

Now, whether that would be true in other blood centers, I don't know, but that was what I noted about your presentation. That piece of information hit me in that this would be probably four to five times higher among our apheresis donors in our particular area than among our whole blood donors.

DR. WILLIAMS: So you are saying the impact on lost donations would be four to five times higher?

DR. GILCHER: I am saying that the impact on donors would be very high. And then the impact on donations would even be astronomically higher because this particular group of donors averages 12 to 18 donations per year as an apheresis donor. So I'm saying the impact in the apheresis donor base in terms of donations I think will probably be very, very high.

CHAIRMAN BROWN: Dr. McCullough?

DR. McCULLOUGH: Alan, back to this table, with the 50 percent of the risk essentially being allocated against those who were in the U.K. between five and 17 years is based on -- you arbitrarily chose

the midpoint of that range to do the calculation. Is that correct?

DR. WILLIAMS: Yes. It's not entirely arbitrary. That's standard procedure when you're working with an interval like that, yes.

DR. McCULLOUGH: Did you choose some shorter periods within that interval and rerun these? If you had used only six or seven years, instead of the 11 years, for that interval, it would reduce the contribution of that group to the total risk and, therefore, would increase some of the other categories. Did you look at the effect on the contribution of risk from some of these shorter stays if you reduced that?

DR. WILLIAMS: We did not do that. It would have the effect you referred to, but I guess it got back to the earlier question: How representative is the midpoint? I think if there was a strong argument that most of the five to 17 year group were closer to five than the 17, then that would be justified, sure. But it would have an impact if you changed that analysis point.

CHAIRMAN BROWN: Dr. Rutherford or Captain Rutherford, would you like to say something here?

CAPTAIN RUTHERFORD: Well, I guess I'm the

only DOD contingent here. Speaking on the DOD for the Air Force as well as for the Army and the Navy, we chose the Air Force. I think we sent out 167 surveys, and 25 came back. Out of those 25, 8 had responded that they had been in the U.K. Three responded that they had been in one month or longer. So that's about a 12 percent.

The DOD collects around 85 percent of its blood usage from active duty personnel. So that would greatly impact us. The thing there, too, is we did not take into account the time periods in '83 through that period of time when we had a large contingent of 300 and some thousand Army individuals in Europe who probably went to the U.K. for some period of extended time. So that wasn't even considered.

The DOD opens all of its bases to the Red Cross and the American Association of Blood Banks and ABC members. So as they come back to the States, the large contingent of Air Force personnel at Langley Air Force Base, Keesler Air Force Base, Lackland Air Force Base in San Antonio would probably greatly impact the donations collected in those areas by civilians. The civilians do rely upon us a lot for blood donations.

CHAIRMAN BROWN: Captain Rutherford, in the collection of blood by the military, so long as

the donors are active military personnel, are those donations used exclusively for the military or is there any mixing with the civilian blood supply while they're still in active duty?

CAPTAIN RUTHERFORD: There is a lot of mixing of blood within the DOD with civilians. They rely on us for blood at times as excesses are in the system. And then we rely on them also when we need emergency units.

All of our donor centers or OCONUS overseas are FDA-licensed. So the blood that's used OCONUS is collected from military active duty or civilian DODs or dependents who are on base and are used only on base. Only in emergencies do we use non-DOD blood of OCONUS.

CHAIRMAN BROWN: Alan, any of the areas which were surveyed, did they include areas in which there was a substantial military component?

DR. WILLIAMS: The one I'm aware of, again, is Oklahoma City. I know we do have a fairly large military contingent there. And it generally lowers their survey response rate because they don't like to return surveys.

How many of their donor base are comprised of military base individuals and what bases are I

think Ron could probably answer.

CHAIRMAN BROWN: I think it might be important in view of the possible bias to this survey with respect to military contributions to get as much information about this as we could.

In other words, what I'm hearing is at least a possibility that the proportion of military donors in the actual real life nationwide donation program for civilians would be substantially affected if the proportion of military were not reflected as a true proportion in view of the extensive military presence in the United Kingdom.

Can anybody illuminate that problem? Bob?

DR. ROHWER: The other thing is: If the military doesn't like to return surveys, are we biasing the survey because we're not getting answers from people who have done a lot of travel?

CHAIRMAN BROWN: What do you think, Alan? Are these legitimate questions or --

DR. WILLIAMS: Yes. I think Bob's point is a valid one. I think that when the data become available, you will find that percentage of military donors as a proportion of the total U.S. blood supply is going to be really quite small, but I don't have a figure for that.

CHAIRMAN BROWN: Just a second, Bob.

Yes, sir?

DR. TABOR: Ed Tabor, FDA. I would just like to second the last comment and emphasize the importance of not basing decisions too firmly on portions of studies that have either very small returns of surveys.

I mean, the military one is not only small, but you don't know, at least we don't know here, the demographics. I mean, were the ones who returned them officers and the others enlisted and so forth?

Also, the data on apheresis is based is very, very small numbers in one location. And I think those are two areas where we really seem to have very little data at present. We should be very careful about drawing conclusions from them.

CHAIRMAN BROWN: Yes, Blaine?

DR. HOLLINGER: Alan, you did a really wonderful job with this, and I know how difficult it was to get all of this data in such a short time. Nevertheless, 50 percent non-response rate is still pretty high. And a lot of the data is being made upon that.

Do you have any idea at all about anything

about the demographics of the people that responded versus the demographics of the particular areas from which they were collected -- they're going to be different in different areas of the country -- to give some confidence that these are similar to what one might expect from donors in general?

DR. WILLIAMS: I don't have the specific demographics of our return rate. I wasn't able to get them yesterday based on your question. Typically in all of the surveys we have done, we have gotten about a ten percent lower than mean response from under 25 age donors and first-time donors and generally about 10 percent above the mean by older donors and repeat donors. And sometimes survey return rates go up as high as 80 and 90 percent when you hit older repeat donors.

So without having the numbers, I would say probably this survey follows the same pattern. And, if anything, there is probably a little over-representation of the older, higher socioeconomic repeat donors.

CHAIRMAN BROWN: Dr. Leitman?

DR. LEITMAN: I'd like to return to the apheresis issue for a moment and to remind the Committee that greater than 50 percent of all platelet

components in the U.S. are collected from apheresis donors, who, as Dr. Gilcher stated, are generally regarded as the most safe type of donor because they donate so frequently -- 12 to 18 times per year is our institute's estimate as well for our center -- and to state that an increasing proportion of non-platelet components, both red cells and plasma, are being increasingly collected by apheresis technology.

So the impact on the U.S. blood supply of deferring, of adding additional deferral criteria to apheresis donors, is much larger than that on whole blood donors. And I think I would like to see that data because the impact will be so huge, and that I think you need a larger number of apheresis donors surveyed to get that, of course.

CHAIRMAN BROWN: Bob?

DR. ROHWER: On this issue of robustness, another way -- this word you don't like, I know -- to look at that is to do the same calculation on the maximum and minimum values in each one of those year bins.

On the preliminary data that you provided a week or so ago, I did do that. And it doesn't vary that much. It just shifts the two tables by one interval one way or the other. But by the time you

get up to around six months, you're still talking around 70 to 80 percent, 70 to 85 percent effect in terms of removing exposure.

The other thing I would like to note is that I think it was mentioned earlier that we have the Canadian experience to refer to. What strikes me is this distribution of exposure is almost exactly the same as the distribution that was obtained in the Héma Québéc study by Dr. Germain, who I think is here, and which again adds some credibility to the idea that this type of distribution of travel exposure among blood donors is fairly consistent across North America.

CHAIRMAN BROWN: Yes?

DR. BURKE: I want to return to the question of the qualitative difference between the travelers and the non-travelers. Your conclusion was that there would not be any change in the risk of the donor pool, that the donors who had been in the U.K. versus those that had not had no change in their other risks, their other deferrable risks.

But it seems that you would have to replace the repeat donors with a number of first-time donors so that there would not be a negligible impact on the donating pool but that there would be at least

a temporary burst of a window there where you had to have more first-time donors who would have higher potential risk.

So my conclusion would be that it isn't a total wash, not a total even risk, but there would be at least a window of a period. Is that a reasonable conclusion?

DR. WILLIAMS: Yes. I think I was careful to say, yes, on a theoretical basis, there is a doubling of risk and if you use that particular cutoff, that two percent would have to be replaced by first-time donors.

I think the message I would like to make is that if you did the analysis, the difference would not be statistically significant, but on a theoretical basis, yes, you're bringing more risk in by bringing in more first-time donors. But it's not measurable given the current resources.

CHAIRMAN BROWN: Dr. Epstein?

DR. EPSTEIN: Alan, can you speculate at all how these data might be extrapolated to source plasma donation? It's a big missing piece. If there is any thought later in the day that we should consider policies differently for whole blood and transfusable components versus plasma and, therefore,

plasma derivatives, the impact on the source material, the availability of plasma for fractionation would need also to be understood. I know it was simply a limitation of what could be done quickly that you went to the whole blood centers, but we still would be faced with a question about source plasma.

DR. WILLIAMS: I think to the extent that the source plasma collectors can supply demographics of their donor population, we could probably do some rough calculations.

Just without having seen any data, my guess is that they tend to be a younger population, probably less financial resources to do international travel and on that basis may well be impacted less, but I think we're going to get a more accurate answer here.

CHAIRMAN BROWN: Just a second. Susan, did you have anything to add about source plasma in terms of demographics? Maybe not.

DR. LEITMAN: No. I was referring to repeat volunteer, non-paid donors. As you know, source plasma donors are paid. It's a completely different group of individuals and risks. And deferrable risk in those donors is markedly higher in paid plasma donors.

CHAIRMAN BROWN: Yes, Jim?

MR. REILLY: Hello. Jim Reilly, American Blood Resources. I'm not sure that I'll clarify any more than you have, Alan, but it's worth commenting at least.

We did make an attempt to collect some data rather quickly. Unfortunately, we didn't have a well-organized structure to do it in, such as Alan. So we didn't really end up with anything that we thought was particularly meaningful.

There are some differences in the population. There are some similarities. The deferral risks are not as different as you might think, but there are differences in the demographics. They tend to be a younger population. The socioeconomic status is admittedly different.

So we have some different travel patterns. And I think on the surface, we would suggest that the percentage that are traveling outside the United States is probably lower. But, similar to platelet pheresis, the frequency with which they donate is substantially higher.

So I think the overall impact of the supply is probably not meaningfully different, clearly would be, but I'm not sure that's really the big area.

I think if we were concerned about anything, it's the developing of a series of additional criteria would invoke all kinds of extra logistical problems with regard to look-back criteria, which probably have just as big a supply impact, if not maybe larger than the actual deferral criteria or the first question that you asked.

The other question that we would begin to raise is: Looking at the total list of questions, are we slowly but surely eroding the quality or the efficacy or the entire screening process? And what is the ultimate risk impact here?

The other difference in plasmapheresis is that the ultimate end product goes through a further manufacturing process, which has additional viral clearance steps. So there are questions about whether the ultimate product risk is the same or different.

I don't think that probably addresses the question that you had, but there are some criteria or questions that we have with regard to how this would be best implemented and what the ultimate value would be.

CHAIRMAN BROWN: Dr. McCullough?

DR. McCULLOUGH: I'd like to go back to the assumption that the donors lost would be replaced

by first-time donors. As I recall, Alan, the survey was done directing the question to people who had donated within the last year.

DR. WILLIAMS: Directed to folks who had donated within the past month.

DR. McCULLOUGH: Month. So it's well-known I think that many -- it seems to me the figure of 50 percent or more runs in my mind -- people who donate the first time do not donate again or there would be a huge cadre of previous donors out there who would not have donated within the past year. They would be the most susceptible to being retrieved and reentered into the donor pool, rather than trying to find brand new first-time donors.

So I think we shouldn't necessarily jump to the conclusion that donors that are eliminated if new criteria are adopted would have to be replaced by people who had never donated previously.

CHAIRMAN BROWN: Are records kept by the blood donor centers about such patients so that they could, in fact, be contacted? Dr. McCullough?

DR. McCULLOUGH: This will vary by different blood centers. Most blood centers would have a list of donors that would date back three to five years approximately. Some might be more. So the

names of those previous donors who haven't donated within the past year would be available.

CHAIRMAN BROWN: Yes. As a practical matter, one has the option I guess of putting an ad in the paper, you know, "You donated blood. Won't you please donate again? We need it" or sending a postcard to the individuals.

Yes?

DR. NELSON: One of your earlier tables showed the heterogeneity in the various blood collection centers visiting to the U.K. in various times. From that, I remember there was about a twofold variation from one to another, saying what you present --

DR. WILLIAMS: That's right, from the low to the high.

DR. NELSON: Can we, then, assume that this being an average curve, an individual blood bank might have -- the curve might be twofold higher if we did a cutoff of one month, six months, or something like that? What's the degree of variation between individual blood banks in that overall curve that you --

DR. WILLIAMS: Well, the range where the mean is 22.6, the overall is 22.6 percent, the range

is 11.2 to 30.5 percent for that total time period. And, if I recall from the December presentation, that tended to cluster more around the urban areas, particularly New York City and San Francisco. So yes, the numbers would be markedly higher in some areas.

CHAIRMAN BROWN: I would like to introduce a qualification to being completely smitten by the notion of person-days, as opposed to time spent, just to point out that person-days depend on the notion that 100 hamburgers, for example, distributed in any way will have the same risk.

That is to say, if one person stays 6 months and eats 100 hamburgers, it is the same overall risk as if the 100 hamburgers were eaten by 100 different people who visited United Kingdom for one day.

That assumes that the risk of a single exposure is the same as the risk to multiple exposures in a single person. And that's an assumption. We do not have any evidence bearing on that question.

So that, for example, if a person is twice exposed within a week, he may be more susceptible to an infection than two different people exposed once during the same time period. So cumulative person-days may not be as attractive a way to analyze

risk as it may be appearing.

Larry?

DR. SCHONBERGER: I was wondering if there was any laboratory evidence to support what you just said. I noticed in the human growth hormone situation, there is actually epi data that would support the cumulative.

I mean, the one risk factor was lengths of treatment. But people often interpret that as meaning that with the longer period of treatment, you're more likely to get the one hit that you need.

Is there any laboratory data pertinent to this issue that you're aware of?

CHAIRMAN BROWN: I think the recent PNS paper with lemurs if I'm -- this is embarrassing because I'm an author.

(Laughter.)

CHAIRMAN BROWN: That would be one little point. One lemur was sacrificed. And I think, but I'm not absolutely sure, that the lemur that was sacrificed and was positive had two doses. Stan may have some additional information.

I'm not aware of any systematic study, although it has been talked about for some time, of analyzing this particular question of cumulative risk;

rather, in the nature of radioactivity. People talk about it. It is expensive to do.

Do you have any information, Stan?

DR. PRUSINER: No. I just want to point out that I don't know of any data where you would take, for instance -- if we add more than one infectious unit, of course, the incubation time goes down. But that doesn't really help answer your question.

The question is: If we took a fraction of an infectious unit, gave that to an animal, and then later gave another fraction of an infectious unit, would we ultimately get one infectious unit? And would the animal get sick? I don't know of a study like that.

CHAIRMAN BROWN: I don't think so. I agree. I don't know. And, of course, that is a very relevant consideration since an infectious unit defined by intracerebral inoculation is well-known to be less. You need more than one intracerebral infectious unit when it is given by a peripheral route, which includes the oral.

So it really boils down to: Do these things hang around and somehow get together? You know, a fifth of an infectious unit once a day for

five days is like medication. At the end of the five days, if you've got one infectious unit, that's enough to do it. There just is no information that I know of.

Stan?

DR. PRUSINER: The one thing we do know, which is unpublished, is that there is clearly clearance from the brain. So it complicates all of these kinds of measurements. And we have no understanding of this from a peripheral route.

That's not helpful. I'm sorry.

(Laughter.)

CHAIRMAN BROWN: We'll, then, go on.

Yes?

DR. CLIVER: This is a continuing concern of mine that we haven't really looked very much at the ingestion route. But, having said that, there is a lore of foodborne disease that differentiates between infectious agents and intoxicants, which is highly dependent on Avogadro's number.

With infectious agents, if all of the infectious material required to produce an infection is present in one ingested unit, then if only one in a million of those succeeds in inducing infection, still you can either feed a million units and get an

infection in one person at high probably or probably you can feed one of these units to each of a million people. And probably one out of the million will eventually get infected.

With intoxicants where you require high redundancies of whatever your disease agent is, the dynamics are very different. And there cumulative exposure becomes much more significant.

CHAIRMAN BROWN: Did you want to add anything, Bob?

DR. ROHWER: That was the point I just wanted to make. And, from my point of view anyway, I don't see how virus or an infectious pathogen can take into account the fact that there are other infectious pathogens in its neighborhood.

They don't gang up like that. I mean, my guess is that's the exact same question as the pooling question, which we have debated endlessly. And I don't think it ever will be resolved without an experiment, and the experiment is an expensive one.

CHAIRMAN BROWN: "Endlessly" is a little too strong a term.

Other questions for Dr. Williams? We are sort of moving into the other term of the equation now and shifting off what Dr. Williams' major subject was.

That is my fault.

If there are any further questions about the impact on blood supply? Yes, Dr. Sayers?

DR. SAYERS: Alan, from what you have calculated about number of donors that have visited Britain, the number of whole blood volunteers there are nationally, the number of transfusion recipients there are annually, I wonder if you could pitch this the other way around and have a graph which would show the likelihood that a transfusion recipient received blood from somebody who had traveled to one of these areas, taking into account the number of transfusions that individual had received.

DR. WILLIAMS: That would be interesting to do. I'm not sure I can do it in my head because there are numerous factors involved that -- to answer your question, no, we haven't done that, but it's probably something we could do.

CHAIRMAN BROWN: Other questions for Dr. Williams?

(No response.)

CHAIRMAN BROWN: It is a little ahead of schedule. It is ten past 10:00. I think we can have the break now and return to our schedule in 15 minutes, please.

(Whereupon, the foregoing matter went off the record at 10:11 a.m. and went back on the record at 10:32 a.m.)

CHAIRMAN BROWN: We now have three further communications before lunch. The first two are by invited guests from the United Kingdom. On the schedule, we have a talk about demographics of bovine spongiform encephalopathy, U.K. regulatory decisions, and the time course of new variant CJD.

I rather like the name Christl. You'd rather be called Christl, would you?

DR. DONNELLY: Yes.

(Laughter.)

CHAIRMAN BROWN: Okay. Dr. Christl Donnelly?

DR. DONNELLY: Can I have the first slide, please? I guess we can think of this whole area and my whole talk as being a discussion of risk, both relative and absolute. And both of those two ways of looking at risk need to be kept in mind throughout this presentation.

I will be also going from an area of relative predictability, relative certainty to an area of relative uncertainty and unpredictability when I shift in the talk from BSE to variant CJD.

You have the even more difficult task of then adding on an additional level of uncertainty. If we knew the prevalence of variant CJD infection in people who lived in Britain for the whole time, what about people who lived there only a brief time or visited? What would their risk be via blood?

I realize all of these things are difficult to put together, but I will try to keep in mind throughout this presentation showing what we know with relative certainty and where we have to do sensitivity analysis to look at the range of what we do and do not know.

Looking at the BSE epidemic through Great Britain, -- and this shows the BSE epidemic of cases, which peaked in 1992 -- you see over 174,000 cases of confirmed BSE in Great Britain.

Keep in mind that it was only in 1988 when the disease BSE became notifiable in Great Britain. So we know through a number of sources that there was under-reporting prior to that.

It was first diagnosed in 1986, but the BSE inquiry, which is ongoing in Great Britain, has identified certain cases that were seen and diagnosed to be spongiform encephalopathy in 1985. So there were even earlier cases definitely documented.

You can see that the epidemic, which had peaked in 1992, has declined considerably since then and is declining to very low levels.

You can see here to some extent the geographic distribution of BSE. This is shown in number of cases per 1,000 cattle. So it just shows the geographic distribution of BSE throughout Great Britain, both that it was geographically disbursed, but you can also see correlation that those counties that had relatively high incidence in, say, 1993 also were the same as the ones that had relatively high incidence in 1991. It's interesting that the disease showed geographical dispersion almost immediately once it was recognized.

I don't think there is a whole lot that can be gained by speculation on where it started because we have the problem of where it was diagnosed versus where it was started. So there would be a period of time when vets were getting to know and recognize the disease that probably determines its earlier pattern, rather than its actual spread of the infectious agent.

In looking at the demographics of BSE, how many cattle were infected, when they were infected, when they were slaughtered. We use a technique called

back calculation. This was first developed to use for HIV and AIDS and is a technique that statisticians use in diseases of long incubation period.

Now, long incubation period is bad in some respects in that the key regulation brought in that turned the BSE epidemic from increasing to decreasing was the ruminant feed ban, which was brought in 1988. That made it illegal for the feeding of ruminant protein to other ruminants.

Now, there is considerable evidence, both through surveys as well as through our own work, that this was not immediately completely effective. But it did turn the tide of the epidemic.

Unfortunately, that long incubation period meant that although the tide of incidence of infections turned in 1988, it wasn't until 1992 that we saw the turn in the tide of BSE cases. And that was a function of this long incubation period.

The long incubation period and varied incubation period means that we can look at cases that we see now and get information about past and even relatively recent incidence of infections. And that helps us do projections of future cases.

So the basic approach is if all animals were infected relatively young, then if we see only,

say, 20 percent of animals survive to age 5, for each case that we see at age 5, that we can think of representing 5 infections. So we can work from the cases that we have seen and the time period that we have seen them over and work backward over to the infections that that represents.

Now, we need information to do that, both on the actual demographics in terms of the number of animals born each year and their proclivity of survival. We also need information or a form for the incubation period distribution. That is the time from when an animal is infected to when it experiences the clinical onset of disease and another distribution that ties together exposure and susceptibility with age. So this represents the sort of age-specific susceptibility exposure to infection.

Now, we could get information about the incubation period through experiments in cattle. And there have been experiments where cattle were experimentally dosed through the oral route and then watched over a period of time to get information about, among other things, the incubation period. That takes an extremely long period of time, a large sample size, to get an idea of what such a varied and long incubation period disease would require.

But also there is reason to think that the incubation period depends on dose. So how would you know the dose that the population of cattle in Great Britain were receiving? So we are going for an empirical estimate of the incubation period borne out to fit the BSE epidemic.

Now, this looks complicated, but it's not, actually. We have got the incubation period coming in. First let me tell you what the formula is actually representing.

For animals born at a certain time, we cross-tabulated all the animals that had BSE in Great Britain that we analyzed by the year in which they were born and the age at which they experienced BSE.

So you imagine this cross-tabulation table. And we know from the agricultural annual census the number of cattle that were born in each year. So we know our denominator. We just need to figure out, then, what the processes were that generated the cases that we saw.

So on the furthest right-hand side, we see an animal that was maternally infected. So there is greater complexity in figuring out what the time-dependent rate of maternal transmission is.

We know through various studies that there

was a rate of approximately ten percent maternal transmission in the last six months of the maternal incubation period. But obviously, then, through time, that depends on how many cows are in that incubation stage.

Those animals that were maternally infected then experienced an incubation period of duration U at the onset of age U. Those that were feed-infected, which is the term, then, further to the left, which we have here, is a combination of the feed risk. And that's of absolute time.

So if this animal was infected at age A, it experienced the feed risk at that time of K at T naught plus A. It had age-related exposure G of A. And that means if it was infected at age A, it had an incubation period of U minus A. That, of course, only applies to those animals that were not maternally transmitted.

So in the square brackets, we have the term for animals being infected and onsetting at age U. We then have to add in the probability that an animal actually survived to age U given when it was born. And we have a survival curve where the majority of animals are slaughtered by three years.

So when we have a long incubation period

disease, that means the majority of animals infected actually were not seen to be clinical cases of disease. So they were slaughtered for human consumption.

We then add an additional term of the probability that a case gets reported because, as I noted, the disease BSE was only made notifiable in 1988. So prior to that time, we have under-reporting, which is important to include.

Through fitting such a model, we were able to get a very good fit to the data. You can see here the data for various cohorts. These are the animals that were born in 1987. And you can see that when we look at the number of cases by age, -- this is age naught to eight years -- you see a very good fit of the model to the data.

We have done considerable sensitivity analysis. I think you have a big pack of publications. What we find in fitting these data is you have to get a very precise fit to the data. That requires very precise estimates of the incubation period. You can't fit the data with an incubation period that differs very much from this in form. It doesn't provide the good fit to the data that we need.

Similarly, the age of infection

distribution representing exposure susceptibility has to have this relatively odd peak form. This peaks between sort of 6 to 18 months of age and suggests this is a key point in the animal's life when it's most susceptible to infection.

Now, the investigation we have done into feeding practices suggests that this is not just a function of when cattle are fed ruminant protein or protein-supplemented feed because it seems that animals typically receive protein supplements from the first few days of life and then receive considerably more protein supplement after the first lactation.

So to have the key time be between 6 and 18 months suggests that it is something biological in their susceptibility. Now, this is key, having an early infection is key, in interpreting what number of infections generated the cases that we have actually observed.

This is our estimated feed risk profile, which is the function I called K in the earlier formula. What it shows, this is plotted in the highest resolution that we ever fit. You actually don't need this much resolution to get a good fit to the data.

The key aspects of this are up through

1988, the approximately exponential rise in infection incidence. Now, you see lots of spikes as well. We believe this reflects the seasonality in the use of protein supplements, that you need more protein supplements in the winter than in the summer, and that's reflected here.

You see the key in this feed risk profile -- and this is feed to cattle -- peaked in 1988. That was when regulations were brought in that turned the tide of this infection incidence profile. And the infection incidence then dropped considerably in 1989 as a result of the regulations that were brought in.

Now, it's important to note that we did not tell the model in any way that regulations were brought in 1988 or what the effect might have been. We used the data to tell us what the feed risk was.

So, although you might look at this and think "Oh, well, they didn't work absolutely" and that is certainly true, there was a belief at the time very optimistically that this would just absolutely stop feed-borne infections. And it obviously didn't.

But 1989 would not have just been the same as 1988. On the basis of these trends, we would have expected it to be considerably higher, going up in an exponential manner.

And since we estimate in the 1988 cohort of cattle approximately ten percent of animals born in the 1988 cohort were infected with the agent of BSE, although 174,000 cases is considerably a bad epidemic, it could have been much, much worse.

So, although obviously the earlier they brought in regulations, the better, had it been a year later, it would have been a considerably worse situation.

So you can see here that then we have blips of infection later. It's really difficult under the most recent years to get good estimates. You have the least information when looking at current cases about the most recent estimates. But the key thing to consider there is that in 1996, in light of the announcement in March of 1996 about variant CJD cases, further regulations were brought in that restricted the feeding of any mammal protein to mammals.

So one of the suggestions for the reason for this leakage of the ruminant-to-ruminant feed ban was that there may have been the use of, say, pig feed, which could contain cattle or sheep protein, feeding that to cattle because it was on the farm, the farmer needed it, looked like pretty much the same thing.

Another possible route would have been the contamination of equipment if equipment in a feed mill was used for making pig feed and then it was used for making cattle feed.

I think the key thing is that it was extremely effective. We have analyzed this data in another way as well, which was -- I don't have time to go into the details, but it was looking at what is called the basic reproduction number. That is the average number of new cases per initial case.

So if each case or each infection generated on average one or more infections, then the epidemic will be stable or grow. If on average one infection generates less than one secondary infection, the epidemic will die out.

Under all of the scenarios we considered, you see the epidemic dropping to basic reproduction numbers well under one. So all of the suggestions we have are that the epidemic is dying out.

Here you can see in the context of the cases that were observed, so in purple is the annual case incidence, the epidemic of infections. That is shown here in red. The green represents at each year end how many infected animals were alive.

The key thing is to look at the difference

in both time shifting from earlier to later and in magnitude that the magnitude of the epidemic of infections is considerably greater than the epidemic of cases.

So we estimated that some 900,000 cattle were infected through 1996. This manifested in over 174,000 cases, as I pointed out. And the difference between those, then, is largely animals that were slaughtered for human consumption. They were slaughtered over a range of incubation stages, which I will address in a moment, but that gives you an idea of the magnitude of the epidemic and the potential risk.

That was Great Britain, constituting Wales, England, and Scotland. Here is a separate analysis for Northern Ireland, which experienced an order of magnitude lower infection incidence. So in Northern Ireland, we estimated some 11,000 animals infected and of those, over 9,000 slaughtered for consumption.

So, again, you see the characteristic shift between estimate of the infection incidence compared to the case incidence. It was earlier and of greater magnitude.

Now, as you may know, the export ban on

Northern Irish beef was lifted before that of Great Britain due to both the lower magnitude of infections and also of greater tracing of animals, which was historically due to greater TB incidence.

So it was interesting to consider the time period over which you are looking for travel. This gives an indication of the estimated total number of infected animals slaughtered per year. So this might be a basis where you start to think of translating the risk from cattle into risk to humans.

Classified here is animals slaughtered over and under 30 months. As you can see, the majority of animals slaughtered for consumption are under 30 months, but as the epidemic progresses and new infections are at a much decreased level, the majority of those animals being slaughtered for consumption are actually over 30 months. This is key because of the regulations brought in 1996, which restricted human consumption to animals slaughtered at under 30 months.

So while they didn't eliminate infected animals, that wasn't their basis, what they did was to distinguish between animals at higher and lower risk. Animals under 30 months were at lower risk because of the infection incidence profile going down

considerably. And also for those animals that were under 30 months and were infected, they would be at an earlier incubation stage, which may lead to less or lower infectiousness.

Now, also, the other reason I showed this was to show the magnitude. If you imagine that all animals slaughtered for consumption that were infected were equally infectious, that would lead to peak at about 1989-1990 for potential infections.

If the key, though, is animals slaughtered in the last year of their incubation period, those animals that hadn't yet reached clinical stage but were near it, then we see the peak of infectiousness. Again, if those animals in the last year of incubation were all equally infectious, it would peak at about 1992.

So it is very difficult to think about: one, dividing up the risk into the '80s and the '90s; but also thinking about if you're thinking in terms of person time that necessarily one year at a certain time equals one year at another because there are temporal changes.

I also show this because you can see the detail of the estimated number of infected animals slaughtered for consumption under 30 months at

extremely low levels.

So if it is these animals that provide the majority of the risk, we're talking a handful of animals. This is particularly important in Great Britain because, in addition to the restriction of animals over and over 30 months, there were regulations brought in 1989 that specified both bovine offal ban, which restricted those tissues believed to be potentially the most infectious, as well as an additional regulation brought in more recently, highly controversial in some areas, beef on the bone. And beef on the bone was banned to restrict exposure to dorsal root ganglia, which is found to infect mice.

Of course, then, in Britain we only worry about animals under 30 months because those are the only ones being consumed. And it was found that dorsal root ganglia was infectious to mice in the last year of incubation period. That is why people were particularly interested in this being just a handful of animals. That ban is still in place but highly under discussion.

This gives you an indication of the confidence intervals for -- these are animals slaughtered under 30 months of age over the recent time period and next year. Both gives you an

indication of those animals in all incubation stages.

So we're talking on the order of between 150 and 50 over this time period as well as just, in green, the handful of animals that are slaughtered within 12 months of onset if you're just considering that last period to be potentially infectious.

Now, that is all looking at what is here, which is a BSE epidemic, where we have considerable data, we have done sensitivity analyses. Everything that fits the data has very similar results to what I have shown you here: a peak in susceptibility; a long, approximately five-year on average, incubation period; and number of infected animals slaughtered each year dropping considerably. But to consider variant CJD cases, you have many steps between the BSE epidemic, over which we know a considerable amount, and how we translate that into variant CJD cases.

For this particular meeting, I should have drawn another arrow from variant CJD cases to blood donors, which would be those people who are preclinical but giving blood.

Now, a number of issues come in here highlighting the specified bovine offal ban, which may have considerably reduced potentially infectious material in meat; heterogeneity in consumption rates,

which may play a role in your deferral decisions, looking at those who ate more or less meat; potential for infection; dose response susceptibility heterogeneity. I bring that up because there was a mention of risk factors, potentially genetic. And you probably know that all of the variant CJD cases that have been identified to date have been methionine, methionine homozygotes. They have that in common with approximately 40 percent of the British population.

It may not mean that it is just those 40 percent who are potentially infected. It may mean that we have genetic effects in the incubation period. So it may be that we have shorter incubation periods for some genetic groups and longer for others.

