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FOOD AND DRUG ADMINISTRATION
NATIONAL INSTITUTES OF HEALTH

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Advisory Committee on:

TRANSMISSIBLE

SPONGIFORM

ENCEPHALOPATHIES

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P R O C E E D I N G S (8:07 a.m.)

AGENDA ITEM: Opening and Administrative Remarks.

DR. FREAS: Good morning. Mr. Chairman, members of the committee, invited guests and public participants, I would like to welcome all of you to this, our fourth meeting of the Transmissible Spongiform Encephalopathies Advisory Committee.

I am Bill Freas, the acting executive secretary for today's meeting.

Today's presentations will be open to the public.

At this time, I would like to go around and introduce to the public the members seated at the front table.

Starting on the audience's right-hand side of the room, in the first seat is a committee member, and also a consumer representative, Ms. Barbara Harrell from Montgomery, Alabama.

In the next seat is Dr. Susan Leitman, chief of blood services, Department of Transfusion Medicine at NIH.

In the next seat is Dr. Lawrence Schonberger, assistant director for public health, division of viral and rickettsial diseases, Centers for Disease Control.

In the next seat is Dr. Stan Prusiner, professor of neurology, University of California School of Medicine.

In the next seat is Dr. Edmund Tremont, professor of medicine, University of Maryland.

In the next seat is Dr. Raymond Roos, chairman, department of neurology, University of Chicago.

In the next seat is the chairman of FDA's blood products advisory committee, who will be working with us today, serving as a temporary voting member of this committee, and that is Dr. Blaine Hollinger, professor of medicine, virology and epidemiology at the Baylor College of Medicine.

In the next seat is committee member, Dr. David Hoel, professor and chairman, department of biometry, epidemiology, at the University of South Carolina.

Coming around the corner is a temporary voting member for today, Dr. Peter Lurie, Public Citizen's Health Resource Group, Washington, D.C.

Next is a committee member, Dr. Donald Burke, director, Center for Immunization Research, Johns Hopkins University.

Next is our chairman of this TSE advisory committee, Dr. Paul Brown, medical director, laboratory of central nervous systems studies, National Institutes of Neurological Disorders and Stroke.

Next is a new member to this committee, and I would like to welcome Dr. Dean Cliver, professor, School of Veterinary Medicine, University of California, Davis.

Dr. Kenrad Nelson, who is a member of the blood

products advisory committee, will be joining us very shortly, and he will be sitting in the seat next to Dr. Cliver.

The next committee member is Dr. Linda Detweiler. She is senior staff veterinarian, U.S. Department of Agriculture.

Around the corner of the table is a committee member, Dr. William Hueston, associate dean, Virginia-Maryland Regional College of Veterinary Medicine.

In the next seat, Dr. Rohwer will soon be joining us. He is not here. That will be his seat. He is director, molecular neurovirology unit, at the VA Medical Center. He is a consultant for today's meeting.

Our next seat is occupied by a member of the Health and Human Services Advisory Committee on blood safety and availability. Today he will be joining us as a guest at this committee meeting. That is Dr. Ronald Gilcher, president and CEO of the Oklahoma Blood Institute.

Next is another guest, Dr. Merlin Sayers, director of the blood bank at the Carter Blood Care in Bedford, Texas.

In the last seat is Dr. Louis Katz, vice president for medical affairs and medical director for the Mississippi Valley Regional Blood Center.

There are two committee members who were not able to join us today. They are Dr. Katherine O'Rourke and Dr. Leon

Fatek.

In addition, Dr. Keith Hoots, another member of the Health and Human Services Advisory Committee on Blood Safety and Availability was to attend this, but at the last minute, he had a medical emergency and will not be here this morning.

I would now like to read into the public record the conflict of interest statement for this meeting.

The following announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting.

Pursuant to the authority granted under the committee charter, the director, Center for Biologics Evaluation and Research, had appointed Drs. Blaine Hollinger, Susan Leitman, Peter Lurie and Kenrad Nelson as temporary voting members for this meeting.

Based on the information made available, it has been determined that the agenda addresses general issues and matters only.

General matters waivers have been approved by the agencies for all members on the TSE advisory committee.

In addition, a waiver has been approved for Dr. Robert Rohwer to participate as a non-voting consultant.

Furthermore, it has been determined that all financial interests in firms regulated by the Food and Drug

Administration, which have been reported by the participating members, consultants and invited guests, as of this date, present no potential for an appearance of a conflict of interest at this meeting.

The general nature of the matters to be discussed by the committee will not have a unique and distinct effect on any of the members' personal or imputed financial interests.

In regard to FDA's invited guests, the agency has determined that the services of these participants are essential.

The following reported financial interests are being made public to allow the meeting participants to objectively evaluate any presentation and/or comments made by the guests and speakers.

These interests will be as followed:

Dr. Katz is employed by the Regional Blood Centers.

Dr. Merlin Sayers is employed by a non-profit community blood center.

Dr. Robert Will is a science advisor on CDJ to an FDA-regulated firm.

Dr. Alan Williams is employed by the American Red Cross.

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 discussions, and the discussions will be noted for the record.

A copy of the waivers are made available by written request under the Freedom of Information Act.

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

So ends the reading of the conflict of interest statement. Dr. Brown, I turn the microphone over to you.

DR. BROWN: Good morning. I think today's meeting should be interesting, possibly more interesting than any of the previous three, for the reason that we are being asked to consider answers to questions concerning blood safety and new variant Creutzfeldt-Jakob disease without a shred of direct evidence about infectivity in the blood of patients with new variant Creutzfeldt-Jakob disease, which you would think would be enough to dissuade us from considering the question.

It is compounded by the fact that we haven't got a clue how many people are walking around incubating new variant disease to begin with.

With these two complete holes in our scientific knowledge, we will make a valiant attempt, early this

afternoon, to come to policy decision recommendations.

Having said that, I would like to turn to our first speaker. Is Dr. Wykoff here? Dr. Wykoff will provide an introduction from the standpoint of the Food and Drug Administration. Dr. Wykoff?

AGENDA ITEM: Introductory Remarks.

DR. WYKOFF: Thank you, Dr. Brown. I am Randy Wykoff, the associate commissioner for operations at the Food and Drug Administration.

On behalf of Commissioner Haney and my many colleagues and coworkers at the FDA, it is my privilege to welcome all of you today.

I welcome not only the members of the committee and our guests, but also members of regulated industry, the media and the general public.

I would like to extend a particular welcome to our colleagues from Canada and Europe who have been able to join us today.

I have had the pleasure of speaking to this group in the past. As Dr. Brown has implied, I think today's meeting will be as challenging and as complex, and hopefully as rewarding as any meeting you have had in the past.

The issue before us today is, we are trying to determine what additional actions, if any, the FDA should

take, to help assure the safety of the blood supply, in the face of a theoretical risk of new variant CJD.

As with so many questions that this committee deals with related to TSEs, this issue is made more complex by the lack of information.

We do not have all the information we might like to have about new variant CJD, particularly its etiology and transmissibility.

This lack of information in no way absolves us of our responsibility to take the most appropriate actions to promote and protect the public health.

To deal with this issue, the FDA has brought together a truly exceptional group of experts. This group of experts, the advisory committee and the invited guests, will hear a series of scientific presentations this morning and then, this afternoon, will discuss in open session this issue, and ultimately will make recommendations to the FDA.

These recommendations are to be impartial and are to be balanced, and are to reflect both the sophisticated scientific capability that you bring to this issue, and also your understanding of the public health ramifications of any recommendations you might make.

To assist the committee in this process, there will be an open public comment period this afternoon. Members of

the general public and others not on the agenda will have the opportunity to make sure that their ideas, their thoughts and their suggestions are heard by the committee.

Additionally, to assist the committee, the FDA has developed a series of questions that will be posed to the committee.

We hope that by your deliberating on these questions, that you will find it easier to give us recommendations.

It is very important for the committee to understand that they can go beyond these questions if they wish to. The committee may explore other ideas, other suggestions, other recommendations if they believe they are appropriate.

Our charge to the committee is simple. What additional actions or activities, if any, should the FDA take to help assure the safety of the blood supply in the face of a theoretical risk from CJD.

As Dr. Brown said, this is a complicated issue. It is going to require all of your scientific capability and your thoughtful deliberation.

It will probably also require the full amount of time allocated on the agenda. In fairness to that time, I will conclude my comments by reiterating our welcome to all of you.

Because I will not be here at the end of the day, let me thank the committee for your thoughts, your deliberations and your recommendations. Thank you and welcome.

DR. BROWN: Thank you very much, Dr. Wykoff. Some further background to this issue will now be presented by Dr. Mary Elizabeth Jacobs, in the CBER section of FDA. Dr. Jacobs?

AGENDA ITEM: NEW VARIANT CREUTZFELDT-JAKOB DISEASE AND BOVINE SPONGIFORM ENCEPHALOPATHY: ISSUES RELEVANT TO THE SAFETY OF BLOOD, BLOOD COMPONENTS AND PLASMA DERIVATIVES.

Background.

DR. JACOBS: Thank you, Dr. Brown. Good morning. Copies of these overheads will be available after the break upon request at the desk.

FDA published a notice in the Federal Register announcing this meeting. In that notice we stated, the committee will discuss possible deferral of blood or plasma donors based on geographical criteria linked to possible food-borne exposure to the agent of bovine spongiform encephalopathy, as a measure to reduce the potential for transmission of new variant Creutzfeld-Jakob's disease through blood and blood products.

The potential effects of such deferrals on the

supply of blood and blood products will be considered as part of the committee's deliberations.

First, let's look at the current status of FDA's policy. FDA provided a notice on September 8, 1998, announcing a change to our previous guidance.

That guidance is entitled "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob disease by Blood and Blood Products."

That guidance covered both CJD and new variant CJD. It is important to note at this time that we have not had any cases in the United States of either BSE or new variant CJD.

In that September notice we stated: It is FDA's current thinking that, consistent with the procedures specified in the December 1996 memorandum, plasma derivatives should be retrieved, quarantined, destroyed, and consignees notified only in the event that in-date products were manufactured from a donor who later developed new variant CJD. That is distinguishing it from conventional CJD.

There is, however, a remaining concern whether donations made during the symptomatic phase of classic CJD also could trigger or should trigger withdrawal of plasma derivatives.

Given that current status of planned plasma derivative retrieval, let us consider what additional actions

FDA could contemplate.

Here we see the strategies which could be considered to reduce disease transmission for any agent. Those include donor screening, donor testing, donor referral, quarantine and release of products, use of GNPs, plasma fractionation, clearance which includes both agent removal and inactivation, leukoreduction, withdrawals or recalls of products, and investigation of errors, accidents, adverse reports and product failures.

We are aware that other countries have taken precautionary measures, particularly in the United Kingdom.

In November 1997, there were three recalls of blood products from new variant donors. In February 1998, they announced that UK source plasma would not be used for further manufacture. In July, 1998, they announced that universal leukodepletion would be implemented over about two years.

Leukodepletion refers to depletion of the white blood cells. I would note here, that here we are using the United Kingdom spelling, whereas in the other overheads we are using the United States spelling.

Before turning to our specific questions on donor deferral, I would like to briefly address leukoreduction in the United States. So, we are going to focus on leukoreduction.

This advisory committee, the TSE committee, is a scientific advisory committee, and we have the blood products advisory committee, which is also a scientific advisory committee.

In September 1998, we asked them to give a recommendation on the following question: Is the benefit to risk ratio associated with leukoreduction sufficiently great to justify requiring the universal leukoreduction of all non-leukocyte transfusion blood components, irrespective of the theoretical considerations of transfusion-transmitted CJD.

That is because questions involving CJD come to this committee. The vote by that committee was 13 yes, zero no, and three abstentions.

We expect that cost effectiveness issues will be discussed by the PHS advisory committee on blood safety and availability, because cost questions don't come to our scientific advisory committees.

Now I would like to look at the questions which are coming to this committee today. Those involve donor screening and donor deferral.

We have specific questions on which we are asking the committee for recommendations. The first of those addresses deferral, and I would like to read those for the record.

Should FDA recommend new deferral criteria for blood donors to attempt to reduce the theoretical risk for transmitting new variant Creutzfeldt-Jakob Disease, by excluding donors potentially exposed to the agent of bovine spongiform encephalopathy.

Under that we have sub-questions. A. Should FDA recommend excluding donors who have resided in the United Kingdom or other BSE country.

B, 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.

C, should FDA recommend exclusion of donors who had less intense exposure to beef product, based on limited travel to a BSE country. When did they travel, how long were they there, and what did they eat.

D, should FDA recommend withdrawal for blood components based on these donor deferral criteria.

E, should FDA recommend withdrawal for plasma derivatives based on these donor deferral criteria.

Next, we would like to look at the question of possible cases of new variant CJD which would be reported to the FDA in the case of a person who has already donated blood or plasma.

I would like to clarify that we have not attached a

specific definition to the term possible here. Again, the question is, FDA plans to refer possible new variant CJD cases to CDC for investigation.

Considering FDA's precautionary withdrawal policy for new variant CJD, A, should FDA recommend precautionary quarantine or withdrawal for plasma derivatives to which a possible new variant CJD donor contributed, pending histological, immunohistochemical or other clinical confirmation of diagnosis.

B, is a tonsil biopsy negative for protease resistant prion protein sufficient to make product withdrawals unnecessary, or to reinstate products to which a donor with a possible diagnosis of new variant CJD contributed.

We have also provided the committee with an issue summary which is available to all of you as well. In that, we are posing a number of scientific questions on which we have not asked for a specific recommendation, but for which we feel committee discussion would be helpful.

Those address some of the other strategies which include donor testing, plasma fractionation, removal and inactivation.

Some, but not all, of the questions in the issue summary are for focus by the committee.

Based on current scientific knowledge, is there a

potential risk of transmission of new variant CJD via blood or blood products.

Do the data support the hypothesis that the same agent is responsible for BSE in cattle and new variant CJD in humans.

Are there laboratory test methods to identify blood products with the potential to transmit new variant CJD.

Are they currently adaptable for large-scale screening. By this, we mean blood screening.

Have any processes been shown to inactivate the agent responsible for BSE, for new variant CJD.

Are there particular fractions or components of blood products which should be considered to carry a greater, a lesser or no risk for transmission of new variant CJD.

Finally, is the risk associated with food-borne exposure well characterized.

Now, let's go to the agenda which has been planned to provide information relevant to the questions. First, we are dealing with new variant CJD, TSE, issues relevant to the safety of blood, blood products and plasma derivatives.

Dr. Robert Will will address new variant CJD characteristics and demographics.

Dr. Robert Rohwer will talk about experimental studies of blood infected with TSE agent.

Professor Aguzzi will speak on the role of circulating lymphocytes in the pathogenesis of TSEs and also comment upon the disease in Europe.

Dr. Lisa Ferguson or the USDA will talk about current status of the BSE epidemic in Europe from the FDA's perspective.

Next, we will turn to donor deferral, product withdrawal and product shortages. Capt. Mary Gufstason will speak about U.S. blood donor deferral policies.

Dr. Jeremy Metters from the United Kingdom will talk about UK policy.

Canadian policies will be addressed by Dr. Douglas Kennedy.

Dr. Alan Williams will talk about the REDS study, which includes information relevant to today's questions.

Dr. Mark Weinstein will talk about effective withdrawal and recall policies on supply of plasma derivatives in the United States.

Finally, I would like to tell you what FDA's planned follow up is after today's committee meeting and recommendation.

First, we will have consideration of the TSE AC recommendations. We will have consultation with PHS agencies in the department.

We will have topical discussion at the PHS advisory committee on safety and available. We will have an announcement of our revised guidance. Thank you.

DR. BROWN: Thank you, Dr. Jacobs.

You may realize that every one of the subsidiary issues that were just mentioned is, in itself, worth a minimum of an hour's discussion.

As we are going to take a vote on the questions that have been addressed to us at 2:30 or 3:30 o'clock, I think that we will go into those issues as they seem interesting or relevant.

If it looks as if they are diluting our focus from the questions we have been specifically asked to answer, we will curtail such discussions.

The first scientific presentation is by Professor Robert Wills from Western General Hospital in Edinburgh, Scotland.

He is at the helm of both CJD surveillance in the United Kingdom and, more generally, at the helm of the Biomed-II European-wide program of CJD surveillance. Dr. Will?

AGENDA ITEM: nvCJD: Characteristics and Demographics.

DR. WILL: Good morning. I am very grateful for the invitation to come and speak at this meeting. I will start

just by giving you some recent, up-to-date evidence on the numbers of cases of new variant CJD, and then go on to speculate a little about the cause of new variant CJD and also something about potential exposure.

The reason that we first suspected that there might be a new type of Creutzfeldt-Jakob's Disease in the United Kingdom was because of the relatively young age of the patients.

This is, as I say, a relatively recent update showing in this histogram the typical age distribution of classical sporadic CJD and here, the new variant CJD. It is a rather different age distribution.

Critically, these cases of new variant CJD also shared what was thought at that stage to be a novel European pathological appearance with neuropathological confirmation.

This shows the most recent update of patient numbers, as of earlier this week. There have now been 34 cases of new variant CJD identified in the United Kingdom, of which 32 have neuropathological confirmation. In two, the diagnosis has been made on clinical grounds, and these cases have been designated as probable cases.

There have been 14 males, 20 females. The mean age at death is 29 years. It is very similar to the original description in the Lancet paper of April 6, 1996. The age

range is 18 years to 53 years at death.

The mean duration of illness is 16 months in these cases, with a range of eight to 38 months. Of course, the mean age of death and mean duration of illness are relatively distinct to that seen in classical sporadic CJD, to which the equivalent figures are about 66 years mean at death, and four months or so mean duration of illness.

This is a map a few months ago of the distribution of cases of new variant CJD at clinical onset. It shows that these patients have been identified from a widespread area of the United Kingdom. This is Northern Ireland and Scotland.

The formal analysis of this type of data does not suggest at present any good evidence of significant clustering of cases, or time and place. It seems that any risk factors for development of this disease are widespread over the United Kingdom.

Now, what is the evidence that new variant CJD and BSE are causally linked? This is a critically important issue.

First of all, I would argue that we have now very good evidence that new variant CJD is, indeed, a new disease.

When the cases were first published, there was a concern that these cases might have been identified perhaps as a result of improved ascertainment through the intensive study

of Creutzfeldt-Jakob disease in one country.

The question arose as to whether this disease might be identified in other countries perhaps in the past.

When we first identified these cases, we were able, through the European surveillance system, to state that in the other countries who were collaborating in the project there were no similar cases in 1993, and with the description particularly of the neuropathology of this condition, a number of studies have been done -- for example, in Europe and elsewhere -- to study archived material to look for cases of CJD with a similar neuropathology.

As far as I am aware, no similar case has yet been identified. I think we now believe that there is good evidence that new variant CJD is a new disease.

If we hypothesize that it is in some way causally linked to exposure to the BSE agent, then most of the cases should occur in the country with the greatest exposure, which is the United Kingdom, and so far there have been, as I say, 34 cases of new variant CJD in the United Kingdom, and only one case in another country, and that was in France.

The timing of the occurrence of new variant CJD is consistent with a link with BSE. If we look at the minimum incubation period in curu and human growth hormone recipients, it is about four-and-a-half years.

We can hypothesize that exposure to the BSE agent in the human food chain occurred in the 1980s, and seeing the first cases of a linked disease in the human population with onsets in 1994 would be consistent with this type of incubation period.

I have already mentioned the fact that the clinical pathological features of new variant CJD are relative consistent, particularly the pathology.

Ever since the original description, the cases in which we have neuropathological material have been carefully studied.

Dr. Ryans(?) and his colleagues feel that the neuropathology of this disease remains very consistent from case to case.

Professor Collinge has analyzed prion protein subtypes in new variant CJDs. He finds, and published that these prion protein subtypes were distinct from other forms of CJD and similar to passaged BSE.

The laboratory transmission characteristics of new variant CJD in inbred strains of mice are similar to BSE and distinct from other forms of CJD. I will just show some of Dr. Bruce's more recent data in the following slide.

Finally, and perhaps least satisfactorily, there is no other hypothesis which adequately explains the occurrence

of new variant CJD.

Here is a relatively recent slide from Dr. Bruce. This is a slide which shows BSE transmissions in a number of different strains of inbred mice, which have different genetic properties which influence incubation period, among other things.

The BSE transmission seems to be relatively consistent and very distinct from previous scrapie transmissions. New variant CJD in inbred strains of mice are similar to BSE and distinct from other forms of CJD. I will just show some of Dr. Bruce's more recent data in the following slide.

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Here is a relatively recent slide from Dr. Bruce. This is a slide which shows BSE transmissions in a number of different strains of inbred mice, which have different genetic properties which influence incubation period, among other things.

The BSE transmission seems to be relatively consistent and very distinct from previous scrapie transmissions.

New variant CJD, in terms of incubation period, has

very similar characteristics also, suggesting that the transmission characteristics of the BSE agent are very similar to the transmission characteristics in these mice of new variant CJD.

We believe that the F1 cross, we have some preliminary evidence that these animals are also dying at more or less the appropriate time.

What about sporadic CJD? I am sorry about the top of this slide, but what was set up perhaps fortuitously some years ago, were studies of transmission characteristics of sporadic CJD derived from cases in the United Kingdom.

Here we have two sporadic CJD cases from the 1990s, two from pre-BSE, three cases of sporadic CJD in dairy farmers, which is why the study was set up, new variant CJD, and in the lower panel, the transmission characteristics of BSE and feline spongiform encephalopathy in the domestic cat, which is thought to be BSE related.

What happens with the sporadic CJD cases, including the sporadic CJD cases in the two dairy farmers, is that the mice just gradually die off without a distinctive incubation period.

New variant CJD has an incubation period that is very similar to BSE and feline spongiform encephalopathy.

We feel this is quite strong evidence that the BSE

agent may be the causal agent of new variant CJD.

There are caveats to the causal link, and here are three which I think are important.

A case of new variant CJD has been identified in France. I would argue that this would not refute the causal link, because France did import large quantities of meat products from the United Kingdom in the 1980s, and also meat and bone meal that might have been contaminated with the BSE agent, and also cattle who may have been incubated with the disease.

We carried out a case controlled study to identify any specific dietary or other risk factor that appears to distinguish the new variant CJD patients from age and sex matched controls.

We really haven't found any meaningful results from this study as yet. Of course, there are major caveats to this.

The numbers are very small. Of particular importance in relation to the dietary study is that we are obtaining evidence from a surrogate witness.

Because of the nature of the disease, it is very difficult to get evidence direct from the sufferers.

We are also interested to dietary exposures, not recently, but years before, which introduces further

inaccuracies in this.

I think the failure to identify any specific dietary risk factor may not exclude the possibility that dietary exposure is the cause of new variant CJD, particularly if there was intermittent contamination of a variety of products in the 1980s. It may be almost impossible to identify specific risk factors so long after.

Finally, the age distribution of cases of nvCJD is not yet explained, although I think it is possible that the age distribution, as Dr. Gore(?) has suggested, may be related to differences in the pattern of dietary exposure.

What is happening with the numbers of cases? What in this slide I have got to explain, these are three month epochs since March 20, 1996, when new variant CJD was first described.

Along the top are all the referrals to the CJD surveillance system, individuals aged less than 50 years, excluding possible familial and iatrogenic patients.

Along the bottom is the number of new variant CJD cases derived from these referrals by three month epochs.

What this shows overall is, first of all, that the number of referrals is very much greater than the number of eventual cases, with a ratio of about five to one.

The proportion of referrals to subsequent cases is

variant, but overall, the number of referrals in this age group is relatively stable.

You mustn't be fooled by the end of this graph, because of course, these recent referrals, we will not have found all the new variant cases from the particular referrals, because of the six to nine-month delay between referral and confirmation.

Overall, we believe that these numbers of cases and current evidence is relatively flat also.

In relation to this consultation, I may perhaps mention some information from the European study. What has happened in Europe, because of new variant CJD and the systematic surveillance systems in a number of countries, there have been an increased number of referrals of perhaps what could be called perhaps suspect cases under the age of 50.

There is one country, for example, that has had over 40 such referrals, of which none have ended up having new variant CJD.

This is another way of looking at the new variant CJD cases. This is not completely up to date I think this is 28 cases.

This graph shows each case represented by a followed line of clinical illness, the triangle death, and the cross

confirmation.

This is plotted according to date of onset, which appears to be relatively steady. This type of data has been analyzed formally by Dr. Farrington and colleagues at the PHLS of London, looking at referral delay, et cetera.

Here is the number of the incidence of new variant CJD onsets pre quarter, which is a more or less straight line, suggesting the concurrent evidence that this disease is not occurring either more frequently or less frequently with time, but there are huge confidence intervals, which is very important to stress.

In my opinion, I think that this evidence is somewhat encouraging but must not be over-interpreted. Mathematical modeling has been done that suggests that it may be some years yet before we will know whether or not there will be a large number of cases in the future. It is still too early to say.

Turning to some evidence in relation to lymphoreticular tissues in new variant CJD and other forms of CJD -- and all this evidence comes from James Einseive(?), my colleague in Edinburgh, a neuropathologist.

Here is a tonsil from a post-mortem specimen obtained from an individual who died from new variant CJD.

This shows positive immunostaining for prion

protein. Furthermore, Dr. Einseive found that there was some positive immunostaining for prion protein in splenic tissue in post mortem tissue from new variant CJD.

I will now present some unpublished data on work that has been done. This is immunocytochemistry for PRT in autopsy tissue from cases of CJD and controls.

What has been done is to look at each diagnostic group, new variant CJD, iatrogenic CJD, sporadic CJD, controls and Alzheimer's disease, in order to look at whether there is immunocytochemical staining for PRT, in spleen, lymph node and tonsil.

What is found is that in new variant CJD, all are positive in these lymphoreticular tissues. In brief, all are negative for iatrogenic CJD, sporadic CJD, controls, and Alzheimer's disease.

These are small numbers, but nonetheless, in current evidence it looks as though the peripheral pathogenesis of new variant CJD may be different from sporadic and iatrogenic CJD.

I would just like to continue, because one of the issues that has arisen in the United Kingdom is the withdrawal of blood products that were derived from donations from individuals who subsequently developed new variant CJD.

It is clearly important for us to do this, not when we receive pathological confirmation of a diagnosis, because

there may be a long delay between referral and final diagnosis, particularly at post mortem, but to consider initiating the withdrawal process at an earlier stage.

What we have been doing is withdrawing or notifying the blood authorities of each case of probable new variant CJD.

What happens is that they then go through the whole blood transfusion system to try to identify whether or not these individuals have been blood donors, regardless of the evidence given directly about whether or not they are thought to have been blood donors.

To put up our current criteria for diagnosis of probable new variant CJD, we have a number of --

DR. BROWN: Before we leave the tonsil, would it be possible to tell us what Dr. Collinge's tonsil results are so far for living patients, rather than at autopsy?

DR. WILL: I don't have fully accurate data on that. I do believe there have been a small number of cases -- I think five or six cases -- in which tonsil biopsy has been done in life, and in which the results have been positive for immunostaining, and also I believe, using protein subtyping, suggesting type 4 protein.

This has been used as a diagnostic test. I should say that currently the recommendation -- but I will come back

to that in a minute in relation to this, if I may.

Here are some pre-conditions in order to diagnose probable new variant CJD. It requires a progressive neuropsychiatric disorder, a duration of illness of greater than six months, routine investigations do not suggest an alternative diagnosis and there is no history of potential iatrogenic exposure.

We then have a number of clinical features. There are five of these. Then we have component three, which relates to investigations. The EEG has not shown the typical appearance of classical CJD or no EEG performed. And B, there is posterior thalamic high signal on MRI brain scan.

In order to have a definite diagnosis, it requires neuropathological confirmation and an appropriate clinical contact.

For a probable you require exclusion criteria or inclusion criteria, four out of five clinical features and 3-A and 3-B. For a possible you require one clinical features but without the investigations.

We currently initiate the withdrawal process or tracking process for blood donations on the basis of a probable diagnosis.

Perhaps I should just say briefly that this issue of posterior thalamic high signal on MRI brain scan is being

closely studied and we hope will be published shortly.

We believe current evidence, although it is not fully analyzed yet, shows that about 85 percent of the cases do have this appearance at MRI scanning. At yet, we have no true false positives in the suspect group.

You will note that tonsillar biopsy is not yet on these criteria. The reason for this is that the WHO had a meeting earlier this year at which it was recommended that tonsillar biopsy, in the light of the relatively limited evidence that was available at that time, was regarded as a research procedure rather than a diagnostic procedure.

Of course, this may change with the publication of new data, which I think will be fairly imminent. I have to say that I think that the issue of immunocytochemical staining in lymphoreticular tissue in new variant CJD is critically important scientifically.

I have my own concerns about carrying out tonsillar biopsies in living patients. In my view, tonsillar biopsy is most unlikely to be of any benefit to a living patient.