Now, I won't go through these formulas because they are even more complicated. The key assumption we made here -- and I am happy to go through this with people at some point later if they want to -- is that we assume a linear dose response.

Because what I am going to tell you and conclude is that we still have a lot of predictability, it can still be an extremely large or extremely small epidemic. The fact that we made a linear dose response assumption has not led to any undefendable restrictions in what could happen.

Our goal here was to find the widest range of potential epidemic scenarios that were consistent with the data. And you see here coded by color in the number of cases between now and 2040 the smallest epidemics, shown in white here, correspond to short incubation periods with a range of standard deviations. So each one of these points represents an epidemic scenario that was consistent with the data that was observed.

This is the annual incidence of cases, 3 in 1995, 10, 10, and 16 in last year. A better way to distinguish these epidemic scenarios is in terms of a parameter we call R. That is the mean number of humans infected by one maximally infectious bovine.

Now, quite logically, if that number is very small, then we will have much more smaller epidemics. And that corresponds to small incubation periods.

As R increases in magnitude, we get larger epidemics. And this may be useful only in that we may be able to get some idea from the meat industry on what the largest potential R could be. How widely is the meat from one infected animal spread between consumers? Is it through a relatively small number or could it be as high as 100 or 1,000?

What we have been able to show through these analyses was that there remains uncertainty. We took forward this analysis because there were people saying they could tell exactly what was going to happen. It was going to be a large number of cases.

One person was quoting in 1996 two million by 2000. He doesn't say that any more. There are also people who say they have looked at the data and they can show that it is absolutely going to be small, there will be no more than one or two hundred cases.

So I think we have to keep in mind that although it is nice to know the answer, we have to admit when we don't. And so far we can't restrict what potential epidemic scenarios could take place.

Over the next one or two years, if the number of cases stays on the order that they are now, predictability will increase considerably and we can put a useful upper bound on the epidemic. Now I would say we are at the point where we cannot.

So thank you.

(Applause.)

CHAIRMAN BROWN: Well, thank you very much for a colorful and I would have to say courageous presentation in view of the mathematical formulas. I think the point is well-taken, and it was missed by a

lot of people when various modeling studies began to be published.

The major point in some of these studies was the point that you just heard. There is almost total uncertainty about the extent of what is going to happen in terms of the numbers of new cases of new variant and the numbers of people who may currently be incubating the disease.

The uncertainty is so great that it almost seems pointless to dot i's and cross t's with respect to how are we going to estimate any possibility of risk to the U.S. blood donor and recipient population. This is the huge, major, complete unknown, and it is not going to get more known before the day is out.

We now have a presentation by Dr. Philip Comer, who will give us the Det Norsk Veritas risk assessment. Dr. Comer?

MR. COMER: Thank you very much, Chairman, and thank you for the opportunity to come and talk about the study that we were asked to do by the Department of Health in the United Kingdom as a result of a recommendation from the United Kingdom's Spongiform Encephalopathy Advisory Committee.

What we were asked to do I think probably was also fairly courageous in the light of Christl

Donnelly's talk, which I entirely agree with her conclusions there.

We were asked to assess the magnitude of the risk that could result from the infective agent being present in blood. That's a pretty tall order, really, when we know very little about quite a lot of the factors that could affect that risk, particularly how many people may be incubating the disease.

Nevertheless, being good consultants, we said: Yes, we'll have a go at this and see what useful information can come out from that because we're not just looking at what the actual numbers might be but what actually are the lessons we can learn, what can we actually learn about the processes, particularly what can we learn about which components of blood and blood components are particularly risk factors. Are there particular groups of patients which may be more or less at risk? And can we say anything about the possible effectiveness of the different risk control measures which could be put in place?

Just to look at the time line of the study that we did, the study was initiated following recommendations from the SEAC Committee back at the end of 1997. There was an expert group meeting of a

fairly wide range of people in the United Kingdom fairly shortly thereafter.

Our study actually started early in 1998. We did a first draft report in April which then went to review by an expert, group of experts, in the external world, including both members of the United Kingdom SEAC Committee, some of the people around the table here today as well.

Then the final report was produced towards the end of 1998 after a fairly long gap, really, waiting for comments on the revised report. And the final report was then produced early this year.

It is useful to sort of look at that together with the times at which particular decisions were taken in the United Kingdom. In February '98 was when the Committee of Safety in Medicines made initial advice about imported plasma and then the decision, final decision, to implement leukodepletion of fresh blood supply was taken in July 1998, so very much in the process of the time we were working.

SEAC back here in 1997 had advised that the government should consider the use of leukodepletion. And there was a lot of work that was done immediately thereafter.

I think it is also worth just thinking a

little bit about some of the reasons for those decisions. Now, I wasn't part of that process, and there may well be others who were more closely involved. But if one actually looks at the press release which the Department of Health issued after that, this is Frank Dobson speaking in the press release, saying that he fully accepts the advice of the Committee of Safety in Medicines. He has decided that the bioproducts laboratory, which is our blood fractionation, plasma fractionation service, will be allowed to import plasma.

And then he says this will reduce the possibility of repeated recalls of blood products in the future and thereby help to maintain public confidence in these products.

So his initial reason was nothing about blood safety. It was about public recall of blood products. And that is reflected very much in the statement from the Committee of Safety in Medicines, from their minutes, where the first recommendation is that a plasma pool subsequently is identified as being strongly suspected of having new variant CJD should be withdrawn -- I'm paraphrasing slightly -- and then to avoid future withdrawals of large batches of medicine or products, including vaccines, manufacturers should

avoid the use of U.K. albumin as an excipient to medicinal products, so again concentrating as much, at least, on the risk of recall and the management issues that that arises as well as the health safety implications of variant CJD infectivity in blood.

Just very briefly -- I'm not going to go down these. These were a range of people whom we consulted during the process of the study, including people to do with the blood supply and blood fractionation service for the United Kingdom, people with the Haemophiliac Society in the United Kingdom, uses from haemophiliac centers, so a range of different people, both experts in variant CJD and people involved in the blood business in the United Kingdom.

And then the review panel involved a range of people, both from the United Kingdom SEAC Committee and others, who reviewed our report in detail, came back with comments, which were then taken into account in our final version. So the study has been fairly extensively reviewed and commented.

When we started tackling this, the basic presumption that we had was that variant CJD infections are caused in some way through exposure to the BSE infectivity through the food chain and that

will result in a number of cases.

What we needed to do was to then look at what that meant in terms of potential further variant CJD infections through the blood donation route, either through blood components or through plasma pools and plasma derivatives. How many patients were going to be exposed? And what is the potential for an effective unit coming in here, resulting in a new infection of variant CJD?

This is rather similar in a more diagrammatic form of the process which Christl put up, of the way in which you could actually try and model the estimate of infections there from the food supply.

In fact, when we started off, we presumed that in order to get certainly any absolute measure of the risk from the blood supply, we had to try and come up with some estimate of the size or the number of people who would actually be incubating variant CJD.

That was probably the big difference between the early draft of our report and the subsequent draft, when we looked at that issue in more detail and we realized that to try and come up with anything like a best estimate, even with significant ranges, was really not possible, that particularly we know little about the cattle-human species barrier.

We know quite a lot about these things pu here, as Christl said. We know the numbers of infected. We know the life expectancy of cattle.

So we know the numbers of advanced infections for the region, but, then, what does that mean in terms of the actual consumption of products and the number of cases which might develop?

So the two big unknowns in there are probably the species barrier between cattle and people and the incubation period for variant CJD when you're crossing a species barrier, in particular.

This slide I won't dwell on. It's, in fact, drawn from the Oxford group's data, again seeing that the peak of infectivity coming in is in 1989. And the bars on here are different ages before infection. Again, I think we're seeing that data already.

When we realized we couldn't come up with any prediction of the number of cases, we decided that the way we would present the risk would be risk of new infection per infected donor. What we tried to do in this slide is just to look at to get some indication of what the potential range might be, which, as we know already, is very large.

What we are seeing here is the fraction of

blood donations infected with variant CJD against time and plotted against the mean of the incubation period.

So we've got increasing incubation period up here. And if you see, at low incubation periods, we really have a very small fraction of donations infected: less than one in a million.

As we go out to larger incubation periods, say, if you look at 30, then we're getting up to a maximum of about one in 1,000. They can increase, and obviously they can increase beyond this, too, if one looks at other longer incubation periods. And that's just against one of the potential variable parameters that we have got.

I am just going to go very quickly over the evidence for infectivity in blood. I think probably that will have already been looked at significantly by this Committee, but it was very much part of the background for what we were doing in the study that we did.

If we look at blood transfusions, we know that all attempts to transmit infectivity of blood, blood transfusion, so across a species barrier, have failed and that within animal models, as far as I am aware, the one case which has been reported by Bob Rohwer is still the only case that I have heard of in

which there has been a positive transmission by the i/v route within an animal model.

Epidemiology studies have shown that's from sporadic CJD. There is no evidence that there has been any transmission through the blood route. And when we look at blood from human CJD cases, primarily sporadic CJD cases and certainly no variant CJD cases, and look at that, their infectivity through the i/c route into animal models, there have been a few experiments which have shown positive infectivity into rodents but negative results from a significant number of studies into primates and other species.

And there have been some questions asked about -- these cases, these experiments all involve very small numbers of animals and some sort of significant questions asked about those and, in particular, the fact that it is a bit odd that we have got no positive infections in the primates, which you might have expected would be more susceptible than the rodents.

Then when we look at actually within animal models themselves, there have been quite a number of cases, experiments where positive infections have been reported from animals infected with some form of TSE and have been through the i/c route

infected in the same species, so again with no species barrier.

So all that we can conclude from that is that the blood from an animal which has been artificially infected with the TSE could contain infectivity. And to some extent, that model may be the one that is most applicable to the situation of people being exposed to a TSE through food exposure.

Again, very briefly, a number of experiments that have been carried out trying to assess what the level of infectivity in whole blood is, ranging here from the low end of about five from some of Diringer's work to over 300 from Casaccia -- again, these are all i/c infective units per milliliter of blood -- and a value of about 10 from the work from Paul Brown and Bob Rohwer.

In deciding what we wanted to use as a base case for the work that we were doing, we decided that it was better to err at the low end. After all, these are all animal models which have been developed to enhance infectivity, enhance the likelihood of infectivity. So when we are looking at the human situation, we would be more likely to be at the low end.

We also have to take into account, as we

have already mentioned, that the i/v route, the peripheral route, is going to be less effective than the i/c route. We took a factor of ten for that, again one of the areas where you have got significant uncertainty.

So we took a value of ten i/c infective units per ml as a base case but with a range of values. And we looked at the uncertainty in that and with a factor of ten of the i/v route being less effective than i/c.

We then needed to know what was the level of infectivity in different blood components and in different plasma fractions. The only experiment which has been done which casts any light on that are the experiments which have been done by Paul Brown and Bob Rohwer. Again, I imagine you have already seen a lot of this data.

Two experiments: the spiking experiment, where you have got a high input of spiked hamster adapted scrapie, into human blood, which was then separated and fractionated and all the products of that titrated. I just want to note there, as I know the authors have done, that only a fraction of the infectivity was actually recovered in the final process and that the endogenous experiment, where

blood was collected from mice infected with a mouse adapted TSE, again separated and fractionated as before, and then inoculated back into experimental animals.

In the endogenous experiment, there was no transmission for some of the fractions, including whole blood and red cells, but the number of animals inoculated was fairly small. In fact, the expected number of infections for whole blood, for example, would have been less than one.

So what we did was to take the estimate of infectivity in whole blood. I'm now going to talk about intravenous infective units per milliliter. So we've got one i/v, i/v 50 per milliliter blood, so about 450 per conventional units of blood.

We have taken the relative infectivity in plasma and Buffy coat from the Brown and Rohwer experiment, from the endogenous experiment. And we have assumed that no infectivity is lost, so a significant assumption there.

If we do that, we can then get a breakdown of infectivity in the 3 components with about 50 percent of that infectivity being in the plasma, initially a surprising result possibly with the remaining infectivity being about equally divided

between red cells and Buffy coat.

Then looking at plasma derivatives, again taking that result for plasma, taking the result from the endogenous experiment, where we could use it for Fractions 1, 2, and 3 together, and cryoprecipitate, and then using the relative infectivity from the spiking experiment for Fractions 4 and 5, we can then get infectivity in the main plasma fractions.

We then wanted to go one step further and look at the infectivity in plasma derivatives, the actual products which were being given to patients.

I have been talking to a number of experts. We felt that there were two alternative ways of calculating that. One was to assume that the infectivity would partition in proportion to the protein content of the product. And the other was to use some kind of estimate of clearance factors from the various processing stages in a blood processing situation.

This slide shows the results of doing that, with the blue bars showing the protein mass content basis and the purple ones showing the estimate based on clearance factors. So this is infectivity assuming that plasma derivative was made 100 percent from infected units. So to get the actual level of

infectivity, you then have to multiply that by the proportion of units which were actually infected.

The red line here is unity. So if you're to the right-hand side of that, if you had 100 percent infected blood, then you would have one infected unit per average dose of each of these products. And if you're to the left of it, even with 100 percent of infected blood, you've got less than one infected unit per dose of product.

You can also see that there was wide variation between the two approaches, sometimes about six or seven orders of magnitude here for intravenous IgG, for example, with the protein mass content level giving a reasonably high estimate because you have got high dose about 90 grams, typical dosage for this product for certain patient groups but with a clearance factor basis having a relatively low estimate. So you have got significant variations here.

In the base case results we shall present in a moment, we used the protein mass content basis mainly because they were the more conservative. They gave the higher values. And we used the clearance factor approach as a comparison.

You can see that these two products, in

particular, for one type of factor, 8, this is the less pure version of Factor 8. Eight is not much different between the two.

You have got a potential infectivity greater than one. So if you've got high levels of a high proportion of donations infected, you could theoretically get infectivity through this route. And intravenous IgG is the other significant potential.

Here, particularly with this one, this difference is very significant because when we calculated the infectivity for the protein mass content, we took no effect of any subsequent clearance through the processing.

So we were just basing it on the initial infectivity and the protein mass content. And we assumed that subsequent processing steps would have no effect on the infectivity and the product, which is not very likely, I would guess.

What we then needed to do was to look at the way both the blood components and the products are used to actually get an estimate of the risk to the patients being exposed. The way we did that was to define a set of representative patient groups.

There were just not the data available that could have enabled us to look at the way the

products were actually used overall in the health service in the United Kingdom.

So, together with medical experts, we defined a set of about 20 different patient groups. We looked at the likely numbers of the patients in each group and the typical dosage to the range of different both blood components and plasma derivatives that they may be exposed to over a treatment period. So these are just some of the patient groups that we identified, and there is more data, obviously, in the report, which you have.

So we defined the treatment and the dose for each of these patient groups, both to blood components and to plasma products. And then by assuming a linear dose response model, we can then estimate the number of new variant CJD infections that could result from that.

And, then, the number of variant CJD cases obviously depends on both the incubation period. And, again, here you're not crossing a species barrier from cattle to people. You're within species. So the incubation period is likely to be less than from cattle to man.

You need to look at the remaining life expectancy of these patients and obviously their

probability of surviving the actual episode for which they are being treated.

I'm not going to concentrate on this because I don't think this is the important thing for this. This result shows the numbers of new infections per infected donation for some of the patient groups. So along the bottom here, we have the fraction of donations infected going from unity, on the right-hand side, to one in a million on the left-hand side.

We can see that for many of the patient groups, we're down here at less than ten percent of patients infected for a very wide range of fraction of donations infected.

For some groups, we are at significantly higher level than particularly the patients being given intravenous immunoglobulins, bone marrow failure given red cells and platelets, and acute blood loss being given significant numbers of red cells.

We see this fall off with the fraction of donations infected because with this group, we have a fairly small number of patients. And effectively we have infected all of them by the time we get up to this level. I think all we are saying in this is that there is a range of exposure for different patient groups but highly dependent on the assumptions that we

have made.

Overall we estimate that the number of new infections for the base case results are about 2.6 new infections, about equally split between the patients for blood components and the patients for plasma derivatives.

That translates into case of about 0.8. So we've got about 2.6 infections and about 0.8 cases because obviously not all of the patients infected survive long enough to become a case.

Obviously all of those results are highly dependent on the assumptions that we have made. And you can get some interesting insights into that by actually looking at the sensitivity to some of those assumptions.

So here is our base case for looking at new infections, about 0.8 new infections split between blood transfusion cases, plasma derivatives in red, and the green is increased because of patients, recipients continuing to donate.

If we reduce the infectivity by a factor of ten, we see that we make very little difference to the risk from blood transfusion, but we make quite a significant different to the risk from plasma derivatives.

If we reduce it by another factor of ten, we virtually eliminate the risk from plasma derivatives. But, again, the risk from blood transfusion cases stays about the same.

The reason for that is that in a blood transfusion case, you're transfusing typically a unit or more of blood. That unit contains, of the assumptions that we have more, more than 100 infective units of blood. So, even if you reduce it by a factor of 100, you've still got a significant risk of infection; whereas, the plasma derivative results are spread over a very wide number of people with a relatively lower level of exposure.

Conversely, if you increase the infectivity by a factor of ten, you then increase the risk from plasma derivatives very significantly, but, again, you don't do very much to the risk from blood transfusion.

If you look at the incubation period, the base case incubation period for blood supply we assumed was 15 years, so a 15-year incubation period for infection through blood supply. If you reduce that to five, you make a modest increase in the number of cases basically because more patients survive because you've still got the same number of infections

but more with a shorter incubation period, a higher proportion of them survive. And, conversely, with a longer incubation period, few of them survive.

So the basic conclusion, the first conclusion, which I think is perhaps important, is that it really is not possible to come up with any reliable estimate of what the real risk of variant CJD infectivity in blood is.

We don't know how many people may be infected, and fundamentally we don't know whether blood from someone with variant CJD could be infective. And we have no evidence to confirm that blood from a person with CJD would be infected. However, evidence with the animal model suggests that there is a potential risk, although we have not demonstrated that that is true yet.

Then looking at the results for the actual study, if there is infectivity in blood at the sort of levels that we have assumed based on the Brown and Rohwer work, then the infectivity that is present in a full unit of red cells would be sufficient to cause infection. That conclusion seems to be valid over really quite a wide range of different assumptions.

Plasma derivatives, the result is slightly different. If we look at the base case and our very

conservative assumption that assuming infectivity is based on protein content and taking no account of clearance factors, then there are a few plasma derivatives which could theoretically cause infection. But that conclusion is highly uncertain and varies very significantly over the assumptions that are made, and many of the assumptions tend to reduce the risk, rather than increase it.

So the overall message from that is that looking at risk from blood, it looks as if there's a high risk from the red cell units from the whole blood transfusions than there is from the plasma derivatives. That conclusion seemed to be fairly generally supported by the blood industry people in the United Kingdom.

In the U.K., we have looked at a number of risk reduction measures, including the initial recommendation from SEAC to look at leukodepletion of red cells on the basis that infectivity is perhaps more likely to be associated with white cells, -- that's perhaps a bit uncertain -- eliminate U.K. source plasma, and then a range of other possible measures, including reducing the use of blood obviously would help. Preventing transfusion recipients from giving blood, breaking the recycle

loop could be important and possible prophylactic treatment, although there's really no real data on that at the moment.

Just looking at the results of those, again, emphasizing very much looking from our base case, if we look at leukodepletion on that and assuming that the effectiveness of leukodepletion would be to reduce the infectivity by a factor of 100, then we actually see a modest reduction but, actually, a rather small reduction. That may be if leukodepletion is more effective than that or if the level of infectivity in the red cell unit in the first place was significantly less, then the effectiveness of leukodepletion would be significantly greater.

So if we looked at the range of possibilities, leukodepletion could be effective over quite a wide range of different possibilities, but it's not necessarily that effective.

Eliminating U.K. source plasma is obviously a pretty good measure assuming that the source of variant CJD is restricted to the United Kingdom and not from possible source countries, including the U.S. or primarily the U.S., obviously.

So that is very effective in reducing the risk from plasma products, but, as I said, the

likelihood is that this risk, the risk from plasma products, is overstated in the study. And it does very little, nothing, in fact, to the risk from blood components.

Reducing the use of blood obviously has an effect in proportion to the amount that you could reduce the usage of blood. There have been some interesting studies in the U.K. where you look at variations between different hospitals in their use of blood for the same operation, and there is huge variation, so obviously a scope there but a sensitive area, I suspect.

Restricting blood recipients from being donators obviously breaks the recycle loop but, again, has some potential implications on the blood supply.

So leukodepletion could have a significant benefit, but the potential effects are uncertain. Eliminating plasma, eliminating U.K. plasma, will eliminate any risk that there is, but the original level of risk might have been extremely small.

And a range of other measures has some possibilities. I think this one received quite a lot of attention in the U.K. recently looking at prophylactic treatment with Pentosan. There seems to be evidence that this could reduce susceptibility in

animal models, but there is an awful lot of work to be done I think before we could say with any confidence that that could work for variant CJD.

Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Comer.

We have time for a couple of questions. I have a question. I know that a handful of patients who have died with new variant CJD have been identified actually as having donated blood at some point during their incubation period. I know that that ranges from a donation made as early as 1982 to donations that were made just within the past couple of years.

I think -- and this is where I need to be made accurate. I think some, if not all, of those donations were one-to-one blood transfusions or packed cells, but I'm not sure. Can you tell me, for example, if that is true or whether these donations found their way into plasma pools?

MR. COMER: I know for sure they found their way into plasma pools. I do not know the answer to whether they were whole blood donations or not. I think the answer to that is yes, but the policy that

they have taken in the U.K. is not to inform recipients, which is a difficult ethical debate, obviously. So I think there has been little publicity about that.

CHAIRMAN BROWN: Right. I know it is wrapped in considerations of confidentiality and patient privacy, but that will obviously be a crucial group to watch and may give you or us the first clue about the reality of whether blood is infectious from patients with new variant CJD.

Of the handful, I think one only or two of the recipients have been alive for more than five years, something like that. I think most of them are just a year or two.

MR. COMER: I think that is right.

CHAIRMAN BROWN: Yes. Questions? Bob?

DR. SCHONBERGER: Could you repeat the answer to the question that you just said? I wasn't sure. It's mostly plasma pools or mostly one to one?

MR. COMER: No. I know for sure that it's plasma pools. I do not know --

DR. SCHONBERGER: It's plasma pools?

MR. COMER: Yes. That is for sure because there were some recalls. I do not know how many were one-to-one blood recipients.

CHAIRMAN BROWN: Bob?

DR. ROHWER: Yes. I wanted to just comment that if I understand you correctly, you are doing your modeling based on the titers that were associated with the crude Cohn fractions in the paper that Paul and I published.

MR. COMER: Yes.

DR. ROHWER: In that regard, virtually none of those materials are used as is. They go through considerable additional refinement before they ever get into people.

We have in the interim completed several spiking-based validation studies, which have some caveats attached to them, of course. Nevertheless, the results have been uniformly very encouraging because we're seeing that in the process of carrying these fractions through scaled-down versions of the manufacturing process, we're seeing the elimination of very high levels of infectivity, suggesting that, at least at the level of plasma fractions, we have another very important additional level of safety that we're getting from the manufacturing process itself.

The other thing I wanted to ask you about was your modeling of the contribution from eliminating donations from persons who had received blood and

blood components previously.

I gather you are just looking at the next donation, you are not looking at the issue of propagation of the infection over time by that practice. Is that correct? Because you are showing very little effect here, and in terms of a safety measure, I have always ranked it as one of the most important things we could do.

MR. COMER: That is true. We didn't attempt to model that really fully. And it was just a very crude estimate over the first year. So yes, it is not a full representation of the effect of that.

Just going back to your first point as well, if we take the results from our estimates based on clearance factors, which I think there will be some differences in detail from the results that you have got now with your spiking experiments, if we base the risk from plasma derivatives on the clearance factor approach, then the risk from plasma derivatives is virtually zero. I mean, there really are very, very low levels of risk associated with that. So yes, you get significant, very significant, risk reduction.

CHAIRMAN BROWN: A couple of points just to bring your experimental data up to speed. Unpublished further experiments on the mouse model

have produced good news and bad news.

The bad news is that we have a disappointingly large number of transmissions following intravenous inoculation of either plasma or Buffy coat. We also have a transmission using whole blood as a transfusion into these mice. So that's not good news.

The other thing that is not too good is that we have now got in this particular model a ratio of five to one, as opposed to ten to one, which was also disappointing.

The only piece of good news in that in terms of experimental data is that we found that, again, in this model, the level of infectivity during the entire incubation period is almost negligible compared to the level of infectivity during the clinical phase of illness. And that is very good news indeed. So these are data that are not yet published but .--

MR. COMER: Can I just clarify that?

CHAIRMAN BROWN: Sure.

MR. COMER: It's five to one between i/v and --

CHAIRMAN BROWN: Yes, i/v and i/c. I mean, we were hoping for at least ten, but that's not

the way it happened. Again, there probably is variability from experiment to experiment. And the next time we do it, it might be 10 or 20 or 3. I don't know, but that's the initial number.

Other questions? Yes?

MR. COMER: Well, just commenting on your last point there about the infectivity through the incubation period, our assumption was that levels of infectivity are basically uniform throughout the incubation period, which is obviously the most conservative assumption you could make.

CHAIRMAN BROWN: Right, right. And, as I say, if it turns out to be the case with the human disease, -- and I'm guessing it probably will be -- with you, I think the likelihood of disease, natural disease, whether it be scrapie in sheep, BSE in cattle, or CJD in humans, is going to be quite a lot less virulent than the experimentally induced disease.

Even under the experimental conditions I mentioned, however, infectivity in all components of the blood during the incubation period is so low that it virtually poses I think no risk, at least in terms of plasma derivatives.

Other questions? Yes?

DR. HOLLINGER: Is it your assumption in

humans and, say, Dr. Donnelly's in cattle, that all infections lead to cases if followed long enough? That is, is there a chronic carrier assumed to be the case; particularly in cattle, that is? Do we know that at all?

MR. COMER: We assume that any animal infected will result in a case if it survives long enough. That is certainly the assumption I think both of us have made.

DR. HOLLINGER: Is there any data following for prolonged periods of time infected animals?

CHAIRMAN BROWN: There is if -- go ahead. I'm sorry.

DR. DONNELLY: Yes. I mean, I made the assumption, like Philip's group, that all animals that were infected would if followed for long enough lead to disease.

The possibility of carriers, we looked into the possibility of different susceptibility classes. Certainly I don't know of any study that has followed them long enough to be able to -- you tend to have them followed for up to seven years. I don't know of any studies that you do where they're followed for longer to look for these.

CHAIRMAN BROWN: The only study that I'm aware of that documents a carrier state is work in rodents in which mice were treated with Substance X. A few mice that were treated with -- it's the Pentosan-type drug I believe were shown -- maybe they weren't even shown to have infection. They died a natural life without developing clinical disease.

Bob, can you correct me or verify this? I'm not aware now that I think of it again of any study in which infection; for example, documentation by Western Blot or immunostaining of the resistant form of prp, where an animal has carried that all of his life and died from an abscess three years later, which would be the carrier state.

DR. ROHWER: Well, there is a recent report from Rocky Mountain Lab showing a situation just like that, where the animal survived its life span without showing disease, but it could be transmitted, then, subsequently.

There are also some very old papers from Alan Dickinson and his colleagues showing the same thing using certain strains of mice and also depending upon the route by which the animal is infected.

I would just like to caution in terms of thinking about preclinical infection, I think from my

perspective, anyway, route and dose could have a very big effect on exactly what we see in these models.

So to date, we have only really looked at the i/c model. I think it behooves us to look at more natural routes of infection before we draw any conclusions about the preclinical state.

DR. EWENSTEIN: I just wanted to make a comment about the use of the plasma derivatives. You have assumed 2,000 units as a single inoculum, I think. I just wanted to make the point that for most patients, there are periods of time when they might receive at least ten times that sort of dose in a matter of days.

Now, I don't know what the cumulative effect is over the space of a couple of days. Over the course of a year, a typical number might be 80,000 units. Again, we don't know the cumulative dose because we don't know the body's ability to clear whatever the infectious agents are.

At least in clinical practice, there would probably be many instances where there would be at least 10 times that exposure in a matter of 48 or 72 hours.

MR. COMER: Yes, obviously what we've done here in looking at the typical -- you know, defining

the patient groups and the exposure is just to give some estimates against which we can base some calculations. And there are a whole range of different variabilities that we could look at.

When we actually looked at the effect of changing some of those assumptions, their effect on the results were mainly fairly marginal. So you wouldn't get a big difference by making that sort of a change.

CHAIRMAN BROWN: We have time for two more questions.

Yes, Dr. Leitman.

DR. LEITMAN: This is for Dr. Donnelly. One of the most compelling pieces of data that there's blood transmission of the agent is through the maternal to fetal transmission in cattle, and you quoted a risk of 10 percent over the last six months of gestation.

That's all from clinically observed information? There's no experimental data on that? That's question number one.

And question number two: Couldn't that not also be due to an increased genetic susceptibility to infection in the same -- passed on from the mother to the calf?

DR. DONNELLY: Well, we looked at two main sources of data in looking at maternal transmission. There was the maternal cohort study which was organized by Ministry of Agriculture staff. And unfortunately, rather than recruiting calves just as they were born, they were actually recruited after they had been in farms for a period of time.

There was a maternally exposed animal and a control animal. About 300 of them were recruited. But unfortunately, those animals both in the maternally exposed and control would have been potentially exposed to infectious feed while they were on the farm.

Now, from that experiment alone, it is quite difficult to distinguish whether or not it's maternal transmission or whether or not it's genetic predisposition. And that's because all the experiment -- or all of the maternally exposed animals were recruited as the last calf, so you didn't have a long period of time, a spectrum over the maternal incubation period.

But, looking at the main database, which has been collected on all BSE confirmed cases in Great Britain, we were able to look at those for whom the mothers had been identified and look at dam calf pairs

of BSE cases.

And if you do that, taking into account survival of both dam and calf, you're able to see an increased risk for those animals born at the end of the maternal incubation period, but no increased risk for those born two or three years prior to onset.

So that definitely suggests that it is maternal transmission rather than a genetic predisposition. And that, I suppose, is something to note as well in the potential for carrier animals is that genetic studies that have been done have -- with one exception, which was not followed up with additional experiments, have generally not shown a genetic link in cattle and predisposition.

CHAIRMAN BROWN: Is this directed to -- yeah, okay.

DR. PRUSINER: I would just like to ask you one question. What do you think the mechanism is for a cow near the end of its incubation time so it now has high titers in its brain and it's more likely to infect a calf that's born to it than earlier on?

That's what you're saying, correct?

DR. DONNELLY: Yes.

DR. PRUSINER: That's the strongest data you have. The first piece of data that you -- I don't

mean to be tough about this, but I think the first piece of data you quote, the cohort study, tells us nothing.

It's zero because of the way the animals were ascertained, they way they were taken into the study. So I think to quote the study constantly is really a mistake. It doesn't -- it's not a clear study. And I think that people in Britain are equally divided amongst what this study means.

So the second study is the one you're quoting now. It's your study. And I don't understand the mechanism.

DR. DONNELLY: I don't understand the mechanism either. I mean, what we were looking at was increased risk as it was associated with incubation stage. And as an epidemiologist and statistician, I don't think we'll ever get at the mechanism in that manner.

One thing that was interesting was an examination of beef suckler calves that John Wilesmith looked at, was to try and look to see what the transmission rate is there. And it was kind of a smallish sample size, but it didn't show any increased risk in those animals that had suckled for approximately a year.

So that suggests it probably wasn't milk because, had it been milk, you would have seen a differential in risk. But otherwise, I don't think that all the statistics in the world and the biggest sample size we'd ever actually be able to tell the mechanism.

CHAIRMAN BROWN: Yes, Linda.

DR. DETWILER: Looking at the database and looking at the calf sample, did you look over the entire course of the epidemic or was it concentrated to a certain point of time with the calves?

Because that might -- exposure to feed, too, during their life span might play a difference in the --

DR. DONNELLY: The data was mainly on BABs, or born after the ban, cases. But we did control for what the risk from feed would have been in their herd. So there was a control for what they probably would have gotten to see the expected number of pairs we would have seen.

So we look at the number of cows and the number of offspring that were cases and how many -- within that herd, how many pairs you would expect. So it is controlled for what you'd expect their feed risk was.

DR. DETWILER: What year specifically, do you have that?

DR. DONNELLY: Oh, born after the ban calves, those would have been -- they were mainly born in the second half of '88, '89 and some in '90.

CHAIRMAN BROWN: Mike, sorry to keep you standing so long. You have a comment?

DR. BUSCH: Thank you. Yeah, just a comment/question.

The hemophilic community often frame themselves as the canaries in the mine, and I think here obviously the British population are the canaries vis-à-vis transfusion transmission potential. We're ten years out from the peak of the BSE epidemic, and I'm just curious, from your models, at what point in time downstream would you begin to conclude that transfusion transmission is not an issue?

As this committee begins to deliberate, I think it's important to consider any ban that might be implemented on U.S. travel to Britain. How long will that be in place, and can the experience in Britain give us some sense of when we could discontinue such a ban were one introduced?

MR. COMER: I don't think we can really answer that at all because we still know very little

about the incubation periods both from cattle into man, so when might the peak of variant CJD cases be in the United Kingdom, and also what the incubation period within the blood supply would be.

We simply don't know the answer to either of those questions. And I think we'll be a number of years yet before we can really use the data to give us a better feel for what those numbers are likely to be. So it's not going to be short.

CHAIRMAN BROWN: Larry, the last comment now.

DR. SCHONBERGER: This would be for Donnelly as well. My understanding is that the oldest new variant case of CJD is in the early '50s. You mentioned that you had data that cattle at different ages had a different susceptibility to BSE.

And I was wondering how strong that data is. You talked about an increase susceptibility between the ages of six months and 18 months, but that the exposures, you implied, were as great under six months and over 18 months as during that period, and yet your statistics didn't show that the cattle were coming down.

Is that what you were trying to say ?

DR. DONNELLY: Well, through the

statistics alone of the back calculation, you can only get what's the convolution or the combination of exposure to susceptibility together. But it's by additional data from looking at farmers and what they say they do in practice that exposure seems to be within one order of magnitude about the same all the way through.

But you do seem to have this window.

DR. SCHONBERGER: You mean after 18 months --

DR. DONNELLY: Yes.

DR. SCHONBERGER: -- exposure was just as great, but your --

DR. DONNELLY: Yes.

DR. SCHONBERGER: -- data does not show that they're coming down with the disease?

DR. DONNELLY: Oh, yes; and if anything, it gets greater at 24 months when the cattle start milking. One thing I didn't have time to get into was the fact in doing our analysis of the variant CJD epidemic, in addition to requiring consistency with the annual incidence of cases, we also require consistency with the age distribution of cases.

And in doing that, we're only able to reproduce the age distribution of the cases observed

today if there is some age dependency. That can take the form of an age dependency in the incubation period distribution, or it can take an age dependency in exposure susceptibility.

Now, it's difficult to imagine what the biological mechanism, even if you could work it out in cattle, would necessary apply to humans. But also with humans, you have considerable difficulty of hard to quantify differences in characteristics of dietary choices with age.

But there does appear to be something. We don't yet know what it is. But through time, in the next couple of years, we will hopefully be able to get more data to tell whether or not we can distinguish between it being an age dependent incubation period and age dependent exposure susceptibility.

But in the cattle, it's very clear: you can't get a fit to the data just on the basis of constant susceptibility, or even susceptibility peaking at birth and dropping right off.

CHAIRMAN BROWN: Thank you very much, both Drs. Donnelly and Comer.

It's now high noon. And I had been reading the agenda from a draft and inadvertently left out a presentation by Dr. Stephen Nightingale about

the meeting held by the Advisory Committee on Blood Safety and Availability about the reserve capacity of U.S. blood supply.

He will speak next, and he will be followed by Dr. Penny Chan. Both speakers have kindly agreed to limit their presentations to 20 minutes so that we can remain on schedule.

Dr. Nightingale.

DR. NIGHTINGALE: And if possible, less.

Dr. Brown, members of the committee, and ladies and gentlemen, what I will try to do, and do in the next ten minutes, is to summarize the meeting of the Advisory Committee on Blood Safety and Availability that was held on April 29th and 30th of this year to examine the reserve capacity of the United States' blood supply and to recommend how it might be strengthened.

But before I change that slide, since Dr. Freas and Dr. Brown raised the issue, let me briefly, within 30 seconds, go over the jurisdiction of the Advisory Committee on Blood Safety.

It was chartered on October 9th to advise the Secretary and the Assistant Secretary on a broad range of issues which include: implications for blood safety and availability of various economic factors

affecting product cost and supply; definition of public health parameters around safety and availability of the blood supply; and finally, broad public health ethical and legal issues related to blood safety.

So I would say, Dr. Brown, yours is, by no means, the only committee which has jurisdiction with which ours overlaps. I am sensitive to the concerns that you raised in your earlier comments and will take them to the Surgeon General.

The committee -- could I have the next slide, please?

Dr. Satcher opened the April 29th meeting of the Advisory Committee by noting what is on the slide here, "that it may be necessary, at some time in the future, to defer, at least temporarily, some portion of the donor pool in order to maintain the integrity of the blood supply."

Dr. Satcher emphasized the need that this be done in a way that would minimize the impact of this action on those who depend on blood transfusions for the health and even their lives. He charged the Advisory Committee to review the state of the reserve capacity of the United States' blood supply and to recommend how it might be strengthened.

He further charged the Advisory Committee to do so before, and not after, circumstances might require use of this reserve capacity. And he concluded his charge by reminding the Advisory Committee that we should never be in a position, as some have suggested we may have been in the past, where we would feel obligated to release a unit of blood if we had any doubt whatever about its safety.

Could I have the next slide, please?

After introductory comments about the current safety profile of the blood supply, Ms. Marian Sullivan of the National Blood Data Resource Center, which is an affiliate of the American Association of Blood Banks, then described the current availability of the blood supply on the basis of data available to her.

She stated that, in 1997, about 12.6 million units of blood were collected and about 11½ million units of red cells were transfused; 93 percent of allogenic units were transfused; 2 percent were discarded because of screening test results; 4 percent became outdated; and 1 percent were unaccounted for.

However, as shown on this slide here -- leave that right where it is. Turn that slide back on, please. Okay, shown on this slide, total blood

collections have decreased by 5.5 percent between 1994 and '97, while the total number of whole blood and red cell transfusions increased by 3.7 percent during the same time.

And extrapolating from the current trends and making the assumption that Ms. Sullivan reiterated several times, the available blood supply in the year 2000 would be 11.7 million units of red cells, and total demand would be 11.9 million units.

There were three substantive comments made during the discussion that followed this presentation. The first was that most outdated units are Group AB blood donations which can only be transfused, I think everybody in the room knows, into a Group AB recipient.

The second comment was the fact that while the overall supply of blood exceeded overall demand during 1997, that did not mean that there were not local shortages during the year. And indeed, there were.

The final comment was that one factor contributing to the trend that Ms. Sullivan described is the aging of the population. About half of all transfusion recipients are over 65. As a result, as the population ages, there will be proportionately

fewer donors and proportionately more recipients.

After that -- you can just leave that there for a while -- Dr. George Schreiber of Westat ~~and~~ National Heart, Lung and Blood Institute sponsored retroviral epidemiology donor study, then discussed how donor retention might influence the reserve capacity of the blood supply.

He began by noting that, while almost half of the adult population of the United States has donated at some time, only about 5 percent donate during a given year. In 1995, about 32 percent of roughly eight million blood donors were first time donors.

Half of these donors never returned, and two thirds of those that did returned during the first year after their initial donation. Dr. Schreiber estimated that if the rate at which first time donors returned for a second donation within one year could be increased by 15 percent, the blood supply could be increased by 10 percent.

The discussion that followed focused on the suitability of these donors that might be induced to return. Dr. Schreiber has found that individuals who had donated only twice had no greater incidence of HIV or hepatitis C than individuals who had donated

more than twice.

A similar observation has been made about paid plasma donors. Paid plasma donors who return only once, regardless of the interval after their initial donation, appeared just as suitable as those who returned more often and/or more frequently.

After that, Dr. Alan Williams of the American Red Cross Holland Laboratories discussed some preliminary data on the use and effectiveness of incentives to increase blood donation. Again, Dr. Williams emphasized that his data was preliminary, and I will emphasize that again for him.

What he did report was he found that the number of donors who report receiving some non-token compensation had increased from 26 percent in 1995 to 62 percent in 1998. And in a survey of blood donors, Dr. Williams found that future blood credit is the incentive that would most strongly encourage them to give blood.

However, donors indicated that lottery tickets might actually discourage them from making future donations, and that cash incentives might tempt some donors not to disclose a deferrable risk.

Dr. Busch then spoke of the Blood Centers of the Pacific, and he discussed differences of risk

factors among blood donors. Dr. Busch, I think, will be speaking this afternoon in the public comment period, and Dr. Busch will speak on his own behalf on that point.

However, I would note that Dr. Busch's presentation was consistent with the observation of Dr. Schreiber and the plasma industry that single repeat donors are as suitable as multiple repeat donors. And Dr. Busch's presentation supported the suggestion of Dr. Schreiber that we focus efforts to expand the reserve capacity of the blood supply on efforts to increase retention of first time donors.

Dr. Gilcher, who is also in the audience and on the committee, did discuss new technologies that might increase yield per donation. He said, however, that because of the increased cost, the increased interval between donations, that this was unlikely to be a significant -- provide a significant addition to the blood supply.

Now, in the public comment and the Advisory Committee discussion that followed, the consensus emerged that retention of more first time donors, as Dr. Schreiber suggested, was the strategy most likely to increase the capacity of the United States blood supply and least likely to increase its

risk.

There was also consensus that it would cost a substantial amount of money and incentives, direct or indirect, to retain these first time donors, and that blood banks could not fund these additional costs from current revenues.

However, no consensus was reached on what, if any, incentives, up to and including paid donations, would be effective, how much they would cost, or who would pay for them.

With that in mind, the Advisory Committee then addressed the issues of what, if anything, individuals with hemochromatosis or the blood substitute industry could contribute to the reserve capacity of the blood supply.

There was substantial discussion on that issue in the long run. The most substantive discussion was by Dr. Al Grindon, who presented a range of estimates of the potential contributions of therapeutic phlebotomies from individuals with hemochromatosis.

These estimates range from 300,000 units per year, or 2.5 percent, of the current blood supply to three million units, or 25 percent, of the blood supply. Dr. Grindon's own estimate was on the lower

side.

After further discussion, the Advisory Committee did unanimously approve a motion that since blood products obtained from persons with hemochromatosis carry no known increased risk to recipients attributable to hemochromatosis, per se, they may be a valuable resource to augment the diminishing supply.

The Advisory Committee recognized the obligate need for phlebotomy can constitute undue incentive for blood donations due primarily to financial considerations. For this reason, the Department of Health and Human Services, they recommended, should create policies that eliminate incentives to seek donation for purposes of phlebotomy, and that, as such undue incentives are removed, the Department should create policies that eliminate barriers to using this resource.

Finally, the Advisory Committee heard presentations from representatives of the blood substitute industry on the potential contribution of blood substitutes to the reserve capacity of the blood supply.

The consensus of these presentations was that proof of principle had been established for these

agents, but unequivocal demonstration of safety and efficacy in adequately powered Phase III clinical trials had not yet been accomplished.

For this reason, it appeared to the committee unlikely that any of these agents would be able to make a meaningful contribution to the reserve capacity of the blood supply within the next two years, but quite possibly they could do so at a later time.

Let me have my last slide, which is a summary of the recommendations that the -- the summary is that demand for blood is increasing at about 1 percent per year and supply is decreasing at about the same rate. The extrapolation from the current trend says demand is expected to exceed supply in the year 2000.

The strategy that appears most likely to increase the reserve capacity of the blood supply -- and again, least likely to increase the risk of blood transfusion -- is to increase retention of first time blood donors.

However -- and these are important. However, there is no guarantee that this goal could be achieved. No firm estimate of how much it would cost and no certainty who would pay for it.

And finally, the complementary strategy to increase the reserve capacity of blood supply is to eliminate undue financial incentives for blood donations by individuals with hemochromatosis. And as such undue incentives are removed, to create policies that eliminate barriers to this use.

However, the potential contribution of this resource, while it may be substantial, is again there is no guarantee that this potential will be realized.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Nightingale, for a lucid and concise presentation of the Advisory Committee's deliberations and conclusions.

Unless there are questions for Dr. Nightingale, we will proceed then directly to Dr. Penny Chan, who will report on the Canadian viewpoint which, as I understand it, is in flux with two meetings bracketing this one as though the Canadians want to see what we're going to do before they make up their mind.

DR. CHAN: Well, what can I say? I promise I won't speak as fast as Dr. Nightingale. Probably not as clearly.

I'd like to thank you first. And I probably -- although this was the meeting that I was asked to speak about held by the National Blood Safety Council on variants of CJD and issues for the blood system, I think I need to talk a little bit about our process and the background that brought us to these meetings before I go into a description of the meeting.

So, if I could have -- what I'd like to talk about is a little bit about what the council is, what the issue was, the process, and the background around which this meeting was set.

I'll go through just the agenda, very briefly mention a few things about the actual meeting, then the recommendations, and, although the meeting was held less than a month ago, what has happened since then.

So very briefly, the National Blood Safety Council is probably the Canadian equivalent to the Advisory Committee on Blood Safety and Availability that Dr. Nightingale was talking about. There are a few differences, some of which I may highlight.

It has 16 members. Three are consumers. Two are from industry. I should stress that none of the members are representatives of an organization.

They were invited for their experience and their expertise, but not as representatives.

And when I say industry, both the members that come from industry come because of fractionation, experience and perspective. And we don't actually have any people from the current operators of the blood system -- that is, the collection blood services.

However, within the group that I've listed under treating physicians, we have an ethicist, we have a hemophilia treater, we have several people with the experience in apheresis. We also have a couple that have been involved in the blood services previously.

We've got a couple of people, public health officials. And this is significant not only because of their expertise, but because of the regional and more local basis for public health. So it gives us sort of a broader dimension to the discussions.

We've got a hospital laboratory technologist, a lawyer and an anesthetist. Our mandate is to advise the federal Minister of Health directly. We are -- independent staff, I guess, is me, which means that I don't work actually for the

federal government.

I'm not within the actual Department of Health. My job is to support the council entirely, so that is a slight difference. And this, I'll get into a little later, means that the council determines its own agenda, the issues that it will deal with.

The history, just very, very briefly. I'm sure you're all fully aware of the Commission of Inquiry that took about four years and focused a tremendous amount of attention on blood safety, on decision making, and, as I'll describe a little bit later, set the background very strongly.

At that time that the report was released, the Minister of Health announced the formation of this council. And it was seen as a means of overseeing blood safety, of helping to prevent such disasters occurring, opening a dialogue, etc.

He named initially just seven members. And there has been a period of probably a year where we've expanded the membership, determined the mandate and all of that.

So, the functions have sort of been broken down into three. These are the functions of the council. One is more or less a watchdog over the blood system.

Now, as we advise the federal minister, it's largely the structural organization and performance of the federal departments, which are the regulator equivalent to your FDA, and the LCDC, which is equivalent to your CDC.

So we have a mandate to watch the actions, the organizational structure, is this the best for maintaining the safety of the blood system. We also have the role of helping to identify any risks to blood safety that the council may consider are not being dealt with.

And we have a very strong role in communication, and this means putting the parties together, having consumers being totally open to the public in information exchange, education, and certainly provide a forum for open debate on any issues.

We have two types of meetings. There are planning meetings which, as I mentioned before, we set out own agenda. It is not set by the government, therefore it takes a time to work out how and what the issues are. And we do have fairly frequent meetings with the Minister of Health.

And then we have open forums. And it's going to be the third of the open forums that I'm

going to be describing. The outcomes are not necessary that we have to come out with recommendations. We're not given questions to answer.

If we think there's a recommendation that needs being made, then council will make it. If the process has been sufficient, the people have got there and talked about things and courses of action become fairly obvious, then hopefully we can facilitate that process.

So the issue that we dealt with in early May was "do variants of CJD pose a risk to blood safety?" And we sort of divided it into the classic variant and others. The others came out of, I'm sure you're all aware, of the scare that we all had over the Utah donor was this a possible chronic wasting disease, etc.

So we just put that issue on the table and let's see where it went. Our process -- we circulated a notice widely to all associations, consumer groups. We've sort of got a mailing list that's growing.

The day before the meeting, there was a flurry of activity. The two blood service organizations in Canada both issued a press release. And I think it was either that day or the day before the regulator had also issued a letter to the blood

services regarding donor deferral and variant CJD.

So I have to tell you that obviously it wasn't council that put this issue on the table. There was a tremendous background that we set our meeting on. And I did already mention the climate that has been set from the Krever report and some significant impact on the way we're dealing with things.

The first, and probably most significant, is there's been a total reorganization of the blood system such that the Red Cross is no longer running the services. We now have two blood service organizations. Héma Québec is in the providence of Québec, and Canadian Blood Services over the other provinces and territories.

And there were some principles -- I've called them principles. You can talk about them as standards, but sort of moral standards that came out very strongly out of the report. And I think there's very heightened awareness of these issues still in Canada.

And these I've labeled the precautionary principle or perhaps safety is paramount. And there were two things that Justice Krever laid out fairly clearly that you should not await scientific certainty

to act, and you should also consider the likelihood and the severity when you're considering risk.

And I'll go into a couple of quotes from the report because I think they're fairly important for a background here. He also talked about "the importance of national standards, but that they should be local variation if it was deemed important for protecting safety and independent decision making."

So that's sort of the general background or environment. And then specifically, on the area of new variant CJD and the possibility of deferring donors who had resided in Britain, at the end of 1998, there was a report released by the Bayer Advisory Council on bioethics in Canada.

And it had 20-odd recommendations, one of which was that donors who had resided in a BSE country should be deferred from donation. And then, subsequently, I think it was in January of this year the LCDC had asked for a risk assessment to be performed on new variant, and that report contained a recommendation also for the deferral of donors from UK.

And then we do have what is called the Expert Advisory Committee on Blood Regulation, which, like your plethora of committees, is equivalent to

your BPAC. It's a more technical advisory committee to the regulator.

Their meetings are not open to the public. And they had also considered this issue and made a recommendation to the regulator on the issue of donor deferral. However, they had asked to await the data on -- now, if you want to know whether that's a spelling mistake, yes, it is, but it could be considered as a -- the implications or the impact so that you have a new word for it -- that's the donor survey.

Now, I've just copied a few -- and I've really cherry picked excerpts from Krever Report, those that were discussed in the meeting that set a sort of a standard here.

And the first excerpt I've chosen was "the operator of the blood supply system and the health protection branch must not wait for scientific certainty about the spread of a transfusion or infusion associated disease and the effectiveness of particular risk reduction measures before they actually reduce risks."

Now, that second part means that just because you cannot totally eradicate the risk doesn't mean that you shouldn't consider taking actions to

reduce the risk if there are actions that are possible.

And the balancing of risks and benefits of taking action should be dependent not only on the likelihood of the risk materializing, but also the severity of the effect if the risk does materialize on the number of persons who should be affected and the ease of implementing protective or preventive measures.

And clearly, the more severe the potential effect, the lower the threshold should be for taking action. So you can see we're setting standards here.

It recommended that Canada "have a national system for the collection and delivery of blood components and blood products." That clearly was not implemented. We have two systems.

However, a national blood supply system will have national standards to ensure that all persons in Canada needing blood components or blood products have access to products of uniform quality.

Now, this poses a little bit of an interesting dilemma. And even within the report, like most things that some people refer to as the Bible there, you can find a quote that says something that's a little bit different.

And so another excerpt says that "the National Office of the Operator must create an enforced national standards, but it should permit its local centers to exceed them."

So, as long as you've got a minimal standard, then regions can take actions or should take actions to exceed those standards if it's necessary.

It's recommended that the "Bureau of Biologics and Radiopharmaceuticals" -- that's our regulator -- "make decisions with respect to the safety of blood components and blood products independently of those made by manufacturers and distributors."

Now this one has a lot of historic significance, and perhaps I've only used it here to say that really the manufacturers and the regulator need to make independent decisions: "Obviously the manufacturers have to meet the regulatory standards; however, they can exceed them."

And that's what the next part is, that "the regulator accept manufacturers' or distributors' decisions to take actions that exceed the standards of safety set by the Bureau." And I think this is the final quote.

"The regulator should never interfere with

the decisions of a manufacturer or the operator to take a risk reduction measure that exceeds its regulatory standards."

I realize that I've spent rather a lot of time on that, and I apologize. But I think the context for the meeting is fairly important. I very briefly, on the next two, outlined the agenda. I've taken off some of the details.

And, as you will notice, your Chair here today was also the person who started our meeting off, and I might say he started it off by saying two things. One is, "I intend to be controversial." And secondly, he also said, "If you're looking for answers, you're not going to get them."

So that having been said about our meeting, the first section was really the overview. It was an information session, but we also tried to capture the experimental data that was available. And following strictly the experimental data, we went into a panel discussion where we asked what's the likelihood of transmission by blood and blood products.

Unfortunately, in the discussion, the distinction was not kept perhaps as clearly as it should have been between the components and the

products. And is it likely to be the same for classic and new variant?

And thirdly, the question was: What is the biological plausibility, from our experimental data, that there will be other variants of CJD? I won't go into the attempts of answering these.

We had a discussion by Dr. Will about the situation in the United Kingdom with respect to new variant and the actions they had taken. We had descriptions of what's going on in Canada, particularly on the surveillance system that we have for CJD in Canada; the current prion research; the precautions; and, for blood safety, our regulatory policy and our policy development.

Then we had time for submissions and discussion, and a panel discussion again.

If we can go to the next slide.

The second day we figured that we would change gears because we were not just looking at the science, but we were looking at the area that Dr. Brown had said: When we don't have the answers from the science, but we still have to develop policies, what are the things we need to consider?

And Dr. Hoots, who is also a member of the Blood Safety and Availability Committee here in the

U.S., did kind of a nice overview of some of the factors that are important.

And Mr. David Page, who is a hemophiliac, and he talked about some of the factors that are very important in the decision making from the perspective of consumers. And one of the critical things, and perhaps why I've gone into the Krever setting the standards, is the tremendous loss of faith in the blood system and the implications for scientists, physicians and people who have to make decisions and why this has to be a factor to be considered when you are making decisions. Then we had the recommendations that I've already described, one from the Bayer Bioethics Report, and one from the Risk Assessment Report that was given to the LCDC. And then we had the impact of deferring donors.

And Dr. Marc Germain and Dr. JoAnne Chiavetta presented the data from surveys that were not unlike those that Dr. Williams just presented. In fact, I believe there was collaboration in the establishment of the types of questions that were asked.

I'm not going into the data here. Dr. Germain and Dr. Chiavetta are both here and any questions about that should really be addressed to

them. I will make just two points. One is that the data vary between the two organizations and, like Dr. Williams said, within regions for each of the organizations, particularly for the Canadian Blood Services.

And perhaps the Canadian Blood Services data are more analogous to those of the -- the one that was conducted here in U.S. I really won't say anymore about that. As I say, the raw data, I think hopefully, will be circulated to you all.

Then we had submissions and discussion on the impact. And the last part of the second day we devoted to look back notification of recipients. And we had a description of a process that had gone on that started from the actual notification, the follow up after the notification, and, I might say, the lawsuits that are still pending over it.

We debated some of the ethical issues, and then we had a very interesting consumer panel which consisted of people who -- we had David Page, who is a hemophiliac, from his perspective. We had a thalassemic who is a constant user of components.

And we had a couple of parents of children who had been notified that their children had received products that were CJD implicated when that was the

policy in Canada.

So that was our meeting. And then I think I would just -- oh, yeah, there you go. That's the data from the survey. It will be circulated, I promise, and we can discuss those.

Finally, the recommendations that council came up with. And the first is a little long winded, but what it's trying to say here is, consistent with the letter from the regulator that went out, as I said, the day before the meeting, that members of Héma Québec and the Canadian Blood Services should get together, and we were prepared to serve as the independent third party, to make decisions about deferral of donors who have resided in the UK such that there is a single, high standard.

Donor deferral policies must be coupled with strategies to increase donor recruitment. So that's really not giving a time, but saying that the two organizations have to work out a single standard and that council would facilitate that process.

The rest of the recommendations I'll go through very briefly. Health Canada had not standardized its -- not finalized its policy on classic CJD, and we advised that they do so.

The blood services should provide clear

statements about the reasons for believing that there are no longer concerns regarding the classic sporadic CJD; that Health Canada and the blood services provide communication regarding all aspects of product quarantine.

And that was because there's considerable confusion over the Utah donor case. Health Canada identify and provide information that all products that contain trace amounts of blood products -- this was interesting.

Many of the physicians did not even know which products that were being distributed contained blood products. We thought this was an important issue. All products can be tracked in the event of an infected donor. And that they take steps to discourage manufacturers from using blood products in the production or formulation of other products.

That mechanisms are developed to ensure that -- oh, this is the surveillance for CJD. That criteria have to be established to determine between classic and variant forms, which I know is the topic that you are going to be discussing this afternoon.

And that these criteria should be very clearly put out to people and it's clear what they do when they get a case.

There was concern about the partitioning of the experimental data regarding the partitioning of the prion with the cryoprecipitate. And this recommendation says that the use of cryoprecipitate should be reviewed.

Finally, I think -- I keep saying finally. I think I'm getting to the end. That the information -- oh, that our equivalent to the BPAC, their recommendations be made more public so that people know when these things are going to occur; that Health Canada take the steps to ensure that notification policies are consistent.

And this was felt very strongly, the next one, from the consumers because notification without education and follow up is worse than no notification at all. All notification programs must include appropriate education and follow up components.

That Health Canada then ensure that the recipients notified in the past are informed of the facts and the policy changes. And that Health Canada ensure the simple, clear education of the public and physicians on CJD as it relates to blood transfusion.

Since May 7, 1999, lots of things have happened. However, the decisions have not been made. There is a deadline of June 10th which the regulator

has asked the operators to decide how long and what deferral criteria will be put in place.

And there are several meetings. The CBS has convened yesterday, I think it was, a meeting of their advisory committee to help them look at all the implications of donor deferral.

And the meeting that's scheduled to have the operators together to make a decision will occur, we hope, next week. There have been lots of other things. But I hope that gives you a little bit of an understanding of our process and perhaps the environment in which we're dealing with many of the same issues that you are.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Chan.

Do we have a question for Dr. Chan? We could probably work any comparative discussion into this afternoon's open public hearing or committee discussion.

Yes, Jay.

DR. EPSTEIN: The issue of elasticity of the blood supply arises any time you contemplate deferring donors. And, you know, there was loose talk about UK exposure related deferral reckoned by, you

know, even just weeks to months of exposure.

And I just wonder, is there any figure that you can provide that represents what you think the Canadians believe can be recovered by new recruitment or increased frequency of donation?

In other words, what percent donor loss through deferral do you think your system tolerates?

DR. CHAN: I will not -- I cannot answer that question, but I can say that the types of -- the two services will have quite different elasticity. There's absolutely no doubt about that. For one, the inventory levels are different between the two organizations, plus the number of donors that would have to be deferred if you drew the line at one month or six months.

These are two numbers that have been bandied around, but I really would much prefer either or both of the operators to speak to that if you want a specific answer. Different is the issue. Maybe 5 percent was the number that was bandied around.

Is that sufficient, or can we -- okay.

CHAIRMAN BROWN: Larry.

DR. SCHONBERGER: When we had the problem with the human growth hormone, the solution turned out to be to switch to molecularly engineered hormone. Is

there any such solution to our blood problem in the near future?

Does anybody have any information on that; that is, using some substitute that would not require the human donator?

CHAIRMAN BROWN: Well, Factor VIII is available as a recombinant. I don't know of any other derivatives are yet available.

DR. EWENSTEIN: Let me comment on that. I mean, you're right, Factor VIII is available. There's still albumin in many of the preparations, although there are movements afoot to slowly release products that don't have any albumin as stabilizers.

There is a Factor IX product that's available without any human component. But there's still a group of patients even in the coagulation area that are dependent on the plasma derived products. There's a recombinant, von Willebrand's product, that's under development, but I would predict would be years away.

And so just licensed, for example, was a product to treat von Willebrand's disease with an intermediate purity, Factor VIII. So I think the answer to your question is we're getting there, but that there are still large segments of the bleeding

disorders community that rely on plasma derived products.

And then, of course, I can't see, at least as a hematologist, any time soon having a recombinant IV Ig preparation.

CHAIRMAN BROWN: This -- yes, Peter.

DR. LURIE: Just back to the question of elasticity of the blood supply. And I apologize. This being raised now raises questions for me about the particularly central slide that Dr. Nightingale presented.

Can you put that one up again? Criss crossing lines. I guess I have first a question for you and then, depending on your response, two or three comments on it.

My question is: Are the extrapolations that you present in that slide extrapolations from just the '94 to '97 period, just those two data points, or are we really looking back further in time?

DR. NIGHTINGALE: The slide is what it is; it's a '94 survey and a '97 survey. It comes with confidence intervals that you can see. It is our current best estimate, and it is understood that this is not a prediction within those confidence intervals.

But I think the message in the slide is

that there's not a lot of slack in the blood supply right now.

DR. LURIE: I think the message in the slide is overstated for several reasons. The first is that the Y axis begins at about 11 million units of transfused blood, and so it makes the -- in a section, look rather sharper than, in fact, it is if you extended it all the way down to zero.

The second point is that you've made an extrapolation based just on two points, as you say; and which, in effect, makes it seem as if the two lines are independent of one another. I like to think that the blood transfusion industry, aware of the change between '94 and '97, is, in fact, reacting in some way, presumably by increased recruitment.

So there is a kind of inevitability applied to all of this that doesn't really quite seem right to me.

DR. NIGHTINGALE: Sure. And the -- what doesn't seem right is that past experience will predict future experience, and that is not the implication. I think the implication of the slide is that there are -- there is a bit of concerning information raised at the meeting.

For example, Dr. Williams' survey finding

-- again, preliminary -- that in 1995, 26 percent of donors reported receiving some incentive; in 1997, that 62 percent reported receiving some incentive.

The conclusion that the speakers in the public comment section brought to our advisory committee was, as I stated at the outset, was that there's not a lot of slack in our current blood supply, and attempts to quantitate that, you make your best effort and that's what I think this slide represents.

CHAIRMAN BROWN: Yes, Peter, that's fine.

Thank you, Dr. Nightingale.

This is certainly going to be heatedly discussed in the discussion period this afternoon. And so I'm going to call time for lunch now, but we're going to come back to that and particularly since there are present on this committee now two or three people who were present there.

And clearly this is an important issue. And we'd like to thrash it out as thoroughly and satisfactorily as possible, and we will.

I'm going to reconvene at 1:30 rather than 1:45. That's 45 minutes. 1:30.

(Whereupon, the proceedings recessed for lunch at 12:45 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:42 p.m.)

CHAIRMAN BROWN: This afternoon's program will begin with several presentations as a part of the open public hearing.

And Bill, did you have anything that you wanted to say about the public hearing part?

DR. FREAS: Nothing other than the fact that we do welcome comments from the audience. And this your opportunity, if you're not on the agenda, to come forth and express your views to this committee.

CHAIRMAN BROWN: Yes, there have been several speakers who have given the FDA notice that they wanted to make a short presentation. And in general, as I recall from past meetings, these presentations should be limited to five minutes.

DR. FREAS: That is correct.

CHAIRMAN BROWN: The first speaker from the Armed Services Blood Program, who you've already heard from earlier this morning, is the Director of this blood program, and it's Captain Bruce Rutherford.

CAPTAIN RUTHERFORD: Good afternoon.

The Department of Defense would like to thank you for allowing us to offer public comment.

I am Captain Bruce D. Rutherford, Medical

Service Corps, United States Navy, the present Director of the Armed Services Blood Program.

On 5 February, 1999, Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs, forwarded a letter to Vice Admiral David Satcher, Public Health Service, the Surgeon General of the United States.

In that letter, Dr. Bailey expressed her opposition and the opposition of the Surgeon Generals of the Army, Navy and Air Force on deferring individuals as blood donors based on "perception" of a "possible" risk of transfusion transmission of the agent for "new variant" CJD.

There has not been a single case, repeat, single case of transfusion transmitted new variant CJD or classical CJD reported in the world in more than 55 years since transfusion of blood products became widely accepted as a treatment regime.

In November of 1991, the Department of Defense issued an advisory recommending that individuals participating in Operation Desert Storm be deferred as blood donors after a number of Desert Storm troops were identified with cutaneous and visceral *Leishmania tropica*.