It may, of course, give some benefit in the sense of getting an earlier diagnosis, but that is not particularly helpful for the patient, as far as I can see.

I personally feel that subjecting people to an anesthetic when they are critically ill is also a difficult

ethical issue.

Nonetheless, I think it is something that will be carefully considered by many groups, I suspect by the WHO when we have more data.

I thought I would end with a bit of speculation. We believe, for the reasons I have suggested, that BSE is causally linked to new variant CJD.

We also believe that the most likely hypothesis is that this was due to exposure to the BSE agent in the human food chain, probably in the 1980s, and probably to high titer tissue; that is, either brain or spinal cord tissue.

What I have done here is to just look at BSE exposure in inverted columns and link this to the timing of the occurrence of new variant CJD.

I must stress that this graph here with the solid bars and then the lighter bars is a surrogate marker for what I believe to have been BSE exposure of the human population in the United Kingdom.

This is derived from Professor Anderson's modeling paper, in which he looked at the number of infections in cattle that were necessary to result in a subsequent epidemic of clinical disease in the cattle population. This is all infections.

Of course, it is true, and probably very likely,

that the great majority of these cases that were infected would not have been relevant in relation to human health, because the great majority would have been slaughtered very early in life prior to replication of the agent in brain, spinal cord and perhaps in any other tissue.

So, these very large numbers -- this is 500,000 at the top here -- I don't really believe that this was the exposure.

There has been a lot of work done by various people to try to analyze what the exposure actually was. This relates to the number of cattle, for example, in the last year of the incubation period, that may have been slaughtered, and particularly older cattle.

The exposure path may have been very much flatter than this, with a peak in the late 1980s and early 1990s.

The SBO ban was then introduced in 1989 in the United Kingdom, which will have significantly reduced any exposure to the BSE agent.

If this measure had been fully implemented, in my view, it would have reduced the risk to the human population almost to zero.

DR. BROWN: I think everybody around the table may not know what SBO means.

DR. WILL: I am very sorry, the specified bovine

offals ban, which was a ban of what was believed to be all potentially infectious tissues from cattle -- for example, central nervous system tissues and a range of other tissues -- that were removed from all cattle that were slaughtered in the United Kingdom, including healthy cattle.

There are small bars here indicating that there may have been a continuing exposure at a lower level to this tissue, which then stops in 1995, because of further legislative action.

Then we have new variant CJD onsets here; with, as I have said already, an incubation period of perhaps six to 12 years.

So, the critical period of exposure may have been -- this is speculation -- may have started around 1983, peaked in the late 1980s, early 1990s, and then declined to very low levels.

There is, of course, some speculation about what may have happened prior to 1983, and there is some argument about whether BSE may have been around for very much longer, which I am not really qualified to discuss.

In my view, I think that the exposure in the human food chain probably was over a relatively limited period.

That is all I have to say. Thank you for your attention.

[Applause.]

DR. BROWN: Thank you very much, Dr. Will.

Actually, we have about five minutes to ask questions of Dr. Will, if anyone around the table has any.

DR. ROOS: I wondered whether you could provide any kind of quantitation of infectivity in those spleens and tonsils versus the brain, or whether that is impossible on the basis of immunohistochemical data.

The question is, how does it compare to the central nervous system, for example.

DR. WILL: Do you want some sort of measure of the relative infectivity of spleen, related to the central nervous system, solely based on the immunocytochemical staining?

DR. ROOS: Or anything.

DR. WILL: I am not sure I can give a figure on that. Others may be able to. Perhaps Adriano would be able to say something about that.

We don't have a measure of infectivity. Transmission studies have been set up in order to try to study this type of issue, but the results will take some years to get.

There is also a question as to whether the immunocytochemical staining in lymphoreticular tissues necessarily means that there will be an increased level of

infectivity in blood, and that is another matter of debate.

I think in relation to bovine tissues -- I don't know if that is quite the point of your question -- but the studies that have been done looking at the pathogenesis of BSE have indicated that in the mouse bioassays the levels of infectivity in the brain are very high, like $10^{>6}$, $10^{>7}$ infectious units per gram, and probably also in spinal cord.

In natural disease, we only have tissues that have been found to be infected include retina, dorsal root ganglia. There is some question about bone marrow in BSE as well. All the other tissue that I was mentioning are negative.

DR. HOLLINGER: Did you say that, were any of these cases -- the 34 cases -- were any of these donors at any time in the past?

DR. WILL: Yes, that is why the withdrawals took place. We had evidence on four individuals who were blood donors with new variant CJD, and all of these donations were tracked back.

In at least one of the cases it was so long ago that they had been blood donors that all the product had been used up.

In the paper that I wrote -- let me just clarify this. When I wrote a paper with Richard Kimberlin(?) we had a fifth case in which the family had said, this person was

definitely a blood donor, and that is why the paper says five.

In actual fact, when the national blood authority tracked back to try to find the donations, they could find no record of blood having been donated.

Of course, this raises the difficulty that we have of relying on evidence that is given with the best of intentions by the family members, but may be wrong, that they believed a blood donation had been given which may not, in actual fact, have been given.

So, we are currently -- this is what is happening -- with every case that becomes probable or definite, that all the blood banks in the United Kingdom do look back through their records to see if there is any history of donation, even if they say they had not been a blood donor. So, validation of this is very important.

DR. HOEL: What about the recipients?

DR. WILL: What has happened is that a limited look back study has been carried out, in the sense that there have been a number of recipients of whole blood products that have been derived from the new variant CJD donations.

So far, we believe that there are six of these individuals who do not appear on our registry of new variant CJD cases.

Of course, this evidence is of very limited volume, because the donations were given relatively recently and these patients are all young. Most of the data is after the age of 18.

The time period between when the blood was given and now is relatively short. If the blood infectivity were a risk, it is likely to be a low infectivity exposure.

We will wait to see whether blood donations actually result in the onset of disease. It may be years or decades before the negative evidence of that would be reassuring.

DR. HOEL: Just one follow up. When did they give their blood? How long ago, and what is the longest follow up that you have in the look back?

DR. WILL: I actually have that data with me. We are talking about, I think, on the order of five or six or seven years, something like that. We are not talking about 20 or 30 years. Therefore, the problem is the negative evidence so far, the very limited numbers, is not necessarily very helpful as a reassurance at the moment.

MR. EPSTEIN: Thank you very much for a very nice summary, Dr. Will. I appreciate your coming.

Can you clarify for us what is known about infectious prion titer in the meat of the BSE animal versus brain tissue?

It strikes me that in terms of trying to understand the human risk, it is a very different situation if we think meat generally was contaminated, versus we think the human exposure was incidental to inadvertent consumption of neurologic or other bovine tissue.

DR. WILL: It is a very complicated issue. As I have already said, in the transmission studies in mice, meat or muscle tissue has not been shown to contain infectivity.

The problem is the sensitivity of the system in which you are transmitting from bovines to mice. It is not a fully sensitive system because of the species barrier.

All that you can say on the basis of that evidence is there may be low levels, maximum, of infectivity in muscle material.

Although I think others are far better qualified than me to discuss all the transmission data from the past, my understanding is that there is really no evidence that muscle tissue contains infectivity in BSE through experimental work. Dr. Brown can comment on that further.

There then becomes the question, which is a critical question, as to whether these diseases are transmitted through high dose exposure, and perhaps a one off exposure, to a very high level of infectivity, or whether chronic low dose exposure, in which the infectious exposure itself would not be

sufficient to effect transmission, whether chronic low dose exposure is a matter of importance in these diseases.

That is a matter of great debate. Again, it is something that perhaps I am not best qualified to discuss.

It is a critical issue when assessing risk, because if you say that there is a threshold below which infectivity is not important for the transmission of these diseases, then it may be that low titer tissues, and even tissues that contain minimal infectivity may not be relevant to onward transmission of disease.

Of course, the final point about this is, enavitoire(?) particularly prior to the initiation of legislative measures, it is possible that material which might not have otherwise been a risk, might have been cross contaminated through the processes that happen in enavitoire.

For example, was there splattering of spinal cord tissue, for example. Of course, that is another issue that is very difficult to address experimentally or directly.

So, I think that there are a range of issues here that are well worth discussing. My personal view, for what it is worth, is that I think we have good evidence or sufficient evidence to suggest that individuals in the United Kingdom were probably exposed to high titer tissue, containing perhaps 10^{10} infectious units per gram.

To me, if we know that that happened, it may not be necessary to invoke all the other tissues that are not known to contain infectivity as being causal in relationship to new variant CJD.

I must admit, that is a personal view. All these other issues that are raised by this question, I am sure would merit discussion.

DR. BURKE: Could you entertain us with the notion of how possible that would be?

DR. WILL: On of the issues that we don't have all the information on is, did bovine spinal cord and brain enter the human food chain in the United Kingdom in the 1980s.

In order to address that, what we are looking at is to find out what is happening to these materials in other countries, and particularly Australia and New Zealand, because they have similar dietary habits to the United Kingdom, at least in general.

We have obtained some information from those countries which suggested that bovine brains have been entering the human food chain, and perhaps organs.

That is important because Australia and New Zealand have demonstrated no BSE, and there is no need to take any precautions at all in relation to these diseases.

What was the case was that in New Zealand, we can

take the information about New Zealand that suggested that some type of spinal cord material was put in a production process in the category of other meat, in which the bones from the animal are removed, and it is put in a large press.

Out one end comes the bone and out the other end comes some pinkish material that can be used for various meat products.

It is therefore possible, by analogy to what happened in New Zealand, that in the 1980s similar things were happening in the United Kingdom.

Therefore, it is possible that exposure to CNS-type tissue did take place, through the consumption of this type of product.

DR. BROWN: Other questions?

DR. LEITMAN: Could you put the incidence rate, that rather comforting two cases per quarter, in terms of a denominator, perhaps the population of the United Kingdom, about 60 to 80 million?

DR. WILL: The population of the United Kingdom is about 57 million.

DR. LEITMAN: That is one in 10 million per year; is that correct?

DR. WILL: Yes, but I think I must be careful -- I am sorry, am I being responsive to your question?

DR. LEITMAN: That is my other question.

DR. WILL: I think it is true, and I think that it is relatively reassuring that after 1996 the number of cases of new variant CJD have been relatively small.

The difficulty with diseases with a long incubation period is that it is too late to say that that indicates that they will only have a small amount of cases.

There is, to my mind, still a possibility that there could be large numbers of cases in the future. We certainly hope not.

In relation to the 1980s in the United Kingdom, as Dr. Brown has already said, the problem is that we do not know how long the incubation period is. There is no way of telling, nor of testing.

Therefore, we have to perhaps use the worst case assumption, and that is why we have taken the measures we have in the United Kingdom. It may turn out to have been unnecessary.

I should say also, perhaps in passing, that there has been quite a lot of publicity recently about various mathematical models.

The first publication suggested anything from 100 to 6,000 cases of new variant CJD. A recent publication suggested that the total number of patients who would ever

have new variant CJD would be 100.

I think it is likely -- if I can just throw this in here -- is that there is such a range of predictions because of the range of uncertainty, that we don't know what the distribution is, we don't know what the exposure was, really, for high titer tissue.

We have such a long incubation period, that we don't know what the exposure was. We don't know if there are subtypes. We don't know if there are a lot of single doses. Maybe there was very high exposure.

There are all these uncertainties. In my own mind, I think it is worth the mathematical models just to state the uncertainty.

I personally feel that to rest too much on that model may be problematic.

DR. LURIE: My question is about the 34 cases that you described. How many of them had, in fact, been donors and what was the impact upon the supply of blood or blood products, and what if any action does the British government plan to take in response to those.

DR. WILL: I have already answered that first question. I think Dr. Metters can answer it further.

DR. BROWN: We can have one more. David, you had a question.

DR. HOLLINGER: With the age distributions, in your risk models, are you comfortable with the difference in dietary habits?

DR. WILL: I have to say there is a divergence of opinion on this. The issue is that the age range, although the age is much younger than 50, the epidemiologists felt that it was specific dietary habits, that spread out the distribution.

A different view was held by Dr. Gall(?), who has published something about the dietary exposures from a few survey 10 years ago, that suggested that it is possible to explain this particular distribution.

I personally feel that we need to know more about the distribution of the food rates, what type of food product was used, in order to get a handle on that.

DR. BROWN: Thanks very much, Dr. Will. The next presentation, experimental studies of blood infectivity in TSE is going to be made by Dr. Robert Rohwer, who spent many years at the National Institutes of Health. He is now director of the molecular neurobiology laboratory at the VA Medical Center in Baltimore.

AGENDA ITEM: Experimental Studies of Blood Infected with TSE Agents.

DR. ROHWER: Thank you. I am going to focus this

talk mostly on several experiments that have been done in the last year or two, both by ourselves and in collaboration with our esteemed chair at the VA.

I will just mention some of the earlier published work and, if we have time, I will say a few things to put this in perspective.

My main point to make about prior work is that there have been off and on attempts over the year to look at this issue of TSE infection in the blood.

You can divide them into two groups, a look at natural infections, the most important ones being the humans to primates, attempts to transmit the disease from humans to primates via blood and blood products.

This included a couple of transfusions of complete units of CJD infected blood into primates. There is some work with mice looking at this. There were no transmissions in any of these cases.

The only transmissions of naturally infected material have been four reports from four different laboratories, claiming to have transmitted the disease from human blood to rodents, mice, rats, guinea pigs.

These reports are quite incredible, when you consider the very low titer that you find in blood, and the fact that there is a very large species barrier between humans

and primates.

There is a lot of reservation about accepting these, unless they were to be confirmed in further studies.

The situation with experimental studies is quite different. Here, it is often empirical. Some people reported transmissions from animals experimentally infected and others have not.

It is hard to sort out what the differences might be due to, but there are bit methodological differences.

Different models were used.

It is always possible that the titers in blood may be sporadic. It may come and go and that could account for some of this variability.

What you can take home from those studies is the fact that when infectivity was seen, it was seen in populations that had very long incubation times, in which some of the animals usually did not come down, indicating significant limiting conditions, suggesting variable patterns were present.

In most of these studies, an attempt was made to concentrate infectivity into a fraction, in order to increase the sensitivity of the assay.

That was usually buffy coat. So, buffy coat has clearly been implicated as a source of infectivity.

One thing from all the experimental work that has been done to date has been that in the interest of expediting experiments and just because it is a standard laboratory procedure, in general, the animals that donated the blood were inoculated with very high titers of inoculum.

The disease was allowed to incubate. Subsequently, blood was removed from that animal and inoculated by an intracerebral route into a recipient animal, to see whether there was any infection in the blood.

The intracerebral route is used, simply because it is the most efficient route of infection. It is not necessarily the way you would get exposed to blood naturally.

If you want to ask the question, is there infectivity in the blood or isn't there, this is the way to do it. All you are asking here is whether you have the presence.

The problem here is that when infectivity was seen, it was at very low titers. It must have been less than 100 infectious doses in the blood itself, and I would revise that down from there at this point.

There is always a possibility that, because of the robust nature of these agents, that what happened here is that the inoculum of the original donor had been re-isolated in the blood, and that is what was being inoculated.

That would account, perhaps, for the discrepancy

between the experimental infection and the natural infection.

On the other hand, in the experimental infections, there is no species barrier that is not a factor. It is still plausible that this is endogenous infectivity as well.

I addressed this in one experiment I showed you here, and we are looking at that in other experiments around titration now.

At the time, again, of these experiments, there were still a number of important outstanding questions. What is the effective route and dose. Those could be big effects.

Low dose, infection by peripheral routes take a lot longer to develop. There is more opportunity for peripheral systems to become involved, and this could be an important factor, and it has not been investigated adequately.

When is infectivity present? That is the crucial question we are all concerned with here, as to whether this is something that occurs in clinical disease, or do people manifest this throughout the incubation period.

What is the titer -- essential for risk assessment -- and what is the distribution among components and fractions.

Transmissibility and distribution in animal models will give us the ability to perhaps generalize what we see in animals to humans.

Now, the first set of experiments I want to show you involved a series of transfusions and titrations of blood.

In all of these experiments, a donor hamster was inoculated, either by the intracerebral route or the interperitoneal route with either a high titer inoculum or a low titer inoculum.

When that animal became sick, or when it was halfway through its incubation period, the animal was anesthetized and exsanguinated by cardiac puncture.

We could reliably get four to five mls of blood out of the hamster. Two mls of blood, the first two mls that were collected, were immediately transfused into a naive recipient.

Another two mls, when it was available were not buffy coated, actually, but white blood type cells were prepared and they were inoculated as a single inoculum into another animal simply to ask the question, is there infectivity in this blood or isn't there.

If we get negatives in these transfusions, they are meaningless, if we didn't actually transfuse infectivity.

So, this was designed to answer the question of whether there was infectivity or not. On the other hand, at the time we began these experiments, no one had actually done a titration of whole blood and there was concern that maybe we were missing something by inoculating buffy coat alone.

So, we also took one milliliter of whole blood in seven different cases and inoculated the entire milliliter into hamsters.

To inoculate a milliliter of blood cerebrally, you can only inoculate 50 microliters at a time by that route. So, you have to inoculate 20 animals to look at a whole ml. So, we inoculated 20 animals.

We looked at both high dose, intracerebral inoculating donors. We had several donors that received a limited dilution, a very low dose.

The importance of this experiment, these animals received so little infectivity to initiate infectivity, that it must have come from infection, and not the inoculum. This gets around the caveat that I spoke of earlier.

Then we used the interperitoneal model because -- Gary is going to show this works -- and these inoculations were interperitoneal high dose, and we bled some of these animals in clinical disease and some of them in preclinical disease.

I will start with the IC inoculations first. The way to look at this chart here is that each line represents the fate of the blood from a single donor animal.

This is the result of the inoculations with blood from this animal, for example. In the blue column here, we

are looking at the results of the transfusion, and the green column is the results of white blood cell inoculations. Over here in the pink, the inoculation of 20 animals with 50 microliters at a time of whole blood.

So, for example, in this animal right here, the transfusion, after 560 days, produced no infection. The buffy coat, or white blood cells, had also produced no infection.

Yet, when we inoculated the blood directly, we had five out of 18 inoculated animals became sick, indicating we have a titer somewhere around five infectious units per ml in this blood.

We were surprised, because every blood that we looked at, with the exception of this one where we ran out of blood before we got a full 20 inoculated, but the bloods in which we inoculated a whole 17 to 20 animals were all positive in this experiment.

They gave titers ranging from about five to 15 or 16 infectious doses, or five to 15 infections per milliliter of blood inoculated.

Yet, these white blood cells gave no infection except in this particular case right here. We weren't expecting this. None of the transmitted from these IC inoculations.

We did see one transfusion transmission from a high

titer IC inoculated donor. That is this one right here.

The blood of that animal also titered quite strongly. You had 12 infections out of 19 animals inoculated, almost a ml inoculated.

These were the results from the low titer donor experiments. These animals received only one to 10 infectious doses. This is the only blood that we titered.

None of these transfusions transmitted, but none of the other transfusions have transmitted either, except for this one.

Then four of these animals did eventually come down with scrapies, suggesting that there is infection derived as a consequence of -- it is there as a consequence of the infection, not the inoculum.

This is just a representation of what the titers of these six bloods would be if they were corrected for the quasi-distribution of the infection process.

As you can see, we found from five to about 25 infectious doses by that criteria. It may be significant that this living version donor was down here at the low end of this and the fast incubation animal was also there, suggesting that there is less infectivity under those circumstances.

That would also suggest that some of the infectivity in the high titer donors could conceivably come from the

inoculum, but presumably it does not all come from the inoculum.

This is a plot of the incubation times of those animals who did get sick from these inoculations. As you can see, our typical intracerebral inoculation gives an incubation time of less than 180 days.

However, at limiting dilutions, these infections take a lot longer, possibly because they are not truly intracerebral inoculations any more.

Intracerebral inoculations, where we do it, a good part of the infectivity does end up in the blood stream and does end up in the peripheral organs. Perhaps the infections originate that way, and that is why we have such a long incubation period.

On the other hand, quite a large proportion of our cohort went out to almost two years, and we saw almost no infection after about 390 days, which gives us the confidence to terminate the study at this time.

This is where the transfusion transmission came down; this is where the low titer donor transmissions came down. There wasn't anything particularly meaty about those infectious tests.

What can we say about this data? There is infectivity in the blood that was present even when the donor

received a small dose.

It was present after IC inoculation with the donor, and we saw infectivity during preclinical disease.

The titer was 14 infections per ml of blood inoculated. Infectivity was not concentrated in the white blood cells, as we had expected it to be, and we did the transmission by transfusion.

What can we say about this transfusion transmission? This was one transmission out of 24. The problem with this type of data is that there is not denominator. We don't know if this is one out of 22 or one out of 22 variants.

Another way of looking at this, this is one transmission out of 44 mls of blood transfused. Each transfusion has one ml of blood.

The donor had received a high titer inoculum, so there is always the possibility that there was something special about the blood that causes transfusion.

The important thing, of course, is that the epidemiology suggests that even though it experimentally suggested here that transmissions can occur, the epidemiology suggests that this must occur pretty rarely.

We are continuing to look at this. We have this little diagram in the laboratory. It is about a third of the blood volume in the hamster that we are moving here.

We have an additional 47 transfusion titrations from low titer donors and another 18 or so from high titer donors, to do a total of 50 more of each class, hoping that we might see some evidence that there is a difference between the high titer and low titer donors.

The next experiments that I am going to discuss were recently published in Transfusion, and they were conducted in collaboration with the NIH.

These experiments were designed to answer the question, where is the infectivity in blood and how does it partition during plasma fractionation.

There are two ways you can go about a study like this one. When we began these experiments, it wasn't clear how we should proceed, so we did them both ways.

The idea here would be to look at blood itself and look at the distribution infected in blood. However, there is hardly any infectivity in blood, as I have just shown you.

The incubation time would be very long, the sensitivity would be low. The advantage is that the infectivity would be in the appropriate context.

Traditionally, the way a study like this is done is that a high source of infectivity is spiked into the vehicle - in this case blood. The blood is then fractionated, and this is tracked by infectivity assay.

The advantage here is that you have short incubation times, high sensitivity, but the relevance is not known.

You don't know, in the case of the TSE diseases, the only source of high infectivity we have is central nervous system tissue.

If we put a brain fragment into blood, for example, are we really fractionating the way blood borne infectivity does in fractionates, or are we just fractionating brain activity in the presence of blood. We can't answer that question.

Both of these experiments were done in a similar way. The first experiment using endogenously infected blood, a large cohort of mice were inoculated with the mouse adapted strain of GSS.

GSS is a Griffen-Strasburg(?) syndrome, a dilutal form of PFE disease, and it has been adapted to mice. The basis for doing this is there is some experimental work that has been done in the past.

A cohort of mice were inoculated, and most of these mice were in clinical disease. The mice were killed or anesthetized, and then their blood was drawn by cardiac puncture and pool.

That pool of 50 mls of blood was then taken through

a component separation and then the plasma was taken through the first steps of co-fractionation and those fractions were also analyzed.

The data are summarized on this table, and I will take a bit of time here. The specimens that were now analyzed are over here in red. So, these are the components over here and down here are the co-fractions.

On this chart here we have the total specimen weight to volume fractionated. We started with 45 msl of blood.

If we jump to this column over here, this is the number of animals that were inoculated and this is the number of positive animals that we discovered.

We encountered a heck of a difficulty in the execution of this experiment, in that most of the components, especially, were toxic on IC inoculation, and they had to be diluted in order to introduce them without killing the animal.

This dilution caused a reduction in the total mass that was actually inoculated and that is indicated here in the fraction that was inoculated.

The important thing to note here is that in the case of whole blood, hardly any was inoculated, less than a tenth of a percent. In the case of red blood cells, the same was true.

In the case of buffy coat, we inoculated about two

percent. About 60 percent was this plasma pellet, and three percent of platelets were plasma.

We did much better with the pellets derived by plasma fractionation, and get about 30 percent of each one of those.

As a consequence of this, these numbers over here, what I have done here is I have corrected these values here in this yellow column by saying, well, in the case of buffy coat, for example, we saw two infections out of 12 animals inoculated. We inoculated as much buffy coat as we could there.

If we had inoculated the whole thing, how many animals would we have seen? Well, we would have seen 101. The same thing here for the plasma pellets and platelet plasma.

The thing that surprised us, and that is disturbing, is that we inoculated a fairly large number of animals with plasma and had a significant number of infections there.

It appeared that a significant proportion of the infectivity was still present in the plasma, that it did not come down with cellular impressions as we had expected.

I don't want you to make too much of this. As you can see, small changes in the number of animals in these fractions could cause a lot of excursions over here on this

side.

Nevertheless, I think we can see that there was infected plasma and we hadn't expected that. When we went through the co-fractionation, such infectivity was recovered and was found primarily in the cryoprecipitate infection 1+, 2+, 3. None was found at 4 or 5, even though we inoculated nearly 100 animals and that is where we got the bulk of those fractions.

In these experiments, again, if you divide the amount of infectivity we recovered by the amount of blood that we had present, we got a number consistent with the hamster result, about 10 infectious doses per ml.

We saw infectivity in plasma in buffy coat. This is an important aspect, that in the co-fractionation we recovered only about 10 percent of the infectivity we would have expected, and we don't know where the rest is.

We have gone on with this experiment and have put it on with a much larger scale, which I am going to show you in a minute.

The data I am going to show you is taken at about 150 days. We are only here in this titration. We have all this time to go before we get to the end of it.

What we have done is, wanting to get a better estimate for the distribution of infectivity of the fraction,

we started this time with hamster blood, 250 mls of it, and carried it into a component separation, and through a component fractionation.

In this case, what we have done is we have inoculated a five ml equivalent of every single one of these components and fractions.

On the basis of the titer we saw in our direct titrations of hamster blood, we expected to see between 20 and 50 infections per five ml equivalent in whole blood, which will give us enough infections to make statistically valid comparisons, hopefully, with the rest of these components, the distribution in the rest of these components.

Everything that is boxed in red here is so far showing infections. All of these samples were inoculated. These were also inoculated. This is the same as this, just look at these right here.

So, these components are all showing infectivity. This is consistent with what we found the first time around. It is too early to talk about distributions.

In the co-fractionations, we are so far seeing infectivity in the cryoprecipitated fraction, of +2, +3, just as you did before.

Everything in pink here has been inoculated at the level of a 5 ml equivalent.

We also have untitrated experiments looking at pure blood platelets in lymphocytes, purified by glycol methods.

Another way to look at this is to spike human blood with rodent infectivity, and then track the infectivity through the same fractionation process.

The fractionation is the same in this case. We used disbursed brain cells. Our prejudice at this time was that the infectivity would be cell associated, so this might be a good way to introduce the infectivity into the unit.

This was done; it was fractionated. In this case, we have lots of infectivity associated with each of these fractions.

So, we have to do serial 10-fold dilutions and then inoculate the animals with each dilution and look for the end point where the inoculate no longer kills the animals.

This is the results of these titrations expressed in terms of fractional recovery. Actually, I have got the wrong one.

This is the total recovery. As you can see, we had about 10^{10} infectious doses in the whole blood sample.

This is whole blood, white blood cells, red blood cells and plasma. The one problem with the end point dilution titration is that it only has a sensitivity of about half a

log and these are not really significant differences.

I am going to show you only the plasma fractionation next.

In the plasma fractionation, we saw significant removals in going from plasma to cryo, 1+2+3, 4, 5 and 5 supernatant.

The only problem with this is that even though we saw several logs of removal, it didn't add up. We didn't recover the infectivity that we put in there, and we cannot account for the infectivity that we lost.

I presume that it is in aggregates and hopefully it is in the cryo 1+1+2 fractions.

Otherwise, the distribution was consistent with the mouse, and the process resulted in the significant removal of infectivity.

One way of looking at all this data together at one time is to consider, given if there were 10 units of infectivity per ml in blood, how would it distribute on the basis of these experiments.

We would have expected, in that case, 5,000 infectious units in 500 mls of whole blood and half of it would be in the platelets or plasma.

We found a fifth of that, or 280 infectious units in cryo, another 10^{th} of 1+2+3. We saw nothing in the mouse

experiment, but based on the hamster spike, we would have seen two infectious units in four, and a tenth of an infectious unit in five.

I will conclude here with some acknowledgements. The transfusions were done largely by Bobby McCauley(?) in my lab. Bryan Hudson did a huge number of western blots to confirm all of these infections.

The fractionation experiments were done in collaboration with Paul Brown, and I would like to acknowledge the continuing support of Bill Rowe and the American Red Cross. That is it.

[Applause.]

DR. BROWN: Thank you, Dr. Rohwer. We are now on schedule and therefore, we will not at this time have any questions for Dr. Rohwer. We will continue immediately with Dr. Adriano Aguzzi, an experimentalist and neuropathologist who comes to us from the Institute of Molecular Biology at the University of Zurich in Zurich, Switzerland, who has conducted a series of interesting experiments at the level of molecular biology, neurosurgery and genetic manipulation in mice to explore the function of the lymphoreticular system in the pathogenesis of TSE.

AGENDA ITEM: Role of Circulating Lymphocytes in Pathogenesis of TSEs. BSE, nvCJD and Blood: A European View.

DR. AGUZZI: First of all, thank you very much. It is a great pleasure to confront you with some of our data.

I must apologize, because in order to make you understand what we have been doing, it is going to be necessary to bring you through some cellular immunology.

Okay, the question that has interested us is the preliminary data, the process by which the infections reach the central nervous system when they are administered to peripheral sites and the central nervous system is the only piece of the body where you can actually find pathology.

So, the assumption here was that specific cell types and perhaps specific polymers of these cells might be involved in the process.

So, we acknowledge that we are using brain grafting and the idea behind it was to take neuroepidermal(?) cells and assess from the brain whether you highly over-express the normal prion protein(?), and transplant such cells into a mouse that is a genetically-engineered mouse that does not contain the gene encoded for prion protein.

So, if you do this manipulation, you end up with a graft that overexpresses prion protein, and we surround it with a region that is devoid of the normal prion protein.

Now, apart from the cerebral inoculation, such grafts do develop disease. What you can see here is that it

is confined to the tissue that expresses the normal prion protein; however, it does not invade the tissue that is devoid of normal prion protein.

Now, this has allowed us to ask the question whether normal prion protein may be necessary for neuroinvasion.

So, the question that we were really asking here is actually whether, if you take out the normal prion protein from the body and now you get a piece of brain that expresses prion protein, and then you can use it the other way, and if you put prion into the periphery, into the peritoneum, will that then reach the brain.

The assumption is that you can anticipate that this was not the case. Apparently there is some piece of the body that needs expression of prion protein for the infection to reach the brain. The question was, what could be this issue.

We know it is some sort of hematopoietic cells like B. lymphocytes, perhaps follicular dendritic cells, but perhaps also the central nervous system is likely to be involved. This is where we started.

The experiment has been adapted and so, is becoming more and more complicated, but this is what we did next.

We took another Prnp knock-out mouse. Now, we had known from previous experiments that if you put a graft that expresses normal prion protein into the brain of this knock-

out mouse, and put infectious prion(?) into the graft, they will not reach the graft. There is some tissue interposed that needs expression of the normal prion protein.

So, we manipulate, in these compound mice, and reconstituted the bone marrow into the lymphocytes and basically all marrow cells, with hematopoietic stem cells derived from mice that contained the gene encoded for normal prion protein.

So, we manipulate in these compound mice and reconstitute with the bone marrow into the lymphocytes and basically all marrow cells with hematopoietic stem cells derived from mice that contained the gene encoded for normal prion protein.

Now the question was what manipulation would restore the revision. I am not going to show you any detail, however, in such mice we could see that the agent had accumulated a large amount, but it could not reach the brain.

I am going to spare you the experimental details, but the conclusion from these experiments is that apparently Prnp expression of the normal prion protein may be what is required on something like hematopoietic cells for them to reach the lymphoid tissues

However, given that this is necessary, it is certainly not sufficient, because a compartment that cannot be

restored by hematopoietic transfer must also express the prion protein for it to reach the brain.

This is still an area for argument, so we are not totally sure, and again, I am not going to repeat the details.

Now we turn to the question of what happens in the lymphoid compartments. So, we have used a panel of immune deficient mice, of mice in which the cellular components of the immune system would be lacking.

We have asked the question whether we could find a specific immune effect that would prevent the revision to occur, that would prevent peripherally administered prion from reaching the central nervous system.

So, the mice that we have been using were, on the one hand, the mice that in various molecules expressed B lymphocytes, such as the CD4 receptor, the CD8 molecule, the beta-2 microglobulin, which is a component of a major system in the immune complex, as well as perforin, which is an effector molecule, as well as the T cell receptor alpha chain.

These are double knock out mice, with the 24 T cell receptor beta and the T cell receptor delta(?) chain. So, these mice are profoundly deficient in B lymphocytes.

We also used mice that were deficient in both the T and the B cells, such as the SCID mice -- SCID stands for severe combined immune deficiency, both the T and the B cell

systems -- as well as the RAG knockout, RAG-1 and RAG-2.

RAG is recombinase inactivating gene. It is important for recombination of both the immunoglobulin genes, the somatic cell combination and the rearrangement of the T cell receptor chains.

So, the RAG mice, just like the SCID mice, had T and B cells.

Now, we also used mice that are exclusively deficient in the B cell development.

When all these mice were inoculated cerebrally, it was found that all developed disease with latent periods after administration cerebrally, that were similar to those of controls.

We conclude from this that the immune status of the animal has no relevance to the development of disease, if the agents are administered intercerebrally.

Now, when the agent was put into the peritoneum, the situation was very different. In this case, all of the T cell deficient mice developed disease, with incubation times that were very similar to those of the wild type mice.

The experiments in totally deficient mice, the T cell receptor beta and delta, is inappropriate, because we don't get data on this.

However, the mice that have neither T nor B cells

all stayed healthy in the SCID mice as well as the RAG knock-out mice, with the exception of some mice that have been not totally stable.

These are SCID mice in a different background, and these mice developed disease, probably because they are leaky. They tended to restore some of the T and B lymphocytes.

Now, the surprise of this is that the B cell deficient mice also stayed healthy upon intraperitoneal inoculation. We conclude from this experiment that the B lymphocyte is crucially important in the process of neuroinvasion, and the absence of B lymphocytes completely prevents the neuroinvasion from occurring.

Now, the next question, which I think is much more relevant to your group is, does this mean that the B lymphocyte itself is infected.

Let me put you straight right now that the studies I have shown you does not allow for answering this question, because those are not designed for asking the question of whether the B lymphocytes are infected.

The experiments I have shown to you were designed to answer whether B lymphocytes may be necessary for detecting infectivity.

Nevertheless, it was important now to ask the question whether B lymphocytes may be infected at all.

Therefore, my laboratory, together in collaboration with Alexander Weisman(?), did the following experiment.

He took spleens from mice that had been inoculated interperitoneally, and I should tell you that this data base is unpublished.

So, he got T and B lymphocytes from spleen using magnetic beads. It turns out that both B cells and T cells contain some rather high titers, something like 10^{3-4} infectious units per 10^6 cells, when the B and T lymphocytes are isolated from spleens.

However, when the same numbers of leukocytes were isolated from the peripheral blood from the same mice, Alexander could not find infectivity.

I should tell, however, you that the sensitivity of this assay is not very high. The most he could have found would have been a titer of 10^2 infectious units per 10^6 cells.

Anyway, the bottom line is that the PMT lymphocytes from spleens contain infectious agents. However, those from peripheral blood seem to contain at least one and a half log less.

Now, one potential use for this experiment is that most of the dysplasia(?) of the protein is associated with follicular dendritic cells in the lymphoid tissues.

In that way, in histochemistry that Professor Will has shown to you, it is also compatible with the inoculation within follicular dendritic cells in humans.

Now, follicular dendritic cells are cells that they stay in the follicle centers of the lymphoid organ. However, they are in strict contact with the B lymphocyte and also with T cells.

So, one possibility is that during the preparation of the spleens, the fragments of membranes from follicular of dendritic cells may have come off and invaded with the B and T lymphocytes.

Therefore, we did a further experiment to clarify this point. We used the wild type mice, and reconstituted them with hematopoietic extensors.

In this experiment, the same preparation was carried out and here we had B and T cells which are knockout genotype that do not contain normal prion protein, and the stroma(?) section is what contains the follicular dendritic cells. This contains the activity, where the B and the T cells now cannot be infected any longer.

We conclude from this experiment that these data in the white head mouse in which the T and the B lymphocytes containing activity are real and do not represent an artifact.

If this was derived from peripheral dendritic cell

membranes, then we would expect to see that also in this experiment.

The next question that we tried to address was whether we can see prion protein in B and T lymphocytes. This is a western blot that shows you an enriched B cell and T cell fraction from splenic lymphocytes separated with beads.

This lane of the western blot is just as the total protein extracted from the B cells and this is 42 days after inoculation. The same thing is done for T lymphocytes.

What we can see from this graph is that there is enough prion protein in B and T cells from spleen that one can even detect it by western blot analysis, which is a not very sensitive procedure.

It is in the same order of magnitude as the immunocytochemical analysis. It is much less sensitive than the bioassay.

So, we conclude that this activity is contained in splenic lymphocytes. Now, that may be bad news for transfusion medicine. On the other hand, we also see that if we look at the same type of cells -- B and T lymphocytes -- in peripheral blood, we can't find infectivity.

Now, we don't understand why this is the case. One possibility is that infectivity may be confined to subsets of lymphocytes that are resident to internal organs and don't end

up in the circulation.

Another possibility is that the infection of lymphocytes with prion may kill them. Therefore, they may undergo apoptosis. However, this is interpretation. I can only show you what the data show you.

Now, the next experiment that we did on this, and the last that I want to show to you, relates to the question of whether you need normal prion protein on the surface of lymphocytes to achieve infectivity.

This experiment was accomplished the following way. Here are various types of immune deficient mice, like mice that contain neither B nor T cells, or mice that have only B cell, or again, mice with severe combined immune deficiency, where they were constituted with bone marrow cells from the knockout mouse.

I can tell you that this manipulation was directed toward the follicular dendritic cells in these mice, and this is an interesting phenomenon.

What we think happens is the B lymphocytes secrete a cytokine called lymphotoxin which accomplishes the terminal maturation of follicular dendritic cells.

Then, the question was whether restoration of the immune system with B or T deficient cells might restore them.

Yes, and indeed it does. These are severe combined

immune deficient mice, being transfused with bone marrow cells that are either B or T positive or B or T negative. This is a control.

You see that in both this manipulation and in this, the normal cells express Prnp and those that do not express Prnp are restored, and this is another experiment in which the RAG-1 knockout mice, lacking both B and T lymphocytes, were reconstituted with cells that either express normal prion protein or do not express, and both manipulations restore immunity.

The RAG-1 mice were restored with cells from which only B lymphocytes but not T lymphocytes would develop, because these mice lack the T cell receptor alpha gene encoding gene.

Also, this manipulation restores immunization. However, if the same mice are reconstituted with bone marrow cells from mice which lack the capability of generating B lymphocytes, then immunization does not occur.

We conclude from this experience that indeed, B lymphocytes are not a crucial component in the chain of events that leads from the transition of infectious prions from lymphocytes to brain. However, B lymphocytes will support immunization independently of whether they express normal prion protein or not.

This may be perhaps because lymphocytes may at least transfer prions because they express a receptor for this protein that is distinct from PRT, or because B lymphocytes may secrete some sort of protector, which may well be lymphotoxin, which then leads to the maturation of follicular dendritic cells.

So, that is where we stand more or less, and I think for me, one of the most important and exciting aspects of this is the neuroconnection may well be a target for secondary prophylaxis.

The idea that I had in mind there is that manipulations of the B cell follicular dendritic cell axis may prevent clinical disease from occurring in individuals who have been exposed to the agent and who actually may incubate the infectious agent in their tissue.

One question one might ask is whether the abolishment of B lymphocytes may prevent infection. We don't know if it works, but we have done some preliminary studies.

Here we have treated the mice that have been delivered infectivity to the peritoneum with strong immunosuppressant drugs.

Here it is a combination of cytotoxin and dexamethasone in very high doses. Of course, this is nothing that would go into clinical experimentation.

The goal of this experiment was to provide a basis for whether this might work, and it does. In this case, the immunosuppressant treatment was started 10 days after inoculation with prions. Even at this time point, at which prion infection is well taken into the lymphoid organs, even at this later time point, the administration of dexamethasone quenches the infection such that no infection is detectable in screens. These are western blots from spleen tissue.

Also, the screens of these mice, were transmitted to indicator mice, and the indicator mice are in this case transgenic mice which over-express the normal prion protein, which are highly sensitive and come down with infection after 60 days. So, that is where we stand and thank you.

[Applause.]

DR. BROWN: Out of the mass of information that you have heard in the last 50 minutes, rather than put off the committee discussion until its scheduled appearance at 10:35, I am going to allow 15 minutes now for questions for the previous two speakers, both Dr. Aguzzi and Dr. Rohwer, and then we will have a break.

So, any questions that anyone has for either Dr. Aguzzi or Dr. Rohwer, please ask them.

DR. ROOS: I just want, hopefully some of the data is

with respect to spleen. We hear about all the different forms of encephalopathies.

What you show, for example, as a positive western blot on these scrapies spleens, and Dr. Will showed us some data showing negative immunohistochemical staining in classical traditional Creutzfeldt in the spleen, versus the new variant.

Are we dealing with just problems with respect to sensitivity of the detection system, or should we, in fact, be very cautious about extrapolating data from scrapie versus Garsman-Straussla(?) syndrome versus new variant versus classical Creutzfeldt, et cetera.

DR. AGUZZI: Thank you very much for this question, which I think is absolutely crucial to the problem. We have exactly the same problem, how can we extrapolate from these data to advise regulatory agencies.

I think there are two problems. For one thing, there is what I call the new approach of prions, that is extremely dependent upon the type of prions you consider, there is no doubt about this.

One of the most surprising effects is that the BSE prions seem to be not lymphotropic at all when they go into cows.

In fact, they stay in cows in various organs of

cows. It has been very difficult, or actually impossible, to demonstrate infectivity with any infections.

However, if we assume that new variant CJD is caused by the same prions as BSE, then we have to follow that BSE prions transmitted into humans are extremely lymphotropic, to such an extent that in all the lymphoid tissue that has been analyzed so far, the scrapie is present at such high levels that you can easily detect it by immunocytochemistry, which again, that is not a sensitive assay.

So, clearly there is a tremendous shift going on here. The other thing that is very striking is that sporadic CJD doesn't do that.

The prions for sporadic CJD do not seem to enter the lymph node with the same efficiency, or actually with much less efficiency. So, that is the first thing.

With the prion strain that we have been using in our studies, they are supposedly RNL prions. They are recognized in the laboratory isolate, and we don't know whether this represents a good model or whether this faithfully reproduces the lymphotropism of certain human proteins.

So, what the purpose is that for these types of organs, and perhaps even for specific cell types within the lymphatic organs is totally unknown.

DR. BROWN: While it is true that the detection of

BRP seems quite distinct between new variant and sporadic CJD, as you know, in primates inoculated with case of sporadic CJD, infectivity is present in lymph nodes and spleen.

Adriano is talking PRP, which is a decent marker for infectivity, but it ain't infectivity, unless it is demonstrated to be infectivity.

While Adriano stressed the differences between strains and their affinity for the lymphoreticular system, it is important not to think that sporadic cases of CJD suddenly don't have infectivity in that system. They do.

DR. AGUZZI: Thank you. I totally subscribe to this. I don't want to be misunderstood. The protein assay, whatever type of protein assay, whether it be western blot or immunocytochemistry, will become positive only if you have in excess of 10^5 , perhaps even 10^6 infectious units per gram of tissue.

DR. ROOS: We were told that the spleen had negative staining in Bragg white cells, by Dr. Will. I wondered -- I just was surprised that that immunohistochemical staining was negative, and your B and T cells would have a positive western blot in scrapies spleen.

DR. AGUZZI: Perhaps I should mention this. In the spleen of a mouse 42 days after inoculation, there is enough that it is easily detectable with the western blot.

DR. ROOS: Really, that suggests that this data can't be just carried without any caution into what might be a model for experimental sporadic CJD. Is that right?

DR. AGUZZI: Yes. I think a better way of investigating sporadic Creutzfeldt-Jakob is to do the experiment in transgenic mice expressing human proteins than to introduce the human pathogen.

The last thing that really intrigues me of Dr. Will's presentation is the consistent infectibility of lymph nodes.

I think that is a very important aspect which I hadn't realized before. It may mean that new variant CJD is a diffused systemic infection of the immune system in the first place.

If I read the data correctly, not all these lymph nodes are in the areas to which the gastrointestinal system drains. It is possible that the agents are throughout the body.

DR. ROOS: I would also point out that in both natural and experimental stages, from those studies, we know that the lymphoreticular system is heavily involved at an earlier point, including different kinds of lymph nodes, different areas, and spleen.

There is all kinds of consistent evidence -- and we

have known for 40 years -- that the lymphoreticular system is crucially involved in BSE infection.

DR. ROHWER: The BRT analite is also very infected in the spleen of the infected hamster. We were extremely surprised, in a collaborative study that we have underway with Gary Vasso(?) and Carl Mallata(?) at FDA, that purified platelets and purified lymphocytes from the hamsters seem to have no evidence of PRP at all.

That is why we have those two studies going on right now, is to see if there is any correlations with this.

Part of the reason we were surprised is we were thinking possibly the reason there was residual infectivity in the platelet or plasma is that there are platelet fragments still within that fraction. We were guessing that maybe there was some of that infectivity that was associated with those fragments.

That there doesn't seem to be any PRP at all associated with platelets is remarkable, especially since there is a very strong signal from human platelets compared the same way at the same time.

DR. BROWN: Are there any other questions for either Dr. Rohwer or Dr. Aguzzi?

DR. ROOS: Something you mentioned about aggregates, you kind of passed over it quickly; in other words, why the

infectivity wasn't encountered for.

If there are aggregates in some fractions, does that mean that you kind of have to inoculate every drop of every sample in order to really clarify if it has infectivity or not?

In other words, it is not homogeneously distributed or you have to treat it before you inoculate it or what?

DR. ROHWER: It is an issue that concerns us greatly. Just to put it into perspective, we have both had the experience with normal viruses, that it is very hard to get a mass balance or an infectivity balance in those types of fractionations as well. It is even harder here.

Indeed, my guess is that we lost that infectivity in the cryoprecipitating or in something else. Each one of these co-fractionations is a series of pellets, alcohol precipitations, and it is begging for aggregation.

The way we are trying to deal with that, in an experiment that I presented that we are doing now is that every fraction was exhausted for re-inoculation, and we inoculated the filtrating type pellets along with everything else, or made an attempted to do that.

Hopefully we will find that stuff somewhere in there and we will get a better mass balance. I would guarantee that we have no empirical way of determining whether or not the

methods that we chose are sufficient to disaggregate that is in there.

DR. BROWN: Have you songregated(?) everything?

DR. ROHWER: We did this in a sufficiently large volume that, unless there was actually some sort of chromatography going on with the polychropian tube, I wouldn't expect that.

Sometimes the tube was appropriate, but typically the geometry of the songregation is important, so we would move it into a tube that was more appropriate for effective dispersion.

DR. SCHONBERGER: When a human gets injected peripherally with human growth hormone and develops central nervous system disease, I guess I sort of assume that somewhere along the line the infection traveled to the central nervous system through the blood.

It sounds to me like you were suggesting that it might be going through the peripheral nervous system? Is that what I heard, and can you expand on that?

DR. AGUZZI: That is, at this point, still perhaps not 100 percent clear, but I think that all evidence indicates that prion seldom reaches the brain straight, by passing the blood brain barrier, and that the peripheral nervous system is very likely to be involved.

One of the reason is that whenever prions have been inoculated to peripheral sites in this experiment -- and this is research some 20 or 30 years ago -- it was always found that the first site of replication in the CNS would be where the nerves enervate the site of injection. This applies both to limbic and to peritoneal injection.

This may be indirect evidence. At the same time, the species barrier is going again from the animal neuropathogenesis, and indicates that when you see prions are inoculated into immune deficient mice, the injection doesn't take or the prions have a very low efficiency, even when this is done intercerebrally.

So, the prions have to go to the periphery and we are suspicion that there is a conversion and then go back to brain.

The other evidence that I think is from our own experience and I think is very strong is that in the knockout mouse harboring a brain graft that expresses PRP, will not develop disease in the graft, upon peripheral immigration, even if this mass has been replaced by bone marrow that expresses PRP.

So, all the evidence points to the peripheral nervous system mediating the enervation, and I think it is very likely that the peripheral nervous system needs to

express normal prion protein.

We are addressing this last issue by introducing recombinant viruses, transducing PRP in and we are constituting a special PRP to see whether there is enervation.

DR. BROWN: Two final points before we take a break. There was an indication in your question, I thought, Harry, that indicated that maybe blood borne infectivity is not as crucial as we thought it once was, because it looks as though in the peripheral nervous system -- it looks like the entry into the central nervous system may, at least in part, be through the peripheral nervous system.

I think the operational term there is in part, for two reasons. First, it is difficult to imagine infectivity as being detectable as it is in organs as far apart as, for example, the thyroid and the kidney and the heart, without explaining that on the basis of blood-borne infection.

I mean, I can't imagine nerves infecting all three of these and blood borne not being a part of it, although we know these organs can be infectious by infectivity measurement.

The second point is that in human growth hormone, most of the subjects who were taking human growth hormone were inoculating themselves like the diabetic, subcutaneously, probably mostly in the leg, although I can be corrected on

that.

The point is that the clinical presentation in this group of patients, as you know, is cerebellar. That is not where I would expect it, a dermatone, to first produce its disease.

I don't think it is quite as clear cut as your questioning is going to. I suspect that blood is involved in the central nervous system infection, and it may be that there are alternate routes.

It could be that there are two routes, a primary and a secondary route. We can't exclude either one.

What we will do now is have a break. It is 10:20. We will be back here and start on the money at quarter of 11:00, in 20 minutes.

[Brief recess.]

DR. BROWN: Ladies and gentlemen, we are ready to begin our next presentation, which will be made by Dr. Lisa Ferguson, who is senior staff veterinarian at the Animal and Plant Health Inspection Service in Riverdale. Her topic will be the current status of the BSE epidemic in Europe, a perspective from the U.S. Department of Agriculture. Dr. Ferguson?

AGENDA ITEM: Current Status of the BSE Epidemic in Europe: USDA Perspective.

DR. FERGUSON: Thank you. I am glad to be able to be here this morning and give a bit of an agriculture perspective.

Those of you who are not familiar with our agency, we are the Animal and Plant Health Inspection Service.

We are the ones who regulate the animal health aspects of animal to animal products going in and out of the country. That is how we fit into this whole scheme of things.

I am going to try to cover very briefly a very large subject that we have struggled with for many years now.

What I am going to try to do is give a very short summary of just some numbers, statistics of BSE in cattle in Europe, then go into U.S. actions, actions we have taken as a regulatory agency, a short summary of what we have done since the disease was first identified in the United Kingdom, and then an explanation of recent changes that we have done and recent evaluations that we have done of the status of various countries in Europe. That will probably be the most interesting.

To begin with, these charts actually are pulled off of the OIE, which is the International Office of Epizootics and International Animal Health Reporting Agency.

These are pulled off their web page, so if anybody really needs to know in the future, you can just search their

web page and they will update these statistics.

The top table is the number of cases reported in the United Kingdom. If you look at this bottom line, I realize that those of you in the back probably cannot read this, but the numbers show the story in the United Kingdom.

It started out with 446, which is 1987 and before. We had a peak here in 1992, with a total 37,381 cases. In 1998, we are down to 1,728. So, things have peaked up and are coming back down.

Now, if we look at other countries in Europe which have identified BSE in native animals, we have Belgium, they reported their first case late in 1997, and have reported subsequent cases here in 1998, up to a total of seven, I believe. Our numbers may be slightly off because there have been some reported very recently.

France reported the first one in 1991, and their numbers stayed relatively stable for several years but now are going up again.

They had five cases in 1991. In 1996, they reported 12 cases. I believe this is actually as of the first part of November in 1998, they had 17 cases.

If you look at the Republic of Ireland, that is the next one down. They stayed very steady for several years, and had a significant jump, it appears, in 1996.

Actually, we have asked the Irish what they attribute that to. They attribute it to a combination of two things.

First of all, obviously, you had exposure due to imported feed and/or animals in the early 1990s. This is what you would expect. Then they started to have a peak.

Also, obviously there has been increased attention and increased vigilance in reporting starting in 1996.

Liechtenstein has identified cases this year, Luxembourg identified one case last year. The Netherlands identified their first case last year. Portugal, I believe everybody is probably keeping up with Portugal.

They identified the first cases were in imported animals. They have significantly jumped up and to date, in 1998, have identified 83 cases.

Switzerland, actually, their numbers look somewhat similar to the United Kingdom. Their numbers peaked in 1995 and have dropped off very significantly. They have reported 13 to date in 1998.

I apologize that these are very tiny graphs. These are also available at the web site, and show the picture very well in the United Kingdom.

This one is confirmed cases plotted by year of clinical onset. You see the first confirmation here in 1986.

You go up and peak and then back off.

These essentially show the same thing but sort of different configurations. The confirmed cases after July 1988 plotted by month of birth.

Here we have confirmed cases with known dates of birth plotted by month of birth. As you can see, the shape of the curve looks very similar to that first one I put up. Obviously, the dates start here in 1982 and follow on.

So, that is a brief picture of the statistics and numbers in Europe. This next slide is a time line of regulatory action.

USDA APHIS first restricted ruminants and their products from the United Kingdom in July 1989. We then extended those same restrictions to any other country that identified BSE in native animals. So, if they identified their first case in 1991, we applied those restrictions in 1991.

In May 1991, we actually started our active surveillance program for BSE in the United States. Things were sort of clipping along fairly well.

I have left off all the activity in 1996. We really did not change our regulatory efforts from APHIS' standpoint at that time.

June 1997, the FDA published their ruminants and

ruminant products ban, and that was effective in August of 1997. In January of 1998, we published an interim rule which extended the restriction on ruminants and ruminant products from Europe.

We were concerned at that point in time, based on information coming out of Europe, allegations of under-reporting coming out of Europe, papers that were published that extrapolated from export data from the United Kingdom what should have been found in continental Europe and what had not been found, the additional research from pathogenesis studies in the United Kingdom, which showed additional tissues, also at the same time, that is when The Netherlands, Luxembourg and Belgium each identified their first native cases.

So, all those things came together and we decided to re-look at our regulatory approach and put restrictions on all of Europe, while we asked those countries to provide us with information about their surveillance and their risk management procedures, so that we could get a more accurate assessment of what was going on and what was actually the risk of products imported into the United States.

I won't subject you to reading a list of the countries that we added. Essentially, it was all continental Europe, from the former states of Russia, and all of

continental Europe was added to the restricted list.

In February of 1998, APHIS began evaluating submissions from countries on their surveillance procedures and risk management procedures.

That is what I will focus the rest of my presentation on, how we did that and what risk management procedures are in place.

We did outline a policy of the information we wanted from countries. They separately needed to do an adequate qualitative assessment of their BSE status.

This doesn't show up. It should actually be 1998. The APHIS BSE working group did these assessments. What we were looking at, we based our criteria on the OIE guidelines.

The OIE has a chapter which outlines necessary requirements for surveillance and risk management. We took those as our basic guidelines and built our criteria for looking at countries on those.

We developed a questionnaire which was basically used to obtain the information we needed. We then developed the criteria and the questionnaires for all the affected countries. Some of them had gone ahead and submitted information prior to that and some hadn't.

To date, we have seven countries that have provided adequate information and have addressed all those criteria,

and we are considering them minimal risks.

As I say, we are in the midst of the regulatory process at this point in time. I think most of what I am saying is pretty much common knowledge, but all of this is going through the regulatory process. So, please don't go out and look for it in the current regs. It is in development. It will be published.

These will be our list of countries. The way our regulations are set up is we have restricted lists in our regs. So, if you are on the list, then essentially there is a problem, or a possible problem, and restrictions apply.

If a country is not on the list, that means either we have assessed them, as in the case of the European country, and we consider that they are in the normal range, or we are considering that the rest of the world does not present a significant risk at this point in time.

I will make an additional comment there. Our Canadian colleagues are going through the same process that we are doing, and we have agreed with them, since our criteria and our classifications are almost the same, that they will recognize any evaluations that we do and we will recognize any evaluations that they will do.

So, the way it comes out is, we will be evaluating most of the countries in Europe and our Canadian colleagues

will be evaluating most of the rest of the world.

Let me just describe briefly the classifications. The top one is regions in which BSE is known to exist. That is pretty straightforward.

This second one, this is the category that was added in our January interim rule. Regions which present an unacceptable risk for introducing BSE into the United States, either because of import requirements less restrictive than those that would be acceptable for import into the United States, or because of inadequate surveillance, or both, or because the regions have provided inadequate information to APHIS, with regard to control factors, such as import restrictions, surveillance and risk management.

This one identifies exactly what we view as important for these countries to be doing with import restrictions.

The third category is one that is going through the regulatory process at this point in time, in response to the comments that we received.

We will be creating this category. In a region where BSE has been reported in native animals, but for which meat, meat products or other animal products may be imported, and in the United States, where there is negligible risk for introducing the disease into the United States due to

mitigating measures, such as active surveillance, acceptable import practices and risk management strategies.