Knowing that *Leishmania donavani* was

transfusion transmissible, and now knowing the extent of infection rate of the "at risk" population, the DOD decided to defer those individuals as blood donors who participated in country in the Persian Gulf.

It was not until December of 1993, or two years later, that the DOD stopped asking leishmaniasis related questions of its blood donors. The cessation was due to a concentrated effort by the military health system in identifying an extremely small number of infected individuals and the follow-on screening questions' ability in identifying an extremely small number of donors with symptoms where leishmaniasis could have been a possibility.

However, a study in the survivability and infectivity of viscerotropic *Leishmania tropica* in human blood donors from ODS participants was later shown to support our concern and was published in the American Journal of Tropical Medicine and Hygiene in 1993.

Transfusion transmission by Leishmania species was a known, not theoretical. We know the calculatable risk of being injured in a car accident, yet millions of individuals a day drive their cars with hundreds of thousands being injured per year and tends of thousands killed each year.

It is the same with airplanes, lightening and other activities.

In theory, anything is possible. I remember back a few years ago when the Institutes of Medicine came out with this HIV report. Yes, hindsight was better, but that has always been true.

I think in this case we have hindsight, 55 years of hindsight. We do not need to institute a UK deferral policy which will only lead to further crippling of our nation's blood supply and more product shortages.

However, what we do need is a concerted research effort by federal and civilian entities to develop human virus-free or non-human products to replace the majority of products that we presently use.

We need Hemoglobin-Based Oxygen Carriers presently in clinical trials moved through the regulatory process at a faster pace. We need better hemorrhage control products such as fibrin or non-fibrin based bandages.

We need more recombinant clotting factors produced in transgenic herds, yeast or bacteria. We need to move away from 80 years of collecting blood.

Thank you.

CHAIRMAN BROWN: Thank you, Captain Rutherford.

Are there any questions that any of the panel would wish to address to Captain Rutherford?

The next presentation will be by Kay R. Gregory of the American Association of Blood Banks.

MS. GREGORY: Good afternoon.

I'd just like to come up here rather than try and fix that microphone to my height.

The American Association of Blood Banks is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members including community and Red Cross blood collection centers, hospital-based blood banks, and transfusion services as they collect, process, distribute and transfuse blood and blood components and hematopoietic stem cells.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety of the nation's blood supply.

The association operates a wide array of

programs to meet the safety priority and is proud to have played a key role in ensuring that the nation's blood supply is safer today than ever before.

The AABB appreciates this opportunity to comment on the potential deferral of donors who have traveled to Great Britain as a means of reducing the theoretical risk of transmission of nvCJD through transfusion of blood and blood products.

The AABB wishes to reiterate its previous position stated at the last meeting of this committee that any measures taken to decrease a theoretical risk must not impact safety by decreasing the availability of the blood supply.

The AABB points out that classical CJD has been the subject of intensive study and notes that current opinion is moving toward a position that transfusion does not transmit this disease. AABB recognizes that data from classical CJD cannot be extrapolated to new variant CJD.

Nevertheless, there are no scientific data to support deferral of donors for new variant CJD. AABB considers it very important to continue to gather and assess data about new variant CJD and was pleased to be able to participate in the survey you heard about earlier today to determine the magnitude of

donor loss should donors be deferred based on travel to Great Britain.

In December, when you met last, this committee recognized that 11 percent of donors, as estimated by AABB and other presenters, would not be tolerable. And you asked for more data to evaluate the impact of imposing different deferral criteria on blood availability.

The AABB would like to call your attention to recent data obtained from the National Blood Data Resource Center on current trends in blood donation and utilization, and you've heard this already this morning. Data obtained from the 1998 blood collection and utilization survey indicate that in 1997 12.6 million units were collected and 11.5 million units were transfused.

For allogeneic units, 93 percent were transfused. Between 1994 and 1997, total blood collections decreased by 5.5 percent, while the total number of whole blood and red cell transfusions increased by 3.7 percent during the same period.

Extrapolating recent trends, the National Blood Data Resource Center predicts that demand will exceed supply by the year 2000 if no changes in deferral criteria are applied. Therefore, even with

no changes in deferral criteria, it is becoming increasingly difficult to maintain an appropriate level of supply.

Spot shortages during holiday periods and during the summer will be even more difficult to alleviate. Any new deferral criteria for donors will decrease the number of donations available. Thus, a policy that defers even a very small percent, such as one to two percent, of available donors will have a detrimental effect on blood availability.

Furthermore, donors deferred for travel to Great Britain would, of necessity, be replaced at least in part by first time donors, a population which has shown to have higher behavioral risk and a higher incidence and prevalence of infectious diseases known to be transmitted by blood.

Therefore, it is possible that the change in the donor base that might occur as a result of donor deferral or travel to Great Britain might increase the risk of transmission of other known or unrecognized transfusion transmitted pathogens.

Another issue that merits consideration is the potential psychological impact of deferring donors who have traveled to Great Britain. A person who is excluded from donation based upon concerns of

transmitting nvCJD may react by becoming anxious about whether he or she might develop nvCJD at a later date.

This is especially worrisome, in that the risk is theoretical, there is no short term intervention or resolution available for the donor, and there is no intervention that can be taken on the donor's behalf to alleviate such concerns.

In conclusion, AABB notes that there is no evidence that nvCJD is transmitted by blood transfusion. There are no cases of nvCJD in the United States. It is unknown whether travel to Great Britain correlates with exposure to or infection with the agent of BSE.

And there is no evidence that any proposed criteria will decrease the theoretical risk of acquiring nvCJD from transfusion. In contrast, there is good evidence that even a one to two percent loss of donors due to new deferral criteria will have a significant impact on blood availability and, hence, on the safety of those transfusion recipients who cannot tolerate a delay in receiving blood products.

The country should contemplate nvCJD deferral criteria only when it is apparent that such a policy would improve blood safety more than the loss of donors and the associated decrease in blood

availability would compromise blood safety.

Thank you.

CHAIRMAN BROWN: Thank you, Ms. Gregory.

The word theoretical has been used many, many, many times this morning and will continue to be used, and it's being used correctly. I'd just point out that, for ten years, between 1985 and 1995, the risk of new variant CJD from BSE was also theoretical.

The next speaker is Dave Cavenaugh from the Government Relations Committee of Ten Thousand.

MR. CAVENAUGH: I'm the government relations person at the Committee of Ten Thousand. The organization is the Committee of Ten Thousand.

CHAIRMAN BROWN: Yes, that's fine. Thank you.

MR. CAVENAUGH: Okay, COTT, which is the Committee of Ten Thousand, is gravely concerned about the industry logic favoring UK donors over additional U.S. replacement donors even with the survey, and even with the lack of data on paid and unpaid high volume pheresis donors.

This morning's discussion showed a glaring omission in the analysis to date of the impact of excluding well paid, highly educated, non-incentive provided pheresis donors in addition to the larger,

understood group of paid pheresis donors.

We've heard quite a bit in terms of the studies and in terms of some of the questions about the likely blood borne nature of this never documented entity of prion and its ability to be transmitted by blood.

There's a perceived link between new variant and beef that's been raised based on proximity, but the BSE classical CJD link should not be forgotten. It should be entertained at the minimum. Living in the United Kingdom in the late '80s seemed to be a major factor, for example.

What was it about living there, that's proximity. Both statistic presenters showed clear risk of new variant in the blood, not even enlarging the scope to include classical CJD. There are no nv cases in the U.S., but plenty of classical -- arguably, much more than the one in one million rate alleged.

Just ask CJD Voice, the patient-family support group which spoke before you 18 months ago. Small then, its numbers have mushroomed. Something is getting transmitted. Can it all be through beef? But most disturbing is the recent news confirming a second mutated form of prions also causing death in under a

year.

This doubling of the number of ways prions can be malformed with fatal results raises our concern levels considerably. The explanation that it is spontaneous sounds like an early catch all. With an entity so new, so unknown and so dangerous, the committee should be providing every protection possible, not bowing to arguments of relative risk.

Thank you.

CHAIRMAN BROWN: Thank you.

The fourth presentation will be by Dr. Michael Busch, who is a member of the Blood Safety and Availability Committee and Scientific Director of Blood Centers of the Pacific.

DR. BUSCH: Yes, thank you. I'm happy to be here and to share a little bit of context because my concern and reason to come to the meeting was to try to put a broader perspective to a focused deferral.

And I think we've learned in the past that focused deferrals can have consequences, and both political and safety consequences. And I just want to share a broader context to these discussions that I hope you'll consider.

There are many ways that we can sort the

donor base toward improved safety, and many of these have been considered over time. And what I've tried to do on these next three slides is just summarize the kinds of donor sorts that have been considered in terms of improved safety.

We have allogeneic and autologous donors at present. For example, autologous donors, their blood is not allowed to be given to other people. There has been great controversy over the years as to the relative safety of directed donors, and you heard today about the potential increased safety of apheresis donors.

Many of these relative safety issues have actually not been recently analyzed carefully. The frequency of donors, the concept that first time donors are higher risk I think is now well established that they're probably two to three fold higher in terms of incidence of the major transfusion transmitted viral infections.

In contrast, among repeat donors, there's a kind of old saw that the more frequently a person gives, the safer. In fact, recent analyses from the REDS group has indicated that the more frequent donors are actually no safer than less frequent donors; and further, that actually apheresis donors are no safer

than frequent whole blood donors.

So some of these theoretical benefits, I think, are not borne out by data. There's good data on regional risk. And for many viruses actually, you can look at the United States and look at different collection regions.

The southeast U.S. versus the midwest, for example, dramatically different: 10 to 30 fold different rates of risk incidence. Collections at mobile sites, at high schools, colleges, etc. versus other sites, urban versus rural.

There's now good data coming forward that show that there's significant relative safety to donations given in different regions. There's a major focus now on incentives. Should we be paying donors to give more frequently or are there other types of payments such as giving donors time off work?

I think Alan Williams' recent data from the REDS survey group shows that actually time off work is a significant predictor of denied risk behavior. So the kinds of characteristics that -- donation related.

Then we can go on to demographic characteristics and I'll show some -- a little bit of data from this, and I think this was distributed to

the committee. But there are dramatic -- significant differences in risk, and particularly the incidence rate of new HIV and other major viral infections distributed by these demographic characteristics.

And I think Alan also showed that the British donor deferral would impact differently on different groups. Again, I'll show some specifics on this. But in general, race ethnicity -- there are some highly significant correlates. The more educated donors are, the lower the incidence.

There's risk associated with country of birth. And just to recall for you the major outcry that occurred over deferral of Haitian donors, and currently there's still in effect a deferral of sub Saharan African donors.

So just the broader context that these geographic-based deferrals have been implemented in the past. Really travel history is what we're focused on now. In the past, there remained deferrals for malaria. There have been intermittent deferrals for travel to HIV risk areas, and now the consideration of British deferrals.

Obviously medical history and behavioral history and surrogate tests are other deferral criteria. Just a little bit of data to illustrate

some of these points. And we're focused here on incidence. Actually, these numbers would be much more dramatic if we talked about prevalence.

Prevalence reflects lifetime accrued exposure to an agent, but the risk of blood is predominantly due to window phase. And therefore, most of our interest in relative risk for established agents for which we screen relates to the frequency of new infections or incidence.

And what you can see actually is some examples of how these potential sorts may be beneficial for one agent and actually detrimental for another. For example, for HIV there's a higher, but not significantly higher, incidence in males than females, but there is a highly significantly increased incidence for hepatitis B in males to females.

On the other hand, both HCV and HTLV are higher incidence in female donors, probably related to secondary sexual transmission from injection drug use. So, what might seem like a safer group of donors for one virus are, in fact, a higher risk subset for another virus.

If you look at age, pretty much across the board there's a age related higher incidence rate in younger donors, but then as donors age, they are less

at risk of being exposed to these agents. Now, as you're aware, the older donors tend to be the better, well off donors who can travel.

As Alan indicated, a British donor deferral would actually bias towards exclusion of older donors and result in the needed replacement with younger donors.

Education is really probably a reflection of socioeconomic status. And again, there is a lower risk of infection with better educated donors pretty much across the board. The one exception is if you focus on high school donors, you need to focus on the younger high school donors who are still high school students versus older individuals who only completed high school.

And once you do that sort, you pretty much see a consistent decline across all viruses with the higher the level of education, the lower the risk of infection with these agents. Again, this is an example where the donors who you're seeing indicate a history of prolonged travel to Britain are the better educated donors, so on offset would occur in replacing those donors.

Race/ethnicity is actually one of the most startling predictors of incidence. Just one example

here, hepatitis B surface antigen with a much higher incidence in black, non-Hispanic and Hispanic donors than in Caucasian donors.

Obviously many of these deferrals are not either practical due to the need to have an adequate blood supply, or ethically or socially acceptable. There's been discussion about exclusion for transfusion. And in fact, in France they've recently implemented exclusion of previously transfused patients from giving blood.

In fact, if you look at prevalence, the prevalence of all these viruses is higher in previously transfused patients, but that's because their risk of acquiring these infections from transfusion predated the introduction of screening.

So now that we're screening the blood supply, this slide just shows from REDS again that the rate of new infections is no different in transfused and non-transfused people. So an exclusion based on history of transfusion will have no beneficial effect with respect to current agents for which we're screening.

If there's an agent that may have been transfused in the past, theoretically there could be a benefit of excluding those donors. But one must be

aware that about seven to eight percent of all blood donors have been transfused in the past.

So an exclusion of transfused donors, somewhat like British donors, would have an incredible impact on blood availability with really, I think, a negligible and non-quantifiable benefit in terms of safety.

I included in the distribution a manuscript that we published a few years ago which actually focused on what was at the time a major controversy. The age deferral issue came up because donors, particularly whole blood sector donors, were later developing classical CJD.

Those reports were coming to FDA, and FDA was taking the position that these products needed to be recalled and/or not distributed, and it was having a huge impact on the availability and financial issues around blood banking.

So what it led to was a sort of knee jerk reaction, well let's just exclude older donors because most of these CJD cases are occurring in older donors. And what we were able to show in this paper and pretty much undermine that policy was that actually the exclusion of the older donors would result in an increased risk; that donors over 50 had a two to

tenfold higher incidence, higher risk than younger donors.

And that, as a consequence, if one were to exclude all donors either under 50 or under 60, you would increase the risk of the blood supply for these known transmissible agents by ten to 20 percent. And I think this was a significant factor in the decision by the blood organizations to not implement this policy and by FDA to eventually reverse that recall policy.

Now, the last point I want to make is that -- is alluding to the impact on donors. And I think until very recently, we've not had data to quantify what notifications to donors that they're deferred indefinitely or permanently on the grounds of non-specific test results or deferral policies has on these individuals.

And recently, the REDS group conducted a survey called the REDS Donor Notification Survey where about 4,000 donors who had been deferred due to test results, various ALT, anti-CORE, false/positive results for various markers were surveyed and asked about the impact of these notifications -- the effectiveness of the notification message and the impact.

And just a few selected results, I think, illustrate that a large proportion of these donors who were being given data that we think is pretty definitive -- we're convinced these donors are not infected.

We've done extensive testing and further testing, and many of these donors are brought up for follow up, additional testing. And they're basically being given a message that you're not infected with this virus, but unfortunately you had some results that are leading us to have to permanently defer you.

And what you can see here is that about 80 percent of these donors, equally split between a lot and a little, indicate confusion when they're initially notified of these results. And the survey actually was conducted in general about five, seven years after the notifications.

And you can see that many of these donors remain confused years later. Again, there's -- about 50 percent of these donors are indicating they're still confused about the meaning of those original notification results, although most of them now are a little less confused over time.

They also indicate a high level of anxiety with about 40 to 50 percent of these donors indicating

that they were very, very emotionally upset when they were told of these results, and another 40 to 50 percent -- 40 percent or so indicating they were somewhat upset.

As with the earlier data, when you ask these donors are they still emotionally upset, this number drops to about half of that level. But many of these donors remain concerned and upset and confused about the meaning of these permanent deferral messages in the absence of any mechanism to reinstate them.

And finally, many of these donors, even though again our message was one of reassurance, have subsequently sought doctors' advice on what to do about this. And unfortunately, in the case of new variant CJD, I don't think we'll be able to give doctors much advice other than trying to reassure these donors.

Coincidentally, I just received a couple letters that I distributed to the committee during the break that are actually from donors that just wrote to my CEO just in the last day.

And I'd ask you to glance at those letters because I think they really point out the intense, you know, emotional experience that individuals go through when they are told they can no longer give blood, many

of them after having, you know, became dedicated donors and feeling that a good, you know, meaningful component of their lives had been giving blood.

And the impact of these false notifications on these donors and the failure of a mechanism to allow these donors to be reinstated and appropriately reassured that their own health and that of their families is not at risk I think is an important consideration as you consider a policy that would impact a very large number of individuals.

Thank you.

CHAIRMAN BROWN: Thank you, Dr. Busch.

I have a question or two for you before you leave. I would imagine that if a statement were crafted that was a little less blunt, it might take some of the emotional backlash out of this.

In other words, instead of sending a note saying "sorry about that, but you're permanently deferred, you'll never be able to give blood again" -- which is unrealistic in the present context. If it were decided to exclude a proportion of British donors, one could send a note saying "you are temporarily excluded from giving blood for the following reason," and put a little paragraph in there why the position was taken.

It's not complicated, complicated. Until such time as we know that this doesn't pose a risk, then we will exclude you, but we will not exclude you permanently. The same thing, I am sure, is going to happen with the screening questions that currently exclude recipients of growth hormone and dura mater recipients.

These are not going to be permanent categories of exclusion. That's the first point.

And the second is that -- did I understand you correctly at the beginning of your speech to say that the data indicates that there is no difference in the risk of having any of these other transfusion related agents between professional donors, volunteer donors, apheresis donors, first time donors and multiple repeat donors?

Did I understand that correctly or did I miss a beat?

DR. BUSCH: Why don't I do the second one first. Yeah, no, there is a quantifiable, increased risk among first time compared to repeat donors. But within the repeat, volunteer donor sector -- so these are the volunteer donors -- although classically people always felt that the more frequently you give, the safer you are and that apheresis donors who are

giving weekly, this kind of special, more committee donation program, are safer than whole blood donors, as we've begun to do analyses in the REDS group with huge databases to try to quantify and validate that, we've been unable to validate that.

There does not appear to be an increasing safety margin as donors give more frequently. This is all data from the volunteer donor sector.

CHAIRMAN BROWN: So, in other words, if you've given twice, beyond that it's a plateau?

DR. BUSCH: That's correct, --

CHAIRMAN BROWN: Okay.

DR. BUSCH: -- that's what our data indicates.

In terms of the first issue, you know, the concern -- from a blood bank operational perspective, that's pretty much what we used to do. We used to tell donors you're, you know, temporarily deferred; that there's a potential that we'll be able to reinstate you down the road.

What that results in is donors frequently calling back and saying "what's happened, where do I stand with this." Eventually, you know, the FDA has in the past come forward with reinstatement programs that allow for donors to go through follow up testing

a year later, for example, that allows them to be reinstated.

In fact, those programs pretty much universally across the country are not operationalized, one, because they're frequently reversed as new tests come in and new questions arise. They're quite onerous in terms of the required testing.

But in addition, they're a regulatory catastrophe. Because if, by chance, eventually a donor who was reinstated gets implicated in another problem, immediately, you know, the FDA comes into your office and the first thing they look for is where's your donor reinstatement records.

And they want to go through those records and verify that those donors were completely, properly reinstated. So, for a variety of reasons, the truth is that donor reinstatement does not occur in this country, with very rare exceptions.

And this is even for agents for which there are FDA approved reinstatement programs. So for these reasons, practically at this point -- and, you know, what's the difference between an indefinite deferral, a temporary deferral?

These are very subtle and often non-

defined distinctions. So at present, even though you can frame it just as you indicated, and we probably would, practically that's why I asked the question earlier.

You know, how long will we need to wait until people are convinced that this is not a problem and we can reverse this policy? And what I heard was, you know, it's probably five or ten years before we'd have a sense.

So, you know, do you want to tell people, you know, call back in a year or two? So I think practically this will be -- you know, unless there is some position of this committee that this should be a two year, you know, revisited, I think it would be inappropriate for the blood banks to communicate to the donors that this is a temporary deferral.

CHAIRMAN BROWN: Yeah, I understand that point of view. At least this is not complicated by the necessity of retesting. I mean, that's at least one thing we don't have to worry about.

DR. BUSCH: It could be viewed as a good or a bad issue. I mean, --

CHAIRMAN BROWN: Both, both. From the point of view of basic science, bad. From the point of view of practicality, good.

The final scheduled -- I'm sorry, is there a question?

Bob.

DR. SCHONBERGER: Mike, I'd like to come back to this question of deferring for history of prior use of blood products, which, as you know, is one of -- I feel is one of the best things you could put in place for building a fire wall between us and the expansion of any inapparent infection that might be occurring through blood and blood products via TSE agents.

And this number that you come up with of seven or eight percent, what I'm having difficulty with this is making that -- it seems to conflict with the experience of Marian Sullivan and trying to do look back studies where it seems like a much larger percentage than that of people who have received transfusions at least have died already by five years or so in the look back.

And presumably, if the people who survived transfusion are such a small cohort, a lot of them aren't going to be healthy enough to give blood anyway. And is that really a realistic number, or could it be smaller than that?

DR. BUSCH: I think that number is

definitely accurate. You know, it's coming from -- we're required to ask donors have you been transfused in the past. So this is a required question of blood donors, and these are compiled, actual reports from blood donors.

I think the issue is -- you're right, you know, half of blood goes into patients who die, but actually only a small fraction of transfused patients die, probably 20 percent. And the distinction is, is that the patients who are dying get a heck of a lot of the blood.

So very ill patients consume a lot of blood. Eighty-percent or so of people who are transfused survive, and those people probably -- many of them, fortunately, currently become dedicated donors because they've benefitted from the transfusion process.

But the number of 78 percent I'm certain is correct.

DR. SCHONBERGER: Well, what if you excluded albumin?

DR. BUSCH: That's not included in that.

DR. SCHONBERGER: That's not included?

DR. BUSCH: No.

DR. SCHONBERGER: Okay.

CHAIRMAN BROWN: Questions from the floor?

DR. TABOR: Well, the question about history of transfusion is the one that predates the availability of most of the serologic tests we have, and it's clearly one that, sometime in the future, could be reexamined.

It's certainly been well documented that most people, for instance, of those very rare cases of individuals whose blood transmit hepatitis B, they've almost never had a history of transfusions themselves. So that question is -- that we ask donors is an anachronism and probably is an anachronism with regard to new agents also.

I'd like to also make a comment regarding the use of the term British donors. We're not talking about British donors. We're talking about red blooded, American donors who happened to have had enough money to go to England or to have been sent there by the military.

Where possible, I think we should not refer to them as British donors because that adds a level of connotation that we're excluding something alien. And we're talking about American blood donors who are going to be impacted by what we decide, and it's the American blood supply is going to impacted.

CHAIRMAN BROWN: For the record, that was Dr. Tabor from FDA.

So the transcript is hereby directed to strike out every use of the phrase British donor, which is, in fact, incorrect; and these obviously are American donors who have visited or lived in Britain.

Although I suppose British donors would still be included, wouldn't they?

(Laughter.)

CHAIRMAN BROWN: We haven't addressed that.

Larry.

DR. SCHONBERGER: I'd like to suggest to the Captain -- I guess it was Captain Gregory that presented to us where -- Rutherford, was it?

CHAIRMAN BROWN: Captain Rutherford.

DR. SCHONBERGER: Rutherford.

CHAIRMAN BROWN: Close.

DR. SCHONBERGER: Okay, sorry about that. Bruce Rutherford.

That when he talks of 55 years of data, you know, where there's been no cases and so on, that it would be more impressive if the military could institute or present sort of a more epidemiologically oriented study.

I would think that they are particularly uniquely suited to potentially get good data on the new variant CJD issues particularly, and they still would have time to set something like that up, since much of the exposure of the U.S. citizens to Europe, I would think, may well be military people who were assigned there during the '80s and so on.

Perhaps the military could identify these people. And certainly the Centers for Disease Control would be happy to help continue the follow up of such individuals if they would want to institute that.

It just struck me when we're talking about all these years of not hearing about things, when, in fact, we search often to look for tighter epidemiologic type of studies, and I would encourage that that be discussed.

CHAIRMAN BROWN: Yeah, I don't know we need to discuss it now.

But Captain Rutherford, you've got an offer for help if you -- from the CDC if you'd like to -- and I think Larry's right. You have an unusual opportunity, in fact, to assess this problem in the near future and CDC is a good colleague to have.

The final scheduled presentation is Dr. Richard Davey, who is the Chief Medical Officer for

the American Red Cross.

DR. DAVEY: Thanks, Dr. Brown. Just before I start, I'd like to correct perhaps one misperception from Mike's presentation. He said that half of patients who get transfused eventually die.

Actually, all patients who get transfused will eventually die.

(Laughter.)

DR. DAVEY: So, Mr. Chairman, the American Red Cross does welcome the opportunity to speak to this committee on this important subject. The Red Cross supplies almost half of the nation's blood supply through the generosity of over four and a half million volunteer blood donors.

We serve over 3,000 hospitals through our national network of 37 blood regions. The Red Cross regards the safety of the blood supply as its highest priority. As such, the Red Cross is currently conducting nucleic acid testing for HCV and HIV throughout our system under an IND application.

In addition, Red Cross scientists are actively investigating possible emerging threats to the blood supply such as Chagas disease and Babesiosis. We've also supported research in the TSEs through direct research conducted by Dr. William

Drohen at our Jerome Holland Laboratory, as well as through -- as well as with collaborative research with both Dr. Brown and with Dr. Rohwer.

The Red Cross actually has devoted more resources than any other private organization to understanding the relationship, if any, between TSEs and blood transfusion. While the safety of the blood supply is our highest priority, the Red Cross also has an additional responsibility to ensure an adequate supply of blood and blood products for the American people.

Indeed, an inadequate supply of blood poses a major safety hazard, as critical blood and blood components may not be available when needed. We view with considerable concern, therefore, any proposal to defer donors who have lived in or traveled to Great Britain during the peak years of the BSE epidemic in that country.

This deferral is being considered because of the theoretical risk of transmitting new variant CJD from individuals who may have consumed beef products in Great Britain during those years. As we know, new variant CJD has not been reported in the United States, and there are no documented cases of this disease being transmitted by blood or blood

products worldwide.

Now this morning Dr. Alan Williams presented data gathered through the REDS and ARCNET systems on the impact on the American blood supply if donors who lived in or traveled to Great Britain between 1980 and 1996 were deferred.

In brief, the percentage of donor travel to the UK varied from 0.4 percent for those who resided in the UK for five years or more to 22.6 percent who were in that country for three days or fewer.

The estimated annual blood resource lost by deferral of donors visiting UK between 1984 and 1990 varies from over 35,000 units lost annually for deferral for a five year visit to 1,939,000 units lost for deferral for a one week visit.

That's just an annual loss, not a cumulative loss, which would be larger if we looked at it over a two or three or four year span.

Now the blood supply today is marginal, at best, with shortages often occurring over the holidays and summer months. A variety of recruitment strategies have been implemented with encouraging results, but the donor base remains barely adequate to meet increasing clinical needs.

Our blood supply actually is not very elastic. Increased recruitment efforts, however strenuous, may not be able to overcome the deficit caused by deferrals of the magnitude being considered by this committee.

New donors would have to be found to replace the deferred donors. As these new donors, as we've heard, would be first time donors, most of which would be first time donors, a group with a higher incidence of deferral risk and disease markers, it's quite possible that these new variant CJD deferrals would actually decrease the safety of the blood supply.

In addition, deferred donors may face possible stigmatization for being somehow unsafe, and may have undue concerns about being at risk for a dread disease. Also, and I think this is important, the message that the committee will send to the public with these deferrals is that Mad Cow Disease is a current blood transfusion safety risk in the United States.

Can we say the new variant CJD will never be shown to be transmitted by blood transfusion? Of course we can't. That would be asking us to prove a negative when we can't do that. But we must act

rationally using the best science and professional judgement in considering these options.

Research must continue in this important ~~a~~rea. Periodic evaluation of our national strategies on blood safety issues must take place. However, given the present body of scientific and epidemiological data, and considering the known impact on our nation's blood supply, any deferral at this time for this theoretical risk cannot be justified.

Now I may just digress from my written comments for a moment. I think this committee clearly has a very important issue in blood safety and it's considering it very, very carefully, to its credit. But I think it's important for us to realize that not having enough blood is a very, very unsafe thing.

In the National Blood Data Resource Center data that wasn't presented today, 8 percent of the hospitals in the United States in 1997 -- 8 percent -- had to defer or cancel surgery because there was not enough blood.

That's a lot. That's within the Red Cross system and across the nation in the independent blood centers, 8 percent of hospitals deferred surgery.

We just don't have enough elasticity to make up for a further major deferral. In the Red

Cross system, we are actually increasing donations. Our donations are up, but the demand is up even further.

We also have to consider again the first time donor issue. We're going to be replacing these deferrals, if we can replace them at all, with first time donors primarily.

And we've seen that they have an increased risk of deferral risk factors three times over repeat donors, increased risk of disease markers of twice that of repeat blood donors, a safety issue of concern.

Also, I think we have to ask is it in the public interest, as Mike pointed out just a few minutes ago, to have to convey a message to our donors, most of whom are dedicated pheresis donors and repeat donors, that we no longer wish to have them as participants in the national blood supply.

We will develop a group of hurt, angry and scared donors. And whether deferral is permanent or temporary, it's going to be very hard to give these folks the message that they're deferred for a risk that really we know nothing about and is purely theoretical.

It's up to the blood centers to have to

deal with these donors. It's up to the blood centers to have to get new donors, and that's going to be tough indeed. And again, I think it's important to realize that public perception of the safety of the blood supply is also at question here, and deferrals will indeed raise the public perception of risk of TSE in the American blood supply.

So I ask the committee to think very carefully about these proposals and to base their decisions on the best science and epidemiology available. Consider the impact of blood safety that may result from significant erosion of both our blood donor base and of public confidence in the safety of the blood supply.

The American Red Cross will continue to conduct and support research on the possible transmissibility of new variant CJD, and we will honor our commitment to help ensure both a safe and an adequate blood supply for the American people.

Thank you.

CHAIRMAN BROWN: Thank you, Jay.

If there is anyone in the room who wishes to make a statement, this is the time to do it.

Oh, I'm sorry, did you -- Peter, a question for the last speaker or a comment?

DR. LURIE: To the assertion that the development of travel restrictions would signal to the public that Mad Cow Disease is a problem, I guess I have two comments. The first is the Institution of Travel Restrictions for Malaria does not seem to have communicated to the American public that malaria is a problem in the blood supply.

What I think the message the American people will take from this is that a group of people have wrestled with the problem and have done the most they can to protect the blood supply from Mad Cow.

CHAIRMAN BROWN: I must say the Chair agrees with Dr. Lurie on this. I don't think it probably is too smart to go that far afield and make a decision on the basis of something which really is a question of education.

I mean, if someone is going to take a decision to defer, let's say, a small number, let's just say, of donors who have lived in Britain as evidence that Mad Cow Disease exists in the United States, I just don't think there's much we can do about it.

That's just a question of not understanding. In any case, we had a question or a comment from the floor.

DR. FREAS: Please identify yourself.

MS. McMILLAN: Certainly.

My name is Melissa McMillan and I'm with America's Blood Centers. And I just wanted to comment a little bit about some of the things that Dr. Davey mentioned. America's Blood Centers is the association of all the independent community blood centers.

And also, like the American Red Cross, we do collect about half of the nation's blood supply. We work with about 3,100 different hospitals and serve about 125 million people annually. I think some of the things that we've heard today -- we've heard a lot of scientific data.

A lot of the things I'm about to tell you are based upon conversations with the communication structures and our members who are located in 46 states, and also based upon some of the shortage surveys that we conduct to try and monitor the status of the blood supply during our tradition shortage periods which are, like we've discussed, the summertime and the wintertime.

We have had several members tell us that, even as of last summer, their transfusion rates increased not just the 3.7 percent we heard today, but 15 percent. Another center in Florida said that their

transfusion rates increased last summer by 20 percent.

Now, if you take it nationwide, you do have a much lower average; but these people are -- and the donor recruiters are spending an increased amount of time and money to bring in donors when their transfusion rates are soaring far beyond the expectations of the recruitment goals that they set based on a typical need.