These are those countries that have identified BSE in native animals, but they have provided information on their risk management strategies, and we will then accept these and other edible products under certain conditions -- i.e., bones removed -- and certification statements about business practices.

So, these are the countries that have provided adequate information, which will be removed from the restricted list: Austria, Denmark, Finland, Hungary, Italy, Norway and Sweden.

There are other countries that have provided us some information. We have requested more information from them. We do not have adequate information at this point in time.

The final section, there are countries with many cases of BSE that will be placed in an acceptable risk to meet imports.

Here we have Belgium, France, Ireland, Netherlands, Luxembourg, Switzerland, and the United Kingdom.

Now, this is a very brief summary of risk management practices which are in place in those countries which have identified BSE in native animals.

There are countries listed on this side. When they

identified their first case is this column right here.

Current controls, that is my shorthand for what are they doing with the animals, either with the herd, with any other animals.

Over here is when they initiated a beef feed ban or a ruminant feed ban, or a mammalian ruminant feed ban.

This third column is labeled SRM, satisfied risk materials. Actually, that is as Dr. Will described earlier, specified bovine offals.

Okay, herd controls. In most of these countries, the entire herd is slaughtered when a case is identified with exceptions here.

The United Kingdom is doing a selected pull of what they deem as at risk animals, and then they are also doing over 30 months. I think most folks are familiar with that.

In Switzerland, if there are infected cattle, they take all offspring, cattle born on farms where BSE is identified.

Specified risk materials. Grants have been issued and SRM controls in 1996. Ireland, same thing. Switzerland has SRM controls and those went into place in 1990, and the United Kingdom had SRM controls starting in 1989.

If I am comment, just from an animal health standpoint, all these countries really do have well

established veterinary infrastructures. They are doing good surveillance. They are out there looking for disease and checking on it.

I believe my time is about up and I believe that was my last slide also.

DR. BROWN: Thank you very much.

[Applause.]

DR. BROWN: I think we will move right along to three presentations that will be focused on blood donor referrals, product withdrawals and product shortages.

The first of these will be given by Capt. Mary Gustafson, director of the division of blood applications in the Office of Blood Research and Review, CBER, in the Food and Drug Administration. Dr. Gustafson?

AGENDA ITEM: BLOOD DONOR DEFERRAL, PRODUCT WITHDRAWAL AND PRODUCT SHORTAGES. U.S. Blood Deferral Policies.

CAPT. GUSTAFSON: Thank you. My presentation this morning will be two-fold. First of all, I am going to give a general overview of donor screening for any non-blood bankers or non-blood donors in the audience, who might not be familiar with blood donations and features.

Then I will discuss the current precautionary measures that relate to CJD.

In the United States, the safety of the blood supply from communicable disease agents is accomplished through a system of five overlapping areas of protection.

The blood safety system begins at the blood collection center and encompasses the manufacturing and distribution of products.

The first layer of safety is donor screening. Potential blood donors are questioned by trained personnel regarding their medical history and behavior that may increase the risk of communicable disease transmission.

Donors are also given a limited physical examination that includes measurement of the donor's temperature, blood pressure, pulse and blood iron level.

Donors may be temporarily deferred from donation for a number of reasons, including having a temperature, high blood pressure or symptoms of a cold on the day of donation or for taking certain medications.

Donors may also be deferred indefinitely from donation. Reasons for an indefinite deferral include providing a history of behaviors that increase the donor's risk for hepatitis or HIV, such as IV drug abuse, male to male sexual practices, and having had clinical hepatitis.

If the donor is not temporarily or indefinitely deferred, the donor is accepted for a donation of a unit of

blood or plasma donor screening for any non-blood bankers or non-blood donors in the audience, who might not be familiar with blood donations and features.

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providing a history of behaviors that increase the donor's risk for hepatitis or HIV, such as IV drug abuse, male to male sexual practices, and having had clinical hepatitis.

If the donor is not temporarily or indefinitely deferred, the donor is accepted for a donation of a unit of blood or plasma.

The second layer of safety is the blood facility's use of a donor deferral registry or list. At some point, before the unit of blood is distributed, the donor's name is checked against historical records to ensure that the donor was not previously deferred.

If the donor was previously indefinitely deferred, the current donation cannot be used.

The third layer of safety is testing of the donated unit of blood. Each unit of blood is tested for blood borne agents, such as hepatitis B, hepatitis B core antibody, hepatitis C, HIV-1 and 2, HTLV-1 and 2, and several others.

The fourth layer of safety is quarantine of untested units of blood in blood testing positive for any infectious agents or otherwise found to be unsuitable for release. Those units are never made available for use.

The fifth layer of safety is the blood establishment's investigation of any breaches of safeguarding, correction of system deficiencies found and prevention of

future deficiencies, as part of quality monitoring and an umbrella system of quality assurance. Blood concerns must report to FDA any manufacturing problems, errors or accidents that may affect the safety, purity or potency of their products.

Problems that do not meet the threshold for reporting still must be documented and investigated.

Error detection, correction and protection is an important part of any quality assurance program.

Today's discussion will focus on the first layer of safety; that is, donor referrals based on donor's history screening, since that is the tool under discussion today.

In modern blood banking, the donor history has been an integral part of determining whether a donor is suitable to donate a unit of blood and prevention of future deficiencies, as part of quality monitoring and an umbrella system of quality assurance. Blood concerns must report to FDA any manufacturing problems, errors or accidents that may affect the safety, purity or potency of their products.

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safety; that is, donor referrals based on donor's history screening, since that is the tool under discussion today.

In modern blood banking, the donor history has been an integral part of determining whether a donor is suitable to donate a unit of blood.

In general, donor history questioning includes questions designed to elicit information about whether the blood donation process could harm the donor, or whether donations from this person could harm any future recipients of components or products prepared through the blood donation.

The substance and extent of donor history questioning has evolved dramatically over the years.

The next slide -- and I am not sure that you will be able to see this -- it is just an example of a donor history screening card submitted to the Bureau of Biologics in 1950.

You can use it to compare the AABB, uniform donor history questionnaire that was in your information packet.

The information requested of the donor in 1950 included limited physical exam -- temperature, pulse, blood pressure, hemoglobin, which is not a lot different than today.

In terms of donor history, very few questions were asked to elicit information about exposure to contagious diseases, recent infections, illnesses, operations, tooth extractions, as well as specific history about jaundice,

malaria, tuberculosis, heart disease, venereal disease, allergies, fainting attacks and pregnancy.

You will note there are no specific questions that are asked. In our files, we didn't have SOPs submitted that had specific questions.

I am not really sure how they elicited the information, whether it was in an organized way or not.

You can compare this to the 32-item, multiple donor history questionnaire that was provided in your packet.

The AABB's uniform donor history questionnaire has received FDA review and approval, and includes questions covering areas specifically contained in FDA regulations and Title XXI of the Code of Federal Regulations.

Regulations have the force of law, so this information is required to be included in the evaluation of whether a donor is suitable for donations or not.

It also includes topics and questions included in various FDA recommendation memoranda and guidance documents issued by the FDA in the last documents.

Guidance documents, in and of themselves, do not have the force of law. However, they often provide the agency's view regarding measures to be taken to ensure that the regulations are met.

If they are adopted by the majority of the industry,

they become the acceptable manufacturing practice of the industry, and they often carry weight in civil procedures.

The example donor history questionnaire also includes AABB industry standards that are not specifically addressed by FDA in regulations or guidances, but are designed to ensure that the donor is in good health to donate.

It is important to note FDA does not dictate the exact questions asked of the donors. For many years, firms would interpret the regulatory requirements and a question format of their own choosing, subject to FDA review and approval of the firm's U.S. license.

In the very early 1990s, we broke that tradition by releasing a set of questions addressing behaviors that placed donors at risk for HIV infection.

The questions had been field tested as part of a study conducted under contract by the American Institute for Research.

This set of questions is, to my knowledge, the only ones subjected to extensive field testing prior to being used by the blood community.

Since that time, the blood industry has requested that wording for questions be provided if FDA-requested information is to be elicited from a donor during the donor history interview.

We have tried to provide questions and recent recommendations. However, due to the public health need to initiate questioning, the questions have not been field tested for comprehension prior to release with the recommendations.

Questions asked during the donor interview cover the following areas: Donor demographics such as name and address -- this is particularly important now, with all the look backs and plans to notify the donors of test results, and whenever they are deferred.

History of previous donations and referrals, questions about general health, if the donor is feeling well today, if the donor has been under a doctor's care, is the donor free of respiratory diseases, queries about medication that the donor is currently taking or has taken in the past.

The information might indicate that the donor has an underlying disease that would put the donor at risk of harm if he donates -- for example, heart disease.

The information might also elicit information that the donor has an underlying disease or risk of disease that could be transmitted by the donated blood -- for example, if the donor is taking malaria prophylactic drug.

The information might elicit information that the donor's blood might not be suitable for a particular blood donation.

For example, if the donor was intended for a donation of single donor platelets and provided a history of having recently taken a platelet antagonist drug such as aspirin.

The information might elicit a response indicative of ingestion of a drug capable of causing birth defects if given to a pregnant drug recipient. An example of those drugs would include aspartame and propitia.

Queries to determine if the donor is free of a disease transmissible by blood, history of viral hepatitis, HIV infection or positive test for HIV, or a history of having had malaria.

Queries about the potential to transmit a transmittable disease, these questions include questions about personal behavior, for example, IV drug abuse, males having sex with males, close contact with persons with HIV or hepatitis, and questions concerning immigration or recent travel to a particular geographic area, such as areas with malaria risk.

FDA first recommended screening for CJD related risk in 1987. Our recommendation at that time was based on a finding in 1985 that three young adults who had received human pituitary growth hormone during childhood died of Creutzfeldt-Jakob's disease.

Between 1985 and 1987, there were four more deaths. The likelihood of young adults developing CJD was considered so remote, that it was considered that the hormone must have been inadvertently contaminated.

It is estimated that approximately 7,000 U.S. children had received the product through a government program, and the product was also available from two commercial sources.

Although pulled from the U.S. market in 1985, the product was still available after that in other countries, and recipients of the product may still present as blood donors.

The FDA recommendation memorandum issued in 1987 advised that blood establishments should develop and implement specific screening procedures to defer permanently recipients of human pituitary derived growth hormone.

The recommendation was issued as a precautionary measure. Transmission of CJD was known to occur through direct tissue contact, but not by sexual means nor from mother to child across the placenta.

Based on experimental animal studies, it was considered that a theoretical risk was possible, and the FDA recommendation then advised that all person who had received injections of human pituitary derived growth hormone should be permanently deferred from blood donations.

The FDA recommendation did not address other risk factors for CJD, and the FDA did not address the question of look back product retrieval or notification.

The next FDA donor screening recommendation occurred in 1995 following referrals of at least nine previous blood and plasma donors having been diagnosed with CJD since 1983. Five of the cases were in the previous year.

In each of the latter cases, the blood centers, having been advised of the subsequent diagnosis of CJD in the donor, voluntarily initiated withdrawal of undistributed products and retrieval of products that were already distributed but remained unused.

FDA presented data regarding the CJD cases to the blood products advisory committee in December of 1994, and to a special advisory committee on Creutzfeldt-Jakob's disease in June of 1995.

On the basis of the deliberations of the committee, FDA developed interim additional precautionary measures to be taken to reduce the possible risk of transmission of CJD by the transfusion of blood products.

Specifically, the August 1995 memorandum recommended donor deferral based on family history and the receipt of a dura mater graft, in addition to the previous referral for the receipt of human pituitary derived growth hormone.

Specifics to this recommendation are as follows:

Prospective donors should be asked whether they are aware of diagnosis of CJD in their family, including all blood relatives.

The screening was recommended because studies demonstrated that approximately 10 percent of all CJD cases are familial.

Persons with a family history of CJD should be indefinitely deferred from donation unless acceptance is based on specialized genetic testing.

The second additional screening recommendation contained in the August 1995 memorandum is that prospective donors should be asked whether they have ever received dura matter transplant grafts.

Prospective donors who have received transplanted dura mater should be permanently deferred from donation.

The recommendation was based on the fact that CJD has been transmitted to man by the transplantation of cornea and dura mater from infected individuals.

FDA did not recommend the deferral of donors with a history of corneal transplant. The position was based on the absence of reported CJD transmission from corneas since the single known case in 1971, and the voluntary screening of cornea donors for CJD or other neurological diseases at least

since 1980.

On December 11, 1996, the FDA issued another recommendation memorandum that contained revised precautionary measures to reduce the possible rate of transmission of CJD.

The recommendation replaced and superseded the earlier recommendation. The revised recommendation did not change the substance of the donor referral history.

However, for the first time concerning CJD, the FDA provided the specific questions to be asked during the donor screening process, and recommendations on the frequency of obtaining the donor history.

The questions had not been field tested, but by that time, there had been considerable experience in asking questions, particularly for pituitary growth hormone, and about a year of questioning on family risk and dura mater.

It was also recommended that the donors be asked the questions as part of their very first donor screening process, and that repeat donors be asked the question at least yearly intervals.

The specific questions contained in the memorandum are as follows, and I tried to make the slide with bullets so they would be easy to read, but I didn't plan on leaving half the first question out, so I apologize.

It should be, have you or any of your blood

relatives had Creutzfeldt-Jakob's disease, or have you ever been told that your family is at an increased risk for Creutzfeldt-Jakob's disease.

It was further explained in the FDA guidance that if the donor is not familiar with the term Creutzfeldt-Jakob's disease, it should be taken as a negative response, since families at risk are generally aware.

Question two. Have you ever received pituitary derived growth hormone.

If the donor seems uncertain about his or her treatment, the following questions describing human pituitary derived growth hormone injections may be asked.

Was the hormone treatment given by injection; was the hormone treatment given at regular intervals, at least once a week for an extended period of time, at least six months.

Question number three. Have you received a dura mater or brain graft. Donors answering yes to any of the questions should be indefinitely deferred pending further investigation.

Donors providing a family risk response may be requalified if it is found that the diagnosis of CJD in the relative is excluded, or that the CJD in the family member is iatrogenic, or that the family member is not a blood relative.

The donor may also be requalified if gene sequencing testing rules out an increased risk for CJD. If the donor is not retested, he should remain indefinitely deferred.

The donor is permanently deferred if the gene sequencing test is positive. The donor should also be permanently deferred if he or she received either human pituitary drug, human growth hormone, or a dura mater graft.

The questions form the basis for donor screening for CJD risk in the United States today. Thank you.

DR. BROWN: Thank you.

[Applause.]

DR. BROWN: The next presentation is by Dr. Jeremy Metters, who comes to us from the Department of Health in London, England. He is the deputy chief medical officer of the National Health Service in the United Kingdom. Dr. Metters?

AGENDA ITEM: Current Regulatory Policies in the United Kingdom Regarding TSEs and Safety of Blood, Blood Components and Plasma Derivatives.

DR. METTERS: Thank you very much for asking me to speak today. I would say that I could have brought some slides.

Since most of what I was going to say is related to test measures included in your pack, I decided not to do so.

I am sorry about that. You will have to bear with me if I read out some of it. Thank you very much for asking me to speak today. I would say that I could have brought some slides.

Since most of what I was going to say is related to test measures included in your pack, I decided not to do so. I am sorry about that. You will have to bear with me if I read out some of it.

What I want to describe is the current regulatory position. In doing so, I wish to show the progressive steps in the way the United Kingdom has put out its regulatory position, as we have been advised by a number of different regulatory bodies.

I will briefly outline the goal of the different bodies of independent experts offering advice to the UK government.

The Committee on Regulation, at the request of the Secretary of Health in the UK took the issue of blood, blood products and CJD under regular review, just as your committee is doing so today.

There is a different position for blood than there is for blood products and derivatives in the United Kingdom, because the blood products and derivatives, the United Kingdom, as a member of the European Union, is subject to the

advices issued by the Committee on Proprietary Medicinal Products of the European Union, of which our committee on safety of medicines is our national equivalent to the FDA.

There is blood and its labile components, platelets and plasma are not currently subject to EU conflicts and regulations. That may change, with the application of the Amsterdam Treaty expected next year.

It is for the Spongiform Encephalopathy Advisory Committee, of which Professor Will is a member, to advise the UK government on the TSE aspects of blood safety, including leukodepletion.

There is another committee, the committee on microbiological safety of blood and tissue transplantation, which I chair, which advises on the practical aspects of intervention policies in the UK transfusion services.

The aim of that committee is to reduce the risk of transmission of infections of all types through blood or tissue or organ transplantation.

I would simply say with regard to TSEs, we have got to follow the advice of the four committees I just mentioned.

In summer 1995, the Committee on Proprietary Medicinal Products gave advice, and this was that after your own committee advised in August of that year a recommendation to recall or quarantine batches of plasma derived from

medicinal products, manufactured from plasma pools from which a donor who had subsequently developed classic CJD had contributed.

The CPMP, in short, did not advise the recall or quarantining of blood products or derivatives that had an implicated donor with classic CJD.

That position has been reaffirmed by the CPMP in October 1997, and subsequently is the latest position in the United Kingdom.

However, to reduce the possibility of donors who might be at risk of developing classic CJD, the UK blood services, on the advice of the microbiological safety committee, added an additional exclusion criteria to the list which they started in February 1989, where they said individuals who have received human growth hormones are permanently excluded from blood donation.

Potential donors who have received recombinant derived human growth hormone need not be disbarred. That is, of course, the artificially manufactured growth hormone substitute.

Further advice was given in 1992, that women who had been treated with pituitary growth hormones gonadotropins, before 1985, should also be deferred from blood donations.

In January 1996, the deferral was further added, all

individuals who have in the past been treated with extract derived from human pituitary glands or who have a family history of CJD, are permanently excluded.

Up to that time, it was up to the potential donor to read the leaflet they were given; they were not questioned.

On the first of August 1996, they were all quite specifically questioned, and they were asked, to your knowledge, has anyone in your family suffered from CJD.

Later, in February 1997, they were all specifically questioned, have you had injection of human pituitary extract before 1985.

In January of this year, they were asked in relation to dura mater, have you had brain surgery. Then in April of 1995, they were asked not only if they had brain surgery, but an operation on a systole tumor, operating on their spine, so you would find dura mater donors who had had a transplant for that surgery on their spinal cord.

Professor Will referred to the withdrawal of plasma when a donor subsequently develops new variant CJD as opposed to classic CJD.

Those amendments were brought into force in January of this year, to stop the donation from someone who has subsequently developed new variant CJD getting into the transfusion chain.

Of course, the likelihood of a donor developing new variant CJD in the five weeks that labile components have been used is pretty small, but nevertheless, to allow for that, if any donor is suspected of having CJD, then the transfusion services will be noted down and those components will be withdrawn.

The reason I will come to in a moment. The use of plasma, we hope, will no longer be a problem, because we do not manufacture blood products from stored plasma any more.

To return to the concern about new variant CJD, the first advice we gave on this was on the 6th of October 1997, when the chief medical officer raised, in a note published by my department:

"One important question is whether new variant CJD can be transmitted from person to person. This is of particular interest where blood and blood products are concerned.

"There is evidence that under experimental conditions it may be possible to transmit CJD. There is no epidemiological evidence to suggest that classic CJD has been transmitted between humans through blood transfusion or the use of blood products.

"We do not know if the same will apply to new variant CJD. One suspected and three confirmed new variant

CJD patients have given blood."

The CJD surveillance unit, which Professor Will heads up, are following this up.

"The government will take any measures necessary to safeguard the integrity of the supply of blood and blood products."

That was October 1997. On the 29th of October 1997, one of our two fractionation centers for blood products had to issue the first recall of blood products because one of the new variant CJD donors had contributed to the relevant plasma pool.

A month later, a second recall had to be made by the blood products laboratory. This led the spongiform encephalopathy advisory committee, on the 6th of November 1997, to advise that recent research suggests that the pathogenesis of new variant CJD differs from classical CJD and the former have more involvement in lymphoreticular tissues, possibly involving circulating lymphocytes.

It is logical that we will seek to minimize any risk from blood or blood products by reducing the number of lymphocytes present.

The committee recommends that the government should consider, as a precautionary policy, extending the use of leukodepleted blood or blood products as far as is

practicable.

It will be for the national blood authority to devise a strategy to implement this policy.

They continue: It is not possible at present to estimate accurately the risk of transmitting new variant CJD by blood transfusion.

The Secretary of State for Health, Mr. Dobson, immediately accepted the advice to proceed and instructed the National Blood Authority to stop work immediately on the extension of leukodepletion of blood, in order that they were prepared, in the event that the committee -- spongiform encephalopathy advisory committee, I will call it SEAC hereafter -- that SEAC advises we should move on the basis of a risk analysis to leukodepleting all of the blood used in the United Kingdom.

The blood service, as I said, were immediately instructed to plan for introduction of leukodepletion and that started in November of last year.

On the 17th of November, there was a further recall of blood products, this time by the company Nikomed(?) Haversham, of their Tomanadge-II(?) product, because this had been manufactured with serum albumen which had come from a donor among many others who had donated to the plasma pool.

That recall involved 44 countries worldwide, and

immediately prompted the Committee on the Safety of Medicines, which as I have said, is the equivalent to your FDA in terms of regulation, to consider what further steps should be taken to ensure there was no threat to blood products or if no threat was impossible, how that threat could be minimized.

On the 26th of February this year, the Committee on the Safety of Medicine gave advice: "Where a donor to a plasma pool is subsequently identified as being strongly suspected of new variant CJD by a national reference center -- that means the surveillance unit -- all products manufactured from that pool should be withdrawn.

"Secondly, to avoid future withdrawals of blood fractions and medicinal products, including that being manufactured, avoid the use of UK albumen as an excipient in medicinal products."

They went on: "The committee, in consultation with an expert group, undertake a risk assessment of each medicinal product containing components derived from pooled human plasma."

That advice was immediately accepted by the government, who agreed that our two fractionating centers, the one in England, one in Scotland, would import plasma from abroad, and they would no longer assume the satisfactory or regulatory place for alternative sources of plasma, they would

no longer issue products that had been manufactured from UK source plasma.

You will clearly understand that it will take quite some time to close down production based on UK sources of plasma, and to find alternative sources of proper products that have to be found, which have to be inspected, and to set up the new arrangements.

The committee on safety of medicines have said that they would look at each product on an individual basis.

On the 13th of May, they gave further advice. They had reviewed all medicinal products manufactured from UK sources of plasma on a case by case basis, and that none should be sourced with UK plasma for the present time.

They continued: "Although there is currently no evidence that new variant CJD can be transmitted by blood, there is nevertheless a theoretical risk.

"There is currently no test that can be applied to donors that can detect the presence of plasma associated new variant CJD.

"It is possible that manufacturing processes used to produce blood products may destroy the agent, although no test is available to confirm this.

"As a precautionary measure, the government is now allowing the two fractionation centers to import plasma until

such times as a test is developed to screen for the possibility of infection, or it is proven that new variant CJD cannot be transmitted through blood products, or that it is proven that the manufacturing process destroys any infectious agents."

On that basis, the two fractionators moved over entirely to sourcing plasma from non-UK sources.

As I said, this takes quite a time to achieve and the Committee on Safety of Medicine has now agreed with the fractionators, a program through which their plants have been sterilized before recommencing manufacturing using non-UK sourced plasma.

Time tables for the transfer to non-UK source production have been recently agreed, and the fractionation laboratories announced that each product will be supplied at the earliest date, consistent with assurance of continuity of supply.

Quite clearly, we had to continue to issue UK sourced product until such times as there was alternative product available, because the need to treat the patients who were dependent for life and health had to come first.

Turning now to blood, the donor selection and screening procedures that have just been outlined to you are very similar in the United Kingdom to those in the United

States.

The labile components, as I have mentioned -- red cells, platelets and fresh frozen plasma -- are not categorized as medicine. SEAC, as I said, advises a couple of months ago that leukodepletion should be introduced, or not be introduced depending on the risk analysis.

The subsequently delivered further advice based on their risk analysis. This advice was given on the 17th of July.

They said then, there is considerable uncertainty about whether or not the infectious agent may be present and what extent it could represent any risk of transmission.

The committee agreed that leukodepletion could be one way to reduce any risk there may be. The precise impact of leukodepletion on reducing the theoretical risk is difficult to assess.

On balance, the committee recommends the government should extend the use of leukodepletion for all blood destined for distribution as soon as is practical.

The government, again, on the 17th of July. I haven't said it on each occasion where advice has been given, but I will say at this time that Mr. Dobson, the secretary for health, said, we will do whatever we are advised to reduce the theoretical risk of the blood supply.

He has said that as each proposal has been made and each time has been consistent, that whatever is advised by the committee on safety of medicines, the spongiform encephalopathy committee further imparts, the safety of the blood supply in the United Kingdom, it will be done.

So, in summary, the position we have reached in the United Kingdom, all donors of blood are specifically questioned prior to donating, to reduce the possibility that the donor may be at risk of passive CJD.

We have not recalled blood products or derivatives where the donor, through a plasma pool, subsequently developed classic CJD.

We have always recalled blood products where a donor has developed new variant CJD, and as you have heard, there are four such donors.

The first one, Professor Will referred to, was impossible to trace. We have in place a system for other reasons whereby we can trace the destination of donations that have been made.

I will simply say that occasionally an HIV positive case slips through there, and we must immediately trace those products. For that reason, there is a computerized system in the United Kingdom to find any derivatives at all.

We have, because of the theoretical risk of

transmission of new variant CJD, stopped fractionating UK sourced plasma.

As soon as sufficient product made from non-UK source plasma are made available, we will transfer quickly to those.

To reduce the possibility of transmission by blood and labile components, we are introducing leukodepletion.

This is a complex task. You can't immediately move through leukodepletion 2.5 million units of blood a year, which is what we would have to do.

That brings me to another point. If there were 2.5 million units of blood available on the New York stock market or somewhere else, we would be glad to find alternative sources of blood.

It is not possible to re-provision the United Kingdom with red cells from abroad. We can certainly look at the possibility.

I have stated what we have done and why we have done it. There are basic questions that you already had to face, too.

We don't know if new variant CJD is transmissible by blood and blood products. We do know that new variant CJD behaves different than classic CJD, particularly with respect to involvement with human transmission.

We don't know how many people in the United Kingdom will develop new variant CJD. As Professor Will has said, it is too early to make any reliable estimates.

There could be only a few hundred cases, as one report in the UK press stated last week. On the other hand, there could be thousands or more. We just don't know.

We don't have a test. Even if we had a test, we don't know how far in the course of the disease that the test becomes reliable, and whether at that stage transmission by blood or blood products would occur or not.

All these factors have led the various advisory committees to make recommendations that I have outlined to you.

The UK government has said it will follow any practical and realistic precautions to protect the health of the public.

The principal objective is to reduce the prospect of transmission through blood or blood products of new variant CJD.

For those who have sadly been infected, we think there will be another generation of patients who will get the iatrogenic disease from blood and blood products.

Mr. Dobson, the UK Secretary, has increasingly made it clear that he will adopt a precautionary principle against

a theoretical risk of new variant CJD. Thank you for your attention.

[Applause.]

DR. BROWN: Thank you very much. Our final presentation, and before we have questions, will be from Dr. Douglas Kennedy, division of blood borne pathogens, Bureau of Infectious Diseases, in the Laboratory Center for Disease Control in Ottawa, Canada.

AGENDA ITEM: Current Regulatory Policies in Canada Regarding TSEs and Safety of Blood, Blood Components and Plasma Derivatives.

DR. KENNEDY: I have been asked to speak on the current regulatory policies in Canada regarding TSEs and safety of blood, blood components and plasma derivatives.

There are a number of Canadian policies in existence relating to TSEs, including those involving identifying the animals, tracking the animals, animal products, and drugs.

There are two that are the most relevant to drugs. One is animal tissue that was made back in 1992. In other areas, there is the national policy for CJD, which was published in November 1995.

Those can be obtained in full at the web site address, www.hc-sc.gc.ca. Basically, the animal tissues policy relates to issues such as source of the materials, the

species and the tissues used.

It also relates to processing conditions and use of product and routes of exposure. The CJD policy is the most specific to blood issues, and defines donors considered to pose a risk for CJD, requires deferral of these donors from further donation, requires withdrawal of blood, blood components and blood derivatives associated with donors considered to pose a risk for CJD, and requires notification of consignees.

I won't go into great detail. The policy is actually patterned very closely to the U.S. policy that was put into place in 1995 and 1992.

It had been recognized that these policies are dated, and there is a new review of all the U.S. policies for consistency; for example, the animal tissues policy, including the manufacturers requirements.

On the other hand, the CJD policy exceeds current thinking, especially in regards to requirements for withdrawal for plasma derivatives associated with donors considered to pose a risk for possible CJD. Interim guidance is currently in the process of being issued in that regard.

The policy didn't specifically refer to new variant CJD, but referred to CJD in general, as it applies. So, there is a question of whether it goes far enough with regard to new

variant CJD.

A team structure has been set up to review and revise all policies relating to TSEs, and it was set up this past year.

Basically, there are three teams formulating the programs. The first one is a TSE team, and that is to develop health risk estimations with respect to prion(?) agents, why it has a risk for infectivity, to generate and evaluate potential remedial approaches or options to prioritize these baseline agreements with the underlying risk estimates.

The other two, the RMSP, which is the risk management strategy and policy team, is mandated to evolve risk management strategies and policies regarding human exposure to prion agents.

This team operates in a broader context than the TSE team, including social, political, cultural, environmental and economic impacts.

The team above all that is the senior policy development group, whose role it is to oversee and guide the policy development process, and support the development options regarding management of risk from prions.

Generally overseeing the process, ensuring integration, coordination between the agencies and the government.

Current activity is most focused on the TSE team, which is developing risk interventions. There are three streams, basically animal TSE stream, CJD stream, and new variant CJD. I would like to take a moment to focus on the latter, because as has been mentioned here, it is a very pressing issue for us as well.

There are a number of inputs to this information process. There are internal committees focused on the subject.

We have discussions with an expert advisory committee which advises us on regulatory matters. We have drafted, or we have had a consultant commissioned to provide a risk estimation, and we have seen a draft, not a final version.

We have had cross cultural consultation with a group of individuals representing consultants, Health Canada representatives from various areas of government, operators of the blood system, and so on.

I have listed lastly the advisory council on bioethics, which you may have heard, which is a group operating in a management relationship, which focuses not on the scientific issues, but on some of the ethical issues.

Of course, the source of our concern is quite clear. I think you have heard a lot on that subject today.

There are a lot of contrasts between new variant CJD and classical CJD that are causing a lot of concern.

Basically, it is a new agent. Unlike classical CJD where we have got decades of experience and sound epidemiology, and while not conclusive, it has given us some reassurance, we don't have that reassurance looking at new variant CJD.

It affects a younger population. The issue here, and perhaps it is more like to occur in the age group who are actively donating blood and plasma for use in drugs.

The agent also may be one that is biologically selective for efficient spread by a peripheral human infection.

It has a peripheral onset, which by occupation of the periphery, may lead to early and protracted preanemia versus possible wait and restriction in classical CJD.

The data from animal experiments has suspicions of the possibility that the lymphoid tissues would be harboring the agent.

Again, there are higher prion levels detected in new variant CJD patients, which again may imply that there is a great risk of infection from them.

There have been a number of proposals that have come out of the various inputs that we have had with consultants,

from consultations we have had with the public and with interest groups.

A lot of them recognize the need for research and that is really not controversial; I think research activity in humans and animals, diagnostics and screening tests, research in prion clearance and incubation, epidemiology and so on.

There is a great tendency for proposals to include a focus on risk reduction, and particularly a risk reduction by donor deferral.

Even if we accepted the premise that that should be considered, there are numerous questions to be dealt with.

In countries of concern, there have been various proposals. The United Kingdom is an area that we should concentrate on, the countries with TSE in native-born cattle, countries with significant TSE and so on.

The time frame of concern is, again, variously estimated by people. I think in general the time frame of concern starts somewhere around 1980, but numerous proposals have been advanced to try to catch the area of concern, from 1980 to the present; again, another question.

Duration of exposure has been a hot issue, depending on the means by which this agent transmits in the human species.

Of course, the big question is, what impact will any

of these policies have, both concerns of impact of supply of blood products, and the impact of deferrals on the donors, and the effects on total volume.

We currently have very little information on the impact. The operating systems are currently doing some surveys which are rather involved in this, in terms of visitation to countries and time frames and length of stays.

Even if one could answer those questions, there is a more important other one that needs to be answered, and that is how do you balance the theoretical risk against potential harm.

I just offer a perspective. Most of the blood products that are used in Canada are produced in the United States. Approximately half the derivatives are actually derived from U.S. donors.

Really, the Canadian perspective and the United States, we are dealing with common problems and there are big common solutions. I look forward to the discussion today. Thank you very much.

[Applause.]

DR. BROWN: Are there questions from the panel to any of the three presentations concerning blood policies, either from this country, the FDA, the United Kingdom, or the policy you just heard from Canada. Questions?

DR. NELSON: I wonder -- the first speaker presented the data on cattle, the BSE. I wondered what the age of onset of BSE in cattle is, and how that would affect the estimate of how many cattle might have been infected.

DR. BROWN: The question is addressed to Dr. Gustafson?

DR. NELSON: No, going back one.

DR. BROWN: To Dr. Ferguson.

DR. FERGUSON: I believe the first case has been in about 20 months. So, we can calculate it from there.

DR. NELSON: What proportion of cattle are slaughtered past 20 months?

DR. FERGUSON: Are you talking about in the United States or in Europe?

DR. NELSON: No, the United Kingdom or places where they have BSE.

DR. FERGUSON: I don't know that I have a good answer for that question. I know in the United States, they are not slaughtered beyond 20 months; not much beyond, but slightly beyond.

We slaughter animals generally younger than they do, so I would say the majority of them would be younger.

DR. BROWN: Do you have anything to add?

DR. PRUSINER: I think the question was not precise,

but 80 percent of the animals, by two years, are slaughtered.

I don't think your answer was very accurate. It is true, that it is seen at 20 months. I don't think that is the question.

I would like you to review for us just a second the last slide. It seemed to me you were saying that the United States based it on the policies, that they were just about to start importing beef and beef products from the United Kingdom, Switzerland, Portugal, Ireland; is that right? That is how I interpreted the slide.

DR. FERGUSON: Yes, that is accurate. We have evaluated those countries that have had BSE in native animals.

Please don't interpret that to mean it is just anything and everything coming in here. There are certain conditions attached to that, that weren't listed on the slide.

Beef and beef products, the bone must have been removed, all nervous system tissue and fatty tissue removed, the animals cannot have been in a region where there were cases of BSE during a certain period of time. There were a couple of other certification statements.

Those provisions actually were in place, until our interim rule in January 1998. We have been evaluating countries in our re-institution program.

DR. PRUSINER: So, how do we protest that?

DR. BROWN: Not at this meeting.

DR. FERGUSON: Right. When we publish the proposal, you can comment on it at that time.

DR. DETWEILER: I just kind of wanted to expand on that. Actually, the majority is seen between four and six years of age in cattle in the United Kingdom, and they range out to 18 years. Again, it drops off more between four and six years in cattle.

DR. BROWN: So, the great bulk of cattle that are allowed to live that long, will show BSE between the ages of four and six.

The answer to the other question, since nobody has contradicted anything, the majority of cattle are slaughtered for consumption before the age of two.

DR. DETWEILER: Just to kind of give you an idea on it, animals that go to slaughter at 30 months of age or older, are prohibited from going into the human or the animal food chain.

Basically, they would be slaughtered, rendered and incinerated, or slaughtered and then directly incinerated.

Now there are over two million animals plus that have been slaughtered under that, over 30 months, in the United Kingdom.

DR. BROWN: So, in the United Kingdom, animals unlucky enough to live to the age of 30 months are slaughtered and rendered.

DR. DETWEILER: And then incinerated. They do not go into the human or animal food chain.

DR. BROWN: They are disposed of.

DR. DETWEILER: They are not forced at 30 months to be destroyed. But at the end of their productive life cycle, if they are 30 months of age or older --

DR. BROWN: So, they are not all eliminated at the age of 30 months, but they age naturally and are then discarded. Other questions?

DR. ROOS: I have a question for Dr. Metters. I guess I just wanted to make sure that I understood the rationale for the present policies in the United Kingdom; that is that there is no pooled plasma products that have UK donors. Nevertheless, there is no curtailment of blood transfusions and labile products from UK individuals.

I just wanted to make sure I understood the rationale for that. That was just -- in other words, if there is a safety problem with a particular unit bearing CJD, then presumably those individual blood transfusions also carry that risk. Maybe you could explain that.

DR. METTERS: First of all, all blood products. At

the moment there are, because we haven't completed the change-over from UK source to non-UK source. Once that change-over takes place, there will be no UK sourced blood products. We are making that change as soon as possible.

The reason why blood products may be different from blood is that, of course, blood products go into an enormous pool.

The potential disbursement of a unit that is contaminated with new variant depends on the size of the pool, whether it is a pool of 500 or 6,500 units.

As I said, we have to find an alternative source of blood products. The most units it would go to is three recipients.

The other point to make is that this relates to the follow up. By far, those who receive blood in the United Kingdom will die from the current disease for which they receive the blood within 12 to 18 months. That is a real problem when you come to holding it up, because of the attenuation and so on.

The blood products, that does present a disbursal factor. As I said, we do actually have steps to monitor who receives the blood, and are taking steps to out-source blood products.

DR. BROWN: Just to add, on the disbursal factor, we

don't know what is going on in new variant. We don't know if there are a million infectious units per unit of blood. We just don't know.

I received this comment about CJD. If new variant is, indeed, like ordinary CJD, there is a logical curiosity about the disposal factor. Infectivity is a functional definition. We don't necessarily know what it is.

So, if there are 15 infectious units, we are talking about 15 transmissions of the disease. It is likely, after all the experimental and epidemiologic evidence that any level of infectivity in the blood of normal CJD is very, very low.

It doesn't much matter if that 100 infectious units is distributed to 10,000 or a million. There are going to be 100 transmissions. The notion that you can dilute out infectivity has no scientific basis.

The other thing, if the unit of blood that is donor is fractionated with an infectious agent, then disbursal may be higher. Unfortunately, we don't know the answer to that yet.

DR. SCHONBERGER: I am wondering if our colleagues from the United Kingdom can tell us what type of screening for blood donors is done to reduce the chances of new variant disease specifically in the donor group.

Is there any kind of screening specifically directed

toward new variant CJD.

The other issue, again, of screening, is there any screening that is done in the United Kingdom that is focused specifically on ruling out somebody who is symptomatic, for example, with new variant.

I understand that new variant's onset can be subtle and not really very apparent for a while.

DR. BROWN: So, what you are asking is whether or not there are any special criteria that are in place or being thought of to reduce the risk of a new variant patient who is either -- according to Bob Will's criteria -- either probable or definite. I can't imagine a definite, but shall we say a suspect.

DR. METTERS: I think the general answer has to be no. There is nothing you can ask somebody. There is, on the other hand, the donor is at least asked about their general health.

Then if there is any suspicion at the time that they are not 100 percent fit, and they have their blood count done before they are accepted.

If someone is physically unwell in any way, hopefully they will not get through the screening system. So, while it isn't specific to that, it is -- I would be doing a very bad job if I let someone who was unhealthy in any way to

get through our screening system.

DR. SCHONBERGER: So, there is no set of questions that is standard --

DR. METTERS: The questions of about CJD are there, right. To avoid getting classes of donors, you may be able to avoid getting classes of donors.

I would be very interested if any of you at the table could answer the question that was asked.

We haven't yet had one who has been identified that in the time that they were labile, was a donor.

DR. METTERS: As you know, most of the patients, or many of them, have psychiatric onsets. So, if their response to the very first question you ask is moo, you know to be suspicious.

DR. ROHWER: I have a question for Dr. Ferguson. When the provisions against importations from the United Kingdom were extended in February of 1998, was there any attempt by the USDA to go back to see what level of exposure the United States had to European bovine products and cattle since 1980, for example, or since 1988 when the provisions were put in place for the United Kingdom?

For example, between 1980 and 1989, apparently we imported some 500 cattle. Now that we have recognized that there may have also been a risk from imports from Europe and

others before this change in policy, have we gone back and looked at how exposed we were from that risk? I mean, how many imports were there, and what kind of things were imported.

DR. FERGUSON: Yes, actually we have gone back and looked at live animal imports from continental Europe at that same time.

They were fairly restricted at that point in time because cattle in Europe were infected with other animal diseases, such as FMB.

There were some animals from Germany and some from France -- maybe somebody can help me out.

DR. DETWEILER: Six from Belgium were put under quarantine.

DR. FERGUSON: Those were fairly recent imports. We did go back and look at the continental imports from 1980.

DR. DETWEILER: There are 38 from Germany that are currently being tested. They were born in 1996.

DR. ROHWER: In other words, the thing that I am concerned about is the carriers are meat and bone meal imported from the United Kingdom.

There was a report by Schroeder a couple of years ago -- last year, I guess -- indicating that there must be a lot of under-reporting there. So, what was the exposure and

what is the exposure.

DR. FERGUSON: As far as what was the exposure to Europe, that is why we took the action in January of this year. That is what we have been trying to look at, the process that we are going through now. What was our exposure.

I think I can say that our exposure was probably very minimal, because we imported -- please, don't hold me to this number -- less than 200 animals from continental Europe at that point in time. There were only about three shipments that came in since 1980.

They were 1982 and 1983. They were basically from France and Germany at that time. We did go back and do a risk assessment on those.

After that time, because of a foot and mouth problem in Europe, and because the importation, one big shipment was cancelled that never came in. It wasn't until 1996 that we had the Belgium shipment and the German shipment come in. So, there was a big void in continental Europe going on.

Of the ones that we imported from the United Kingdom, about half of those were from the Republic of Ireland and not from Britain.

MR. EPSTEIN: I think this is a question for Dr. Will, or anybody can answer it. Is anyone doing an experiment to take blood from the new variant CJD cases and attempt to

demonstrate infectivity in any animal, especially in primates.

I know that these kinds of experiments have yielded controversial results for controversial CJD. I think they remain important to do and it is worth knowing if they are ongoing.

DR. WILL: I think there are plans to do that with primates. The other issue is whether we should try to inoculate this material.

The mice that were used in these experiments that I showed earlier, indeed, those experiments are going on also.

I have a concern that I think these experiments must be done, but I don't think you should over-estimate the chances of their giving us the full answers to this question.

We are trying to transmit it across a species barrier, possibly with low rates of infectivity. A negative result may be interesting, but it may take many years to achieve. Dr. Brown has more to say about that.

DR. BROWN: This is a good time for me to put something on the public record that has bothered me for some time.

That is the USDA position, the United States Department of Agriculture position, that any research conducted on new variant done in this country will have to be

done under conditions of what are called biosafety level III.

They made that decision in December of last year. They made it on the basis of consultations with a number of people and organizations outside the USDA, which was appropriate.

I have to say that it is very unfortunate that, amongst the committee that made the decision, there was no single person who actually was an experimentalist in the field of transmissible spongiform encephalopathy.

The decision was made because TSE is an exotic disease in this country. New variant CJD appears to be the result of infection with BSE.

The thought was, obviously, that working with new variant CJD was tantamount to working with BSE, and therefore presented a potential risk to the U.S. cattle population.

What was left out of this decision is the fact that -- and to back up just a second -- the biosafety level III conditions versus the biosafety level II conditions are chiefly designed -- in fact, almost exclusively designed -- to prevent air borne infections.

It doesn't sound like much of a job to go from II to III to prevent air borne infections, but let me tell you, it is some job.

It requires months and months of ventilation duct reworking. In short, it is a real difficult thing to do.

What was missing from the USDA decision was that, in 40 years of experience working with BSE, no one has ever gotten it via air borne transmission. That is epidemiological data and laboratory data.

Had the USDA chosen instead to allow us all to work as have for decades with biosafety level II, with laboratory facilities using biosafety level III precautions, we would be, in this country at least, a full year ahead of where we are.

Some of the questions that are most urgent to this committee would probably already have some scientific information.

Having said that, we will break for lunch and come back at 1:15. After lunch, the committee can discuss anything that they have so far heard.

[Whereupon, at 12:15 p.m., the meeting was recessed, to reconvene at 1:15 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:17 p.m.)

DR. BROWN: Okay, this afternoon we are going to hear first from Alan Williams from the American Red Cross. He will bring us up to date on the so-called REDS study. Dr. Williams?

AGENDA ITEM: REDS Study.

DR. WILLIAMS: Thank you very much. Thank you for the opportunity to present this afternoon.

As mentioned, the data that I am going to present are derived from the Retrovirus Epidemiology Donor Study, known as REDS.

We were able to take the opportunity, as part of our 1998 general donor survey, to insert some questions which are relevant to the topic.

What I am going to describe for you is both the data derived from the survey and some extrapolations related to blood safety and availability that might result from a deferral of donors who traveled or resided in Britain during the 1984 to 1990 time period.

The retrovirus epidemiology donor study is sponsored by the National Heart, Lung, Blood Institute. It has been in place for just about 10 years now.

It is a multi-center, multi-component study. I won't go into all the components of it. One of them is a survey

research program, to capture data about our blood donor population, and specifically targeted to some of the risk factors that are in our current donor base.

I would like to specifically acknowledge Dr. George Nemo and Paul McCurney(?) at the institute, who have been particularly supportive of the research.

The clinical coordinating center is Westat located in Rockville, Maryland, and Danny Yamaki, Steve Schweinberg and Sno Lin(?) have been particularly involved in the analyses of the data that we have today.

At this stage, blood centers, there are five REDS centers that have been the long-term participants, and three additional centers were added for the purposes of the 1998 survey research.

I will just go through them by geographic area. They include Baltimore/Washington, the Detroit metropolitan area, the Los Angeles area, San Francisco, Oklahoma City, New York City, San Bernardino and Lifeblood in Memphis.

I would like to acknowledge the contributions of the staff of each of these centers, which have worked very hard to make the survey possible. It takes a lot of work.

Specific to today's discussion, our objectives are, one, to estimate U.S. donor travel or residence in Great Britain for the defined time period relevant to the BSE

epidemic.

Secondly, to correlate this travel or residence in Great Britain with other donation variables to estimate the impact of deferral on blood safety and availability.

Additional objectives, which are secondarily related to today's discussion, are to show you some data determining the donor understanding of the Creutzfeldt-Jakob Disease deferral questions, which were shown to you earlier today by Mary Gustafson.

A question that arose out of a letter to the Lancet regarding ingestion of mammalian brain, estimate the prevalence of mammalian brain ingestion by blood donors, and I have some interesting data related to that.

The survey methods which we derived over a period of years, we use anonymous mail surveys which are sent to donors within a month of their active donation process.

So, these are accepted blood donors who have proceeded with donation, and then they are sent out a survey form, requesting information both about their experience with the donation process, their behaviors and demographic characteristics.

Because the survey is anonymous, we can't relate that directly to the identifier or to their registration demographics, so we collect all of that separately.

We use a weighted random sample. REDS, as part of its structure, has a very sensitive donor/donation data base on each of their sites, so that we can select a highly representative sampling frame for work such as the survey, and even over-sample certain demographic groups if it is determined that we need to.

It is conducted in monthly waves, and the actual process is to provide some publicity about the survey at the donation sites, and then on the selected sampling frame, we send out an advance letter from the blood center, followed by the survey form with an additional cover letter, and follow that by some sort of follow-up procedure, which also may result in a new survey form being received by donors who haven't previously responded.

We have now gathered quite a bit of experience conducting surveys. Our first feasibility pilots were done in late 1990 and 1991.

We ran a large survey in 1993. The results of some of that were published in JAMA in March of last year.

We ran a large pilot in 1995 to look at some preliminary data related to incentives for blood donation, and we are running another large survey between April and October of this year, and we are just in the tail end of that data collection.

Because cleaning processes and so forth take a period of months, the data I am going to show you reflects data collected for donations between April of 1998 and June of 1998, and the number of respondents was 22,500, so it was quite a large survey.

Traditionally, the survey is showing a 65 to 70 percent return rates. The survey we used this time was several pages longer, so I think we are probably closer to the 63 to 65 percent response rate in this particular survey.

I think it is important to point out that we do tend to get a lower response rate from first time versus repeat donors. I will show you how we have corrected for that and some of the extrapolations that we have made.

Question categories. We collected demographics of the donors, donation history, questions about how they reacted to their donation experience.

We have collected quite a bit of information about past and current behaviors, including questions which essentially reiterate the exact time frames and questions of the ones that were asked at the time of donation, and I will tell you in a moment why we pursue that.

We also, for this survey, added a question about travel or residence in Great Britain, which is shown here.

I have a couple of comments about the format of the

question. The survey was literally at the printers when this issue sort of heated up.

We had some discussions with the FDA about the desirability of putting in such a question, and in fact, worked with them collaboratively about constructing the question.

Unfortunately, it doesn't address all the issues that the committee has to talk about this afternoon in terms of variable time frames and geographic areas and so forth, but this is the information we were able to collect.

The question is, did you ever live in or travel to Great Britain -- England, Scotland, Northern Island, Wales, Channel Islands -- in the seven-year period between January 1984 and December 1990.

The reason we chose the time period was, this was defined as the peak of the dietary BSE risk in a report in the Lancet by Collee and Bradley.

1990, as was mentioned earlier today, was immediately following the specified time that precautions were taken, so we had a reason for doing the cut off then.

The risk was probably reduced dramatically. To the extent that some of these practices continued, it might not have been complete.

In channeling this time period, we felt that the

data could reasonably be extrapolated from other time periods if need be, and we probably weren't specifically locked into the data from this time period.

We did not ask specifically about beef ingestion, as well as other details, primarily because if you are asking someone about details that are 10 or 15 years old, the likelihood of getting an accurate response after that time period is probably pretty low.

Even remembering if you have been in Britain is probably tough enough.

There are estimated to be -- in one report I saw on the internet -- about 12.4 million U.S. vegetarians. Just as a rough measure, perhaps six percent of the population could be assured of not having had meat in Britain.

So, what are the data related to this question? Yes responses were received from 2,600 of 222,57, for an uncorrected total of 11.7 percent of the respondents.

Not sure were received by .6 percent and no by 87.7 percent.

Possibly the most dramatic stratification that we made was dividing the responses up by geographic region.

As you can see, the urban areas of the country on both the east and west coast have quite higher levels of donors who reported travel to Britain during that time frame.

The highest is San Francisco with 16.3 percent, New York City very close, Baltimore and Washington, all above 12 percent, and then going down correspondingly to some of the midwest and coastal areas.

So, keep in mind that this isn't going to be uniform impact across the country.

Our second breakdown was by first time and repeat donor. I think the findings are not unexpected. Among first time donors there was about 6.4 percent reported, on repeat donors 12.1 percent.

This is logical in that first time donors probably tend to be younger. It is not unreasonable to see that difference.

It is important for use of these data in any further extrapolations, because we do get a differential response from first-time donors.

Now, the first thing I wanted to mention briefly is our attempts to look at the safety of donors that might be removed or might be left or have to be re-recruited by a change in deferral policy.

REDS has currently two ways of assessing transfusion safety. Something that is hepatitis C, HIV, hepatitis B cases are something on the order of anywhere from one in 100,000 for the hepatitis factors to one in a million for HIV.

Two ways we have of measuring them is using the survey as reported in the JAMA paper. We are able to derive a population of donors who come through the donation process, and admit in the subsequent survey that they have risk factors that should have prevented their donation.

This was reported in 1.9 percent of the donor population in the 1993 survey, and I will show you the data in a moment for the current survey.

We use this as a measure of potential risk in the donor population, because the ability to transmit to a recipient probably comes out of this population that does have residual behavior risk.

The second way is to look at marker incidents, by observation through the data base of repeat donors who have been negative at one donation followed by a positive donation subsequently.

As I mentioned, deferral risk is a cumulative factor for risk that, if identified at the time of the screening, would have resulted in deferral of the individual.

That was reported as 1.9 percent in 1993. It is higher in males, in donors who use the confidential unit exclusion process, which very briefly, is the donor who designates, just before going into the donor room, that they wish that their blood products should not be used for patient

support because there might be some question in their mind about its safety.

It is also higher in donors who have reactive blood for a screening test.

Among donors who responded in the 1998 survey, the deferrable risk among donors who traveled to Great Britain in 1984 to 1990 -- that would be travel or residence -- was two percent.

Among donors who did not travel to Great Britain 1984-1990, also two percent.

Among all first-time donors, really paralleling the 1993 data, deferrable risk in first-time donors was about twice as high as repeat donor population.

So, on a deferrable risk basis, we could not demonstrate a difference between these two populations.

Looking at the educational level of donors who reported travel to, or residence, we again see fairly major differences in these three categories.

Those who report high school or less education, some college, or college and above, you can see 5.2 percent had high school or less in the traveling group, 21 percent some college, and 72.5 percent college and above, compared to those who did not travel; overall, a higher level of education.

Other data that we have within REDS, as I mentioned,

we were able to look at observed incidence by seroconversion to certain markers, and we were able to relate this to educational level of the donors as well.

For HIV, the three categories, again, here, high school or less, some college, college or above. The first group here is HIV.

You see some variation in the numbers. The only significant difference here was in the college or above group, which was significantly lower than the other two.

Hepatitis C, again, you see differences. The only significant difference here was the high school or less group, which was a significantly higher level of HCV incidence than the other two groups. Hepatitis B, some differences but none significant.

On a theoretical basis, one could consider that, if one is excluding donors with a higher level of education and then re-recruiting donors who are first time and did not have that selected higher level of education, on a theoretical basis one could be, in fact, influencing the ability to have incident infection and transmit, say, an infection to a recipient for one of these markers of concern.

I would like to say a couple of words about the effect on resource and adequacy of the blood supply.

Starting out with numbers derived from the American

Association of Blood Banks and generally accepted, there are 13 million allogeneic units donated per year in the United States, made into 22 million components.

This reflects donations from eight million donors and four million recipients.

Roughly, 32 percent are first time donors. Of first time donors -- this is derived from the Red Cross ARCNET data base, and those are the numbers reflecting that break down.

Using those 2.6 million first time donors, the 6.4 percent traveling prevalence in Great Britain times the average donation per year for each first time donor, the loss is about 215,000 units.

Going through the same calculation for repeat donors, 5.4 million repeat donors in a year's time, times 12.1 percent prevalence of travel during that time period to Britain times 1.8, the average donation, would result in the loss of about 1.2 million donations.

Putting these together, the impact of deferral based on that criteria would be 1.4 million lost units, or 10.7 percent of the blood supply.

It would result in 819,000 lost donors. The breakout for first time to repeated I just showed you. Because of the differential in average donations per year, one has to consider that loss of repeat donors would have to be

countered by recruitment of first-time donors who, in general, have lower levels of donations per year.

So, we put in a correction factor and estimated that about 1,080,000 new donors would have to be recruited in response to deferrals for that question.

In conclusion: Indefinite deferral of blood donors who traveled or resided in Great Britain during the 1984-1990 time period would result in the loss of 10.2 percent of the U.S. donor base, 10.7 percent of the annual blood supply.

I think some of the blood organizations have comments this afternoon which would say more about the actual impact of those numbers.

Donors lost by deferral would need to be replaced by more than a million newly recruited first time donors.

Based on estimates of deferral risk and infection incidence, the risk of transmitting known infections such as HIV, hepatitis B and hepatitis C will increase, only due to the fact that first-time donors are clearly shown to be higher in both deferrable risk and incidence.

About the CJD-related donor screening question, it is worded: At the time of your last donation you were asked about the CJD question. We have information to say that 60 percent of the respondents either felt they didn't have sufficient information or weren't sure about that.

I won't say anything further about that, since the FDA takes this as meaning that donors who have experience with Creutzfeldt-Jakob's disease would recognize it. I will end there, and thank you very much.

[Applause.]

DR. BROWN: It appears to me that maybe the Achilles heel of British travel appears to be that if it is true that the greatest susceptibility to -- actually, that is not what I wanted to say -- the greatest vulnerability, the greatest exposure in Great Britain was in the low end consumption, or the consumption of low end meat.

It stands to reason that since we are talking about a comparatively up-scale group of travelers, we are not going to get many travelers who eat much low end meat.

We are talking about people who, even if they lived in Great Britain, would not have low end meat on the table.

So, we will have the next presentation -- actually, the last presentation. So, this is by Mark Weinstein, Dr. Weinstein, the director of the division of hematology in the Office of Blood Research and Review, CBER, in the FDA, and he will speak about the effects of withdrawal and recall policies on the supply of plasma derivatives in the United States.

AGENDA ITEM: Effects of Withdrawal and Recall Policies on the Supply of Plasma Derivatives in the United

States.

DR. WEINSTEIN: In this presentation, I will talk about the effects that excluding donors who have traveled or resided in the United Kingdom would have on the supply of blood derivatives.

First, I will talk about the effects on the availability of plasma to groups who manufacture, if donors are deferred because of travel or residence in the United Kingdom from 1984 to 1990.

As you heard, those dates were chosen because it encompasses the peak period of the epidemic in the United Kingdom.

Also, I will be giving some hard data about plasma donors who meet the risk criteria that Dr. Williams has just presented.

I will then discuss the effect on plasma derivative availability if product is withdrawn because of United Kingdom travel or residence control criteria.

Regarding the availability of plasma for manufacturing, the institution of such a deferral may or may not be different for recovered versus source plasma.

Recovered plasma is plasma that is derived from whole blood donations. It is generally obtained from volunteer donors with a yield of about 250 mls per donation.

General, more donations are used per lot to make a recovered plasma product than are used to make source plasma products.