Now, this is something we need to look at. There are a lot of things that we need to, you know, think about. And some of this data we don't have. For instance, what are these transfusions being used for, what types of surgeries?

This data is not readily available, but it could give us an incidence as to what are the types of people that need surgeries and maybe also give us some sort of correlation among the people who are donating.

For instance, we have liver transplants on the rise. With an aging population, we're going to have an increase in the number of knee and hip replacements. These surgeries require a lot of blood.

Now, I've had many reporters over the years ask me, "Has anybody ever died from a lack of blood?" The answer is no. But do we want to take a chance in saying that? We have to possibly say yes if

we defer a percentage of the population who are good donors.

I just think it's something we need to think about.

Thank you.

CHAIRMAN BROWN: Is there anyone else in the room who would like to make a comment?

Yes, middle of the room, left-hand side.

MS. SULLIVAN: Thank you.

I'm Marian Sullivan from the National Blood Data Resource Center. I was sitting back there trying to decide which of my data to defend first here today, and I decided to speak for a couple of minutes about our year 2000 projection.

The projection, which has been quickly flashed on the screen a couple of times here today, could benefit from being put in better perspective, I think. Without the benefit of the other slides that led up to its presentation at the advisory committee meeting, it's a little bit difficult.

The projection resulted from an 18 month data collection and analysis process which involved 2,400 U.S. hospitals and blood center participants. As a result of this 1998 nationwide blood collection and utilization survey, the NBDRC and Westat produced

national estimates for blood collections and transfusions in 1997.

These data were compared primarily with data from the Center for Blood Research -- which had been collected by the Center for Blood Research for 1994, the last year for which national data were collected prior to our survey.

However, we have also conducted an analysis of historical trends going back well into the 1980s. Considerable fluctuations are evident over these years. The year 2000 projection graph which you say today illustrates the trends in supply and demand for the most recent and most relevant period based on the 1994 and 1997 data.

The supply declined by 4 percent, or 1.3 percent per year, in this period. If I had my slides with me today, you could see that if we plot whole blood collections back to 1989 through 1997, the overall decline is 11 percent, or 1.4 percent per year, from 14.2 million to the 1997 figure, 12.6 million.

In fact, the slide which you did see today actually extrapolates the available supply rather than total whole blood collections. And this has somewhat softened the negative slope which you might have seen.

And that's due to the fact that we have seen, during this period, a significant decrease in the test loss percentage which has softened the slope if we plot available supply, and that has been taken into account in our projection.

Regarding transfusion demand, the extrapolation which you saw illustrates a 3.7 percent increase in transfusion -- units transfused between 1994 and 1997, or 1.2 percent per year, which is not statistically significant.

In fact, if I had chosen to plot allogeneic, meaning community units transfused, you would see an increase in transfusions of 7.1 percent, which is significant. But the projection actually included all types of donated units transfused.

In fact, if you can once again imagine my absent slide showing historical trends back to the early '80s, what you see is that annual transfused units have actually leveled off since the early '90s. And prior to that, there was a very steep increase in the early '80s followed by a decline that began about 1986.

We do not believe that we have overstated this issue in our year 2000 projection. The assumptions we made were based on the most recent

trends in collections and transfusions.

In fact, after I presented these data at the advisory committee meeting last month, a number of committee members, some of the speakers and some others closely involved in blood banking commented and seemed to agree that I had actually understated the problem.

And if, in fact, we had included other factors and prepared a more complex model, other factors such as the population increase and the redistribution of the population, as well as blood group availability -- if we had factored these things into our model, then the projection would have only been strengthened.

Thank you.

CHAIRMAN BROWN: Thank you very much, Marian, for a well tempered riposte to the criticisms.

I think -- Ray, is it about this? Because I was going to suggest that all of the people who have made public presentations stand ready to answer questions when this aspect reappears, which it will, almost immediately, if that's okay.

Marian, you'll probably be recalled to the stand, okay?

That concludes the public hearing part of

our day and we now enter into deliberations, which is always the most amusing part of each day.

(Laughter.)

CHAIRMAN BROWN: And I have a plan. And it will probably get sunk, but I want, before we make these deliberations, to summarize for you and the committee members my own view of the framework for the following discussion.

We have, on the one hand, to evaluate the risk of disease transmission from the blood of patients with new variant CJD. That is the issue before the committee. And here is what we know and don't know about that side of the equation:

We cannot yet predict the magnitude of new variant CJD in the United Kingdom. We cannot quantify the risk of infectivity versus the period of potential exposure. We do not know the proportion of new variant CJD cases that will have infectivity in the blood, if any.

We do not know the level of infectivity, if any, in the blood during the incubation period of new variant CJD. We do know that there is probably a much less degree of risk in plasma derivatives than in blood components based, as a generality, on what we know experimentally from what you've heard a little

bit of this morning and a good deal of in December, this being based on both the distribution of infectivity in TSEs, transmissible spongiform encephalopathies, in general within blood components.

That is to say, largely present, but not exclusively present, in the Buffy coat. Plus the fact that processing of plasma for derivatives has been unequivocally shown to result in very large losses of any infectivity that might have been present in unprocessed plasma.

The second part of the equation is the effect of any exclusion on blood supply. And we've learned that we have a good quantification of the effect on voluntary donor supply. We have no information at all on the effect on paid donor supply.

And that's what I come away from this morning's education as the main elements of our consideration. It therefore appears to me that if any exclusion is, in fact, recommended, it is going to have to be done as a pragmatic decision.

In other words, can any cut be made to obtain a maximum reduction in risk with a minimum effect on the blood supply? I propose to ask the committee -- and Bill, if you want to put that slide on now -- to immediately consider a reversal of the

draft questions in which we will consider question 2(a) first.

And what I'd like to do -- as you see, this is a query about doing any exclusion for the purpose of plasma derivatives. And it's possible that we can dispense with this question immediately. It's possible we may not be able to.

I therefore wonder if the committee would agree to answering that question even before discussion with a yes or a no. If the majority of the committee feels that there is no need to recommend new criteria for deferral with respect to plasma derivatives, we can dispense with question two all together and concentrate on question one, which is the same question focused on whole blood donors.

If the committee decides that question two needs discussion before any decision is made, we will go ahead and duly discuss it. This, by way of perhaps spending more time on what appears to me, at least, to be a question of -- that is arguable on both sides, that is question one.

If the committee would like not to do this, please let me know. If you'd rather just sort of take it 1(a), 1(b), 2(a), 2(b) as it's written, then we'll go ahead and do that.

Stan.

DR. PRUSINER: I would like to argue that we go as planned in the beginning, 1(a), 1(b), 2(a), 2(b), because I think that there's some -- there can be some arguments made with the first group of assumptions that you made, pieces of data that you threw out about prions being largely in white cells, blood product titers being lower.

So I would suggest that we don't change the order, --

CHAIRMAN BROWN: Okay.

DR. PRUSINER: -- that we don't do this.

CHAIRMAN BROWN: Bob.

DR. ROHWER: I also think we need to consider, in general, the intent of dividing this into two categories and what the significance of that is. In other words, I'd remind you that the British right now are not deferring for fresh blood. They're only deferring for plasma.

It's just the opposite of what the intent, I believe, of this -- of the focus here is. And there are important implications of that, and I could begin by discussing those right now or we can resolve this issue of whether we're going to discuss them first.

CHAIRMAN BROWN: Well, is the committee

more or less agreed that it would be a better idea to just go through 1(a)(b), 2(a)(b)? I hear lots of heads shaking.

Okay, the Chair stands demolished.

(Laughter.)

CHAIRMAN BROWN: And we will therefore open the discussion with a discussion of question 1(a): Should the FDA recommend new deferral criteria for whole blood donors to attempt to reduce the theoretical risk of transmitting new variant CJD from transfusions based on foodborne exposure to BSE in the UK?

The question is open for discussion.

Yes, sir.

DR. CLIVER: I'm going to get this in sooner or later anyway, so now's as good a time as any. I've been hearing wish lists of things that need to be researched. We also heard don't wait for the science, but eventually all of these things are going to be resolved, we hope, by scientific investigation.

We're dealing with a pyramidal hypothesis here that is all based on a broad assumption about food transmission. And as I said at the previous session, I'm really dissatisfied with the way this aspect of the question was being addressed.

I think we need to know more about that, if we can. But just the idea that now we're going to focus on transmission from person to person via blood and give up, as it seems to me, on some fundamental aspects of how people got infected via food in the first place I think is not the way to go.

So just to give you an idea of the things that I think we ought to be trying to know more about with regard to peroral transmission in beef, if you will, or animal products -- one, I understand that there is some work that addresses the question of the level of agent in tissues -- specific tissues eaten.

I'm hoping that that also addresses the question of -- the degree to which this is a function of the stage of the infection. We're hearing that perhaps the last year or so before onset is the time when the agent is going to be at peak, and I'd like to know whether that's universally true or whether it's even applicable to the perceived edible portions of a carcass.

Second, we don't know anything about the digestibility of the various tissues that may harbor the agent and how those are going to be processed during the digestion in the GI tract.

Third, assuming that the agent gets to a

susceptible portion of the intestinal mucosa, and we don't know what that is, why then the question is what is the interaction between the agent and the intestinal mucosa?

That's just one cell defending us from all the things that go through our bodies all our lives and this is a pretty critical aspect.

Finally, it seems to me that we ought to be addressing the question of age and other host factors. That is, as people, how differently do we process these things?

When I hear that onset of something that might be CJD in someone under 55 is probably diagnostic or at least highly suggestive of new variant over 55, it isn't seriously considered, this says that something happened to me a while ago and, if I want to go back to England and eat beef, I've got a carte blanche now because I'm 64 and it ain't going to happen to me.

So, you know, I should be able to donate blood forever, except, unfortunately, I had something 12 years ago with a melanoma that kind of negates that. But we need models. We need to be trying to find experimental means of addressing these and I'm sure additional questions.

And they aren't going to solve any problems real fast. But all the same, to proceed with the top of the hypothetical pyramid and ignore the base, I think, is dead wrong, too.

End of sermon.

CHAIRMAN BROWN: Yes, Bob, I'll call you in just a second.

Dr. Cliver, it's possible that there's a misunderstanding here. We are not here to discuss how people get new variant CJD in Great Britain. We're not concerned about how they got it. We're just concerned that they got it.

And what our main concern is, what our only concern is, is whether or not such patients are capable of transmitting CJD through the blood.

DR. CLIVER: But risk assessment is a well established part of the way these kinds of decisions are made in the regulatory arena, and we don't have the bases for risk assessment vis-à-vis how long somebody stayed in the UK, what they had to eat, how they at it and so on.

So I think it's a valid and significant part of the risk assessment process.

CHAIRMAN BROWN: Yes, you're suggesting that we really ought first to decide -- have a

consensus on how new variant -- whether or not living in the United Kingdom is a risk factor?

DR. CLIVER: I didn't say that. We're talking about quantitative risk assessment, and I didn't say that the data are in hand to be able to do it.

All I said is while we're prescribing or wishing for research that would clarify some other aspects of this hypothetical pyramid, that neglecting the base of the pyramid by saying that's not relevant, we've got to get on with business, is incorrect.

It is just not the way risk assessments are done -- quantitative risk assessments.

CHAIRMAN BROWN: What way are you suggesting that we do here now?

DR. CLIVER: I'm suggesting that we at least add this to our wish list of things that need to go into a longer term perception and understanding of whether someone in this country who happened to spend a few days a few times in England, as I did, is at risk as a blood donor and is endangering his fellow citizens by giving blood.

CHAIRMAN BROWN: Right. So, again, I don't think we disagree. Everybody would like to have that, and we probably will have it too late.

DR. CLIVER: Well, okay. But all I'm saying is it isn't -- I haven't heard it even mentioned on the wish list at this point.

CHAIRMAN BROWN: Okay.

DR. CLIVER: I think it is significant --

CHAIRMAN BROWN: Okay.

DR. CLIVER: -- over the longer run.

CHAIRMAN BROWN: Bob.

DR. ROHWER: I wonder if Dr. Cliver would be satisfied if the word foodborne was just struck from 1(a)? I would certainly prefer that because I don't believe that it has been established that that's how new variant cases are acquiring this disease. And then we just go with exposure.

CHAIRMAN BROWN: Yes, I thought the wording on 1(a) probably could have been -- towards the end there, you can probably scratch the entire "based on foodborne exposure to BSE in the UK" and substitute "the theoretical risk of transmitting new variant CJD from transfusions from" --

DR. ROHWER: Based on exposure.

CHAIRMAN BROWN: -- based on exposure or --

DR. ROHWER: Period.

CHAIRMAN BROWN: -- residence in the

United Kingdom. No, exposure or travel or residence to the United Kingdom. But I think we all understand that. It's just a question of words.

Yes, Peter.

DR. LURIE: It seems likely that any restriction that this committee might come up with is going to be right censored in the sense that it would be -- I'm told 1996 or some other period and include the period before that.

Now, that being the case, and particularly seeing as though people who are blood donors are disproportionately older, what this means is that any impact upon the blood supply is going to be one that will be maximal when first implemented.

And that within a period of time of some ten to 15 years, the impact of that will just kind of work its way through the population and will decrease with time until it has no impact at all. So we should look at these as really maximal impacts upon the blood supply.

CHAIRMAN BROWN: Ray.

DR. ROOS: I just wanted to give my own opinion about the whole blood versus blood derived products, which I guess maybe is a little bit of a different perspective than I think you were getting

at, Paul.

And that is, from the point of view of safety, although there may be reasons for thinking that with fractionation you're going to lower the titre and be safer, on the other hand one clearly has the -- if, in fact, the agent is in the blood, one has the danger of disseminating it far more widely with respect to the blood derived products than unit to unit transfusion, and perhaps that was one of the reasons that guided the UK to make the decisions that it did.

And so we're poised now very uncertain about what the risk is here, whether we should be guided by the data that we have, which is, of course, from classical Creutzfeldt rather than new variant. And if we worry about the risk, I think we have to take into consideration what's going to be our most dangerous action here, which I think might relate to the possibility of releasing contaminated blood derived products.

I also worry and, you know, maybe I need some education here, but does everything get fractionated? In other words, there's still, I guess, fresh frozen plasma; and, in that situation, one really doesn't have the benefit of fractionation.

Just thinking about that whole option of the -- of blood versus blood derived products and safety versus any threat to our blood supply, I wondered whether the blood bank people could educate me again.

And that is, when somebody gives blood, is it clear what that blood is going to be given to? In other words, can you ensure that units that are given might be given for whole blood or red cells or platelets and keep particular units from going into blood derived products and into this big, big vat?

And that way one might not be able to decrease the number of donors, but just redirect where those donations come from -- go to.

CHAIRMAN BROWN: Dr. Gilcher.

DR. GILCHER: I think Dr. Katz and I are going to address probably similar issues, and I really wanted to expand on the point that you had just raised.

I think question one and question two need clarification. Because the real issue in question one is should FDA recommend new deferral criteria for directly transfusible blood products. It has nothing to do with whole blood donors because it could be an apheresis platelet donor, an apheresis plasma donor.

It's a direct, transfusible product. Question 2(a) should then go to a pooled product that is used that is subsequently fractionated. That would clarify the questions.

CHAIRMAN BROWN: Could I interrupt you for just a second and ask Jay if that, in fact, is the intent of the question?

DR. EPSTEIN: That is our explicit intent.

DR. GILCHER: Because this -- and Jay, you may want to comment -- is analogous to malaria, which, in fact, was raised by the Chairperson. In malaria, if you have been potentially exposed, your plasma can, in fact, be used even in that case for direct, transfusible purposes, but certainly can be used for plasma fractionation.

Whereas, the red cells or cellular products specifically cannot if they contain red cells because that can transmit malaria. But I think the intent here is that we're talking about direct transfusible versus a pooled, subsequently fractionated product.

And the reason that's important is that on the whole blood donor side -- or let me say on the directly transfusible product side, the plasma from the donors would, in fact, be able to be fractionated.

And when you look at the amount of plasma that goes to recovered plasma fresh/frozen, and I'll give you the statistics from my center, approximately 80 percent of the 80 to 85 percent of the plasma that is derived from whole blood ends up as recovered plasma fresh/frozen.

The remainder is used as a transfusible product. So the majority of plasma derived from whole blood, at least at my center, and I suspect that's true for most of the ABC centers and probably the Red Cross as well, that plasma ends up as recovered plasma fresh/frozen, which is subsequently fractionated.

And that would not be a deferrable issue if number two were, in fact, allowed to stand.

CHAIRMAN BROWN: Right. I have a question.

Susan, you said that most of the platelets that you recover are recovered from apherese plasma. Or at least a lot of it is, huh?

DR. LEITMAN: They're not recovered. The donor is recruited and donates specifically for that purpose.

CHAIRMAN BROWN: For platelets?

DR. LEITMAN: And not only -- in my institution, 100 percent of the platelets are derived

by platelet pheresis of apheresis --

CHAIRMAN BROWN: Okay. Under those circumstances, of course, the platelets are not pooled with any other --

DR. LEITMAN: No.

CHAIRMAN BROWN: And what happens to the plasma, it goes back to the patient?

DR. LEITMAN: The pheresis product is collected in 200 to 500 ml of plasma and that's a platelet pheresis product. We don't -- most centers do not do concombinant plasma donation at the time of platelet pheresis.

CHAIRMAN BROWN: Okay, so I wanted everybody to understand this. This is a plasma pheresis. Ah, excuse me, a platelet pheresis, so to speak. It's not plasma pheresed where at least you're removing platelets and then directing the plasma to a pool.

DR. LEITMAN: That's correct.

CHAIRMAN BROWN: This is a one to one donation?

DR. LEITMAN: Platelet pheresis donation is a one type of donation.

CHAIRMAN BROWN: So the wording would -- the preferable wording, Jay, would be: Should the FDA

recommend new deferral criteria for directly transfused products?

Is that correct?

DR. EPSTEIN: Well, it's deferral of criteria for donors of blood components intended for transfusion use.

CHAIRMAN BROWN: Stan.

DR. PRUSINER: So Ray just said unpooled. That's the key word here, isn't it?

DR. EPSTEIN: Well, it isn't quite because there are transfused components that are pooled.

DR. PRUSINER: How big are the pools?

DR. EPSTEIN: They're small. They're, you know, about ten to a dozen would be typical for safe platelets.

DR. PRUSINER: Okay, so under 25?

(Laughter.)

DR. EPSTEIN: Well, I think we shouldn't get too hung up on the words. What we're talking about here in questions 1(a) and (b) are the directly transfused products. You know, whether they're given in individual units or small pools, notwithstanding.

DR. PRUSINER: Okay.

CHAIRMAN BROWN: So again, I think the words actually are important because they imply

they're important to know why ask both questions. So let's get exactly the wording that everybody can appreciate.

DR. PRUSINER: So how about, Paul, individual or as small pools, which I was saying?

CHAIRMAN BROWN: Deferral criteria for -- well, I guess all donors are individuals.

DR. PRUSINER: Right.

CHAIRMAN BROWN: For donors whose donations or who -- how do you want to word it? I know what everybody sort of understands, but I'd like to really get it down exactly.

DR. LEITMAN: I'd like to make a suggestion. It could be for components which do not undergo further processing. Pooled platelets or pooled cryoprecipitate don't undergo further processing other than some units may be frozen and then thawed.

But --

CHAIRMAN BROWN: You say pooled platelets?

DR. LEITMAN: You can get a unit of platelets from a unit of whole blood and pool six to ten such platelet units and get --

CHAIRMAN BROWN: From the same patient?

DR. LEITMAN: From different donors. A

whole blood unit can be fractionated into packed red cells, plasma and platelets.

CHAIRMAN BROWN: Yeah, you taught me that. But I thought you just said pooled platelets.

DR. LEITMAN: There's two kinds of -- there's two ways in which platelets are manufactured. One can gain the entire amount to be transfused from a single apheresis donation, or you can pool single, random donor units of platelets derived from a whole blood donation.

CHAIRMAN BROWN: So there could be several donors --

DR. LEITMAN: Up to ten.

CHAIRMAN BROWN: -- contributing a pool, and this is what you were asking. A pool of 10 or 12 donors whose platelets then are pooled.

DR. LEITMAN: The same would be true of cryoprecipitate. When one transfuses that component, there's a pool of anywhere from six to 12 units. But those products don't undergo further processing the way plasma derivatives do.

They're not fractionated, they don't go over columns, there aren't any activation steps. There aren't cuts made of the product.

So perhaps components that don't undergo

further processing would be a better way of stating it.

CHAIRMAN BROWN: Okay, and another -- yes, a question. Is it also possible historically and today, that cryoprecipitate, for example, could wind up in pools of 10,000 to 100,000. That is to say, it would be prepared from huge pools, just as, for example, IgG as opposed to ten donors?

Is cryoprecipitate a kind of special case that could have little pool or huge pool.

DR. LEITMAN: Its the cryoprecipitate when pooled, is the starting material for making pastes from which the fractionated derivatives are made, but that's not transfused as an unprocessed component. There's further processing involved.

DR. BUSCH: Still? Because in the past --

DR. LEITMAN: To make the plasma derivatives, yes.

CHAIRMAN BROWN: Yes, historically cryoprecipitate, as was given as such without further processing, huh? Paul?

DR. ROHWER: The key distinction here is that these pools, the pools that Dr. Leitman's talking about, I believe, go into one person. In other words, you pull these units together for one transfusion. So

there's only one person exposed.

They're expose to ten people, but it's the difference between having a huge pool where one person can expose thousands of people or hundreds of thousands of people or something like --

CHAIRMAN BROWN: I hear you, but that's not exactly the same thing that Jay was saying. Jay was emphasizing processing. You're emphasizing number of recipients.

Which do we want to consider, Jay?

DR. EPSTEIN: Well, --

CHAIRMAN BROWN: Which do you want to consider?

DR. EPSTEIN: I think that if we simply say deferral criteria for donors of transfusible components, it's clear enough to FDA what we're talking about because we only have two categories of donor deferral criteria, One we call whole blood, the other we call source plasma.

Now there are subsets of apheresis components for transfusion, but they follow the donor criteria for whole blood. So, you know, it's actually simpler than it seems. But I think we can correct the language just by saying new deferral criteria for donors of transfusible components, --

CHAIRMAN BROWN: Okay.

DR. EPSTEIN: -- and it will be true for that set that the products are either in single units or small pools.

CHAIRMAN BROWN: Okay. And question 2(a), how would you word that, for donors of pooled products, of what?

DR. EPSTEIN: Well, typically we would call those fractionated products. That would be another way to describe it.

CHAIRMAN BROWN: So it would be donors of --

DR. EPSTEIN: Well, I think it's correct as stated, of source plasma and recovered plasma intended for fractionation.

CHAIRMAN BROWN: Okay. I'll ask the committee if everybody understands this distinction.

Okay, Jay.

DR. EPSTEIN: Yeah, I guess the idea is that they're further manufactured into injectables. That's where the processing issue comes in. Because we do have at least one pooled product, namely solvent detergent treated plasma, which is not technically fractionated.

There's no fractionation. However, it is

further treated.

CHAIRMAN BROWN: I am clear about what you want. I think there is a contradiction in separating the second from the first. And one is that it's pooled, therefore it has the capacity to infect zillions of people.

And the other is that, despite being pooled, it's processed, so it's going to reduce all the infectivity to zero. So you've got two contradictory risk factors.

DR. EPSTEIN: Well, first of all, not all processing is equal.

CHAIRMAN BROWN: No, of course not.

DR. EPSTEIN: For example, solvent detergent and plasma has no fractionation, and yet the pools can be as much as 2,500 donors.

CHAIRMAN BROWN: Right. But your point of making two questions out of a single question --

DR. EPSTEIN: Yes.

CHAIRMAN BROWN: -- is clearly designed to make us appreciate that there is a distinction in potential risk --

DR. EPSTEIN: Yes, we --

CHAIRMAN BROWN: -- in these two situations.

DR. EPSTEIN: We reflected on the way we had framed the questions in December, and we felt that we had somewhat muddied the issue by not distinguishing for the committee that the risk/benefit equations might differ significantly.

When you're dealing with transfusion components, you have all the infectivity from the unit collection going into the recipient. Whereas, in the situation of processed products, you have large pools, you have higher risk that the infectivity would be present in the product.

On the other hand, titre is lowered. On the other hand, it goes into many more people. And layered on top of that is that the percent of donor loss would be different in the two populations as well.

Although, I think it's reasonable to speculate that the percent donor loss would be less in source plasma for any criterion that we imposed in the two settings given the younger age and lower socioeconomic status of the source plasma donors.

So, we simply felt that by having failed to make that distinction, we deprived the committee of the ability to think through the possibility of different policies in the different settings. That's

why we've split it now.

CHAIRMAN BROWN: Okay, so let's have the committee think through donors of transfusable components, right?

DR. EPSTEIN: Well, but so let me suggest --

CHAIRMAN BROWN: Yes, yes. Go ahead, Jay.

DR. EPSTEIN: -- just the wording of 2(a). For donors of source plasma and recovered plasma for further manufacture into injectable products.

DR. NELSON: I have a technical question that maybe some of the prion experts can help me with. And that is, my understanding was that this agent was fairly resistant to disinfection or treatment, and yet you're telling us that the processing will eliminate infectivity to almost zero.

And somehow, I don't -- I can't appreciate how effective is the processing with regard to removing infectivity because obviously if it's, you know, only partially effective, then we're increasing the risk by allowing pools.

On the other hand, if it's highly effective, then that's --

CHAIRMAN BROWN: Bob, why don't you produce some numbers.

DR. ROHWER: Well, the point here is that there are two ways to get rid of infectivity. One's to kill it, and the other one -- and the other way is to partition it away from your product.

And fortuitously, in the case of these agents anyway in the couple of instances in which we've been able to do this experiment, the partitioning went in such a way that the infectivity didn't go with the product.

However, there's always a denominator on that number. It depends on how much infectivity you challenge the process with to begin with. You can't claim that you removed more than you put in. And also, some steps in the process are more efficient than others and there's some question about how multiplicative those steps are.

And for technical reasons, it's not always possible to test that aspect of the fractionation over the full range of the process. So there are some uncertainties in this.

And by way of a caution, we have to realize that even though we demonstrated high levels of removal for Factor VIII, for example, for a Factor VIII process, a particular Factor VIII process that we validated, on the other hand, we know from experience

that that didn't happen in the case of HIV, otherwise we wouldn't have had this high rate of exposure of hemophiliacs to HIV.

So it's not a foregone conclusion that it will happen in every single fractionation, every single time, and it probably means that every single one of these steps ultimately has to be validated by direct testing of some sort.

And there are other caveats associated with this type of experiment -- whether the spike was appropriate, that type of thing. There are many different ways in which you can conduct it.

But all I'm trying to convey here is from the data that we have in hand today, it was very encouraging that actually there is probably a great deal of benefit at least that's derived from going through the refinement process for these products.

CHAIRMAN BROWN: Yes.

DR. PRUSINER: Bob, I would like to say that I think that, you know, the committee -- I mean, obviously when you make a statement like that, the committee is very influenced by it. And it seems to me this is very preliminary data from what you're telling us.

That's what I'm understanding. And

secondly, I want to emphasize that it's the physical state of the prions that's very important because these are proteins. They aggregate to many different size particles.

And what you choose as the spike, as you very carefully said, can influence enormously how it's cleared. And usually these particles are -- these are non-ideal particles. They're not even like HIV where we have a particle which we -- we have one HIV virus, then we have another one, and another one, and another one and they all behave the same pretty much.

That's not true with the prions. So I think that we're -- that people are getting a little false sense of security here with very preliminary data, unless you have much more data than I know about.

DR. ROHWER: Well, I would like to agree with you to the extent that we've done one experiment using one spike modality for one of these -- well, we've done four different products, but we've done one spike modality, one animal model for each one.

I think it would be much better to look at several different spike modalities in several different models, several different processes before you come to any final conclusion as to how much

security you can get from these processes.

The only thing I wanted to communicate is that compared to the crude cone fractionations which have already been published in the transfusion paper last year, these things have -- the products that are actually injected undergo a lot more refinement than the fractions that were mentioned in that paper -- that were assayed in that paper.

And we're not starting with very much infectivity to begin with. I mean, that's the other part of this equation, though that again is based on animal models and there is some question about new variant CJD.

And certainly Neil Cashman has made a very strong argument that the titers may be much, much higher in new variant. I'm not sure why he can't discount that argument, but --

CHAIRMAN BROWN: What is that argument?

DR. ROHWER: That argument -- his argument basically is that PRP RES concentrations seem to be much higher, and if infectivity directly correlates with PRP RES, then there must be more infectivity there.

CHAIRMAN BROWN: Higher where?

DR. ROHWER: In the brain, but also it's

found in RES organs -- you know, the tonsils and appendix and places where you don't find it in classical CJD.

CHAIRMAN BROWN: Would you agree that an alternative, equally plausible explanation is that this is the result of route of exposure?

DR. ROHWER: Yes.

CHAIRMAN BROWN: Larry.

DR. SCHONBERGER: Yes, I was just trying to get -- clarify what I think I heard Stan say.

Are you saying that the data that we're hearing about, the clearance of the GSS agent or other agents in the model, may not apply to new variant CJD prions? Is that what you're saying? I understand the differences in the arguments about titre and where the agent is.

But are we saying that those differences between new variant CJD and other prions are such that the clearance data should be looked at with a grain of salt?

DR. ROHWER: Well, I agree with that. All these things should be done over again using the new variant model. But again, it will be a new variant mouse model. It's not going to be a new variant monkey model or a human model simply because -- well,

it can't be a human model.

And the monkey model would just be -- it would be impossible to do this type of experiment in monkeys.

DR. PRUSINER: Yes, I think that the protein, the prion protein, the disease causing form, PRP SC in BSE is really quite different than many of the others. So it's a different strain. Because we think that strains are different confirmations of PRP SC.

And we have some recent data which is unpublished, but it has been presented at a Uri Saffire, excuse me, Mike Scott presented this data in Geneva a couple months ago, so we're trying to prepare it now for publication -- where we've been able to transmit new variant CJD into mice that express bovine PRP with incubation times of about 250 days and all of the animals get sick.

So there is, I think, a model for the future now to be able to look at this. Strangely enough, these mice have the same neuropathology as mice that receive bovine BSE prions, and much different neuropathology than these same mice that receive natural scrapie.

So I think it may be possible in the

future to get some of these answers. What I was really reacting to though -- I don't think this is really important right now. What I'm really reacting to is not being overly influenced by some early optimism that may or may not be correct that Bob Rohwer's telling us about.

I mean, I think that's all very interesting and all very encouraging, but I don't think we can make decisions based upon one time experiments. And I'm not sure that we want to do that. I think that might be a mistake.

It places a big burden on Bob Rohwer's data. And I think he would want to at least replicate it before we start making decisions based upon this kind of information.

CHAIRMAN BROWN: Yes, I don't really think anybody disagrees that we never have enough data, and this data is certainly early data. On the other hand, it seems to me early data is better than no data at all.

DR. BOLTON: Paul.

DR. PRUSINER: I don't do -- I don't think we want to debate that, but let me just say I disagree.

DR. BOLTON: Paul.

CHAIRMAN BROWN: Yes, I'm sorry.

DR. BOLTON: It seems to me that if -- this is slightly off the subject, but on the general subject. If we vote to put in deferral criteria in the first case and not in the second, aren't, in fact, we redirecting those donors from either whole blood or direct transfusable donations into pooled donations?

CHAIRMAN BROWN: Yes, that's an amusing twist. Hadn't occurred to me, but that's probably what would happen.

DR. BOLTON: Then I guess the question is: Is that acceptable to the blood banks, and is that a good outcome?

DR. NELSON: I said that's the reason for my question.

CHAIRMAN BROWN: We have a comment here.

DR. EWENSTEIN: Well, I was going to ask just a little bit more on the fractionation procedure just as a point of information.

Do you have mass balance at this point on those experiments? And also, you know, sort of -- it begs the question in the commercial operation: Where are these infectious particles now? I mean, they're still on the cow?

DR. ROHWER: That's an extremely

perceptive question. We do not have mass balance, and I don't believe we're ever going to get mass balance using these types of experiments and these types of models simply because to do the experiment on the scale on which you have to do it in order to get a mass balance would be prohibitively grandiose.

And so we're only going to get a glimpse of what's going on in these things.

No, these experiments will -- I really don't think there's much hope for them ever meeting the same standard that would be applied to a conventional virus. I don't think -- unless we can come up with an in vitro assay or something like that that allows us to actually do the assays on the same kind of scale that you can do them for in vitro work, I don't think that's going to happen.

CHAIRMAN BROWN: Yes.

MR. COMER: Thank you, Chairman. I just thought it might be worth informing the committee that I was at a meeting of the World College of Physicians in Edinburgh about two weeks ago and the Scottish National Blood Service were reporting a series of experiments that they have been doing on clearance factors for fractionation.

I don't have the paper with me and it was

at a meeting, not a published paper, but they are doing quite an extensive series of work, again obviously using mass model, but I believe getting very similar results to those that Bob's reporting.

So there are at least other data that support the -- we're getting similar sorts of results. Six full log clearances for many of the processes within the fractionation area.

CHAIRMAN BROWN: One further point is that in the paper that was published that Bob referred to in which a spiking experiment was done and a parallel experiment was done using an endogenously infected model, one could have predicted the other, which is just a little point in favor of at least that spike being a pretty good spike.

That spike happened to be intact, infected brain cells. And the distribution was very similar to that found in endogenously infected mice -- that is, mice that weren't spiked, but the infectivity was within the cell -- excuse me, within the blood naturally.

Yes, Ray.

DR. ROOS: I wonder whether that study was done on BSE and new variant or another one of the spongiform encephalopathies?

MR. COMER: No, it was a scrapie mass model.

DR. ROOS: Okay. Because I just want to mention we have run into problems in the past with the spongiform encephalopathies with pooled material such as the dura mater, lyadura event and growth hormone.

We've also had problems with the unit to unit approach, obviously, but the toll there is far less. And I do think the data is good. And in fact, I think that the data that we have from Paul and Bob have clearly clarified a lot of things.

And I don't think we would be struggling with some of the issues here if we hadn't had that data -- that is, that the agent is in blood, and that even the intravenous route works, and that this is a cause for problems.

But I am a little cautious about the issue of the fact that it isn't in -- it isn't the new variant agent that we're dealing with and that some of the rules may be different.

CHAIRMAN BROWN: Well, this is exactly why we're here today. Dr. Satcher and the other groups have already decided that this is not worth significant worry with respect to classical CJD, and that new variant was an unknown.

And so that's why we're considering specifically new variant because we don't have information specifically on it. I mean, everything we don't have information on becomes a subject for this committee.

(Laughter.)

DR. McCULLOUGH: I'd like to go back to the two different groups of donors. I think if the committee made different recommendations for the plasma donors versus the transfusible product donors, it seems unlikely to me that we would divert donors from one group to the other.

They're generally different -- fundamentally different groups of donors, and I think there's very little cross over back and forth between those groups is point number one. And point number two, that even if blood centers decided to start to generate most of their plasma for fractionation by plasma pheresis, they really aren't set up to do that.

The equipment is limited and the economics are marginal with volunteer donors. And so I think that the concern that we might divert donors from one group to the other is probably not a practical one.

CHAIRMAN BROWN: Dr. Epstein.

DR. EPSTEIN: Well, two comments, first on

this point. To prevent diversion, what we would do or could do is to recommend that if a donor of blood components for transfusion is identified to have this risk, that that donor's plasma not be distributed as recovered plasma for fractionation.

That could operate coincident with a system where source plasma donors aren't asked that question. So you'd have no diversion, but you'd still have two different systems operating. And I think that's the way we would reconcile it to prevent, you know, diversion.

Back to the point of consistency among studies of partition during fractionation. FDA has seen a second complete data set from one of the fractionators with experiments that were designed similar to the ones that Drs. Brown and Rohwer organized and those data were entirely consistent.

They, of course, suffer from similar limitations. As Dr. Prusiner said, you're using a particular type of spike obtained in a particular way. It's artificial compared to natural infection.

But still, if you look at the logs clearance at highly specified steps of processing, the consistency was near absolute in the two different experiments. Now those data are not public.

CHAIRMAN BROWN: Bob.

DR. ROHWER: But I would also like to make perfectly clear that I would not propose intentionally ever challenging the plasma fractionation with blood from new variant CJD cases just because you didn't know what else to do with it.

That is not my intent. It's just that there is an additional margin for error in any refinement process or margin of safety. Whether it's absolute or not is still open to additional verification.

CHAIRMAN BROWN: Yes.

DR. EWENSTEIN: I was wondering whether there were other data, the IV Ig processing as well, the other high risk recipient group.

DR. ROHWER: There is for the Nietschman Kissler process. We've presented that several times now and we're preparing that for publication. This is a process that's used by the Swiss Red Cross for making IV Ig.

And again, we saw, oh, four to six logs of removal at several steps in that process.

CHAIRMAN BROWN: The committee seems to have run out of gas on this rather early. I hope not.

DR. LEITMAN: I have a different question.

CHAIRMAN BROWN: Yes. I'm sorry, where are we?

DR. LEITMAN: I'm over here, Dr. Brown.

CHAIRMAN BROWN: Oh, sorry.

DR. LEITMAN: We seem to be extrapolating the partitioning data of classical CJD -- the agent of classical CJD to the agent of new variant CJD. That may or may not be okay.

I'd like to ask Dr. Prusiner if we can at all extrapolate the lack of transmissibility through blood components of classical CJD agent to new variant?

DR. PRUSINER: I don't know that I'm qualified to answer this. I can only tell you that the little bit of work that we've done now on new variant CJD says that it is a dramatically different strain of prion. That means that the confirmation of PRP scrapie is dramatically different than anything else we've studied.

So let me give you an example. We've looked at 40 different cases of sporadic CJD, and we know that there's several different confirmations there at least. And all of these are transmissible in about 200 days to either mice that have a human PRP gene or have a chimeric mouse human PRP gene.

If you look at new variant CJD, it takes more than 500 days and only about 60 percent of the animals get sick. Now, as I said before, if we take new variant CJD and we passage it into a mouse that expresses a bovine PRP gene on a null background, then all the mice are getting sick in 240 days.

The piece of data I don't have that you want is you want to know if I take sporadic CJD or familial CJD cases and passage those into mice with a bovine PRP gene, do they get sick? And the answer is I don't know yet.

But clearly, when we look at mice with human and chimeric mouse human PRP genes and we inoculate those with new variant CJD, the mice are very resistent. And there's a little bit of data from John Collinge, which has been published, which is in agreement with those findings.

Then if we take this and inoculate it -- these inocula from new variant CJD, inject them into mice with a bovine PRP transgene, they get sick. So that says that it's dramatically different than anything else that we've seen that comes from humans.

CHAIRMAN BROWN: But what I think Susan really wants to know is if you took new variant CJD and inoculated it into humanized mice, and then took

the blood from those mice and put it into a further group of humanized mice, would it transmit disease as opposed to the bovine transgenic or any of the other transgenics?

DR. PRUSINER: And the answer is I don't know. But I think there's another lesson. I mean, I agree that the work that you and Bob have published is most interesting. But there have been a lot of studies where people have taken blood -- so these are mice that are intracerebrally or hamsters intracerebrally inoculated.

And then people have gone to try to recover infectivity from various fractions or from whole blood, and this is exceedingly hard to do. I suspect that there are many, many more negative results out there where people were unable to do this than positive ones.

And the negative ones, of course, don't get published. In our own experience, which is not huge, we've had very non-reproducible data, which is why we've never published any of it on the recovery of prions from blood.

We haven't done yet the experiment you suggest, Paul. I mean, we will do this. But I feel very uncomfortable about the assays for prions in

blood. I don't know what's going on. I don't understand. There's a piece of scientific information that's missing there. It's a methodology.

CHAIRMAN BROWN: What specifically?

DR. PRUSINER: Well, the fact that we get variable results. I'll just give you very quickly our own experience for the congressional record. We did an experiment a number of years ago, and this dates back about three years, with hamsters.

And we isolated white cells and plasma, whole blood. And we inoculated white cells into additional hamsters. And these were -- the plasma was taken from animals that had just showed the first signs of clinical illness.

And the titers were fairly high. And when we corrected this per gram of protein, we had about 10^4 infectious units per gram of protein. So we were like three logs or two logs below brain. And then we tried to repeat this study.

We did a very large study taking samples at various times after intracerebral inoculation in the hamster, and then we went through this series of bioassays trying to repeat what we had done and we never found any infectivity the next time.

And I don't know what the difference is

between the first experiment and the second experiment. And then we did a series of experiments to see whether or not the feicol that we were using or the percol we were using to separate out the white cells or the edta or the citrate -- if any of these were important, and we never figured this out.

We saw if we took brain extracts and we added these various chemicals to them, we saw some small decrements in infectivity occasionally, but nothing consistent that would explain why we couldn't reproduce our data.

So I feel very uncomfortable that I don't understand this, and so I always look at these blood studies with big question marks. And if you go through an make a table -- I think Bob Rohwer's done this, or you've done it, where you compile all that's available.

And I know Hank Barron, who is here -- or was here -- he's done this. Maybe he'd like to speak to this. But you get -- you see that the results are not totally consistent, and I don't understand this. I'm concerned.

CHAIRMAN BROWN: Well, if I had experiments that you describe, I'd be uncomfortable as well.

(Laughter.)

CHAIRMAN BROWN: That in riposte to your comment about being interesting, which I always interpret from you as being as damning with faint praise.

I think the explanation for the inconstancy and variability is that you're probably dealing at threshold levels of infectivity. At least I think that's a major contributing factor. I think it's not worth discussing at length, but I will add what has been implied, but not clearly stated, that we have replicated now the experiments in mice two more times with consistent results.

Three separate experiments. So I'm much more comfortable with that set of experiments than you were with the hamsters. I will also say, in favor of variability, that our results, in certain respects, are consistent with Bob's work with hamsters.

In certain other respects, they differ. It would be very nice to have the hamster work and the mouse work consistent right down the line. They are consistent in terms of the level of infectivity that Bob is finding in hamster blood and I'm finding in mouse blood.

And incidentally, the mouse model, for

those of you who -- is a human strain of TSE. It happens to be from Gerschman Sträussler and it's a mouse adapted strain. Bob is using the typical ~~s~~crapie, high titre, 263K strain.

Irrespective of the two strains, the level of infectivity in the blood is consistent. It's ten to 20 infectious units per ml of blood. Where we differ dramatically is that in the mouse model, IV transmissions are fairly commonplace.

They're not as commonplace as intracerebral transmissions when you put blood in the brain, but we got a lot more than we bargained for. Whereas, Bob's hamster experiments, he has, I guess, still just a single transmission out of somewhere of 50 -- between 50 and 100 attempts.

Granted, there are certain technical differences, but that's an illustration of the fact that two different rodent models can, in fact, differ. And we're not going to solve that today. I mean, that's biology.

Yes.

DR. BELAY: How do you compare the clearance process of the different fractionation states? Is there more clearance at the first -- at the last fractionation state compared with the first

one, for example?

CHAIRMAN BROWN: Well, I can talk about just a simple Cohn fractionation, yes. It's a cumulative thing. I mean, each precipitation builds on the previous precipitation. Cryoprecipitation leaves a precipitate in the supernate.

The supernate is then reprecipitated and you get fraction one, two, three. It's a little more complicated than that. By the time you get down to four or five precipitations and albumin, you'll just about run out of infectivity even when you started with ten to 20 infectious units per ml.

That's just a physical following of this infectious agent with precipitate. And that's consistent. We know that years and years and years of all kinds of experiments that have nothing to do with blood have consistently shown that precipitation tends to take out this infectious agent.

Yes, Blaine.

DR. HOLLINGER: I think you bring to mind one of the concerns that I always have about using mouse adapted models and other things, which may not be equivalent to natural disease. It could be concentrations of virus much more than what we see naturally.

And, I mean, we see this with albumin, which was supposed to be very -- which is very safe. But you can overwhelm the system by putting in lots and huge concentrations of virus and end up with an albumin product that will transmit hepatitis B, for example.

Has anyone, Paul -- anyone here. Has anyone done any experiment -- I mean, the BSE problem has been down now around since 19, what, '83 and patients have been around since maybe '93 or '94. Has anyone done any experiments with just calves that are infected taking whole blood from calves and infecting other calves?

They don't have to come from -- they can be calves from another source where there would not be any disease, but infected those to see about transmission of this disease through whole blood. It seems like that's a natural experiment that would be relatively easy to do.

CHAIRMAN BROWN: Not easy to do. It is a natural experiment. It's on test, as I understand it, at Weybridge in the United Kingdom. And the calves, so inoculated, are still on test. Calf blood has been injected into mice so that you've got a species barrier.

That hasn't worked. And the calf experiment is still incomplete.

If there's anybody from the UK that has more up to date or correct information, that's as far as I know. So yeah, you're right. I mean, that was an obvious thing to do.

One of the problems is people didn't get interested in blood until a little bit later than they should have. And as you know, in this country, although we've been interested in a timely way, we've bene unable, due to the prudence of the USDA, to work with it.

Bob.

DR. ROHWER: Paul, it seems to me that the issue before us is to decide first whether we want to make a distinction between blood for use in directly transfusible products versus pooled products. And then if we decide we're not going to make that distinction, then we can move on.

CHAIRMAN BROWN: Is the committee -- Ray. And then after you say something, I'll ask the committee if they're ready to take a vote on whether or not we recombine, in spite of Jay's best efforts, both questions into a single question.

Ray.

DR. ROOS: I wasn't -- we've seen several times this figure that Steve Nightingale showed of the issue of the dangers to our blood supply and the risks. And I got a little confused with respect to transfusible components versus pooled products and how that figure related to those two different groups.

You know, we've spoken a little bit about issues related to safety of those two groups, the risk of those two groups, but I'm not quite clear about the availability and whether the -- whether we should lump them together.

CHAIRMAN BROWN: Yes, that's a good point.

Marian, why don't you defend -- or not defend, but clarify that. The data that went into your figure is based on what group?

MS. SULLIVAN: Based on whole blood collections, whole blood and red cell supply and demand. And of course, the products -- our data include -- our other data include components that are made from those whole blood donations and also pheresis -- specific pheresis donations.

But the figure --

CHAIRMAN BROWN: But it's based on whole blood --

MS. SULLIVAN: -- that we're talking about

is whole blood and red cells.

CHAIRMAN BROWN: -- donors rather than apheresis donors?

MS. SULLIVAN: Usually considered to be a good indicator of available supply.

CHAIRMAN BROWN: No, but is that correct? That is, this data is based on a population of whole blood donors?

MS. SULLIVAN: That's correct.

DR. ROOS: So what can I derive with respect to these pooled products? Do we know about their availability and what's anticipated for the year 2000?

MR. REILLY: Jim Reilly with ABRA.

We didn't publish the way that Marian did, but we recently collected some data which gives us some insight, but not absolute, definitive numbers on supply. First, there is, as probably everyone is already aware, a fairly substantial shortage of immunoglobulin.

Most of that is a bottle neck at the plant, but there is a very delicate supply and balance between source plasma supply and the fractionation capacity. Last year our estimates are that we were down about 13 percent overall.

And so for this year, it's just anecdotal, but it would suggest that we are probably down a little bit to even with last year. So we are in a very precarious balance and supply situation right now.

CHAIRMAN BROWN: Jay.

DR. EPSTEIN: Well, Bob, if I could comment though, is it not true that only half of the source plasma collected ends up in U.S. products? In other words, roughly -- there's roughly twice as much plasma is collected for fractionation than is utilized for U.S. products.

Worldwide, I recognize that there's still a shortage and that, you know, you meet needs of international customers. But still it remains true that the U.S. supply of plasma for fractionation is twofold greater than the U.S. consumption for U.S. use.

MR. REILLY: Yes. I don't recall off the top of my head whether it's half, but it is clearly in excess, yes.

DR. EPSTEIN: But vastly in excess compared with the situation of collection versus demand for --

MR. REILLY: Yes, Jay.

DR. EPSTEIN: -- blood component.

CHAIRMAN BROWN: At the microphone and then Dr. Sayers.

DR. DAVEY: This is a comment about recovered plasma or whole blood derived plasma. All of that material is used for U.S. consumption essentially. And I think if we are considering a deferral for that particular material that's going for further manufacture, the committee should consider the problem of post donation information.

We, at least in the Red Cross, often hear back from our donors days or weeks after a donation that there's some information that they forgot to tell us or whatever that impacts on how we handle those products that have already been obtained and perhaps sent for further manufacture.

So we will hear from donors that -- of the millions that we have, that gee, I forgot I was in the Army in England for a year or something or other. And we are going to have to deal with that information then in terms of market withdrawals.

Perhaps that plasma has gone into a big pool that has been manufactured into Factor VIII, IV Ig, whatever, material that's in very short supply. So post donation information has to be considered,

especially with its impact on the blood supply.

CHAIRMAN BROWN: Jay.

DR. EPSTEIN: Well, the committee voted in December that there should not be derivative withdrawals based on post donation information related to residence or travel in the UK, and the FDA has accepted that recommendation.

So I don't think that scenario presents itself.

CHAIRMAN BROWN: Dr. Sayers.

DR. SAYERS: Thanks, Paul.

I just wanted to say something about availability now that we've gone onto that. And it looks as if, judging by the way some of the conversation has gone, that the committee might end up with trying to make a decision about how much additional deferrable is tolerable against the background of this relative inelasticity of the nation's blood supply.

And I think cynics could reasonably argue that that's just making some sort of token concession to this issue. But I'd hate the committee to come up with some decision about what is tolerable in terms of a deferral rate if they assume that some of the other comments about the availability of additional donors

are indeed true.

And the comments that I'm referring to are the fact that one could be pardoned for thinking that the first time donor who is now a lapsed donor is somebody that could easily make good for any additional deferral that CJD criteria would superimpose on the nation's blood supply.

I mean, that idea flies in the face of what has been an incredibly aggressive attempt to recruit former donors, lapsed donors, recent donors, donors of any marking whatsoever. Community blood programs' attempts to recruit have been, as I say, aggressive.

What we're understanding is that part of the reason why those attempts are failing and part of the reasons why we see those two lines on that graph that Steve Nightingale intersecting -- part of the reason for that is that the whole donation process has become so alienating.

I mean, donors now find themselves spending twice as long during the donation process as they spent as recently as five years ago. Donors find themselves being given health information history which they very correctly perceive to be in total contradistinction to how they feel about themselves.

Donors find themselves being deposed. They find themselves involved in lawsuits. They find themselves being sent off to their physician and then incurring costs in terms of understanding what the health implications for some of the information is.

And I heard you say, Paul, that this is an issue of education. It certainly is. But it's not been against the background the blood programs have been less than resolute in attempting to apply this education.

The problem really boils down to this: when you tell a donor who has been deferred for any number of a whole host of reasons tied up with non-specificity that he or she can no longer donate, but you give that individual the reassurance that you're satisfied that he or she is healthy, when that donor comes back with an astute comment like "well, if I really am healthy, Doctor, why can't I donate," and you have no answer to that, then no amount of education is really going to be successful.

So I'd hate to think that this is going to come down to a decision about how many more donors can we defer, assuming that it's going to be easy to make up that deficit.

CHAIRMAN BROWN: Yes, Stan.

DR. PRUSINER: I'm really uncomfortable with these arguments that you just made. In fact, I'm exceedingly uncomfortable because to end the conversation with the patient by saying what you just said is just not accurate.

There are large numbers of answers. I mean, we went through this at the University of California and a whole set of discussions with a committee to try to set a policy. And the fact is that there's a lot of scientific information, and then there are a lot of clear unknowns.

And the unknowns have to be clearly stated to the patient. And for you to stand there and say what you just said I think is unfair to the committee, it's unfair to the population of the country, and it's really not accurate.

CHAIRMAN BROWN: We're warming to the task now.

DR. SAYERS: Let me blow some air on the embers, then.

(Laughter.)

DR. SAYERS: I'm mindful of what Dr. Tabor had to say about how we should accurately define "donors." And as an immigrant to this country from the UK, I think I can reasonably define myself as a

variant UK donor.

That aside, would that the donors that we deal with whose health history is significantly impacted by what is tantamount to the largest public health exercise in the world -- I mean, 40,000 people a day get tested by six or seven markers of infectious disease.

They get tested for markers of infectious disease like HTLV that the American College of Obstetricians and Gynecologists doesn't even regard as something which should be part of a pregnant individual's antenatal workup. And yet, we have to give those donors, if they're reactive in that assay, advice about whether they should be breastfeeding or not.

Now, these are not responsibilities that we have taken willingly or enthusiastically, but our issue really is that the donor's understanding -- his or her perception of what constitutes good health -- is not a perception based on the incredible insights and understandings that the pooled members of this group can represent.

To say that my remarks do a disservice to the donors, or to the committee, rather, without elaborating on it, I would have to say that any

deferral of donors, for reasons that are not rooted in science and for reasons that can securely steer us away from a further erosion of the blood supply, any decisions made on that basis are going to be a disservice to the three or four million transfusion recipients that we have to be concerned of annually.

CHAIRMAN BROWN: Okay. That's a pro and con.

Before we have any further discussion, I would like to ask the committee if they would be prepared to vote on the following question. Is our current knowledge insufficient to permit us to vote separately on questions 1 and 2? And is that -- I think this is the sense of one of the avenues of discussion that has occurred this afternoon.

Do we really know enough to be able to make this distinction, to be able to distinguish between risks from question 1 and question 2? So would the committee like to vote on whether, once again, to combine these into a single consideration of donor deferral -- blood donor deferral? All bets off, just no further distinction than that? Yes?

DR. BURKE: My question bears directly on that, and it's for Jay. And could you please review any precedents that there are for deferrals that are

-- where that's differentiated already, where there are FDA precedents for taking one class of donors and saying they're deferred for exactly the same age and then not deferring them in another donation setting.

DR. EPSTEIN: Yes. We currently screen donors of transfusable components for the anti-core marker for hepatitis B. We do not screen source plasma donors for manufacture of derivatives for that marker. We currently screen donors of transfusable components for antibodies to HTLV. We do not screen source plasma donors for markers of HTLV.

We do recommend, however, that if recovered plasma is obtained from an HTLV positive donor that it not be sent for fractionation. However, we do not prevent releasing anti-core positive plasma as recovered plasma for fractionation.

And then, as was mentioned earlier, we defer donors of transfusable components if they have risk factors for malaria, and we do not screen them, nor do we interdict recovered plasma based on risk factors for malaria.

DR. BURKE: So in every case where there is this exception, it's on the assumption that the agent poses less of a risk and is inactive -- and can be inactivated in the pools.

DR. EPSTEIN: Absolutely. That has always been the guiding principle.

DR. BURKE: So the issue of having it as a pool, and, therefore, putting a greater number of people at risk is not a precedent so far.

DR. EPSTEIN: Well, as I tried to say earlier, we could avoid that situation by adopting the posture we have for HTLV, which is that if you're screening the donor of transfusable components, and you have a risk factor based on exposure in the UK, that you would then interdict the recovered plasma. So you wouldn't fractionate it or transfuse it.

So we don't have to cause a situation where we have divergence. But at the same time, you could have the policy where you are not screening the source plasma donor for that history.

CHAIRMAN BROWN: Let me, Blaine, say something, because the committee is starting to go around in circles, which we often do at these meetings at some point in the afternoon.

I think we have imperfect -- very imperfect scientific knowledge on which to make any decision we are going to make today. We do have a couple of pieces of information that bear on this distinction.

In animal models -- rodent models -- we know that most of the infectivity is in the white cell component and comparatively less is in plasma. In rodent models, we know that it takes at least five times more infectivity to produce an infection when given IV than when given IC; that is, intracerebral. This means that a dilution effect in pooling can operate.

Yes, go ahead.

DR. PRUSINER: Did you say five times or 10^5 times?

CHAIRMAN BROWN: No, no. Five. Five. Five.

DR. PRUSINER: All right.

CHAIRMAN BROWN: Just five. Not very much but enough so that when you do the arithmetic you find that the likelihood of having five intracerebral infectious units in a single vial of product is very low, much -- I mean, phenomenally lower than if you had just one infectious unit -- was enough.

So pooling and its dilution effect, with respect to getting five IC infectious units together in a single dose, is a real thing and it's a safeguard. On the other hand, it is in rodents. It has only been demonstrated twice, two independent

experiments. And it's in a model which is not new variant CJD.

I mean, this is where I'm talking about imperfect. We go two or three steps back.

Robert?

DR. ROHWER: Paul, I would encourage us not to invoke the pooling argument because I strongly disagree with it and do not feel that that's likely to be playing a role. And we could go on and on about it, and try to resolve it here, but it is a technical issue that it is possible to take two different positions on it. And I don't think it's possible to resolve it here, so I don't think it should be invoked.

I think we should consider the -- it is a worst case situation that if you take a 10^4 infectious units and disperse them into a pool, you have the potential of distributing that to 10^4 individuals ultimately in separate product units.

And I'd rather work from that point of view. If there's any value or any safety that can be taken from plasma, it's from the refinement process itself. But I do agree with Stan that we've only looked at a couple of different processes by a couple of different models. It's not a closed situation.

And I certainly myself would not be in favor of invoking that as a reason for making this choice. I think we'd have -- it's more important to look at this from the standpoint -- really, from the same standpoint that -- well, actually, the British didn't use that rationale, but we all thought they did at first. But the idea that the directly transfusable products expose far fewer people than pools may expose and make the decision on that basis.

CHAIRMAN BROWN: Well, it's just -- you know, it's --

DR. ROHWER: There's no distinction.

CHAIRMAN BROWN: Yeah. Right. I don't disagree that it's arguable. I don't know how you argue against data but you do. My point then goes back to the original proposition, let's assume we don't know a damn thing.

You're telling me that the pool dilution argument is arguable. The partitioning of infectivity in blood is arguable. The relevance of spiking experiments is arguable. The appropriateness of rodent models is arguable. Do we have enough information to warrant considering questions 1 and 2 separately? That's the first question. Can we take a vote on that?

If people think we have enough information to consider question 1 apart from question 2, let's get on with it. If we don't, let's combine them and simplify our lives.

DR. ROHWER: Right.

DR. ROOS: Well, the two things we know is, as Bob says, if there's 10^4 infectious units in the pool, we have the possibility of infecting a thousand people versus 10^4 in one sample. And the other thing that I think --

CHAIRMAN BROWN: That's what I argued with. But go ahead.

DR. ROOS: No. Really, the infectious unit is defined by an intercerebral infectious unit. If you need five of them together when you give it intravascularly, then you're not going to get it if you dilute out to one in a million. You'll never get five in one vial. Well, I --

CHAIRMAN BROWN: That's what we don't want to discuss here.

DR. ROOS: Okay. The second thing that I -- well, there are issues related to those issues and the different routes. I guess the other thing that I think I heard was -- from Jay was that, in fact, we have enough pooled plasma derived products in the

United States -- that is, that the issue of risk of shortage in the United States seems not to be present in the pool derived products but certainly is present in the transfusable components. There's a different issue of availability of these two that I think also makes them different.

CHAIRMAN BROWN: Okay. That's a good point.

DR. LEITMAN: Could I object to that? There is a great difficult getting IV Ig. No matter what the manufacturers may say, we've had to cancel protocols because our pharmacy is unable to get IV Ig for new experimental IND -- you know, IRB approved indications. You can barely get it for the approved indications.

And if you speak to patients and consumers who use the IV Ig, such as those on the BPAC Committee, they are very concerned about any additional deferrals on donors based on that.

CHAIRMAN BROWN: Is this going to be passionate, Larry?

DR. SCHONBERGER: Yes. I was just going to suggest that we keep the issues separate. I think that each of these questions raise different issues. They do not necessarily mean that an individual would

have to change the criteria for 1A versus 2A. But the vogue will be based on different issues that they're weighing. And I think we could move on and just --

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: -- proceed to go with the way Jay had had it.

CHAIRMAN BROWN: Okay. Barbara, we'll hear from you, and then we will, in fact, take a vote on 1A and go on from there.

MS. HARRELL: Okay. As a consumer representative, I've sat here and I've listened because I tried to -- I'm probably the only non-scientist on the panel. And I'd just ask my learned colleague a question.

CHAIRMAN BROWN: Which one?

MS. HARRELL: Is there a --

(Laughter.)

CHAIRMAN BROWN: No. I'm -- do you mean all of us?

MS. HARRELL: Just this one, right here.

CHAIRMAN BROWN: Oh. Oh, okay.

(Laughter.)

CHAIRMAN BROWN: I wasn't being smart. I just didn't know which one you were talking about.

(Laughter.)

CHAIRMAN BROWN: Go ahead.

MS. HARRELL: Well, I asked him the question, was there a deferral -- was there deferral criteria for blood donors for classic CJD for people who have either resided or visited the UK.

CHAIRMAN BROWN: I'm sorry. Repeat that, the question.

MS. HARRELL: Is there a deferral policy for blood donors to attempt to reduce the risk of transmitting classic CJD for people who either resided or visited the UK?

DR. SCHONBERGER: The answer is no.

MS. HARRELL: And if there is no risk, if we think that there is no risk of transmitting the whatever to -- for CJD, what makes this different, for new variant CJD much different?

CHAIRMAN BROWN: That's the first time, Stan, you'll ever hear of prion referred to as a whatever.

(Laughter.)

CHAIRMAN BROWN: I mean, I've heard it referred to as a lot of different things. I'm --

DR. PRUSINER: You've said that many times, Paul.

(Laughter.)

CHAIRMAN BROWN: It may be that --

DR. PRUSINER: Is that in the Congressional Record?

CHAIRMAN BROWN: The issue is not about sporadic CJD. That is the issue we can sort of generically say CJD. Presumably, if the blood from a patient with new variant CJD were infectious, the disease that it would transmit would be new variant CJD. So it's not --

MS. HARRELL: Okay. So CJD is not transmitted through the blood is what you're saying?

CHAIRMAN BROWN: We have no evidence from looking at populations that that has ever happened. The question is: since we know it can happen when we use experimental models of CJD, we can take CJD blood from one animal and produce the disease in another animal.

So there is the "theoretical possibility" that this might also happen in humans, particularly with a different strain of the disease, which new variant is, about which we don't know a whole lot. That's the question.

DR. SCHONBERGER: Isn't the answer to her question that the incidence of CJD, REDS, classic CJD, is not influenced by whether or not you've lived in

the UK between 1980 and 1996 --

CHAIRMAN BROWN: Yes.

DR. SCHONBERGER: -- but the incidence of new variant CJD is?

CHAIRMAN BROWN: Yes, 40-love.

(Laughter.)

CHAIRMAN BROWN: Stan?

DR. PRUSINER: Maybe, Paul, it would be useful for you or someone else to just summarize what went on in December, the background for this, why new variant CJD may or may not pose a risk to the blood supply, because this all went on in the last meeting.

We had all of these consultants come and talk about this, and maybe there are other people at the table who really aren't up to speed on this, because this is really the background piece of information upon which this whole discussion is based.

MS. HARRELL: I was here. I've just forgotten. That's all.

(Laughter.)

DR. PRUSINER: That's fair.

(Laughter.)

MS. HARRELL: But the other thing is that there has been discussion back and forth, and we really don't have enough data to -- I don't think to

make a decision. But I do go along with the Canadian -- Ms. Chan's presentation that in light of -- without having the data, that you take a conservative approach in that you do not wait for the scientific certainty. That as a representative for the community, or for the consumer, that they want to reduce their risk as close to zero as possible.

As far as it affecting the blood supply, I think that that is something that may be totally separate that we will have to consider. But first, we don't want anything to come into the country that is not already here. And if there's something that we can do, then we should do that.

CHAIRMAN BROWN: Okay, Barbara. I think without further ado -- we're really running out of time, Susan.

DR. LEITMAN: Let me return to the apheresis donor issue. There is some level of decrease in -- or deferral of the whole blood donor population that the American blood supply will tolerate. Maybe that's half a percent, one percent, 1.5 percent, but it probably could be tolerated.

I don't know what the apheresis donor population would tolerate, but we just heard from Dr. Gilcher earlier that that might be as high as a four

to five percent or higher deferral of repeat donors. Is that enough of a problem that this committee thinks it might need more information on that population of donors of transfusable products before it started making deferrals based on time spent in another country?

CHAIRMAN BROWN: Is the committee ready to vote on question 1A? Bear in mind that the vote on question 1A implies an answer to question 1B, and that if you -- if you recommend that the FDA recommend new deferral criteria, you are automatically obliged to recommend what those criteria should be.

DR. ROHWER: Paul?

CHAIRMAN BROWN: Yes.