In 1998, GAO reported that 1.8 million liters of plasma was obtained from 8 million volunteer donors.

We have also learned from the REDS survey that 12 percent of recovered plasma donors traveled to or resided in the United Kingdom from 1984 to 1990.

No, in contrast to recovered plasma, source plasma for further manufacture is obtained by plasmaphoresis.

Donations are in the range of 800 mls of plasma for donation, and donors are generally paid. The 1998 GAO report indicated that 11 million liters of plasma were obtained from 1.5 million donors.

Eighty to 85 percent of the plasma for derivative manufacture in the United States is obtained from source plasma.

Currently, the supply of plasma in the United States for derivative manufacture is in excess of the amount used.

At least a third, and probably more like a half of the plasma in the United States is exported. U.S. manufacturing plants are working at full capacity, although for some this capacity right now is limited because of compliance issues.

Assuming that 12 percent of those sources of recovered plasma donors traveled to or resided in the United Kingdom between 1984 and 1990, a decrease in the supply of plasma for manufacturing by 12 percent should still exceed the U.S. use.

The cost for plasma may rise precipitously, as the U.S. demand has the potential for being met. This is contingent on plasma exports being reduced.

Plasma distributors may decide, however, to honor contracts that they have with foreign manufacturers rather than to supply the U.S. need first.

The assumption that the 12 percent figure is true for both the recovered and the source plasma donor is questionable, because the source plasma donors probably have a lower socioeconomic level and are perhaps less likely to travel.

However, the source plasma donor industry is attempting to target college students and military personnel, a highly mobile group, that may have traveled extensively and resided in the United Kingdom for some period of time.

What would happen if the plasma derivatives were withdrawn under the donor deferral criteria. First of all, no plasma derivative would be available for at least 90 days after the imposition of the deferral, until derivatives could

be made from new plasma donors.

This is because plasma derivatives are made from pooled donations from 5,000 to 60,000 donors. Every plasma derived product on the market would contain plasma from at least one of the roughly 900,000 deferred donors. It takes about 90 to 200 days to manufacture a plasma derivative and make it available for sale.

After the initial large withdrawal of product, there would be a long period where withdrawals would occur because of adverse information received after donation.

If we assume that only one in 10,000 donors report post-donation -- which is a very conservative number -- that they met the donor deferral criteria, this would lead to approximately 100 withdrawals from recovered plasma donors.

This is more than all the CJD withdrawals that took place between 1995 and 1997, which amounted to 63.

Similar calculations for source plasma donors would predict 22 withdrawals because of post-donation information.

Although the CJD withdrawals for recovered plasma products are more frequent than for source plasma products, because there are more donors per product, the impact on source product availability becomes much greater when a source plasma donor is identified with a risk factor and a pool of products is withdrawn.

This is because the source plasma donor gives more frequently, and in larger amounts, than the recovered plasma donor, and therefore, more lots of products are likely to be affected.

The next slide gives you a sense of the numbers of donors who had various CJD related risk factors that led to the withdrawal of plasma derivative products.

In 1997, there were approximately 40 withdrawals. This model shows the percentage of annual production of various products impacted by those relatively few CJD withdrawals.

Five to 25 percent of the annual production of the anti-hemophilic factor, IGIV and albumen were subject to withdrawals in this period.

Over roughly five percent of the products were actually returned to the manufacturer. Large amounts of material in intermediate manufacture and in the inventory -- and therefore, never distributed -- were affected by these withdrawals.

The last slide shows the number and distribution of IGIV for 1998. The various boxes indicate the amounts distributed by individual manufacturers.

I have altered the amounts actually distributed by individual manufacturers to preserve anonymity, but the totals

for each month are after it.

The line labeled projected indicates the amount of material needed to meet demand. This was calculated by using the 1996 distribution figures and multiplying by an estimated 10 percent increase in demand per year.

Currently, we are about 30 percent below the estimated level necessary to meet demand. You can see that the last three months or so they are below the level that they need for this year.

Any deferral or withdrawal recommendations have to be made in light of this, that products will not be available to treat patients. Thank you.

DR. BROWN: Thank you, Dr. Weinstein.

[Applause.]

DR. BROWN: I totally agree with Dr. Weinstein's last comment, but we are asked to be a scientific committee, and it is my judgement that it is the FDA that has to take these other considerations, and that our input is to the base on the science in this case, such as it is.

In our discussion and deliberations, we should deliberately exclude any considerations of trade off and society concerns and political concerns. That is the business of the FDA.

They are the ones who are going to make the policy.

They are the ones who are getting our advice. We now have, I think, open discussion.

DR. FREAS: As part of the FDA advisory committee procedures, we hold an open public hearing for members of the public, who are not on the agenda, who would like to make announcements and presentations to the committee.

Mr. Chairman, at this time, I have received five requests to speak during the open public hearing.

The speakers will be called in the order in which the requests were received. The presentations are to be kept to five minutes.

The first speaker requested an additional five minutes for presentation of data.

We ask that all the speakers, in the interests of fairness, address any current or financial involvement with any firm or products with which they are involved.

Our first speaker is Dr. Steve Peteway from Bayer Corporation.

DR. BROWN: These presentations will be how long?

DR. FREAS: The first one will be 10 minutes.

DR. BROWN: You have 10 minutes, Doctor.

AGENDA ITEM: Open Public Hearing.

DR. PETEWAY: Thank you for giving me an opportunity to come this afternoon and describe some of the experiences

that we are having at Bayer Corporation.

Looking at the capacity of plasma biotechnology manufacturing processes, to clear TSE, to clear modeled TSE.

This is sort of a follow up to the talk that Bob Rohwer gave, and Bob very nicely addressed the issues and the caveats for these studies. I am not going to go back and reiterate that, only to say that the points that he brought up are very valid, and we agree with those.

Current validation studies or current clearance studies are being done today looking at the potential to clear TSEs.

As most of you know, we follow a standard validation format. That is, scale down, characterize the manufacturing processes, high titer responses, and clearance determined by bioassay.

We have taken a little different approach at Bayer to speed things up and to try to address the feasibility of these studies.

What we have done is to develop a more rapid in vitro assay, essentially a western blot, to detect pathogenic isoforms of prion protein.

It is a quantitative end point dilution western blot. I will tell you right now that the sensitivity to detect is around 10^3 infected units per ml of infectivity.

We apply this in in vitro assays to identify process steps with the greatest potential to clear TSE.

So, we first look at the in vitro assay and then we come back and validate the identified clearance steps of the bioassay. It is important to show that the two correlate. So, we have two independent parameters we are measuring here.

Just a brief summary of the assays that are specific with the hamster 263K. In fact, it uses a 3F4 monoclonal from Richard Rubenstein in New York, and we have done this in collaboration with Richard.

The titrations for this are linear. They are consistent with bioassay titrations. Importantly, the linearity of titrations is reproducible.

Each one of these is a half log deletion. It is just like any other end point dilution. The only difference is that our end point that we are detecting is prion protein in pathogen form.

So, we address three questions, then. Can this assay estimate clearance. Does PrPsc clearance correlate with TSE infectivity clearance, and is there a significant clearance in any of these products.

This is a schematic of some of Bayer's processes, beginning with cooling, cryoseparation that you have heard about, the processes that lead to the different products.

We have evaluated the process steps that are outlined in green, and I will show you a little bit of that data and summarize it for you.

Let me just say right now that the data that you will see from us is very consistent with the data that Bob presented, that Paul Brown and Bob Rohwer reiterated, for partitioning of endogenous and spiked TSE.

This is a first experiment. You can see that there are five links to titration here, 2.5 logs of prion protein went into the original starting material.

After fractionation, the effluent or supernatant goes onto the product. It has three rings. Very importantly, the precipitant has five rings. This is a one log clearance, or a one log partitioning.

What is important about this, is that we were able to carry out 10 separate fractionation materials, that demonstrate reproducibility in this partition.

So, each one of these represents a separate experiment. What you can see relative to clearance is that in each one of these you get consistent clearance, one log clearance.

You can see that in this one we have .5, and in this one 1.5, which is in the variability of the assay, the average being one log. This may be one of the important features of

being able to use an in vitro assay.

At the other end of the spectrum, we looked at our IVIG process, and one of our fractionation steps. I think it is very clear to see that with the sensitivity of this assay, we are able to titrate out about 4.5 logs of prion protein.

This is the starting material. After fractionation, this is the effluent that goes onto the product. You can see that there is nothing detectable over 4.5 logs. Then we are able to regain that material, and show mass balance.

You heard Bob refer to that this morning. I think this is critically important for interpreting these experiments.

Again, this experiment was done multiple times, and the result being an average of about four logs partitioned.

The next question of critical importance, then, is how does this partitioning relate to the infectivity partition. Are they the same and do they correlate.

This is another process step to be looked at. In this table, after fractionation, looking for bioassay or infectivity, all the infectivity in this particular fractionation ended up in the precipitant. None was detected in the effluent in two separate experiments using bioassay.

When we did the same experiment looking at PrPsc, the prion protein, we found exactly the same results. All

prion protein ended up in the precipitant; none was detected in the effluent; the two correlate exactly.

DR. BROWN: Steve, could you bring that back again?

DR. PETEWAY: Sure.

DR. BROWN: Earlier, you said that bioassay was approximately five-fold more sensitive than the western blot. This slide indicates it is 10-fold more sensitive.

DR. PETEWAY: To the extent of this assay it is. It probably is. This is what was detectable after spiking, and after separation from the bioassay.

DR. BROWN: You have got five logs of infectivity and you can dilute to four logs.

DR. PETEWAY: There was 100-fold less infectivity using this bioassay than there was using the western blot. That is the difference.

This is just to summarize some of the studies that were done to date. Cryoseparation, cryoprecipitated separation, fraction 3, fraction 4.1, and importantly, one we call fraction 4.4. It is in the chart on the way to albumen.

What you can see is whether we identified a single log of partitioning for clearance, or whether we identified 2.5 or 2.4 or 3, or four logs.

In every case, the western blot or the PrPsc partitioning correlated directly with bioassay partitioning.

So, we were able to show two parameters and demonstrate reproducible clearance at all of these steps.

I know that there are some people in this room who would not be surprised at all if PrPsc partitioning correlates with bioassay partitioning, but I think in this context it is incumbent on us to demonstrate that.

In conclusion, then, this western blot assay and the in vitro assay can measure clearance of prion protein over a four to five log range.

Importantly, in the context of this complex mixture, this plasma, there is a direct correlation between prion protein and TSE infectivity clearance as a result of plasma, and in fact, some of our tech manufacturing processes.

Importantly, there is significant clearance of experimental TSE prion that occurs as a result of plasma and biotech manufacturing processes. Thanks.

DR. BROWN: Thank you, Steve. Would you put the previous slide up again, please? I am just looking to see whether, in this schema, there is at least one step that reduces infectivity within three to four logs in the pipeline of every one of the end products that you show on the slide. Are there any that escape? Are there any that are on there?

DR. PETEWAY: Yes, for cryo. This is really only about 1.5 logs total.

It turns out that we have now completed studies of fraction 2+3 and there is greater than four logs clearance for that step, which you would expect; right?

So, you found all your infectivity going to this place, and significant infectivity there, and our results match your results exactly.

So far, the IVIG with these two steps with four here plus four here, that is significant. I will tell you also that there are four there, and there are four here.

So, for all of these processes beyond what we call fraction one, then there is at least six logs or greater clearance for each one.

DR. BROWN: So, the only product really, which is not being devastated is the cryo.

DR. PETEWAY: Yes, and I will tell you that we haven't finished evaluation of these process steps either. So, we don't know.

DR. BROWN: So, that may or may not be, but that is still uncertain. The other products at the bottom all have four log intervention at some point in the pipeline.

DR. PETEWAY: Right, they have at least one step that has four logs, and most of them have two.

DR. BROWN: Any other questions for Steve Peteway? Okay, the next request is from Chris Healy from the American

Blood Resource Association. From here on out, the comments will be five-minute comments.

MR. HEALY: Good afternoon, and thank you. My name is Chris Healy and I am the director of government affairs for ABRA.

ABRA is a trade association that represents the nation's source plasma collection industry. ABRA members include more than 375 community-based source plasma collection centers across the United States.

These centers collect just under 11 millions liters of source plasma annually from approximately 1.5 million donors.

Source plasma donors are valued members of society, and provide the nation with many raw materials for many life saving and life enhancing products.

Maintaining a safe donor population is the industry's primary goal. Throughout the 1990s, great strides have been made in excluding high risk donors and increasing the quality of the donor base.

The greatest achievements have resulted from the industry's self-imposed voluntary standards including, among other things, the quality plasma program, the qualified donor standards, the biomarker standards, the inventory hold standard and PCR testing.

As a result of industry's efforts, plasma derived therapies are safer today than ever before. Today, the likelihood of a potentially infectious window period donation entering the manufacturing pool prior to viral inactivation is 1.47 per million donations for HIV, 3.32 per million donations for HCV, and 53.84 for HBV.

Once inactivation steps are complete, the viruses present nearly no risk.

Notwithstanding these safety gains, the industry recognizes the need to remain vigilant about potential health risks from emerging and newly-identified pathogens.

Industry monitors the scientific literature closely for information that may implicate blood and blood products, infections from emerging pathogens, and as you saw from Dr. Peteway's presentation, many industry participants perform their own substantial research on emerging pathogens such as CJD.

The industry stands poised to take whatever steps are necessary to address any threat to the nation's blood derived therapies.

With few exceptions, the route for transmission of the CJD pathogen remain theoretical. In a recently reported longitudinal study, CDC reported that there is no association between long-term infusions of blood infected concentrates and

classical CJD.

Furthermore, despite frequent travel to Great Britain by many Americans, no cases of new variant CJD have been reported in the United States.

Finally, worldwide, there has never been a case of CJD associated with the infusion of blood products.

To date, the greatest health threat to plasma product users is product availability. While the supply or source plasma has not been a concern to date, preliminary evidence shows a 15 percent decrease in donations this year as compared to last year.

The data also suggests a downturn in the number of new donors reporting to the collection centers. Many segments of the industry report increasing difficulty in recruiting and maintaining donors.

Further reducing the existing and potential donor base could have a detrimental impact on the blood supply.

Furthermore, much of the industry's recent donor recruitment and retention activities attempted to attract college students and military personnel.

These individuals tend to be educated, healthy and reliable source plasma donors. In many respects, they represent the donor profile that the industry is striving to attract and retain.

However, they are also the most likely to travel abroad. The deferral of these donors could exacerbate the donor selection efforts that we are undertaking today.

In conclusion, I would like to thank you for the opportunity to speak about this important issue. Once again, assuring source plasma safety and the maintenance of a safe and adequate donor base are the industry's paramount concerns.

While the industry believes that Great Britain's experience with new variant CJD warrants close scrutiny, current science suggests that deferral of individuals who traveled to or lived in Great Britain is not warranted at this time. Thank you.

DR. BROWN: Thank you. Next is Dr. Steve Kleinman. He represents the American Association of Blood Banks, commonly known as AABB.

DR. KLEINMAN: Thank you for the invitation to speak. I am chair of the transfusion transmitted disease committee of the AABB.

The American Association of Blood Banks is a professional association for approximately 2,200 institutions engaged in the collection and transfusion of blood and blood products, including American Red Cross blood service regions, independent community blood centers, hospital-based blood banks and transfusion services, and more than 8,500

individuals engaged in all aspects of blood collection, processing and transfusion.

Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country.

Throughout its 50-year history, the AABB's highest priority has been to maintain and enhance the safety of the nation's blood supply.

The AABB appreciates the opportunity to participate in the dialogue about measures that may prevent the theoretical transmission of the CJD agent by blood and blood products.

Based on recent evidence and concerns that new variant CJD may be associated with the ingestion of BSE contaminated beef, the British government, as we heard today, has required that plasma collected in Great Britain not be used for further manufacture of injectible products.

However, citizens in Great Britain can donate blood for transfusion as blood components such as red cells, platelets and MFT.

In Canada, recently, the Bayer Advisory Council on Bioethics recommended deferral of donors who had resided since 1980 in geographic areas with significant incidence of BSE or new variant CJD.

The assumption underlying this geographic exclusion presumably is that residence in -- and by extension, travel to -- Great Britain may serve as a surrogate risk activity for theoretical food-borne exposure to new variant CJD, and its theoretical risk of transmission through blood products.

The comments in this position statement are in response to the FDA's request for information regarding the impact on the U.S. blood supply of such a geographic exclusion.

Data that we heard a few minutes ago regarding travel to or residence in Great Britain are from the National Heart, Lung and Blood Institute's Retrovirus Epidemiologic Donor Study and there is additional data from the Department of Defense.

In the ongoing REDS survey of current blood donors, 11.2 percent of approximately 22,500 survey respondents indicated a history of travel to or residency in Great Britain between 1984 and 1990.

Blood donated by Department of Defense personnel augments the civilian blood supply, and the military relies on collections among military personnel to support its own transfusion program.

At any given time, 1 percent -- that is about 12,000

people -- of active duty staff are stationed in England, and 50,000 military personnel are stationed in Europe.

Based on these figures, the DOD estimates that five to 10 percent of active duty military personnel have either lived in or traveled to Great Britain since 1980.

Because FDA regulatory criteria also apply to the military, it is thus likely that five to 10 percent of active duty personnel would be deferred as blood donors.

Extrapolating the REDS and DOD data to the general donor population, it is conceivable that at least 11 percent of prospective blood donors would be deferred for travel to or residency in Great Britain.

In addition, since a repeat donor contributes, on average, 1.6 units of blood per year, an estimated loss of 1.4 to 2 million units could occur each year as a result of applying these exclusionary geographic criteria.

This represents the approximate number of red cell units required annually to support the transfusion needs of patients undergoing coronary artery bypass surgery or bone marrow transplantation.

The AABB believes that such a loss of units would have a major impact on blood availability in both civilian and military populations, and would exceed by historical proportions previous losses that resulted from interventions

directed toward other potential infectious risks.

For example, implementation of testing for antibodies to hepatitis B core antigen initially resulted in an annual loss of two to three percent of donations; ALT testing previously accounted for another 1.6 percent loss. In a blood supply that is already marginal, a 10 percent deficit could be irremediable.

It is also possible that blood safety may be negatively affected by implementing such a deferral.

Donors deferred for a theoretical CJD geographic risk would, of necessity, be replaced by first-time donors, a population in which higher behavioral risks and higher infectious disease incidence and prevalence rates have been documented.

Thus, by deferring these predominantly repeat donors with theoretical CJD food-borne risk and by recruiting first-time donors to replace them, it is possible that implementation of the geographic exclusion criteria under discussion will negatively impact blood safety as it pertains to HIV and other known transfusion-transmissible infectious diseases.

The decrease in safety and availability issues are the AABB's overriding concerns, but the potential social impact of implementing a deferral for travel to or residency

in Britain is also an issue that deserves consideration.

In the past, geographic exclusions have been perceived as discriminatory, and those affected by such deferrals have voiced concerns about stigmatization.

Currently, of those geographic exclusions in use, that for malaria is likely to remain indefinitely, but these donors are deferred for no more than three years, and the current HIV group 0 exclusion will be lifted when licensure of screening tests with enhanced HIV group 0 sensitivity occurs, presumably in the not-too-distant future.

A geographic CJD exclusion criterion not only risks stigmatization of those to whom it is applied, but it may unnecessarily and unjustifiably raise public fears about the safety of travel to an industrialized nation, as well as raise fears in individual donors who give such a travel history, with regard to their own future health.

In conclusion, the AABB believes that the deferral of blood donors who have traveled to or lived in Great Britain may sacrifice a measure of protection from known infectious agents for protection from a theoretical risk, and will significantly decrease blood availability in the United States. Thank you.

DR. BROWN: Thank you, Dr. Kleinman. The next speaker is Dr. Richard Dailey from the American Red Cross.

DR. DAILEY: Thank you, Mr. Chairman. I am Dr. Richard Dailey. I am the chief medical officer of the American Red Cross.

The American Red Cross welcomes the opportunity to speak to this committee on this important subject. The Red Cross is the largest supplier of blood plasma and tissue products in the United States.

We supply almost half of the nation's blood supply through the generosity of over 4.5 million donors. We supply over 3,000 hospitals through our national network of 38 blood bridges.

The Red Cross regards the safety of the blood supply as its highest priority. Red Cross scientists are actively investigating possible emerging threats to the blood supply, such as Shitis(?) disease, and we will soon be implementing nucleic acid testing for HCV and HIV.

We have also been active in research on transmissible spongiform encephalopathies, and we have devoted more resources to this effort than any other private organizations.

We have supported Dr. Rohwer's research. We have supported the work of Dr. William Groeing(?) in our own lab, and we have worked closely with Dr. Brown of the NIH.

The Red Cross also has the responsibility to ensure

an adequate supply of blood and blood products to the American people.

We view with concern, therefore, proposals to defer donors who have lived in or traveled to Great Britain during peak years of the bovine spongiform encephalopathy epidemic in that country.

This deferral is being considered to reduce the theoretical risk of transmitting new variant CJD from an individual who may have consumed beef products in Great Britain during those years.

New variant CJD has not been reported in the United States, and there are no documented cases of the disease being transmitted by blood or blood products worldwide.

The REDS study has studied the impact on the American blood supply if donors who lived in or traveled to Great Britain between 1984 and 1990 are deferred.

Dr. Williams presented these data earlier today. In summary, of 22,257 donors who completed the mail survey, 2,603, or 11.7 percent, met the criteria for deferral.

Considering the number and donation frequency of both first time and repeat donors, the REDS group estimates that 1.4 million units would be lost.

In addition, 819,000 donors would be deferred, incurring the unnecessary fears of these donors, and

increasing the concern of the public regarding the safety of the blood supply.

Over one million new donors would need to be recruited. Moreover, these would be first time donors, who have a higher incidence of referral rates.

It is likely, therefore, that taking this step in response to a theoretical risk may actually decrease the safety of the blood supply.

We are also very concerned about a decrease in recovered plasma for further manufacture derived from Red Cross volunteer donors, with the corresponding impact on the supply of plasma derivatives.

The Red Cross produces approximately 20 percent of the plasma derivatives used in the United States and is the sole producer of derivatives made entirely from volunteer donors.

Essentially, all Red Cross plasma derivatives are used within the United States.

The loss of 11 percent of our donors would result in the loss of over 175,000 liters of plasma. The ability to produce concentrate, plasma, albumen and IVIG would decrease accordingly.

In addition, market withdrawals of derivatives manufactured from large plasma pools would increase

dramatically, as post-donation information is received about travel to, or residence in Britain.

Tracking the authenticity of this information would consume considerable time and resources of blood collecting organizations.

So, the impact of decreased production coupled with an increase in rapid withdrawals would occur when plasma derivatives are already, as we have heard, in short supply.

This action of proposed deferral on the supply of these essential derivatives to prevent a theoretical risk must be undertaken with full consideration of these clinical consequences.

The dramatic loss in donors and potential increase in risk, therefore, will have a major impact on the American blood supply.

The blood supply today is marginal at best, with shortages often occurring over the holidays and in the 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.

It is highly unlikely that increased recruitment efforts, however strenuous, will be able to overcome the deficit caused by this deferral.

These proposals, therefore, will have a devastating effect on the American blood supply, to prevent a problem that has never occurred.

The American Red Cross will continue to conduct and support research on the possible transmissibility of new variant CJD.

We will honor our commitment to ensure the safety of the blood supply. However, an adequate supply of labile blood products and plasma derivatives must be maintained if we are to meet the needs of the patients who depend on us.

Therefore, the Red Cross cannot support proposals to defer donors based on a theoretical risk of travel to or residence in Great Britain. Thank you, Mr. Chairman.

DR. BROWN: Thank you, Dr. Dailey. I am sure the committee, like me, is just so sad that the REDS questionnaire didn't include three other words -- and how long.

I have a feeling that all these phrases like tragic, catastrophic would disappear if we knew, as we might expect, that the phrase travel in or reside will be 90 percent made up of people who have spent two weeks or less in Great Britain.

If, instead of 1.5 million or 1.4 million exclusions, we had 140,000 exclusions, it would change the whole picture.

We don't have that information; just one more thing

we don't know.

The final speaker is Richard Vogel, from the Hemophilia Association of New Jersey.

MR. VOGEL: I would like to thank you for this opportunity to voice my concerns over the decision to allow classic CJD into our country's blood supply.

First, I would like to introduce myself. Second, I will explain why I believe it is a bad decision and ask a few essential questions, and lastly, I will suggest what can be done.

My name is Richard Vogel and I am a trustee of The Hemophilia Association of New Jersey, as well as a trustee of The Hemophilia Federation of America.

I come before you today as a 42-year-old severe hemophiliac who is HIV positive and infected with the ABCs of hepatitis.

Having been infected with HIV through blood products in 1983, I am considered a long-term survivor. I am also one of the first hemophiliacs in this country to have used lyophilized product -- dried factor VIII that is then reconstituted with saline.

That product was first introduced in 1970 and I have been using it ever since. That is 28 years of infusing millions of units of blood from as many donors.

Each vial of factor VIII is manufactured from a pool of donors that exceeded the 20,000 donor pools we were led to believe by 580,000 donors.

In other words, as Congressman Shay's committee uncovered, the donor pools exceeded 600,000 donors. This is a significant number to keep in mind, as I will explain in a moment.

I believe the decision to allow classic CJD into our blood supply by not screening donors is a bad policy.

We know CJD has a 30-plus year incubation period; yet this policy was based on a 17-year study/lookback.

Somehow, this seems to be an incomplete study. When I bake my Sunday morning muffins, they take 10 minutes to bake. If I take them out in five, they are just batter, in other words, incomplete.

As I mentioned before, myself and a handful of hemophiliacs have been using pooled product since its inception 28 years ago.

Again, with a 30-plus-year incubation period, we may just be beginning to see the tip of the iceberg. Would it not make sense to screen for classic CJD a few more years to make sure, like my muffins, that the study is fully baked.

We are so close to being certain, why not wait a few more years. We have the perfect group, the hemophiliacs to

gather our data from.

Since the transmission of classic CJD through the blood, through plasma, has not been scientifically ruled out, I will go under the assumption that it is transmitted through blood.

We know that CJD manifests itself in brain. How else would it travel through the body to get to the brain after being ingested, if not through the blood?

If we accept the logical fact that CJD is transmitted or at least travels through the blood, the argument still surfaces, that classic CJD only infects one in a million.

Well, now we go back to the pooled product and the size of the donor pools. If we say 600,000 donors are in one pool and you infuse two vials at a time -- which is a conservative estimate for a severe hemophiliac -- you are infusing the equivalent of 1,200,000 donors.

Now, the one in a million doesn't seem so astronomical. If we multiply that by 28 years, I do not see how many severe hemophiliacs in my age group dodged the bullet and were not infected. I hope I am wrong. However, we will not know for another few years.

Is the same effort being made to irradiate CJD in blood products as was made to lobby for the reversal of the

CJD withdrawal policy?

Can anyone tell us the status of the research being done for the identification and elimination of CJD in blood products?

Why is the United States last instead of being at the forefront of implementing safety measures that secure the blood supply?

As of July 17, 1998, Britain decided to remove white blood cells from all donated blood. Britain joins Ireland, France, Norway, Portugal and Austria. The United States plans to follow suit in the next two years. Why? Why not now?

Finally, I would like to make a few recommendations on what can be done.

Withdrawal of blood products for classic CJD should continue for five more years. At that time, a review of the hemophiliac community should yield the results needed for an informed decision, medically, scientifically and morally.

Money spent for lawyers and lobbyists should be redirected to the research effort.

Some effort should be made to communicate and update people dependent on blood products as to the research studies being done. What is happening to the studies with iodine? The days of "we just don't know" are no longer acceptable.

The United States should follow the leadership of

Great Britain and other European countries in implementing blood filtration as soon as possible.

In conclusion, we at the Hemophilia Association of New Jersey and the Hemophilia Federation of America urges this committee to recommend the reversal of the CJD policy on blood product withdrawal. Thank you.

DR. BROWN: Thank you, Richard. We continue to have some available time for the open hearing. I would like to ask now if there is anyone in the audience who would either like to make a presentation, or who have comments that don't qualify as a formal presentation, but they would like to say. Yes, sir? Please.

MR. CAVENAUGH: My name is David Cavenaugh and I am the government relation staff for the Committee of 10,000.

We would just like to draw your attention to something that we have been saying at the blood products committees and blood safety committee meetings for several years now, which is that the process of regulating the blood supply need not be based on a graph where there is a zero sum between safety and supply.

It is necessary to split those two in your deliberations. Things will happen. We do not have a new variant in this country. We have a recent case of a youthful person with classical CJD.

The question becomes, is this another variant that isn't being discussed. We don't know that yet.

That question is in the air in 1998 or 1999. Is there a western hemisphere variant that we don't know about yet.