DR. ROHWER: I would like to raise one other point before we vote on this, and it's to a remark that Barbara has just made here about getting as close to zero risk as possible. I don't think we should fool ourselves. Whatever we come up with here this afternoon is not going to be anywhere even close to zero risk reduction or zero exposure reduction.

It could go all the way to zero in terms of geographical exposure. We're talking about 20, 30 percent deferrals, which I don't think is likely to happen.

And in any case, no matter what we come up with, we have to recognize that whatever policy we put in, whether tomorrow, next week, or next month, we've been living without that policy for the last 19 years of exposure to this agent. From 1980 to 1999, the period that was in the REDS study travel questionnaire earlier, that's a 19-year period where we have already assumed that exposure.

We have already had that exposure. We've already had those donations. We've already had people who have received blood from those donations donating again. That has already taken place.

What we're doing here is mitigating further exposure to some extent, and to what extent that is we have no idea, really. And so I don't think we should -- I think we have to keep that in mind. The advocacy of what we're doing here is a little bit questionable in my mind. It seems to me that if we can do something that has very little cost attached to it, we should, but that is the proviso.

CHAIRMAN BROWN: Okay. Were you finished or -- yeah.

Dean, I just want to say that you could argue the same way, and you're right. But someone who smoked 20 years and is told, "You've smoked 20 years;

there's no real rationale for you stopping," I think there is.

DR. ROHWER: I agree with that. And I would like to add one other thing, and that is that I have proposed at various times before this committee and various committees that one way to build a firewall between us and our prior exposure, which has the same attributes as the feed ban that was so effective in bringing the -- turning the BSE epidemic around, is to defer donors who have already been exposed, i.e. people who have already received blood and blood products.

And the problem with that is I have not been able to get a good sense that that is at all practical. But it is something which I would hope that we could consider at greater length at some time.

CHAIRMAN BROWN: The committee should bear in mind that we have exactly two minutes, if we want to remain on schedule, to take votes on 1A, 1B, 2B, and 2A.

Dean?

DR. CLIVER: One thing I'm not hearing is when we talk about the impact of deferral of, for example, 2A, we can choose to minimize risk, but you've got to be first. And the UK was first. They

have already made their decision on this 2A question. In part, I suspect, why we're processing a lot of plasma for -- not to be used in the United States is we're already being outbid for plasma products that are going to the UK.

Now, are we prepared to cut off our supply, or diminish our supply, and hope we can outbid them to bring our own stuff back or keep it? This is -- I think we're not supposed to think about economics. But all the same, if you're going to be very conservative on these points, it pays to be the first one to --

CHAIRMAN BROWN: Yes. No, I think the FDA has given us carte blanche to consider anything we want to on this particular issue -- economics, tradeoffs, risks.

Does the committee want to punt, or do they want to vote? The Chair is finding it a little difficult to refocus this and decide exactly what we should do to try and satisfy the legitimate demands of the FDA for our advice. Yes?

DR. PRUSINER: So why don't I just preempt this and say I'd like to make a motion that we vote on 1A.

CHAIRMAN BROWN: Well, that's what I was

going to suggest. Is that -- is the committee satisfied to finally take a vote on this issue, imperfect as the basis for our judgments --

DR. LEITMAN: I have one last comment. I've heard Jay Epstein say that there will be no product recall. So whether there is post-donation information, or whether a donor comes in the next donation and then gives the information because they're asked for the first time whether they have ever been in England and they say that they lived in England for half their life, for example.

But the previous products or fractionated products are not recalled. So if they're not recalled, it's hypocritical. The whole policy is hypocritical. You prospectively defer, but you have vast amount of product, especially fractionated product, derived from the same donor that you don't recall.

If you have such a hypocritical policy, then my conclusion from that is that this is simply a gesture, a public relations gesture, without any scientific data or any perception of real risk by anybody sitting here, without making an across-the-board removal of product from such donors.

CHAIRMAN BROWN: I think "hypocritical"

probably is too strong a word. It may not be fully logically consistent.

DR. LEITMAN: Illogical is --

CHAIRMAN BROWN: Okay? Is that better?

DR. LEITMAN: Illogical is good enough.

(Laughter.)

DR. LEITMAN: Yes, Ray?

DR. ROOS: I think that a lot of our decisions are based on risk benefits. And if somebody comes in the door and you determine that they are from the UK and you say, "You can't contribute to the pooled blood here," we only lose one donor, whereas if -- so the risk is relatively slight, whereas the recall of a large lot from 50,000 to 100,000 people, because of that one donor that's knocked through, there's an enormous burden that we pay for it.

So I don't really find it hypocritical. I think it's trying to sort out the whole risk benefit issue here.

CHAIRMAN BROWN: I agree. We're starting to vote, and we'll start with Larry. Hold on. All right. The question is: should FDA recommend new deferral criteria for donors of transfusable components, to attempt to reduce the theoretical risk of transmitting new variant CJD from transfusions

based on donor exposure to BSE in the UK?

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Incidentally, just to remind the committee, it is possible to vote punt; that is to say, you can vote yes, no, or no vote -- abstain.

DR. HUESTON: Well, for my own benefit, I suppose, to walk through the logic -- and maybe for the benefit of Barbara because I think she raises a good point about how we proceed -- we have a situation with a small number of known cases of variant Creutzfeldt Jakob, all but one of which are in the UK.

However, we know there is a potential for widespread exposure to BSE that has already occurred. Therefore, we expect more cases, but we really don't have a good idea of the magnitude of the epidemic that we're going to expect.

Part number 2 says, "While there is no known whole blood or blood product transmission of classical CJD in humans, variant Creutzfeldt Jakob differs substantially from classical CJD." So we recognize that there is the potential for transmission of some of the transmissible spongiform encephalopathies via blood, albeit controversial

We have an animal model, and we can

identify infectivity in lymphoid tissues with variant Creutzfeldt Jakob, which is different from classical Creutzfeldt Jakob.

At the same time, it has been pointed out many times by a number of people that there have been no observed risk -- or no observed cases at this point of transfusion or blood product related variant Creutzfeldt Jakob cases in the UK. I think that's a little premature. One might say the absence of evidence is not evidence of absence.

At the same time, there are look-back studies in place in the UK, and there is a natural experiment -- a huge natural experiment ongoing in the United Kingdom, where if, in fact, there is a risk, I believe that the risk will first be apparent in the United Kingdom far before we would see it anywhere else.

At the same time, in looking at the precautionary principle --

CHAIRMAN BROWN: Is this the preamble for a vote?

DR. HUESTON: Yes, sir. You got it.

(Laughter.)

DR. HUESTON: If our goal is to be precautionary, but at the same time we have to

preclude having more negative impacts for any action that we take, then positive -- in other words, impacts on the blood supply. And I have struggled through the whole time, but I'm going to vote no at this time.

CHAIRMAN BROWN: Could I urge the remaining members of the committee --

(Laughter.)

CHAIRMAN BROWN: -- to vote rather than -- I appreciate it, and I let Will, you know, chatter on because he hasn't said a whole lot, and I wanted to hear what he had to say. And so thank you, but we'll never get through if we continue to explain the reasons for our votes, each one and all. So, Susan?

DR. LEITMAN: I take the opportunity to disagree with what you just said. I think the vote at this table is so critical, it will have such a huge impact potentially on the way America collects its blood, that if we go beyond our designated time it's worth it.

And I was influenced, and it was helpful to hear the last speaker's discussion. So I think if any of us have discussions or points to mention now, they might be valuable.

The deliberations of this committee are among the most difficult of any advisory committee

I've ever been on because there are simply inadequate data upon which to base a decision. For myself, in the absence of data suggesting or, rather, documenting risk, I cannot vote yes based on assumptions, perceptions, possibilities, uncertainties, theoretical risks, and potential risks.

On the other hand, there are tangible measurable data that deferral of any percentage of donors, whether it's half, one and a half, two percent, will lead to replacement by donors by a small proportion of donors that are at increased risk for measurable diseases such as hepatitis B and C. So I vote no.

CHAIRMAN BROWN: Dr. Leitman votes no. Dr. Prusiner?

DR. PRUSINER: I would like to vote yes, and I would like to say I have 23 points that I want to go through.

(Laughter.)

DR. PRUSINER: I only want to say very quickly that I don't think that economics and the availability of donors is a reason to vote yes or no in this. I think that the economy has a way of solving these problems, and I think that will happen. I think the real problem here lies that we have a very

imperfect data set, and we're dealing with a disease which is universally fatal. This is really the problem that we face.

CHAIRMAN BROWN: Dr. Prusiner votes yes. Dr. Roos?

DR. ROOS: I think we're dealing with a situation in which we have no evidence of any transfusion that has transmitted either classical or new variant Creutzfeldt. And we have a situation where there are risks involved with blood transfusions that the donors accept at this point.

That is, we were informed about -- I guess about 14 percent of individuals do donate blood that have I guess the recipients. About 14 percent of individuals that donate blood have some risky behavior. And maybe I might include living in UK part of that risky behavior.

And so I kind of accept this as, at the moment, acceptable risk for donated blood and I am awaiting evidence to prove that there is more danger involved. So I'm voting no here.

CHAIRMAN BROWN: Dr. Roos votes no. Dr. Belay?

DR. BELAY: I'm concerned about two issues. The first one is the studies that showed the

presence of the new variant CJD agent in lymphoreticular tissues. And the second concern I have is the absence of evidence against blood-borne transmission of new variant CJD. The kind of data that's available for classic CJD is not available for new variant CJD, so I vote yes.

CHAIRMAN BROWN: Dr. Belay votes yes. Dr. Lurie?

DR. LURIE: Really, what we're doing is balancing one risk against two others. The two risks are the problem of the replacement donor, which is not zero but it is probably very small, given that we're only talking about one, two perhaps, percent replacement of donors here, depending on what happens in B if we get that far.

The second has to do with the diminution in the blood supply itself. And, again, there are scenarios available to us under B that allow us to minimize that. So we really have, on the one hand, two small risks that can more or less be quantified, and on the other hand we have another risk, which may itself be small, but if we are wrong could be very, very large. And that's really the benefit -- the risk benefit calculation that we're making.

For me, there remain too many

uncertainties, and so I vote yes.

CHAIRMAN BROWN: Dr. Lurie votes yes. Dr. Hoel?

DR. HOEL: Yes. I'm changing my vote from last time, and I'm going to vote yes, mainly because of what I see in the epidemiology data of the cases in England and the modeling work. I think this needs to be monitored further to see how it comes in because the risks could be quite large, and so I would vote yes.

CHAIRMAN BROWN: Dr. Hoel votes yes. Dr. Bolton?

DR. BOLTON: I believe that there is insufficient documentation of the risk at this time. And in light of that, I can't -- I don't think that the information warrants changing the current policy. I vote no.

CHAIRMAN BROWN: Dr. Bolton votes no. Dr. Nelson?

DR. NELSON: Well, this is a pretty difficult vote. Last time I voted no, and I'm going to vote no again, although I am -- really, it's disturbing that there is no really good data at this point.

And I am impressed with a comment that was

made earlier, and that is that there is an experiment in the UK of many people who have been exposed to UK donors over a period of many years. And I am somewhat reassured that there have been no cases, and I'm also reassured with the quality of the epidemiologic surveillance and data from the UK.

I think that that has been well done, carefully done, and presumably it will continue to be closely monitored. You know, if a single case had occurred, we would really need to change our policy immediately. That's number one.

But the other problem I have is if I voted yes, then I would have to make a decision on 1B. And the only --

(Laughter.)

DR. NELSON: -- the only reasonable decision on 1B would be to remove -- to exclude all donors who had lived in the UK. I see no basis for any arbitrary decision. Once you go down that route, then you have to exclude anybody from the UK or who visited the UK or Ireland during this period. I don't see any alternative.

CHAIRMAN BROWN: Dr. Nelson votes no. Dr. McCullough?

DR. McCULLOUGH: I agree with Susan. This

is one of the most difficult groups I have had to deal with. I'm impressed by the epidemiologic data. I'm also impressed by having sat through in 1983 and 1984 discussions of there ain't been a case reported yet, and also that we are concerned about the impact on the blood supply.

And possibly also, I'm influenced by having been the fodder for congressional hearings and 60-minute expose on things that might have been done differently at some of those times. So I'm going to vote yes. I have tremendous confidence in the blood systems of this country that they will be able to -- not easily -- respond if changes are made.

CHAIRMAN BROWN: Dr. McCullough votes yes. Dr. Brown votes yes. Dr. Ewenstein?

DR. EWENSTEIN: Yes. I'm impressed by the modeling data. I believe that we have biologic data as well as at least the potential epidemiology coming out of England to suggest that this is a new disease and on that basis should be handled with a lot more caution, because we don't have the comfort that we have with the long-standing classical CJD. And so I'm going to vote yes.

CHAIRMAN BROWN: Dr. Ewenstein votes yes. Dr. Detwiler?

DR. DETWILER: I'm going to vote yes, because with these diseases, a long incubation and the lack of a pre-clinical screening test, that the day you find out there is transmission you're already years too late, and you can't easily clean up the problem. And I think they found out that even with the human transmission because that was based on there is no theoretical -- or it's only a theoretical risk until 1996.

CHAIRMAN BROWN: Dr. Detwiler votes yes. Dr. Piccardo?

DR. PICCARDO: I would vote yes because all of the data from classical CJD cannot be extrapolated into the new variant.

CHAIRMAN BROWN: Dr. Piccardo votes yes. Dr. Williams?

DR. WILLIAMS: I'm going to vote no. I think that this is truly a balancing act, and it's a tradeoff between a known problem, I believe related to the blood supply, and the problems that may follow from a reduced supply and the perception of a risk of new variant CJD.

And I completely agree that an experiment is going on right now. Those data are going to come in, and, obviously, there is going to be close

attention paid to those data, and that surely this committee and FDA will respond should information indicate that we need to take another look at the issue.

CHAIRMAN BROWN: Dr. Williams votes no. Dr. Hollinger?

DR. HOLLINGER: I'm voting no also, for the same reasons that have been addressed. I think there is -- by doing something now doesn't mean that everything is going to be turned around and you don't have to worry about it, if you do have a long incubation situation and one can wait to see if there is some risk down the line, and I think we do have those things going on -- natural and experimental -- in England. So I'm voting no.

CHAIRMAN BROWN: Dr. Hollinger votes no. Ms. Harrell?

MS. HARRELL: Okay. Sitting next to my ex-learned colleague --

(Laughter.)

MS. HARRELL: Okay. I'm voting to be prudent, and I think that this will buy us time to get the data in and have it analyzed from the UK. But right now, we don't have time, and so I vote yes.

CHAIRMAN BROWN: Ms. Harrell votes yes.

Dr. Cliver?

DR. CLIVER: No.

CHAIRMAN BROWN: Dr. Cliver votes no. Dr. Burke?

DR. BURKE: This is a balancing act, and I can -- there are measurable negatives here. In the face of a theoretical, I vote no.

CHAIRMAN BROWN: Dr. Burke votes no. Dr. Tramont?

DR. TRAMONT: I vote yes.

CHAIRMAN BROWN: Dr. Tramont votes yes. Twelve yes. Nine no. Well, at the least, Dr. Epstein can come away from the day with the understanding that he has not been given a mandate.

(Laughter.)

DR. FREAS: Can I just make a comment? I did verify the count. There are 21 voting people at the table. Dr. Roos is a non-voting participant. And the total does add up to 21.

Excuse me. I apologize. Dr. Rohwer is --

CHAIRMAN BROWN: I don't have to ask Bob what he would have voted, had he been allowed to vote.

(Laughter.)

CHAIRMAN BROWN: But I will if you'd like to put it on the record.

This is simply a question to Bob, since he's at the table. Were his vote to be counted, what would it have been?

DR. ROHWER: I'll use this soapbox opportunity.

CHAIRMAN BROWN: Uh-oh.

(Laughter.)

DR. ROHWER: I am very concerned that we may be facing the grave possibility of an epidemic of new variant CJD, an epidemic that, if it occurs, could be made much worse through the mechanism of interspecies transmission, such as would occur through blood products. But I recognize the real risks of insufficient supply.

However, I am impressed by Dr. Donnelly's warning that if the feed ban in the case of BSE had been delayed just one year, the epidemic would have been vastly worse than it was. And, therefore, I feel we should take whatever opportunities for implementing mitigating measures that we can that do not simultaneously jeopardize the supply unduly.

So I recognize that what we have -- the opportunity we have here is very, very imperfect, but I feel like it is possible to do something, and we should do it.

CHAIRMAN BROWN: Jay, you wanted a recount, or just a reexpression?

DR. EPSTEIN: Just a reexpression.

CHAIRMAN BROWN: Okay. The vote on question 1A is 12 votes yes, nine votes no. Therefore, the committee is obliged now to consider what deferral criteria might be recommended. And presumably, based on the evidence, the only deferral criteria that are offered us that make any sense are duration of residence in the UK.

DR. LURIE: It's also duration and when.

CHAIRMAN BROWN: Yes. But it's -- the "when" will be 1980 to 1999.

DR. LURIE: As long as that's established, I would agree with that. But --

CHAIRMAN BROWN: Yes, that's the only information we have. In other words, the question is: have you lived in the UK during the period 1980 to 1996? And, if so, how long? And the answers and the distribution of those answers has already been presented to the committee.

Do I hear an opening bid on time? Larry?

DR. SCHONBERGER: I'd like to point out that all cases to date in the UK have lived there for at least four or more years, and been potentially

exposed. And most of them, as I understand it, have been there for 14 years or more during the 17-year period.

The one that I'm more concerned about for the shorter exposure -- and I tried to get more details about it; maybe Bill has some more information on it -- was supposedly a person who was a -- who claimed to be a vegetarian since late 1985, at least that's how it was reported in the newspapers.

And Will has not contradicted that, although he indicated to me that there is vegetarians and there is vegetarians, and he was not totally convinced that this particular individual might not have been exposed later. But that person would have certainly been there through the 19 -- I'm getting a note here. The point would be that she would have been exposed, then, during the '80 to '85 period.

I just bring that out. Meanwhile, I'm sure there have been many travelers to the UK. There have been military people from the U.S. that have visited shorter periods of time. We haven't seen any cases in that group yet, but at least it offers me some sort of rationale, again not to totally eliminate risk, but to have some basis for modifying the risk. And, of course, I'm also concerned of the impact on

blood supply.

So I was thinking in terms of a three- to five-year category; that is, as I understand it, that would include about .7 percent of the donors in the United States, and that probably would be tolerable to the blood system in the United States and get well over half the person days of risk and give us some modification of the risk in the United States.

Obviously, if we start getting cases among travelers in shorter times, we would need to tighten that even further.

CHAIRMAN BROWN: Just for the committee's information, there has also been one case in France that never visited the UK.

DR. SCHONBERGER: That's right. There is one case in France that never visited it, so that illustrates the point that our whole -- this whole policy is not 100 percent protection. I think that point was raised by Rohwer, and so on.

CHAIRMAN BROWN: Well, to the extent that we have not imported British beef products for the past 10 years, it is.

DR. HUESTON: More than that. We haven't imported it for more than that.

CHAIRMAN BROWN: Right. Maybe ever since

-- you know, 15 years. So, whereas, 20 percent of beef that the French eat, or ate, was imported. In other words, the French case -- clearly, the implication is the French case got their disease because of exposure to British beef. That doesn't happen here.

Stan?

DR. SCHONBERGER: Yes. I was referring to, obviously,, the protection that one gets from the screening criteria.

CHAIRMAN BROWN: Yes.

DR. SCHONBERGER: Those screening criteria that we can come up with is -- that's practical --

CHAIRMAN BROWN: Going to be total.

DR. SCHONBERGER: -- can give you 100 percent protection. We're just trying to make a judgment where to draw the line.

CHAIRMAN BROWN: Exactly.

DR. SCHONBERGER: I just -- you said to throw out an idea. That was my proposal.

CHAIRMAN BROWN: Okay. Well, that's fine. Stan?

DR. PRUSINER: I have a slightly different analysis of this, but not much. If one looks at Alan Williams' handout, the second -- third-to-the-last

page of slides, and put up this graph which I thought was very informative on residual variant CJD risk --

CHAIRMAN BROWN: Is that the zoom-in slide?

DR. PRUSINER: Right.

CHAIRMAN BROWN: The one that --

DR. PRUSINER: Exactly.

CHAIRMAN BROWN: -- goes from one year to one week?

DR. PRUSINER: Exactly.

CHAIRMAN BROWN: Okay.

DR. PRUSINER: That's the one. So I think if people look at that slide -- I mean, we can start thinking about everything from one week to one and a half years with this slide. And I think everybody -- most people, I would argue, at this table would argue that one week is too severe, and this creates something which is intolerable for the blood supply.

And it may well be that even one month or three months do that. I'm not sure. I'm not totally convinced of that.

But clearly, by six months, if one looks at that, and then one looks at this handout that Alan Williams provided us that was not stapled, if one picks the number six months, then of all of the -- if

you look at the cumulative person days, then almost 95 percent of the cumulative person days are eliminated by picking a figure of six months.

So I would think that for purposes of discussion --

CHAIRMAN BROWN: Where is six months on the handout?

DR. PRUSINER: So it's five to eight months.

CHAIRMAN BROWN: That's the one?

DR. PRUSINER: Yes.

CHAIRMAN BROWN: Okay.

DR. PRUSINER: Right? So that's 84 percent.

CHAIRMAN BROWN: So you're suggesting a split between the one to four above and the five to eight below.

DR. PRUSINER: Yep, something on that order. I'm zeroing in on between six months and three months. This seems to me to be a very reasonable way to achieve a 90 percent reduction in risk without making a huge dent on the blood supply.

CHAIRMAN BROWN: Okay. Further comments?

DR. ROHWER: I would second that.

DR. EWENSTEIN: I would also second that.

I was just going to ask for clarification whether we were talking about cumulative time in the UK, and I know that was an issue, or whether we're talking about longest stay.

CHAIRMAN BROWN: I think we were talking -- you were talking cumulative, huh?

DR. EWENSTEIN: If we're going to use the person years, and it's cumulative --

CHAIRMAN BROWN: I think we shouldn't also forget the table before. It's on the flip side of that. In fact, it's exactly backing the figure you just talked about -- blood resources lost by deferral of donors. And even at a year there, the loss is one and a half percent.

DR. PRUSINER: That's right.

CHAIRMAN BROWN: Yes.

DR. PRUSINER: And it just rises very modestly if we pick six months, or even three months. It's when we start getting down to a month that things start to get very -- the curve starts to change dramatically.

CHAIRMAN BROWN: Other comments? Bob?

DR. ROHWER: The only comment I'd have was -- is the 1980 to 1996. I am not comfortable myself with limiting this deferral to 1996. I mean, I would

run it right up to the present. I don't feel like we've come close to really proving that the way that new variant -- the new variant cases get this disease is from eating contaminated meat.

And, in fact, my understanding of the CJD surveillance unit attempt to do so is that they couldn't make that correlation. And there are some very peculiar things about this disease; namely, that it seems to affect young people preferentially, suggesting that there may be some risk factor that babies or infants are exposed to that we just haven't identified yet that puts them at special risk for this disease.

And because we haven't nailed it down, I don't think we should consider necessarily that the exposure is over. We don't know where it's coming from. And I would extend it right up to the present until we know better.

CHAIRMAN BROWN: It occurs to me that a vote on question 1B could be a very heterogeneous vote. We could have people saying one to three days versus five to 17 years. It seems to me that procedurally the best way may be to work up from the least restrictive to the most restrictive, and get a consensus on each separate category.

So that if we had, for example, every -- since we're obliged to work with some sort of a cut, if we can get everybody who is voting to agree on at least eliminating five to 17 years, then we can move on and see where the threshold is when the committee decides enough is enough. Susan?

DR. LEITMAN: Those of us who voted no on question 1A are now faced with an illogical option of telling --

CHAIRMAN BROWN: No, you can abstain.

DR. LEITMAN: Oh.

CHAIRMAN BROWN: No, I'm serious. I understand that that puts you folks in a very difficult position because you would prefer that this not be done at all. And I think you have the right to abstain.

Or if you want to be very logical, you have the right to stick with the least restrictive, if you want to kind of still have an influence. I mean, wouldn't you agree, these are the sort of two options that you have?

DR. LEITMAN: Yes, I agree.

CHAIRMAN BROWN: Stan?

DR. PRUSINER: Could I make a suggestion, and then maybe we could accelerate all of this? If I

make a motion of four months, which really splits this point that I've been talking about, and if there's a second, and then there's a vote, we don't have to do this systematically. If we can't come -- if you're unable to call the question because there is too much discussion, then we have to do it your way.

CHAIRMAN BROWN: Peter?

DR. LURIE: Maybe a simpler one. If we apply to this the same method of analysis that Alan applied to the blood donors, we could just have a descriptive account of where each of us individually thinks the cutoff should be, and then FDA will know that X percent of the 17 voting of us -- you know, what the cutoff would be.

CHAIRMAN BROWN: That's not a bad idea. Jay, would that be satisfactory, do you think, as kind of an accelerating compromise to this question? You would then have at least -- well, you'd have raw data rather than pooled than pooled data.

(Laughter.)

DR. EPSTEIN: Well, we can deal with being advised either way. It's easier for us if there is a consensus of the committee. If there isn't, then I think what we default to is a set of opinions.

CHAIRMAN BROWN: Okay. Let's do it this

way, then, Peter. Why don't we go around the table. Those who wish to commit themselves to a suggested cutoff, we'll take the cutoff down. And it's conceivable that the first round will get a consensus. And if it doesn't, we can then decide whether we want to continue to try and reach a consensus.

Yes? Is it very relevant? Okay.

MR. COMER: Thank you, Chairman. I just thought that it was relevant just to make a comment from the sort of risk perspective of what you all are going to -- just about to be deciding on or voting on. We're talking about a very uncertain risk.

If we're going to make any risk reduction strategy, then it has got to be a significant risk reduction to make any sense at all. And, in my mind, the minimum that you could be talking about that would be a significant risk reduction will be at least a factor of 100, because if it -- talking in factors of 50 percent, even 90 percent is actually not a very significant risk reduction when we talk about all of the uncertainties that we have.

And I suspect that when you start talking about really significant risk reductions, we're getting into the area -- and I agree completely, I think, with what Kenrad Nelson said -- where we have

impracticality.

That possibly does not help your decision making, but I think it is just relevant that what we need to have, if we're doing this, is a significant level of risk reduction, if it's worth doing anything at all.

CHAIRMAN BROWN: Paul?

DR. HOEL: What we're talking about is risk benefit here, not risk reduction.

CHAIRMAN BROWN: Let's change the order. Dr. Tramont?

DR. TRAMONT: Four months.

CHAIRMAN BROWN: Four months? Dr. Burke?

DR. BURKE: Is it either/or four months or can we give another option?

CHAIRMAN BROWN: Any time cut that you would like to vote on or --

DR. BURKE: Six months.

CHAIRMAN BROWN: Six. Dr. Cliver? And, again, you needn't vote if you would prefer not to on this question.

DR. CLIVER: Abstain.

CHAIRMAN BROWN: Mrs. Harrell?

MS. HARRELL: Six months.

CHAIRMAN BROWN: Dr. Hollinger?

DR. HOLLINGER: I guess eight -- greater than five years.

CHAIRMAN BROWN: Dr. Williams?

DR. WILLIAMS: This seems rather arbitrary, but I'd say a year.

CHAIRMAN BROWN: Dr. Piccardo?

DR. PICCARDO: Four months.

CHAIRMAN BROWN: Dr. Detwiler?

DR. DETWILER: Four months.

CHAIRMAN BROWN: Dr. Ewenstein?

DR. EWENSTEIN: Six months.

CHAIRMAN BROWN: Dr. Brown? One year. Dr. McCullough?

DR. McCULLOUGH: Six months.

CHAIRMAN BROWN: Dr. Nelson?

DR. NELSON: Six months.

CHAIRMAN BROWN: Dr. Bolton?

DR. BOLTON: Five years.

CHAIRMAN BROWN: Dr. Hoel?

DR. HOEL: Six months.

CHAIRMAN BROWN: Dr. Lurie?

DR. LURIE: Six to 12 months.

(Laughter.)

CHAIRMAN BROWN: So six would be the cutoff, right?

DR. LURIE: That's fine.

CHAIRMAN BROWN: Dr. Belay?

DR. BELAY: One year.

CHAIRMAN BROWN: Dr. Roos?

DR. ROOS: One year.

CHAIRMAN BROWN: Dr. Prusiner?

DR. PRUSINER: Four months.

CHAIRMAN BROWN: Dr. Leitman?

DR. LEITMAN: Greater than or equal to five years.

CHAIRMAN BROWN: Dr. Hueston?

DR. HUESTON: One year, between '85 and '95.

CHAIRMAN BROWN: Dr. Schonberger?

DR. SCHONBERGER: Three years.

CHAIRMAN BROWN: Was that one of the cuts, three?

DR. SCHONBERGER: Yes, three years or greater.

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: Or greater than two years.

CHAIRMAN BROWN: Greater than two?

DR. SCHONBERGER: That looks like what the --

CHAIRMAN BROWN: It depends actually on what you're working from. But yes, so that would be three to five, that would be --

DR. SCHONBERGER: Yes, three or more. If you've got three --

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: -- years, you're out.

CHAIRMAN BROWN: Well, the most hits were on six months -- seven. But that is not a quorum, or it's a quorum but it's not a majority. So there were eight votes favoring a cutoff of one year or greater. There were seven votes for six months or greater. There were four votes for four months or greater. And I think that's 19 -- that's -- I'm sorry, there was one abstention, that gets us up to 20.

DR. LEITMAN: You're counting those who voted greater than five years as voting greater than one year, but --

CHAIRMAN BROWN: Just for the moment. I'm just tallying this out. I'm not trying to cheat you, Susan.

(Laughter.)

CHAIRMAN BROWN: Specifically, there were -- if you want the exact tallies, there were three votes for greater than five years. There was one vote

for greater than three years. There were five votes for greater than one year. There were seven votes for greater than six months. And there were four votes for greater than four months. I still may be missing one. And there was one abstention. So that's 21.

Have we any suggestions from the committee as to where to -- how to proceed now?

DR. LURIE: Yes, the median is six months. The median is six months.

CHAIRMAN BROWN: The median is six months. Is that a good consensus, Jay? No? Yes?

DR. EWENSTEIN: You could just ask for one year versus six months at this point.

CHAIRMAN BROWN: Well, Jay has the raw data, and we've already got a statistician that has calculated the median.

(Laughter.)

DR. EPSTEIN: Which also adds up to a majority.

CHAIRMAN BROWN: And it also -- so I think we've done enough, frankly, on this question. And I would like to go directly to question 2A. Can we immediately, without further discussion, proceed to a vote on question 2A?

All right. Larry?

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Oh, I thought you were answering me.

DR. SCHONBERGER: No.

CHAIRMAN BROWN: That's a vote, is it? Okay. Question 2A, Schonberger votes yes. Dr. Hueston?

DR. HUESTON: No.

CHAIRMAN BROWN: Hueston is no. Dr. Leitman?

DR. LEITMAN: No.

CHAIRMAN BROWN: Leitman is no. Dr. Prusiner?

DR. PRUSINER: Yes.

CHAIRMAN BROWN: Prusiner is yes. Dr. Roos?

DR. BELAY: He just walked out.

CHAIRMAN BROWN: A pitstop. Dr. Belay?

DR. BELAY: Yes.

CHAIRMAN BROWN: Dr. Belay votes yes. Dr. Lurie?

DR. LURIE: Yes.

CHAIRMAN BROWN: Dr. Lurie votes yes. Dr. Hoel?

DR. HOEL: Yes.

CHAIRMAN BROWN: Dr. Hoel votes yes. Dr. Bolton?

DR. BOLTON: No.

CHAIRMAN BROWN: Dr. Bolton votes no. Dr. Nelson?

DR. NELSON: No.

CHAIRMAN BROWN: Nelson votes no. Dr. McCullough?

DR. McCULLOUGH: Yes.

CHAIRMAN BROWN: McCullough votes yes. Dr. Brown? Yes. Dr. Ewenstein?

DR. EWENSTEIN: Yes.

CHAIRMAN BROWN: Dr. Detwiler?

DR. DETWILER: Yes.

CHAIRMAN BROWN: Dr. Piccardo?

DR. PICCARDO: Yes.

CHAIRMAN BROWN: Dr. Williams?

DR. WILLIAMS: No.