I urge you to not say, oh, we haven't seen one yet. Therefore, our surveillance proves it is not going to happen. Thank you.

DR. BROWN: Thank you. Are there other comments from the audience? Two people are standing.

MR. SHEARER(?). Thank you, Mr. Chairman. My name is Graham Shearer. I am the vice president of medical affairs for the Community Established Canadian Blood Services, which is part of the operation of the Canadian Red Cross in Canada.

Jim, I would like to respond to the comment you made a few minutes ago about adding three crucial words to the survey we heard about from Dr. Williams, the words being, and how long.

Suggesting that if visitors to the United Kingdom were there for less than two weeks and that might account for more than 90 percent of the deferral figures we heard about, and in fact, we would not be talking about 1 million or 1.4 million, but perhaps maybe a couple hundred thousands.

I think this is precisely the issue which none of

the experts on TSE have yet been able to find the answers to, namely, what is the duration of exposure to risk required in order for there to be any risk to a donor and to a recipient.

In the absence of such data, it is, I believe, erroneous to claim that adding a deferral criteria for travel or residence in the United Kingdom or in any other geographic location adds any safety to the system, even if the impact on inventory can't be managed.

What such a deferral criteria may do is add to a perception of risk and safety, not to the added safety itself.

If there is any definitive data as to what exactly the risk is and the duration required to get such risk, this is information that I believe the committee should consider in its deliberation; namely, the distinction between managing the risk and managing the perception of risk. Thank you.

DR. BROWN: Thank you. There is one other spectator who would like to become a participant.

MR. CARMICHAEL: Thank you, Mr. Chairman. I am Lt. Carmichael from the DOD armed services blood program office.

Our office's job is to set policy for the Department of Defense, and ensure everyone's concern for the safety of the blood supply, and have implemented on occasion more restrictive screening and deferral policies and lookback

policies than our civilian counterparts.

Our office is strongly opposed to deferral of donors based on travel to or residence in a specific geographic area for an as-yet undefined time period, to reduce the theoretical risk of new variant CJD.

We believe further research is required to provide evidence to support the risk of transmission and the potential benefits of such a deferral policy, before such a policy is implemented. Thank you.

DR. BROWN: Thank you. Further comments? Further questions?

DR. WILLIAMS: One thing that we wrestled with a little bit in framing the question we asked was the extent to which British beef was distributed throughout the United Kingdom in the 1980s.

We assume that it was distributed extensively. If that is true, is it curious that the new variant CJD cases are clustered in England?

DR. BROWN: I must admit to you, I don't understand the question.

DR. PRUSINER: Or worldwide. You didn't say that.

DR. BROWN: Would you repeat the question, please?

DR. WILLIAMS: We are basically interested in information about the extent to which British beef was

distributed outside Great Britain. To the degree that those distributions occurred, are they in synch with the observed new variant cases.

DR. BROWN: As there is only one new variant case outside Great Britain, any correlation is going to be dicey. Go ahead.

DR. WILL: It is an important question. My opinion is that the relative exposure to BSE was very much higher in the United Kingdom than in other countries.

It is true that some food was exported to other countries, which may explain the French case. My personal view is that it is possible that there have been exposures indigenously through some cases of BSE in other countries which have already been commented upon.

Even so, I believe that the relative exposure of the at-risk population has been very much higher in the United Kingdom than in other countries.

Of course, one of the reasons for doing European surveillance is to determine the relative proportions of new variant CJD cases in other countries, should they, indeed, occur.

My final point is that the timing of exposure to BSE agent may be different in different countries than in the United Kingdom.

DR. BROWN: I had heard some time ago, Bob, a number of 20 percent for the consumption of beef in France. That is to say, 20 percent of beef consumed in France at that time was supplied by Great Britain.

DR. WILL: I think it is important to further define what do you mean by beef. I personally do not believe that the major risk of new variant CJD is through beef. My opinion is that it is through beef products that contain high titers of tissue. That is another issue that has to be considered in relation to exposure of other countries.

It may be that beef itself was exported to a range of countries, not only Europe. My own personal view is that the risk of beef is likely to have been very low, perhaps negligible, perhaps zero.

The question I would like to know is, was beef product containing categories other than meat exported widely. That has never been addressed.

DR. BROWN: And I doubt that anyone will ever learn the answer to that question. You might, for example, hypothesize that most of the cases of new variant CJD came from pate in which the mechanically recovered meat was a constituent.

The idea that you will ever find out how many kilograms were consumed in France to possibly explain the

single French case is just hopeless. It is the sort of thing that one will never know.

It seems to me that all we can say at a minimum is that British beef or beef products did find their way in a significant amount into France in the period in question.

DR. DETWEILER: The high risk that was presented just a little bit ago was from 1984 to 1990. I would assume that the 1990 was because of the SBO to humans in 1989.

If you look at the epidemic in cattle, it really did peak in 1992-1993. You have seen the figures on kind of the route of the ban and compliance, where it wasn't really very, very strict compliance until 1995 or 1996.

Not only with the SBO ban, but would you cut it off at 1990? My gut would be to go a little bit further than that. Are there figures for looking at how much it was enforced right away from 1989?

DR. WILL: I think there are a number of factors that interact. One is the efficiency of the introduction of the SBO ban.

It is quite clear, I think, that when it was first introduced, that the SBO ban was not really enforced, in relation to feeding those materials to cattle.

The general view is that the failures of the SBO ban mainly applied to cattle, not to human food. There was a

concern that some spinal cord had been left and there were measures and investigations of what was happening.

There were occasionally pieces of spinal cord being left, and that was done in 1995. That would go over into the human food chain.

There is a possibility, in my opinion, that there were small gaps in the SBO ban in relation to the human food chain. I personally don't think they were very great in relation to the SBO ban per se.

The other factor that is important is the distribution of infectivity and also the gathering of that has to be taken into consideration, which was not in the SBO at that time, and also the number of cattle that were in the latent stages of the incubation period, rather than the total number of infected cattle.

People have tried to work on this type of model to see what the relative exposures may have been. I think it is true that the exposure probably started in the early 1980s, may well have peaked in the late 1980s or the early 1990s, and then I think declined to a very much lower level.

I think there are a number of interactive factors that here. The other thing that I would say is that, of course, that many of the measures like the SBO ban or the SRM ban were not introduced in other countries in Europe at the

same time. Some came along somewhat later.

Of course, we also know that there may have been some recycling of the cattle feed in other European countries, because they had no need, perhaps, to introduce their own feed ban.

There is a view that currently the risks to the human population in the United Kingdom are negligible for BSE. That may not be true in other European countries.

DR. METTERS: On the question of the SBO ban, I think undoubtedly it wasn't the cause of the decline like that in 1989. If you look at it, it came down like that in 1989, when the ban was first introduced.

There was a tail, and there was another dramatic drop in 1996. The introduction was undoubtedly where the risk came down very, very significantly, and then increasingly, and then again, in 1996. So, it wasn't steady.

I think the real exposure was before the ban brought good controls.

DR. BROWN: Thank you. We are going to have a discussion on that. It is a question to any of the speakers, people who just spoke.

PARTICIPANT: I have a question for Dr. Williams. You mentioned, I believe, that there is data on the consumption of brain tissue. You didn't present any data on

that.

DR. WILLIAMS: I ran out of time before I got to show the last two slides. We asked the question, whether donors had --

DR. BROWN: Would you like to show those slides?

DR. WILLIAMS: I can do that. I think I can probably do it verbally. The question was to donors, whether they had eaten food or dishes prepared with mammalian brains, and then parenthetically we identified the animals of interest, namely, sheep, goats, squirrel, cattle, et cetera.

The responses to that question were 8.6 percent indicated that they had consumed the brain of one species, 1.6 percent had consumed two species, and 0.6 percent three or more species.

For this analysis, we had gradients of the individual animals involved. Those data are available, but we didn't put all that together for this meeting.

DR. BROWN: Is that eight percent of the 11 percent that visited?

DR. WILLIAMS: No, nothing to do with travel to Britain.

DR. BROWN: One in 10 people who traveled to Britain ate brains.

DR. WILLIAMS: This has nothing to do with travel to

Britain. This is overall.

DR. BROWN: In general. In other words, there are eight percent brain eaters in this country.

DR. WILLIAMS: This is a follow up to the letter in the Lancet, which reported a history of squirrel brain ingestion in five cases that they had observed over a relatively short period.

We felt that if this was the next emerging issue, that we should get some data on it.

DR. BROWN: I think that answers the question. Other public comments?

DR. SAYERS: I would like to ask Dr. Williams a question. There does seem to be some inconsistency here. On the one hand, we are looking at how we might introduce new strategies to prevent something that hasn't happened, namely, transfusion transmitted CJD.

Then, what we are being given is information on how to tussle with that conundrum. You showed us that 1.9 percent of donors should ostensibly not be donated. That could be something that could be revealed at the time of donation.

If you take that against the background of the risk for HCV and HIV, it is one in 100,000 for the transfusion recipient.

I am wondering, what is the relevance to that

information that you gave, the 1.9 percent that should be deferred at the time they presented.

DR. WILLIAMS: As you know, that is an area that we have been working in for several years. It is a difficult population to reach, those who deny an infectious disease related risk factor for one reason or another at the time of donation.

This is undoubtedly is the source of infections that do occur. We find that time and time again on interviews with individuals who are found to be seropositive at the time of donation; that they, in fact, also had risk factors that should have prevented donation.

Quantitatively, certainly, given the numbers, it is a larger issue. Also, on its own, it is a very difficult issue to address.

I think the National Heart, Lung and Blood Institute is looking at potential initiatives to look at the behavioral side of some of these issues in the future.

DR. BROWN: Is it fair to say that probably most of those people who shouldn't have donated blood would be found to have not revealed things by virtue of embarrassment.

DR. WILLIAMS: There is a wide range of reasons why this happens. Most of the data come from interviews with seropositive individuals.

Some of it is due to embarrassment, a perception of a lack of privacy at the time of screening, discomfort with the person doing the personal interview.

We know that some individuals come to the blood bank seeking an HIV test, and they are there for their own reasons and go through the donation process on that basis. It is a wide range of reasons.

DR. BROWN: So, until visiting Great Britain carried a pejorative implication, probably the same two percent would be much lower.

DR. SAYERS: In the interests of public disclosure, I have to admit that I did have a tourist relationship with Britain. I would hate to think that that is going to provoke a lookback or recall on my previous 20 years of donations.

DR. BROWN: That reminds me to say that I am sort of hoping we are going to enter the open discussion now. I hope the community will not approach it the way it has been in some ways recommended, with really preordained opinions, either a blanket yes or a blanket no.

Personally, I came to this meeting with quite an open mind. I really don't know how the committee is going to move on this.

I hope it is not that we give up because we can't possibly define lines, although it may come to that. I will

now open the committee discussion and close the public discussions.

AGENDA ITEM: Committee Discussion and Vote.

DR. BROWN: I would like to, with the speakers present, ask for definitions that this committee can use in its considerations, definitions of three different kinds.

If we just look at questions that we are being asked to answer, I hope the questions that I am asking are questions that other members of the committee would want answered, too.

Under the first broad question, the sub-heading A, should the FDA recommend excluding donors who have resided in the United Kingdom or other BSE country.

I would like somebody to make it clear to this committee what the committee should consider, for purposes of answering this question, other BSE countries. That is the first question.

The second question is about B, periods of higher versus lower risk. As long as we have our speakers here, I would like again, the committee to come to some agreement about what a period of higher risk versus lower risk is.

There were some questions raised just a minute ago about extending that 1990 out beyond it. We can't answer the question until we all know what the terms of the question are.

The third question is concerning, under two, the

word possible. You heard the criteria from Dr. Will this morning about what is considered a probable case of new variant, and a definite case of new variant.

The word here is possible. I would like the committee also to have a clear understanding and an agreement about what we are considering possible diagnosis of new variant CJD.

These are the questions of clarification that I would like answered at the outset. Obviously the committee will have many other questions about many other things.

MR. SUDIERY(?): My name is Sal Sudieri. I am the vice president for medical affairs at the New York Blood Center.

Regarding this section A, there is a piece of information that I think is important for you to have.

For the last 25 years, the American Blood Center has had a program with Switzerland, Holland and Germany, where centers that produce plasma derivatives in this country collect units of whole blood from volunteer donors.

They became licensed centers, collection centers, from the New York Blood Center, by our FDA license, and they will ship us the red cells, where we do the processing, dedicate the plasma and the plasma is fractionated.

About 30 percent of the blood, or about 200,000

units of red cells a year, come to New York through this method.

DR. BROWN: Is the committee happy about what everybody considers and knows to be an other BSE country or do we want to get clarification of that?

DR. LEITMAN: Clarification.

DR. BROWN: Are we talking about the United Kingdom plus France, plus Portugal, plus the whole of Europe? What are we talking about?

DR. LURIE: Who is to make that decision?

DR. BROWN: That is what we want to know. Is that a decision that is going to be made? If they can't tell us what is meant by other BSE country, we can't really answer the question.

DR. LURIE: The procedural approach would be to vote on it separately. I think the vote is more providing guidance.

DR. BROWN: Good suggestion. Ditto for periods of higher and lower risk, I suppose, and ditto for possible versus probable. We can move along in that way. That is a good idea.

DR. LURIE: Another parallel type suggestion would be, I think the question that we do need some clarification on is the definition of reside.

While obviously it is more efficient to exclude residents from Britain and visitors from Britain because, a, there are presumably fewer residents than there are visitors, and the duration of exposure and presumably severity of exposure would be different.

DR. BROWN: Maybe the best way to do it is to go piecemeal and nibble, in which case we might, for example, phrase the first question, should the FDA recommend excluding donors who are British citizens and see what you get in answer to that, and see just how far the committee is willing to go.

On the other hand, that is going to require about 117 votes this afternoon.

DR. HOEL: There is another approach. First, we have to answer the first question first.

DR. BROWN: I know. That was going to be my next point. Depending on our answer to one, we can either dismiss A through E or take them up. I think that is why Dr. Epstein phrased these two questions in this way. Maybe I am wrong, but that is the way it is going to be done.

If the committee is ready to vote without further discussion on question one -- not A, B, C, D and E, but just question one as a question -- we will then vote and see what we then have to do, or we can have a little, a moderate or a large amount of discussion before we get to that.

DR. LEITMAN: I have always had a problem with reducing a theoretical risk or reducing a hypothetical risk or reducing a potential risk, because perhaps, as I was talking to one of my colleagues earlier today, perhaps it is a speculative risk and not a theoretical risk that, in actuality, hasn't occurred.

How do we reduce speculative risk? How do you reduce zero?

DR. BROWN: That is an interesting kind of semantic question. It is the virtual reduction of a theoretical risk. Does anyone want to get into semantics?

DR. CLIVER: Clearly question one turns on the perception of nvCJD as a food borne disease that is somehow derived from cattle.

I think I am prepared to accept that. The period of emphasis ending at 1990, though, I think is not indicated. The observations that Dr. Detweiler had before, the data on this would have been very valuable for risk on people on farms, however, there is no imputation here that the risk was associated with people on farms with cattle.

I am not convinced that I have heard anything definite to explain why the distribution pattern is seen within CJD.

At the very least, I have seen that as more and more

cattle were in fact in stages of incubation, that the risk had to be higher in 1992 or 1993. That would not have been an appropriate cut off for risk to consumers.

Beyond that, how long has it been at risk, I think, is adding a dimension to our certainty, that we would not be able to deal with this with any of the knowledge at hand.

If we can't say that even being there is a risk by two weeks or two years or whatever, it doesn't make any difference if you are a citizen or if you were stationed there for two years in the military.

We can't put that dimension on this and expect to gain anything by it at this point, because there is no data base on which to quantify risk with time.

On the other hand, something that I have not heard mentioned that I thought was very significant -- again, I didn't have all the facts, and that is why I was hoping that our UK experts would still be with us -- is that as we look at the species barrier and what presumably resulted in transmission of BSE over sentinel groups, they have been cats; not dogs but cats, were getting spongiform encephalopathy, presumably as a result of exposure to BSE, or ingesting BSE tissues before any nvCJD was noticed.

It would seem to me that in all probability the cats were getting -- I don't know if it was only in the United

Kingdom -- a higher proportion of the beef products.

On the other hand, depending on the social acceptability of experimentation in cats, one, the incubation period is shorter, and two, they aren't carnivorous enough that they would probably be willing to eat any part of a BSE carcass that they were fed, whereby some of these uncertainties about which tissues carried the infectivity could be dealt with, using cats as surrogates rather than rats and mice, or gerbils and mice, or hamsters and mice.

Anyway, I think that to the degree that our decisions here may turn on our perception of how BSE is transmitted to humans via food, we need to be asking some of these questions that I haven't heard asked so far.

DR. BROWN: The British may want to add another dimension to it. One of the things that wasn't gone into as background material for your understanding of this issue is that cats and zoo felines and zoo ungulates and other animals that died from exposure to BSE, were dying from that exposure not as a result of being infected with meat, but being exposed to nutrition supplementation from meat and bone meal made from rendered carcasses.

DR. CLIVER: One point is that even if they were getting beef products rather than beef, quite clearly they were not as exempt from the species barrier as, say, dogs are.

Therefore, one could use comparative eating trials with cats using different parts of the BSE carcass, to determine where the infectivity lies.

DR. BROWN: Where the infectivity lies --

DR. CLIVER: Is it in blood, the periphery -- how are we going to evaluate how much of this --

DR. BROWN: They have done better than that. They have used cattle.

DR. CLIVER: I am not sure that is an analogy.

DR. BROWN: It avoids species barriers considerations all together.

DR. CLIVER: Clearly.

DR. BROWN: In cattle, the distribution of infectivity is very limited and doesn't include blood. Now if you inoculate mice or you inoculate cats, you could do a whole systematic study species by species.

If you are just concerned with species barrier, that experiment is done, inoculating cattle specimens into healthy cattle.

DR. CLIVER: I was not concerned with species barrier. I was saying, when the species barrier becomes moot, we can take different parts of the BSE carcass, including voluntary muscle, if you will, and compare that with the alleged contaminants to voluntary muscle. A cat would be an

ideal -- well, you could do it in cattle if you wanted to do cattle, but I don't think the analogy fits there.

DR. BROWN: They have been exposed to or inoculated -- well, I don't know -- you can tell me that better, probably. They have been compared with all of these things that you have mentioned, including muscle, including brain.

To date, the only infectivity in cattle assay in cattle was found in the central nervous system, the retina, the intestines, possibly bone marrow, and the blood brain barrier.

DR. WILL: Perhaps I could just say, I think what you have said is correct. The experiments we have set up for cattle to cattle transmission, the results are not through all tissue.

DR. BROWN: Not totally, but they are five years down the line.

DR. WILL: No, they are not. That is the problem with this. The original indicator animals we used, the mice as you know, and the cattle to cattle experiments, have been set up.

DR. HUESTON: The cattle to cattle were taking the tissue and intercerebral inoculation in cattle are underway, but not all tissues. It is a massive undertaking and they have started with what are considered to be the high priority

tissues.

I think the longest of those -- I think they are 18 months underway.

DR. WILL: The real critical question is that any experiment that can be done in any animal species that will tell you what the species barrier is between bovines and humans, I am afraid I do not think that is the case.

There is no way of directly measuring the species barrier because you have to do experiments in humans.

The hope is that the transgenic mice experiments might get over the species barrier and might allow a more sensitive measure of what the species barrier is.

I think as far as the feline spongiform encephalopathy is concerned, the presumption is that it was due to exposure to high titer bovine tissue in pet food. That was the cause of the epidemic.

I don't think that necessarily, in my opinion, does tell us anything about human disease. I hope it does, because there has been a relatively limited epidemic as far as the cat population, which is a carnivorous population.

It looks like it is going away, despite extensive exposure. That may be true, that in humans the same thing will happen.

I don't think that we can measure the species

barrier between bovines and cats, and even if you did do that experiment, it would not tell you what the species barrier was between bovines and humans.

DR. BROWN: It could be transgenic mice, as you said, and preferably non-human primates, and hope the results in both those kinds of animals converged.

Let's get back to the issue at hand. Are there other questions about number one? Forget the sub-letters.

DR. BURKE: The question on the table -- I am uncomfortable with the idea of weighing benefit for cost and that is fine; we don't have to worry about the dollar cost.

I am very concerned about trading benefits for other kinds of costs in other diseases. One of the things that I was concerned about in your data, it appeared that you had a five or 10 percent change in the demography of the donor pool.

Then you would shift it to a population that had a much higher incidence of hepatitis C or HIV. So, the net effect of this five or 10 percent change in the demography of the donor pool might have a marked increase on these other things.

Did you actually calculate that, or do you have any models on it?

DR. WILLIAMS: I think the first comment, I don't think it is a change in five to 10 percent in the demography.

It is a change in demographics of five to 10 percent in the donor population.

We did not at this point attempt models. Number one, these are preliminary data. The survey isn't complete yet.

To do that in a meaningful way, you probably need to use multivariant analysis, consider donor age, race, and probably three or four other factors before you could really equate that with any change.

DR. BURKE: I fully agree with that. The first glance at that data that you provided strongly suggested that there would be a change in the donor pool, and that that might, in turn, have a net negative effect, rather than the positive effect that was sought.

Is that a reasonable interpretation that needs to be investigated?

DR. WILLIAMS: I agree with that.

DR. PRUSINER: I would like Dr. Metters to respond to this. Let's say that we did not -- we voted no, so we voted against deferral criteria.

Then I would like to respond to how the United Kingdom would receive that. Would they still be very happy with plasma and plasma products coming from this country.

Then I would like him to respond to the issue of,

let's say we define residence as an accumulation of one year of time in the United Kingdom during that six years, and then we voted again no on deferral. What would you think.

The question is whether to extend what they have done in Great Britain to the United States.

DR. METTERS: In answer to the first question, we always recognize that in resourcing plasma from non-UK sources, whatever those non-UK sources might be, there could be in the donors people who have been in the United Kingdom and have been exposed to the same risk as UK citizens for a variable length of time.

We always recognize that we could not say there will be no donor contributing plasma to a non-UK source pool who has never eaten beef in the United Kingdom pool who has never eaten beef in the United Kingdom.

The number, the proportion of those who would have eaten beef in the United Kingdom and then donated in the United States or in Europe, for example, if we were getting plasma from Europe, would be small in comparison to the total number of donors that would be in the United States or elsewhere in Europe.

Our policy is one of risk minimalization, to the extent that it is practical.

To say to a center providing us with plasma that you

must take out all those people who have been resident in the United Kingdom for any length of time, is simply not something that was reasonable or practicable.

So, I come back to the point, this is minimalization, and we recognize it isn't total avoidance, because the total avoidance is not possible.

To your second question, I think it is entirely wrong for us in the United Kingdom to tell you what you should do. I would rather not voice an opinion.

If I do, I will be accused of taking the United Kingdom's interests above those of the United States, which I decline.

DR. BROWN: That is very kind, Dr. Metters. The reverse has not always been true.

I think the question of time of exposure is a legitimate question and a legitimate consideration. I have always thought of the time of exposure in terms of risk as not being related to something like radioactivity, where there seems truly to be a cumulative risk.

A cumulative risk, it seems to me, with respect to TSE and most other infections, is a game of Russian roulette.

That is, one hit and you are dead. The question is, what are the odds of getting a hit. It is like a six shooter. The question is whether it is a six shooter or whether it is a

stet gun with 100,000 bullets in it, 100,000 chambers, only one of which has a bullet. I think that all we need is one bullet. The question is when are you are going to get it. The longer you are exposed to the possibility of getting it, the greater your chances of getting it.

DR. SCHONBERGER: I would like to remind the group that in the study of human growth hormone, the one risk factor that we worried about identifying was the duration of treatment.

DR. BROWN: Exactly.

MS. HARRELL: This may be totally unrelated to what you are now contemplating, but I had a question about maternal transfer or maternal transmission of new variant CJD to an infant or to a fetus.

DR. BROWN: You are talking about new variant?

MS. HARRELL: Right. Is there a case?

DR. BROWN: The question, Robert, is there any instance of maternal transmission of new variant CJD?

DR. WILL: The answer is no, although tragically, at least one of the individuals was pregnant when diagnosed with new variant CJD.

MS. HARRELL: Was she delivered?

DR. WILL: She did delivered. The child is alive and well, but we are only talking two or three years. Of course,

therefore, we rely on previous evidence, which does not suggest that there was maternal transmission.

DR. BROWN: It is an interesting question. If it were to have occurred, it would be one more very striking example of a particular biological behavior of new variant from sporadic.

We have information about half a dozen children born to patients who were sick with CJD on delivery, who now have -- they have lived for as long as 30 years after that event -- that is, after they were born -- and are quite healthy.

So, in sporadic CJD and in experimental CJD, all the evidence is against maternal transmission. It would have been very interesting, had it been different.

DR. HOLLINGER: I thought there was some data -- perhaps Dr. Will can answer it -- but I thought there was some data of transmission of BSE to the offspring.

DR. BROWN: That is a can of worms, Robert; I will give it to you.

DR. WILL: There was a thing called the cohort study, in which a certain number of calves that were born to BSE-infected animals were put on a farm, and a similar number of animals from non-infected BSE animals were put on a farm and we waited to see what happened.

It sounds like a simple experiment. You compare the

frequency of BSE in one group to the other group.

Of course, there was a clear evidence of an increased risk of BSE in offspring of BSE-infected animals.

However, the experiment was set up at a time when there were still potential feed exposures to BSE agent.

The relative risk in the cohort at various times from 1980 to 1989 seems to decrease with each cohort, depending on whether they have food exposure.

So, it is a very difficult experiment to interpret. All I can say is that the information was reviewed by I think six different epidemiological groups and expert people in the United Kingdom, and the conclusion was, there might be maternal transmission in about 10 percent, and there might be genetic inheritance of susceptibility to feed or something of that sort. They didn't reach any definite conclusions.

I think the answer is the experiment was perhaps necessarily flawed because of the way it was set up, but there may be some evidence of maternal transmission of BSE.

However, if that were the case, its volume does not not suggest that we extend the duration of the epidemic in cattle.

DR. BROWN: Thank you. I think we will terminate maternal transmission. It really is flawed. The main focus, since there is no evidence for it, we can't say for sure. It

is certainly one of the unknowns. It is unlikely, but it is unknown.

DR. ROOS: Just a couple of comments. To review, it sounds like we are not quite certain whether blood is contaminated or not in the new variant.

We are not quite sure about the efficiency of the transfusion as far as a route of transmission. It looks like fractionation certainly helps as far as decreasing infectivity. So, basically, when you think about a 10 percent decline in donor acceptability, I have got a concern, just from my own personal perspective, in neurological patients that I have, the current availability of IVIG is in question, and if a patient asks me why she was spending so much more money for IVIG than she had in the past.

Looking now, not at both travel and residence, but just residence in the United Kingdom, my concern has to do with recall.

If we decide, okay, we are not going to accept people who have resided in the United Kingdom, what is that going to do with the levels of the donor pools. I have a question after this and that is, does it make sense to look at residence in the United Kingdom, those individuals, and maybe exclude them from the plasma pool, but allow them with respect to labile blood products.

Does that make sense? Then we don't have the stigmata -- does that make sense?

DR. BROWN: That made sense to Dr. Epstein and that is how it was phrased. The first question, overall, has to do with donor deferrals. The second question has to do with withdrawals. It is an issue and the questions are separated.

DR. ROOS: I am just taking it, allow them to donate but only use the blood for labile blood products, rather than for the plasma, the exclusion of residence in the United Kingdom.

DR. BROWN: Okay, let's archive that and keep it in mind.

DR. HOLLINGER: The first question has to do with an exclusion. A screening test -- I would ask the expert panel here anyway, to get some feeling for whether this is available or something near in the future in terms of screening test, and the practicality and so on, for the new variant CJD or anything else, in terms of bloods.

DR. BROWN: I think this is a very interesting subject. There are several labs working on it. It is at least a half hour for that, and I think Stan would agree with me, today, as we speak, and when we make a decision, there is no screening test.

Now, whether there will be one next month, next year

or five years from now, we don't have one now.

DR. LURIE: I want to get back to Don's question. Really, as I understand this, we are balancing what we might call theoretical -- for lack of a better expression -- risk is against two possible other risks, that of blood or blood product shortage and the other would be that of changing the donor pools in such a way that it is disadvantageous.

It seems that the first part of this is extremely difficult to quantify, in fact, probably not quantifiable all together.

We should try to quantify what is going on at least on the other two side of the equation.

I am frustrated that we don't have an answer to Don's question because it does seem like an answerable question.

It does seem like an answerable question. We should be able to have a sense, based on the likely changes in the pattern of the donor pool, quite what the increment of the risk for hepatitis B and HIV would be.

My guess is that it would be actually quite small. We started off with risks, depending on the infection, of about one in 500,000. We have an excluding procedure that, while imperfect, it is probably more likely to yield accurate odds with respect to whether or not you get improvement than

whether or not someone engages in illegal activities like injection drug use, or sex with another man.