CHAIRMAN BROWN: Dr. Hollinger?

MS. HARRELL: Pitstop.

(Laughter.)

CHAIRMAN BROWN: Did he leave a vote on this at all? Probably not. 2A? Dr. Hollinger would -- Dr. Hollinger votes no. Ms. Harrell?

MS. HARRELL: Yes.

CHAIRMAN BROWN: Dr. Cliver?

DR. CLIVER: No.

CHAIRMAN BROWN: Dr. Burke?

DR. BURKE: No.

CHAIRMAN BROWN: Dr. Tramont?

DR. TRAMONT: Yes.

CHAIRMAN BROWN: Exactly the same tally, 12 to nine. Boy, consistency. Oh, well, good for the Chairman. Dr. Roos is -- all right, 12 to eight. So whatever Dr. Roos' vote will be, we're obliged to consider question 2B.

Should we proceed directly to find out if the committee feels that precisely the same criteria should be applied to question 2A as were applied to question 1B -- 2B and 1B, identical? Therefore, I can simply ask the question. The question is: shall we apply the same criterion for question 2B as we applied for question 1B? Larry?

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Will?

DR. HUESTON: No.

CHAIRMAN BROWN: Susan?

DR. LEITMAN: What are we voting on?

(Laughter.)

CHAIRMAN BROWN: The vote on the first

question, question 1A, which was decided to proceed and suggest a cutoff, those cutoff numbers were a variety. And the vote now is to determine whether the committee agrees to use the same cutoff on this question with respect to pool products.

DR. LEITMAN: So is each timed vote -- or each interval voted on by each committee member? We're voting on whether we --

CHAIRMAN BROWN: That's right.

DR. LEITMAN: -- use the same interval --

CHAIRMAN BROWN: That's right.

DR. LEITMAN: -- right now?

CHAIRMAN BROWN: That's right. That's right.

DR. LEITMAN: So if I say yes, then I'm saying it's whatever my interval was --

CHAIRMAN BROWN: Exactly. Each individual is --

DR. LEITMAN: Could you please frame the question?

DR. PRUSINER: No, that doesn't make any sense, Paul.

CHAIRMAN BROWN: What?

DR. PRUSINER: That doesn't make any sense. Let's just find out if everybody wants six

months or not, right around the table. Six months is the number we agreed upon in 1B, right?

CHAIRMAN BROWN: That was not -- that was not my understanding at all.

DR. LEITMAN: No. We gave the raw --

CHAIRMAN BROWN: We gave the raw data.

DR. PRUSINER: I thought we had a consensus.

CHAIRMAN BROWN: Well, no, there was no single number that had a majority.

DR. EWENSTEIN: Can we rephrase it another way, then? Can we just -- because I think it will be very difficult to have two different criteria, even though Dr. Epstein had come up with a solution to that. So can we at least recommend that whatever the FDA adopts in 1B they be consistent in 2B?

CHAIRMAN BROWN: That's the sense of what I had, that the criteria that we are -- that each person suggested for question 1A, individually that they would use the same criteria for question 2B.

DR. EWENSTEIN: And it can be rephrased to just say that the same criteria should be used in both situations.

CHAIRMAN BROWN: Yes.

DR. BURKE: I'm not sure that -- it will

be impossible to achieve a consensus. I think we might achieve a consensus on 1B if you were to revote on six months, yes or no.

CHAIRMAN BROWN: Well, I think we can. We could have done the same thing on -- actually, on question 1A, but I chose not to. I just think that, you know, for example, Susan would certainly not agree to a yes vote on six months for question 2B.

DR. BURKE: But several of the people who voted one year or four months might switch, and that way we can present with a consensus and then we can actually have internal consistency of a vote for the second -- for 2B.

CHAIRMAN BROWN: Without having it for 1B.

DR. BURKE: Well, I'm saying I think we can at least try to see if we can get 1B, take one more vote to see if we can get a consensus for 1B. If we cannot, then fine.

CHAIRMAN BROWN: Well, let me ask a question to every member of the committee. Would you, given the opportunity, change your cutoff criteria for question 2B? Change it from what you suggested for question 1B? Is there anybody who would say, for example, five years for 1B and three days for 2B? I don't think so.

In other words, is the committee actually -- would the committee be voting the same cutoffs individually for question 2B as they voted for question 1B? If there is any dissent to that, let's hear it.

DR. BOLTON: Paul?

CHAIRMAN BROWN: Yes.

DR. BOLTON: I think that there are really two different issues here. One is whether we are going to try to give a recommendation or this collection of votes for each 1B and 2B, or whether we give them the numbers and allow the FDA to make that decision and then just ask that they make it consistent for both 1B and 2B.

CHAIRMAN BROWN: Yes.

DR. BOLTON: Do you see the difference?

CHAIRMAN BROWN: I don't quite see the difference. I think we're both asking for the same thing in a slightly different way. Is there anybody else on the committee that would like to give the Chair guidance on this question? How would you like to phrase the vote on 2B? Stan would like to phrase it, "Let's take a vote on six months."

DR. EWENSTEIN: I would like to phrase it that we -- that the same criteria be used for 2B as

for 1B.

CHAIRMAN BROWN: Okay. I think that makes sense, and that's what we'll vote on. Should the FDA use the same criteria for question 2B as was or will be used for question 1B? Larry?

DR. SCHONBERGER: Yes.

DR. HUESTON: Yes.

DR. LEITMAN: Yes.

DR. PRUSINER: Yes.

CHAIRMAN BROWN: Dr. Roos, long pitstop. Okay. Dr. Belay?

(Laughter.)

DR. BELAY: Yes.

CHAIRMAN BROWN: Dr. Lurie?

DR. LURIE: Yes.

CHAIRMAN BROWN: Dr. Hoel?

DR. HOEL: Yes.

CHAIRMAN BROWN: Dr. Bolton?

DR. BOLTON: Yes.

CHAIRMAN BROWN: Dr. Nelson?

DR. NELSON: Yes.

CHAIRMAN BROWN: Dr. McCullough?

DR. McCULLOUGH: Yes.

CHAIRMAN BROWN: Dr. Brown? Yes. Dr. Ewenstein?

DR. EWENSTEIN: Yes.

CHAIRMAN BROWN: Dr. Detwiler?

DR. DETWILER: Yes.

CHAIRMAN BROWN: Dr. Piccardo?

DR. PICCARDO: Yes.

CHAIRMAN BROWN: Dr. Williams?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: Dr. Hollinger?

MS. HARRELL: Pitstop.

(Laughter.)

CHAIRMAN BROWN: Someone better get after these two people. He had a no on 2A. Okay.

(Laughter.)

CHAIRMAN BROWN: Okay. Oh, that's right. Dr. Hollinger left. Dr. Harrell?

MS. HARRELL: Yes.

CHAIRMAN BROWN: Mrs. Harrell, excuse me. Dr. Cliver?

DR. CLIVER: Yes.

CHAIRMAN BROWN: Dr. Burke?

DR. BURKE: Yes.

CHAIRMAN BROWN: Dr. Tramont?

DR. TRAMONT: Yes.

CHAIRMAN BROWN: Unbelievable. Unanimity. I thank very much the committee for -- excuse me?

DR. ROOS: Yes.

(Laughter.)

CHAIRMAN BROWN: Okay. I am obliged, unfortunately, to depart now, and I'm going to turn the chairmanship over to Dr. Roos for consideration of criteria used for the diagnosis of new variant CJD. And he is eminently qualified to do this as a long-standing clinician with research interest. Dr. Roos?

DR. ROOS: Thanks, Paul. I hope this section goes more smoothly and quickly. I guess -- Bill, are we going to have a presentation? So we're going to have a presentation from Dr. Dorothy Scott on the operational definition of possible new variant case for quarantine of blood and blood products.

Dr. Scott?

DR. SCOTT: Well, I think the committee is relieved to hear that this is not for a vote but only for your discussion and thoughts. So what I want to introduce is just a proposed FDA operational definition of a possible new variant CJD case for the purpose of deciding whether there should be a quarantine or withdrawal of blood or blood products from such a possible case when information is missing that would lead to a firm diagnosis of new variant CJD in a blood donor.

This is just to summarize what has happened previously. I think most people here are familiar with it. That is, in August 1995, and then revised slightly in December 1996, the FDA issued a memorandum recommending deferral of all donors with CJD risk factors from donating that included family history in one or more family members, or if they were pituitary growth hormone recipients or had received dura mater.

And it was also recommended to withdraw all products, including plasma derivatives, if a donor developed CJD, had a positive -- strong positive family history with two or more family members with CJD, was a pituitary growth hormone recipient, or a dura mater recipient.

This was all revised and the revision was announced in late August 1998 by Dr. Satcher. And this revision was based on epidemiologic evidence. It was extensively reviewed, which you've already heard about, or at least has been very much alluded to, would show that there was no evidence so far of any transmission of CJD by blood products.

And this was supported by lab-based scientific evidence which showed at least a diminution of titer of the CJD or TSE agents in processing of

plasma.

So you've already been through this today. Obviously, our concerns about new variant CJD is that there is a lack of experimental data showing whether or not blood can transmit this particular infection, and also we don't know much about partitioning during manufacturing of the new variant agent. In fact, we don't really know anything yet.

In addition, we do know, as Dr. Prusiner has pointed out several times, that the new variant agent is biologically different from the classical CJD agent, so we can't necessarily extrapolate all of the information that we have on classical CJD to new variant.

For example, he talked about the differences in the protein and its behavior, and we also know that there is enhanced expression of the new variant agent in lymphoid tissues compared with CJD. And we don't know much about its virulence or infectivity compared with the classical CJD.

And, of course, we haven't had time to get or enough patients or subjects or transfused people to get the kind of epidemiologic data that we have which tells us that transmission of classical CJD by blood or blood products at worst is rare and may not occur.

So, currently, the diagnosis of new variant CJD is based upon neuropathology, and these are the three most characteristic features -- numerous widespread kuru type amyloid plaques, which obviously can occur in a few other kinds of CJD but are quite common in new variant CJD; spongiform change, which is predominant in certain areas of the brain; and a high density prion protein accumulation, especially the cerebrum and the cerebellum by immunohistochemistry, and tonsillar biopsy may ultimately play a role in this diagnosis as well as analysis of prion glycoforms.

You can't see the top of this, but actually it's in your handout. And what I have there is CDC suspected new variant CJD case definition for use when pathology is not available. In other words, there isn't always going to be a neuropathological specimen to examine, or it might not be big enough, I guess.

And so we do need clinical criteria to try to tell if we have a possible new variant CJD case, and the CDC has developed such criteria and this is mostly based on the findings that are described by the CJD surveillance unit in the United Kingdom.

And I want to point out that this kind of

list is going to be subject to change as clinical and diagnostic methods and experience evolve. However, the current CDC definition -- the suspected new variant CJD case would include all nine of the following -- current age, and, of course, we're talking about in donors for our purposes, but the CDC is also using this kind of definition for their own surveillance.

Current age, if alive, or age at death, less than 55. Since the typical age of a new variant patient is about late 20s, and the typical age of a classical CJD patient is about 65, this is one criteria that is useful. And new variant patients tend to have persistent painful sensory symptoms early in presentation and/or psychiatric symptoms.

I can go into this further if people want to know about it. But there were a couple of articles published in the Lancet from the CJD surveillance unit in September 1997, which goes into this in great detail.

In addition, the patient must have dementia and a delayed development of neurologic symptoms, particularly movement disorders, about a four-month delay. And, again, this is somewhat different from classical CJD in its course. They may

have a normal or abnormal EEG, but not the diagnostic EEG, which is a pseudo periodic sharp wave that's often seen in classical CJD.

The duration of illness should be greater than six months. Again, this is in marked distinction to most cases of classical CJD which average four to four and a half months of duration. Whereas, the new variant case typically is around 14 months duration, although there is a spread.

In addition, routine investigations will not suggest an alternate diagnosis. And this is a criteria, really, for the U.S. There should be history of possible exposure to BSE; that is, consumption of local beef products as resident or traveler to a BSE-affected country.

And there is only two more. No history of iatrogenic exposures that are related to development of classical CJD, and, finally, of course, such a patient, if they had a prion protein gene mutation, it was associated with familiar CJD. That would not fall under -- that would not be a patient that we would worry about new variant CJD in.

Certainly, other criteria may be added, as I mentioned, in particular the CJD surveillance unit is expected to publish something about MRI studies,

looking in great detail at certain areas of the brain which might be very useful in making the clinical diagnosis without neuropathology of new variant CJD.

Well, if we used all of those nine criteria to consider whether or not we should quarantine or withdraw a blood product in a case of -- a suspected case of new variant CJD, we might run into a problem.

And one of the possible problems is that two of these criteria are time-based, so one is the time course of disease greater than six months and the other is that a period of four months should have elapsed before development of neurologic symptoms but after the initial symptoms.

And it's conceivable that a true new variant case could come to our attention where this time has not elapsed. And, secondly, travel history and symptom history might not be available or they might not be very accurate.

So from the FDA point of view, what we have been considering is whether or not to lower our threshold for considering withdraw and quarantine of a product, where we don't even have all of the information needed for the CDC criteria for suspected new variant CJD.

So we have proposed the following that -- and, again, I'm sorry, the heading is missing. But that for such a case to be considered even as a possible, or I should say potential, new variant case, it will be a donor who had a physician's clinical or pathological diagnosis of either CJD or new variant CJD.

And the donor would be young, less than 55 years of age. And, of course, such a donor would not have risk factors for classical CJD. And that's what we would call a possible new variant CJD case. And I should point out that although we would include all three of these criteria, from the point of view of reporting to the CDC, we would want to ask plasma establishments and blood banks to also report donors who were young but had risk factors for classical CJD that came down with disease.

And the proposed actions for possible new variant cases with this low threshold of consideration by FDA for disposition of blood and plasma products -- the actions that we would propose would be an immediate investigation and review by CDC and FDA of all of the available case information, and followed by an expeditious decision by the FDA on a case-by-case basis as to whether blood products from such a patient

should be withdrawn as a precaution.

So just in summary, obviously, this is already built in, that any definite new variant CJD case would result in quarantine and withdrawal of all products. In addition, we're proposing that suspected cases meeting all nine of the CDC criteria would also be quarantined and withdrawn.

And that criteria for possible CJD, the young age, the diagnosis of any kind of CJD, would trigger a rapid investigation followed by an expeditious decision about a precautionary withdrawal and quarantine of material.

So that's what I have, and I open it, then, to discussion or comments.

DR. ROOS: Thanks, Dr. Scott. So we're not asked to take a vote, but just to discuss these issues. Yes?

DR. NELSON: I'm concerned a little bit about the explanation for the age criteria, and I can see that this is very useful because the one thing you do know, when somebody gets sick, you can estimate what their age is. And so that's an easy -- you know, an easy early marker for a possible case that's not classical.

And I assume that probably the reason for

the classical CJD patients being much older is that the incubation period is so long that they probably had an exposure much longer. But as this epidemic -- or as the -- if it's exposure to the BSE agent from the epidemic, it seems like over time this age criteria will probably change, and that the under 55 may no longer be a useful criteria 10 years from now or 40 years from now.

And I just wonder if Larry or anybody could comment on that.

DR. SCHONBERGER: We definitely agree, and it underscores the evolving nature of these diagnoses. All I can say is the age is an excellent and easy criteria for us to use now. All cases, as you know, in the world of new variant CJD have been under age 55. In fact, I think the oldest was -- I think the median age is like 29 or so, 28 at onset and 29 at death. So that's why that particular criteria came into existence.

However, obviously, if the epidemic should change and we should start seeing older cases, then, obviously, we would have to change.

There is some semantic problems. We actually investigate every case under 55. So, in a sense, all cases under 55 in the United States could

be regarded as under investigation or possible. We have not used the word "probable," in part because that's the word they use in the United Kingdom, and they count those cases as amongst the cases of new variant CJD that we count.

The 40 cases in the UK, I think, includes one, is it? One probable? That was a case in a teenager whose brain tissue was unavailable for study. And they indicate that it's too early in the epidemic. Their experience is too small for them to be absolutely sure about that, but they're willing to -- at this point to call it a case.

And I've been told that with these new MRI criteria, and so on, that maybe we'll be able to call cases without necessarily having the tissue, depending on what they find the specificity and sensitivity of those to be. So all cases essentially under 55 right now are under investigation.

Plus, we have established amongst pathologists the concept that any case that has the pathology of new variant CJD, regardless of age, or even regardless of whether they've diagnosed it as CJD, should be reported. And those two would count as new variant even though they are not under 55.

DR. ROOS: Just a quick question, Larry.

What is your timeframe of reporting, or what is the goal here? Obviously, with respect to these new guidelines, you want to identify these cases fairly quickly and make some disposition as far as blood products.

DR. SCHONBERGER: Precisely because we are looking at all cases under 55, I was encouraging FDA to encourage the blood establishments -- or the first to identify these cases at least, and that has been the history -- to report to us any case of CJD under 55.

Once we get that report, it may be very easy for us and very quickly making it -- to very quickly make a determination that we're dealing with, say, a dura mater case or a human growth hormone case. But then, another part of FDA will probably become interested in that.

So we think it's worth the blood establishments reporting all of their cases in donors. There just are not that many CJD cases that are going to occur among donors that the blood establishment is going to be able to identify that quickly. But if they do, we want it reported right away.

DR. ROOS: Just a quick question. So, I mean, how about if this patient donates to some large

blood pool or has donated whole blood? It doesn't go back to the blood establishment. It goes to a neurologist, gets diagnosed, etcetera. What's the timeframe then?

DR. SCHONBERGER: Well, frequently, our experience with the withdrawals -- and I'll use the Utah case as an example as that came out -- we handled that very, very rapidly. But even handling it very, very rapidly, you'll find that huge, huge numbers of recipients were exposed to this donor's blood products.

So the withdrawal program is relatively inefficient, compared to what we just did, which was to get deferral criteria. And I think that's why it was important to try to be preemptive in a sense and have the deferral criteria up front.

The withdrawal procedure, even when you do it very quickly as in the Utah case, I would not encourage people to depend on that for considerable safety. What we will do is we will modify and ameliorate the situation. But it certainly won't eliminate even the majority of the risk.

DR. ROOS: I just think it might be good to publicize these new policies widely to the neurological community, so that they alert you, Larry,

or the FDA quickly. The Utah case, in fact, was kind of a very aberrant case. It could be that there are other cases that get less sophisticated care. And if you really want to identify things in a timely manner, you obviously have to publicize the program and new policies to the neurological community.

DR. SCHONBERGER: Well, let me clarify that the primary group doing the surveillance on this are blood establishments. And if this group wants to recommend that blood establishments, you know, provide blood donors with cards or something that would, you know, speed up any type of reporting, that's possible.

The surveillance that CDC is conducting is not designed for that type of rapid turnaround or rapid identification in reporting. That's another weakness of the system and relying on this withdrawal system for tremendous protection of the population.

DR. ROOS: Peter?

DR. LURIE: My question/concern is whether or not requiring all nine of these criteria is too restrictive a set of criterion. I guess the data question that I have is: of the 30-odd new variant CJD cases in Britain, how many of them have met all nine of these criteria?

DR. SCOTT: Well, could I also respond to

that question?

DR. LURIE: Yes, please do.

DR. SCOTT; I don't know the answer to how many have had all nine of those criteria, but most. However, the CJD surveillance unit has somewhat altered their criteria with time such that the current organization is similar to this but not the same. And most critically, they have gotten rid of the age criteria and added an MRI criteria. But this is not yet published material, and it's very recent. We just got that information on May 31st.

And I think the other thing to mention is that we weren't considering only using all nine criteria. But, really, that's the purpose of the third way, if I can say it, which is to have a very low threshold for identifying even potential cases and then to make a rapid decision on a case-by-case basis.

But what we're anticipating is probably what you're thinking, that not all of those criteria are going to be met, just due to a lack of information, time hasn't passed, we don't have material to analyze. And so I think what we're anticipating is that we would be -- we would err on the side of caution unless investigation showed us that it was most unlikely that this was a new variant

case.

DR. LURIE: I'm still left -- I'm afraid after that answer, it -- which may be the best you can give. I'm still left with uncertainty. I mean, it seems to me that that is a basic question. And if independent of data that are unavailable for the reasons that you point out there are people who do not have myoclonus, or whatever, and they don't have the right time course of disease, etcetera, we might -- and they may be too restrictive.

I think, at a minimum, it would be interesting to find out the answer to that question, and that might inform us better.

DR. SCOTT: Right. I can also tell you that in terms of the course of the neurologic progression, they reported I think it was 14 or 17 patients, and three of them would not have met, for example, that criteria because they got their movement disorders before four months had elapsed.

So you're absolutely right. Likewise, it was the psychiatric. So we would not be using the nine criteria per se in a potential case, as including or excluding the possibility of withdrawal.

DR. ROOS: Yes. I guess I kind of agree with Peter that I might have felt more comfortable if

all of the cases satisfied the criteria of suspected cases, plus others that then turned out not to have new variant.

In other words, you want to throw somewhat of a larger net to take care of a lot of the comers, especially when you only have 40 cases that have presently been identified.

DR. SCOTT: That's right.

DR. ROOS: Yes?

DR. BELAY: I just wanted to say that all of the new variant CJD patients in the United Kingdom meet all of this criteria. In fact, in addition, a certain proportion of classic CJD patients could also meet this criteria, all nine criteria. So by no means this criteria is just specific to new variant CJD.

The only criteria that we added was item number 7, which is a history of possible exposure. Again, even in new variants we get patients that would -- that would still be present, because most of them resided in the UK.

DR. ROOS: Yes, Will?

DR. HUESTON: Three thoughts. One -- if, in fact, a case meets the three -- the three criteria for definite CJD diagnosis, you don't need to go through the rest.

DR. SCOTT: That's correct, yes.

DR. HUESTON: Right. So some of the cases were identified because they met these criteria. They were defined without going through all of the rest of the history.

Point number 2, in terms of the nine -- and I just mentioned to Larry -- for all practical purposes, I think number 7 ought to be simply revised to say, "Resident or traveler to a BSE-affected country." The bottom line -- you do not know what you've eaten.

(Laughter.)

DR. HUESTON: You don't know to what you've been exposed. So it's -- the second thing is it draws -- I think it gives a false sense of security and directs, potentially, attention to the wrong products, because the average person thinks of beef as primal cuts of beef. And that's, at this point, the least likely of the sources of exposure, given meat products.

The third comment is that I personally am very concerned about the proposed -- this criteria of possible new variant CJD by FDA. And I have two major reasons for that. The first is that I see the potential for conflict arising between FDA and CDC,

where FDA is stepping forward or making a pronouncement of possible new variant CJD, and at the same time CDC says, "We're still investigating; you know, it's premature."

And I think that puts the FDA in a very awkward position, and I think an inappropriate -- Larry is telling me that they are investigating 25 --

DR. SCHONBERGER: There's about 25 cases under 55 a year.

DR. HUESTON: So my fear -- here is my fear based on my experience. Item number 2 says, "Donor has physician's clinical or pathologic diagnosis of CJD."

DR. SCHONBERGER: They're not all donors, by the way. Very few of them are donors. Okay?

DR. HUESTON: Okay. Fair enough. But once you get a terminology like this established, my concern is that it's going to spread further, that people are going to say, "Well, the FDA would have called this a possible case."

Number 2 says, "Has a physician's clinical or pathologic diagnosis," it doesn't say anything about the physician. And no offense to my distinguished colleagues, but there are a number of physicians that are simply not in the position to make

a clinical diagnosis or a pathologic diagnosis of Creutzfeldt Jakob. That has not precluded some of these same physicians from making a proclamation.

Third, I think that the public health and the risk communication implications of this are potentially massive. And having been on the firing -- you know, on the other end of trying to deal with these, you know, the press grabbing hold of a case and blowing it totally out of proportion and creating a great deal of concern, I don't see why you need another term.

I think you coordinate with the CDC, you coordinate your investigation when it comes back from a blood collection center that you have a donor less than 55 years of age, where you have some suspicion of Creutzfeldt Jakob Disease. You go through the same CDC workup, and you base -- on a case-by-case basis, you base your decision on that coordination with CDC.

DR. SCOTT: Right. So we would leave those products on the market if the patient hadn't had six months of disease, for example. You see, there has --

DR. HUESTON: I'm suggesting that you do it on a case-by-case basis --

DR. SCOTT: Right.

DR. HUESTON: -- in association with CDC. And you may decide to take action prior to meeting all of those criteria.

DR. SCOTT: Right.

DR. HUESTON: I'm concerned about putting forth yet one more term that I believe will be misinterpreted. It will create more misinformation than it will help clarify the situation.

DR. ROOS: Just so I understand, Will, the term is this possible new variant. So maybe it could just be stated that cases were under investigation at that point, rather than label it potential or possible. And I must say, I kind of thought FDA and CDC were working together on these cases. That was kind of my assumption. Okay. So -- Dr. McCullough?

DR. McCULLOUGH: I have the same concerns from the standpoint of the blood banking system. It isn't clear to me exactly when the process of the market withdrawal begins. But if it starts earlier than the resolution of the case by -- based on the nine criteria, what we have under the proposed criteria is someone that some physician says has CJD and is under 55 years of age.

And if something close to that triggers the market withdrawal, potentially involving very

large amounts of plasma derivatives, and all of that sort of thing, I have a lot of concerns about that. I think those actions need to be much -- to be initiated much farther along in the investigation of the case. So I have the same concerns about these very minimal criteria.

DR. SCOTT: Well, if I could interject -- I think what I intended to convey was that those small, three criteria would trigger an investigation that the FDA would be involved in, but not necessarily a withdrawal.

DR. McCULLOUGH: I'm reassured if you can assure me the FDA wouldn't, from time to time, decide to start things sooner, which could happen, I think.

DR. ROOS: Yes?

DR. EWENSTEIN: I think we should also remember that these patients, whatever their subsequent diagnosis, may be the recipients of products that the FDA regulates, and not just the source of products. And so I think it's important to have a low sensitivity for the -- I mean, we talk about hemophiliacs never having been diagnosed with CJD.

Well, you need a low sensitivity to make sure that you're not missing that sort of thing.

There are, obviously, other groups that are certainly in a high risk in terms of receiving biologic products.

DR. ROOS: I had a question. I didn't see any real criteria used related to the abnormal glycoform of new variant. And it was my understanding that all new variant cases had a specific electrophoretic mobility after the proteinase treatment. And why isn't that one of the definite criteria here?

In other words, if you did a brain biopsy that was normal, let's say, or looked pretty normal, or had, you know, just minimal changes, and you saw this distinctive glycoform, would that be adequate by British standards, or should it be adequate by our standards?

Larry, do you want to --

DR. SCHONBERGER: I don't know of any of the cases that don't have the definite diagnosis criteria -- that don't have that and have the glycoform alone. I've had it the other way around, for example, even with the Utah case. We did it based on a biopsy, and there was insufficient material, as I recall, to get the glycoform --

DR. ROOS: No. I had heard that it was --

it was -- it did not look like a BSE new variant.

DR. SCHONBERGER: No, I'm --

DR. ROOS: On the basis of --

DR. SCHONBERGER: No, I understand that. What I'm saying is we had an inadequate specimen for the glycoform. We were able to get the Type I protein fragment at 21 KV, which sort of ruled out the new variant. But we were not able to get the glycoform pattern, certainly right away. I don't know if he ultimately got it. I don't think he even ultimately got that.

Do you remember that, Ermias?

DR. BELAY: I'm a little concerned about adding this glycoform ratio as a case definition for two reasons. The first one is there is no standardized kind of methods that are being used by different groups. That the group in the United Kingdom -- namely, Collinge group -- would use a different criteria compared with other groups within the United States.

So that part of the, you know, method -- the immunoblotting or the Western Blot method -- has not been characterized or has been -- has not been standardized. And the second concern I have is there are other diseases potentially that could have the

same kind of glycoform ratio. And Dr. Pedro probably can correct me on this. FFI, I think, has been reported to have a similar kind of glycoform ratio also.

DR. PICCARDO: Yes. Let me back up for a second. First, I agree with what you've said. If the standardization of prp res, Western Blotting, is -- it is still under discussion.

So the UK -- Collinge group -- has one classification, up to seven different forms of normal prp while in the UK. In the U.S., basically, there is a Type I and Type II that have been recognized. So that is under intense discussion as we speak right now. So I would not base the diagnosis on that. That's for sure. And even at the pathologic level -- let me see, I had to walk out for a second because I had to get a taxi, but -- so I have to ask you a question. You were talking about that Utah case, and you were talking about the biopsy, right?

So I think at this point in time for the pathologist to make the diagnosis we'll need the full autopsy. I mean, with a small piece of tissue, with a lot of spongiform changes, with plaques, even in that biopsy, even with florid plaques, I would not feel comfortable in making the diagnosis, because you

can have rare forms of sporadic CJD in which you have a lot of spongiform changes.

And if you have a minimal amount of amyloid of plaque there, it will be florid, because it will be surrounded by vacuoles. So I think in order to make the diagnosis of new variant from a pathologic point of view, you need the full autopsy.

DR. SCHONBERGER: Generally, I agree with you. We were able in this instance, however, to show that it was not a Type II protein, but, rather, a Type I, which was -- which gave us hard data that was inconsistent with the new variant as reported in the UK. But generally, obviously, most pathologists are going to want the entire brain to deal with.

DR. PICCARDO: I'm not arguing against. All I'm saying is I think we have to be extremely careful. And the only way to be sure about all of this would be the full autopsy. And then work the -- the ratios, glycoforms, etcetera, etcetera -- I mean, we need more time for that.

DR. ROOS: Larry, the definition of suspected and definite -- this corresponds to the CDC classification at the moment or --

DR. SCHONBERGER: Yes. In fact, they had asked us to come up with this definition, and that's

where that comes from.

DR. HUESTON: It's compatible with the Brits, too.

DR. SCHONBERGER: And it is definitely compatible with the UK, although I'm in fairly regular touch with Rob Will, and he tells me that they are changing their criteria and that's why I was emphasizing that people have to regard these criteria as something in progress. It's a model being made.

DR. ROOS: Good point. Any other questions? Peter?

DR. LURIE: Just to be clear, if any one of these nine criteria is not present for reasons of the examination not being done, like an EEG, or not enough time having elapsed, it will count as if it is, in fact, present, right?

DR. SCHONBERGER: Yes, that's right. We would not count the absence of information as being negative. So that's why if a person is alive at five months, that doesn't -- he hasn't really lived greater than six months, that doesn't rule that case out.

DR. ROOS: But it sounds like the action that might be taken by the FDA in a particular case is done on a case-by-case basis. In other words, we are leaving a certain amount of discretion up to them in

their investigations, which I think at this point is probably appropriate, rather than putting every little detail --

DR. SCHONBERGER: I'm sure if Jay saw that we had five months, and that was the only difference, we'd be withdrawing that blood.

DR. ROOS: Yes?

DR. PICCARDO: I think we have to be very careful and very flexible with all of this. Setting the criteria now I think is good, as a working thing. But I think we have to be extremely careful, because in the unfortunate event in which heterozygotes nv will start developing the disease, they might have a completely different phenotype.

So this is just a work -- in my opinion, this is a working hypothesis, and we've set this criteria and we will have to modify that accordingly. I think that's the way to go.

DR. ROOS: It sounds like we are all in agreement about this being a good template to follow, and that maybe we shouldn't introduce a new term probable or possible Creutzfeldt Jakob, and that the FDA should look carefully and on a timely basis at these cases.

I would suggest that you do publicize

these actions to the neurological community because I think they're the ones that probably are going to have these cases come to them, rather than blood banks specifically.

Yes?

DR. ROHWER: Ray, I just wanted to draw attention again to number 7. It seems to me like while that's very helpful in implicating a case, it shouldn't be an absolute criteria for putting it in this category because it eliminates the possibility of discovering cases which may arise de novo from other causes in our midst -- for example, this Utah case.

DR. ROOS: I agree. If there are no further cases, I guess I'm going to call this session to an end and thank the committee members and other discussants.

Tomorrow morning is?

DR. FREAS: Tomorrow morning we will reconvene at 8:30 in the morning. I ask the committee members not to leave anything on their desks. The hotel may clear off the table tonight, and we do not want you to lose any of your papers. Thank you. See you tomorrow morning at 8:30.

(Whereupon, at 5:43 p.m., the proceedings in the foregoing matter went off the record.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in

the matter of: MEETING

Before: TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

Date: JUNE 2, 1999

Place: GAITHERSBURG, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.