It seems to me that -- I am frustrated by the lack of that. My guess is, having said that, that the increment with regard to the HIV, HBV, et cetera, would be some very small number, not one in a million, perhaps, but perhaps something lower than that. Does anybody want to comment on that? Dr. Williams, can you comment on that?

DR. WILLIAMS: Again, I hesitate to quantitate something without doing the math and running the models. I agree, it needs to be done.

I think you are looking at something that impacts 10 percent of the donor population. The numbers as they exist, the incidence is quite small in the donor population as a whole.

We are looking at 10 percent. I think you are probably right. Quantitatively, it is small, plus the industry is moving toward genome amplification testing in the near future, which will reduce risk further.

Without doing that, I think we can't put a number on it.

DR. NELSON: Right now, without genome amplification, the estimate is that there might be 20 to 50 transmissions per year of HIV, people in the window period,

and that is more than one in a million, but there are 12 million donors.

If we were to increase that by 10 percent, that is likely to have a total adverse equation when we relate that to how many new variant CJD cases we might prevent, when there have been none so far related to transfusion.

As soon as there are one or two or three cases, the equation changes. We have to do it with the data we have now, even though we know this is a long incubation period.

Nonetheless, there have been cases of food borne new variant CJD, and so, you know, it is not inconceivable that had transfusion been a risk, that we would have seen the cases already. It seems logical to me.

DR. BROWN: Of CJD?

DR. NELSON: Of CJD. So, it seems to me that the equation, that we probably would have maybe five more cases of transfusion transmitted HIV using the current screening test, from if we went to first time donors, or something like that? Would you agree with that?

DR. EPSTEIN: I apologize. Could you repeat the last question again?

DR. NELSON: I think we would have a handful of HIV transmissions if we went to increase the first-time donors by 10 or 15 percent, not a large number, but there would be some.

Hepatitis B, hepatitis C, together there would be 20 or more transfusion transmission infections.

DR. WILLIAMS: The problem is that you know both donor and recipient transmissions, the confidence intervals surrounding these things are so broad that year to year it is just really difficult to tell if there is a change or not that is real.

DR. BROWN: I would like to address sort of questions taken from Drs. Epstein and Weinstein. You see what you have done, in wanting us to consider both sides of the equation, which is what is happening.

If you want us to continue considering both sides of this equation, we will do it, because we are at your service. You see what is happening.

We will do whatever you want, but if we are going to continue doing both sides of the equation, we are not answering your questions.

DR. EPSTEIN: I guess the problem for the FDA is that we have to factor into our thinking all the possible consequences of a change in policy.

The reality is that we have an inelastic donor pool, that we have product shortages, and then we have some predictable large impact on the donor pool, that leads to some more extreme versions of the deferral policy.

I think that to the extent that the committee can give us a recommendation which is global, that is very helpful.

To the extent that it can't, an opinion on scientific grounds, whether donor deferral would be of scientific value, would itself help.

We will be left with other questions, but we will be left with other questions regardless. I would say that if it is your sense as chairman that we are not going to be able to get to a point of advising the agency, if we press the issue of balancing the risks, then I would say that, although the question won't go away for FDA, let's deal with opinions on the separate parts.

Let me also say that I don't think the committee needs to be tightly locked into the questions that the FDA framed.

We framed them a certain way because that is how they appeared to us. I think that if the committee members can conceptualize the issue or perhaps break it out in a different way, that is fine.

Just make sure that whatever you vote on is recorded in writing, so we know what you are voting on.

I do think the up front question is whether we should have donor deferral policies at all. I think that is a

clean answer.

If the answer is yes, then we get into the more difficult problem of how do we apply it. Do we apply it only for plasma? Do we apply it for plasma refractionation as well as for whole blood? Do we distinguish residency for greater than some period? Do we limit it to the country with highest known risk, et cetera.

I think those can be essay questions, if you will. We can listen to opinion around the table and not call for votes, because it will get very complicated if we need to revise the question.

I am sympathetic to the observation that it is very hard to balance risk. I know that; that is what our jobs are all about at FDA.

If it is going to confound reaching closure on any of these issues by the committee, I would say, let's set that aside.

DR. BROWN: Yes, that is like the prosecutor who asks an outrageous leading question and the judge says, that is overruled; jury, don't pay any attention to it.

There is no way that this committee can just consider the scientific evidence of new variant CJD and come to a decision on it. So, we might as well open up the whole can, and everybody will take these things into consideration.

The question is, since we have virtually nothing to do on with respect to making a judgement on new variant CJD, should we concentrate on the right side of the question, which is prospective shortages and increase in other infection.

Evidently we can't do that either, because we don't have any solid data on what other infections are doing.

DR. HEALY: In fact, we do have something. There are already shortages. We are already rationing blood for reasons that go beyond just DJC deferral. It will get worse with any measurable impact on the size of the blood supply, whether it is CJD or anything else. We are already rationing product based on lack of donors. It will get worse.

DR. BROWN: I am sorry I didn't recognize you. Maybe we should have an initial vote that we should even address the issue of FDA deferral criteria for new variant CJD.

I mean, the subject of new variant CJD; maybe that is the first thing we ought to find out, whether the committee thinks it is worthwhile even to consider deferral criteria for new variant CJD, period.

Let's have a vote on that, on question one. We are voting on question one. If we say no, we are not taking the issue any further. If we say yes, then we will. Very well,

we will have a vote.

You may vote. You may choose to abstain. That is to say, you may have a yes, a no, or an abstention. Barbara, this is a vote.

MS. HARRELL: I hate to be in this first seat, to start it off.

DR. BROWN: Do you want me to start at the other end?

MS. HARRELL: I have got to do what I have got to do. It won't change.

I will start by saying that the reluctance to reduce the repeat donor pool to reduce the theoretical risk of HIV allowed that disease to become epidemic in the United States.

Also, being the consumer rep on this panel, I also must give great weight to the wishes of groups such as the one represented by Mr. Richard Vogel, and also to address the concerns of those who took the time to write to this panel.

For those reasons, I vote yes to question number one.

DR. BROWN: Very good. Ms. Harrell votes yes. Dr. Leitman.

DR. LEITMAN: My vote is a very clear no. I am influenced by two considerations. One is that the risks right now of nvCJD by transfusion is zero. Everything we have heard

this morning says zero.

If we increase the donor population by 10 percent first-time donors, the rates of transfusion transmitted viruses will not be zero. It might only be five, 10 or 20, but it won't be zero. I find even a single case unacceptable as a trade off.

My second consideration is that nothing is demonstrated in the cellular endocrinology literature.

I think this is true. Paul, correct me, taking the blood of a laboratory animal in the pre-clinical stages of disease and infusing it intravenously into another laboratory animal has never resulted in disease in the second animal.

It is cerebral to cerebral, cerebral to blood, blood to cerebral. Blood to blood, when blood comes from the preclinical -- I thought it was from you.

DR. BROWN: I think Bob's single case is a clinical case; is that not so? That is a clinical case.

DR. LEITMAN: So, the transfusion correlate is a preclinical donor, donating blood from blood into the recipient.

DR. BROWN: It is more correct to say we don't know. We don't have preclinical intravenous experiments.

DR. ROHWER: Six of the animals were preclinical.

DR. BROWN: We don't have any data. We don't have

any data on anything that we are talking about.

DR. LEITMAN: It is a no.

DR. ROHWER: Paul, could I make one more comment? It is also important to realize that there is no difference when we have a blood infectivity in preclinical animals and clinical animals. We found infectivity both times.

Because we really have only looked at a very small number of animals because we had a small amount of blood, I am not sure you can say anything about it.

DR. BROWN: You would still vote no, even with that said? Larry?

DR. SCHONBERGER: I, myself, agree with Susan about not wanting to create any real risks in an effort to try to avoid some theoretical risks.

I also find that Barbara's concern about the theoretical risk is reasonable because of all the absence of data.

So, I am going to vote yes, but say that when we do make our recommendation, that we do it in such a way that we absolutely minimize the concerns that Susan was concerned about.

I think that there are probably some ways that we can do that. One way would be that we develop criteria that would never lead to withdrawals, withdrawal of derivatives. I

think that has a very negative effect.

Concentrate on the screening, and that screening criteria be designed in such a way that it gets repeated and reviewed, and that it maximizes the incumbency of the cases that are, in fact, occurring.

We need to find some criteria that covers as big a group of the cases that are occurring -- which for example might be right now like five years' residence in the United Kingdom between the period, say, 1980 and 1995, the period of risk that we are talking about.

Virtually all the cases in the United Kingdom would meet that criteria and that would give us an effect on our system that would be considerably smaller than the type of data that we heard in the questionnaires.

Again, we are not talking about a complete and total avoidance of the problem; we are just sort of adjusting to ameliorate it.

DR. BROWN: So, the vote itself is yes?

DR. SCHONBERGER: Yes.

DR. BROWN: The vote itself is a yes vote with a suggestion for a lot of discussion. Okay.

DR. PRUSINER: My vote is yes and I will say it in two sentences, so I won't prolong this. I think we have such an imperfect understanding of what is going on, what concerns

me the most is that when we look at animals, just so everyone is clear about this, in the preclinical phase, when you look at every single lymphoid work, the spleen, the thymus and lymph nodes are positive.

The titers in those organs are the second highest in the animal. It is the brain, and only the brain, that is higher.

I think there is a lot of concern here. I am still concerned about what to do about sporadic CJD. I don't think that this reversal is exactly the right thing to do.

I don't have a perfect formula, and I agree with Larry, the things he said. I won't repeat them.

DR. BROWN: So, your vote is yes, we should.

DR. TRAMANT: I voted yes as well, for comments that were made. Ultimately, hopefully we will get a test that will allow us to make a rational decision.

At this point, it is how much risk do you want to take. I think the risk at this juncture should be on the side of conservatism.

DR. ROOS: I vote yes. I agree with what Larry said. There should be other ways to minimize the impact on blood.

For example, as I mentioned, take all comers, but exclude residents for pooled plasma, taking them for blood

donations, really a similar situation to what is presently being done in the United Kingdom.

DR. HOLLINGER: My vote is no. I believe that we should continue to monitor very closely what is going on in England in terms of transfusion associated disease, but right now I don't see any particular risk that would be contained by that. I vote no.

DR. HOEL: I would also vote no. I don't think the numbers come together here, particularly this idea of 10 percent differences in the two populations, the 10 percent residents here. I think I might exclude long-term residence, but I would not come close to approaching this 10 percent exclusion.

DR. BROWN: Okay, that would be no, a no, but. It sounded like maybe a no to one, but a yes to 1-C or something like that. We will take your stipulated no.

DR. LURIE: I would vote yes, but I would like to get to vote on some of the more specific issues here. I think there are ways of reducing risk that are not as egregious as a 10 percent reduction in the donor pool, or perhaps as large as a 20 percent increase in viral transmissions.

I would also like to say that it would be -- just to reiterate the notion, some of the sort of part of the equation is unquantifiable.

I think I would like another option, to have people go back and actually do their homework for us on, a, what the impact upon the donor pool would be and, of those 10 percent of people who have been to Britain, what percent of them have been there for a substantial period of time.

I think the answers to both of those questions would allow us to tailor any subsequent recommendations in ways that could minimize the risks in terms of the blood pool and the viral transmission.

DR. BURKE: I would vote no, but I would have a couple of different thresholds for voting yes sometime in the future.

Those thresholds would be the appearance of a blood transfusion case in the United Kingdom and/or the first case of new variant disease in somebody who had traveled or been a short-time visitor to Great Britain.

At this point, having not heard any of either case or any of those evidences, I vote no.

DR. BROWN: I vote yes. I have exactly the same feeling as Donald, but I am coloring it by the fact that there is a long lead time between cases and what you can do something about.

I think there is an outside chance that there may be a wild epidemic of new variant CJD in Great Britain.

If there is, I think we will look back and very much regret that we didn't take that into consideration when we had a chance to.

I will subsequently, in the discussion, if the yes votes hold, be prepared to tailor that and restrict it very much in terms of residence, for example.

I would throw out all the visits at this point, and simply exclude the residents of Great Britain, or long-term residents; not necessarily citizens, but long-term residence. I don't think that is going to reduce the donor pool very much at all. So, the vote is yes.

DR. CLIVER: I vote no. I have heard some very elegant research on hypothetical modes of transportation.

I haven't seen anything that I thought was really modeled for oral transmission to humans, and since every sub-point here comes down to our perception of the infection, we aren't modeling it, I don't think we have any indication that this is a problem.

DR. NELSON: I vote no. Like Don Burke, I am certain I would rapidly change my vote if there was a case in factor VIII with hemophilia or a transfusion transmitted infection.

I am concerned about the possible differences between new variant and classical CJD. There must have been

many exposures from blood transfusion and blood products over the years of classical CJD and there has never been a single case that has been identified.

Again, this is a new disease and I may be wrong, but so far, I don't think the evidence supports the exclusion.

Hopefully there may be a screening test in the future that might be more specific. It is always a problem, using the geographical exclusion.

DR. DETWEILER: I vote yes. I think there has been so much work on the field of TSEs since the mid-1980s.

There are two reasons. One would be, more times than not I have heard with these diseases, especially BSE, we have to wait until we get all the evidence.

Unfortunately, with the long incubations, by the time we get all the evidence we are usually five to 10 years behind the curve, so you should have done it yesterday.

The second is, something that was done with BSE and scrapie, scrapie was not known to be a human pathogen, and we heard that all the way through. It is not going to be, it is not going to be, it is not going to be, or there is no evidence that BSE is a risk to human health.

That went on in the mid-1980s all the way up to 1996 when it was made public. Again, there are some reasons.

DR. HUESTON: I vote yes. I think the question

provides the flexibility to be more responsive when data is not available in the scientific evidence.

I am concerned that a vote of no by the committee may hamstring the agency in terms of its ability to respond to new evidence.

I would, however, agree that I think the yes ought to be qualified, based on the lack of data.

DR. BROWN: The tally is nine votes yes, six votes no. The yeses carry. We will continue therefore to consider the various questions that one raises.

DR. SAYERS: As a non-voting individual here, that, however, doesn't prevent me having an opinion. I would like to give an opinion on this previous question.

DR. BROWN: Absolutely.

DR. SAYERS: Speaking to this issue as a blood banker and as a consumer, more than 20 years ago when Congress had other things on their slate, they actually endorsed what was referred to as the national blood policy.

The national blood policy addressed issues such as volunteerism, paid donors, distribution, and it also addressed availability.

I think it said something that we could well consider still today. I am not sounding hysterical when I say that the national blood supply is teetering on the brink of

inadequacy.

For us to entertain even a five percent additional donor deferral rate to prevent something which, as I said before, has not happened, is going to be a national experiment doomed to failure and it is going to jeopardize patient care.

I feel I am saying this against the background of a lot of really, truly elegant science, but it is science which is totally removed from the whole issue of donor improvement, and the recognition on the part of a few of us that we are not meeting the challenges of donor recruitment, in spite of putting our best efforts toward it. End of sermon.

DR. BROWN: I think now we can talk about who, when, where, why and what. The first question is, in the consideration of deferral criteria, can we briefly, I hope, discuss first of all, the question that is phrased here under A.

That is, are we going to consider just the United Kingdom or the United Kingdom plus other countries.

If we can get through that, we can start on the next possibility.

DR. ROOS: Can I make a motion? Let's just confine it to the United Kingdom and not to other countries.

DR. BROWN: Okay, is there a second to that?

[Motion is seconded.]

DR. BROWN: I think we will have a hand vote on that. We don't need to go around the table. Everyone who would like to confine the at least immediate following discussion to a consideration only of Great Britain or the United Kingdom -- which is slightly different from Great Britain -- the United Kingdom, rather than the United Kingdom or other BSE countries.

In other words, we are now only talking about the deferral criteria with respect to the United Kingdom. All those in favor of limiting the discussion to the United Kingdom, raise your hand.

[15 hands raised in favor.]

DR. BROWN: Unanimous. Shall I push my luck and say, from here on in we are only going to be talking about the United Kingdom, and that we can therefore -- can I interpret from this vote that we no longer wish to consider other BSE countries? Okay.

Then we will cross off other BSE countries and we will answer yes to the question, should we -- well, we have said we are just considering the United Kingdom.

So, now question A becomes: Should the FDA recommend deferring donors who have resided in the United Kingdom. Now we come to the word resided. What are we going to talk about in terms of time of exposure, is the next

question. Do I hear an opening remark?

DR. LURIE: May I make a suggestion? For myself, I usually see a distinction between residing and visiting.

I suspect that if one were to do a survey, which is what I am in fact suggesting, of what the visit patterns and living patterns are, of donors who have been to Britain, we would probably find they are two quite distinction populations, I would think.

My guess is that with such a survey in hand, one could make a rather nice cut that would remove most of the risk and retain most of the donors.

DR. BROWN: I think you are right. Does anyone want to hazard a time cut that could be rational?

DR. HUESTON: Two weeks.

DR. BROWN: I hear two weeks.

DR. LEITMAN: I just want to say, this is so arbitrary.

DR. BROWN: It is.

DR. LEITMAN: Now all you are doing is playing perception against the ability not to jeopardize the blood supply.

A change of the perception of the American public that we are going to do something that would increase the safety of the blood supply, again, I think that is perceptual,

versus our true desire not to jeopardize the supply.

Given my feelings, I would say a year. I can see why we could say two weeks. As you said before, it is probably a Russian roulette hypothesis. It could happen in a single hit. You just increase the likelihood of that hit, the longer you are exposed to it.

DR. BROWN: I can see this carried to its logical extremes. I can see all kinds of possibilities.

That is to say, two weeks with lots of pate, six weeks with an occasional hamburger, a year with a steak.

It is, as you say, almost a fantasy, until we can establish some kind of cut off. I would propose that we talk about residence as to say, who have lived in Britain during this period; not five years, not seven years, not one year, but just have lived in Britain and for some reason find themselves in the United States and are wanting to donate blood.

I wouldn't establish a time cut off. I would make it total.

DR. HUESTON: My comment on two weeks related only to answering the question that was asked, what would be the cut off to separate the visitors from the residents.

That is the only point I was trying to say. I would guess from what I have seen, two weeks, pretty clearly, for

those two weeks, to separate the visitors from residents.

DR. BROWN: I would think also.

DR. CLIVER: Except for military. What are we going to do about military.

DR. BROWN: This is another sort of -- if only we had this time curve, we could eliminate all this guess work.

I suppose we have a member in the audience here, that most of the U.S. military in Britain is there for some time between one and two years; is that correct, or does it vary all over the map?

LT. FITZPATRICK: It is quite variable. The primary group stationed in the United Kingdom is air force. They are typically there between 18 months and two years and three years with extensions.

The navy tours run about three years and the army tours run about three years.

You also have numerous individuals in the air force who go for 90 days for temporary duty. It complicates our problems significantly in terms of those donors we can collect from and which ones we cannot. It complicates our civilian counterparts.

Many of those individuals that go for 90 days are reservists, who go into the civilian population. If I might suggest, there is a corollary with malaria travel that the FDA

has already grappled with, and you might ask them to apply that corollary.

DR. BROWN: Could we quickly have that corollary? What is the time for malaria?

DR. EPSTEIN: I don't know that it really applies. We know a lot more about the risk of acquiring malaria and we know a lot more about the types of symptoms of malaria.

Although I can tell you the time frames, I don't think it is applicable.

One easy cut off that would vary -- it might be six months, it might be a year, it might be seven years -- might be to ask the question, have you ever used a British address. Generally speaking, residence implies you are sleeping and living in a residence. That might be a rational cut off.

DR. LEITMAN: One of the standard operating policies for transfusion policies is that the people in this group need a time frame; they need guidance.

They are technologists and nurses and they will say, what is the time line. Is it two weeks, six months or a year.

DR. BROWN: Okay, so practically, that doesn't work. Stan?

DR. PRUSINER: I would like to suggest a different approach here; that we ask the AABB to go back and look at the survey, the people who responded yes, they have been outside.

Come back and question these people. Now, maybe they will get 80 percent or 90 percent or 70 percent of the people to respond. We would have some data for the next meeting.

This could be done or a new study started. I mean, this is a two-month interval in which all these questionnaires were put out.

We are talking about six months from now, in June having the next meeting. I think we would have some data and that is what everybody would like to see.

We have no data whatsoever, and all the questions that we are bringing up would be framed in the questionnaire and the appropriate data acquired.

DR. BROWN: I think that is a good idea.

DR. CLIVER: I think we ought to put a time window on when the exposure stopped and started, too. I think 1985 to 1995 rather than 1984 to 1990, but maybe we can refine that further. The 1984 to 1990 time window is an inappropriate one.

DR. BROWN: I think that was the sentiment, to the effect that we have not and cannot, on the basis of evidence, establish a specific year of start and a specific year of stop.

We are in the same situation as how long during that

period people are going to stay there.

DR. CLIVER: I don't see how we cannot, though. I think if we are going to include people who lived there in the 1970s, you are getting off into territories where there is no reason for concern.

DR. BROWN: I don't think that was ever a question, to include the 1970s.

DR. CLIVER: We have got to have a time frame in which you will do your analysis.

DR. BROWN: I couldn't agree more. The question is what that time frame is going to be. That is one of the questions we were trying to assess.

What I just added to that is that that is a good suggestion and that we haven't yet established what we are going to consider as the period of high versus low risk. That is one of the things we have to talk about.

Can we at least throw out the question, what did they eat? There is no possible way that the Red Cross screening questionnaire is ever going to get a reliable answer to what did you eat.

Can we have a hand vote that this is something we don't want to deal with?

DR. WILLIAMS: There is a group who would be vegetarians. There are a lot of Indians and south Asians, and

there would be no reason to exclude them. I don't know if that complicates it or not. We don't have to ask them what they eat. Are you a vegetarian or not.

DR. HUESTON: There are a lot of vegetarians that can't be defined.

DR. BROWN: It is just a totally impractical thing to ask the Red Cross or anybody else to go through thousands of questions, what did you eat. Are we asking questions and getting dietary histories from the donors?

DR. METTERS: One of the new variant CJD cases was a vegetarian.

DR. HUESTON: However, she only became a vegetarian at age 11, if I remember correctly.

DR. METTERS: I think that is a matter of uncertainty. During the period you are talking about, she might have been a vegetarian over that time frame.

DR. SCHONBERGER: Wasn't it 1984 that she ate beef and meat and 1985 when she became a vegetarian?

DR. BROWN: Let's stay on focus. We are never going to solve --

DR. METTERS: I am sorry; I don't think you should ask those questions.

DR. BROWN: I don't think so either. Let's dismiss the vegetarian and non-vegetarian. It is almost impossible

ever to find out, so let's not even worry about it. Is it agreed, we can cross out at least that? Okay, that is a cross out.

So, under 1-C, we are just crossing out what did they eat. That is just not a practical thing to do.

We are still left with a period of risk. I haven't forgotten your suggestion, Stan, but I think we are going to have to hammer out the committee's feelings on whether or not we want to do anything in advance of data.

Maybe the question to ask the committee now is, having limited the question on the table to donor exclusions - - we are not talking about withdrawals or destructions, we are talking about donor exclusions.

We have narrowed it down to whether or not we can make a recommendation that incorporates during what period and for what length of time.

Does the committee want to continue to labor this or labor its activities to these two elements. Do we want to, as they used to say, punt until we get a little more information and consider it in the next meeting when hopefully REDS or some other source of information will give us some numbers to talk about?

The question is on the table. Do we further consider question one, or at this point not?

DR. PRUSINER: I would make a motion to punt

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DR. PRUSINER: I would make a motion to punt.

DR. BROWN: Do we have a second to the motion to cease consideration of question one until we get further data, with the caveat that it is going to be next time and not next year?

DR. EPSTEIN: Question one has a number of different parts. I understand the desire to want more data, but I think the experts in this group could potentially give us some guidance, at least on the risk in the United Kingdom, while recommending that any implementation be postponed until we have more data on how long people traveled and/or resided.

DR. BROWN: Since the proposal hasn't been seconded, can we defer that proposal and see if there is any further guidance that we can provide to the FDA in terms of what period and how long.

Let's take what period first. I think that is probably an easier question.

DR. ROHWER: I have a comment to make on that issue. I have always been struck by this MAFF graph which Lisa Ferguson showed earlier today, applying the incidence of the BSE epidemic against the date of birth of the diagnosed cattle.

These are just the cows that were confirmed BSE. But when you look at that plot you realize that in 1985 when the first BSE case was identified, there were already thousands of animals infected.

If you apply Anderson's extension, his estimate that for every diagnosed case of BSE there were five to 10 other cattle which were slaughtered before they got BSE, then you are in the neighborhood of 10,000 or more animals that were infected at the time that the first case was observed.

Those birthdays go back to 1982 or 1981, I believe; perhaps even earlier; I am not sure. So, in picking a date, I think it would be smart to err on the side of conservatism.

I don't think we will lose much by doing that, especially if we follow the criteria on the basis of residence and relate it to some sort of citizenship or something like that. My guess is it won't be a very large group of people.

On the other hand, I am not sure what the other end should be. What about the SBO ban? What about at the time the SBO ban was absolutely instituted and recommended.

I think it would be a mistake to put a limit on the other end. We don't know whether this disease was propagated, regardless of the BSE epidemic and decline in the BSE epidemic. That is one of the risk factors.

DR. CLIVER: I think that the SBO ban removed the source of infections to cattle, but you have got up to six years of incubation in cattle. Even up to 30 months, there were a lot of infected cattle out there. Until 1995, the problems were not infected cattle; there were feed problems.

DR. ROHWER: I agree. I think the real point is that if the whole idea here is to mitigate risk from a theoretical infection of the UK population, then we have to assume that people who are in the United Kingdom right now, there may be a significant number of people who are infected. Why would we want to limit that at the upper end of the range?

DR. ROOS: So, if somebody lived in the United Kingdom over the last two years, let's say, wouldn't the exposure be far less than 10 years ago?

DR. ROHWER: You are saying that they would have to be exposed by some other route.

DR. BROWN: I recognize the man at the microphone.

MR. BUSCH: I think this discussion is critical in terms of guiding how a blood center's surveys can frame the questions.

You are looking at how can you maximize sensitivity and looking at what the impact of various sensitivity limits would be on the loss of blood donors.

I think the reality of these blood donor surveys, the survey that Alan Williams presented for the group that I was involved with, was an anonymized survey.

So, we can't simply go back to those donors who indicated they were from Britain and re-question them about the details.

We would have to initiate a whole new survey and that has to go through OMB approval. The whole process of just designing and getting OMB approval to release this survey would take over six months. There is no way the survey could hit the streets within the next six months through these mechanisms.

DR. BROWN: So, the consequence of that is we would probably not have it. Is there any other source for this kind of data that would be available?

MR. BUSCH: You do have the survey mechanism that has been developed. It is very rigorous with a good coordinating center to capture and compile the data.

For one to try to build a whole new structure, the organizations have some capacity to participate in this process, but getting going and started with a whole new

mechanism, I don't know if those mechanisms could accomplish it.

DR. BROWN: Suppose the Red Cross, for example, that supplies half the blood supply, suppose the Red Cross, without a whole lot of bureaucratic layering, simply started asking the questions.

I mean, do we have to have six months to set up a protocol for these things? Isn't there any way to get things done quickly any more?

DR. FREAS: Could you identify yourself, please?

MR. BUSCH: Michael Busch from UCSF.

DR. WILLIAMS: I think it depends on the degree of sophistication you want to get out of the survey. If you are just looking for prevalence of donors who had residence in Britain for a certain period of time, sure, we can do that in a quick and dirty fashion.

What you won't have is extensive demographics on that population. You won't have the risk information. If you can accept that trade off, yes, we can certainly get the time information. To get the whole package requires a very involved effort.

DR. BROWN: I don't really care whether they went to college or not. I just want to know how long they have been there and where.

DR. METTERS: Just about the SBO ban, that is 1996 that you are talking about. That is very close to the 30 months.

DR. BROWN: I am sorry, I missed the first part of what you were saying.

DR. METTERS: The SBO ban first came in 1989. That is when it was supposed to be done. The very tight controls were put in in 1996.

There was some leakage in the SBO ban through the early 1990s. That came to an end in 1995. Since 1996, it has been very tight.

I am giving you this as sort of fractured information, because clearly, it varied.

DR. HUESTON: Could I clarify, that I think we are confusing two SBO bans. One relates to materials going into the animal food chain and the other relates to materials going into the human food chain.

DR. METTERS: I am talking about the human food chain, not the animal food chain. It is a different feed ban, which has a different type period after it. The dates I was giving related to the human food chain.

DR. SCHONBERGER: So, the human risk period is in -- there is a change after 1992.

DR. HOEL: Would it be easy to get some of this

information from customs or immigration office, say, in the United Kingdom? They would have a distribution of how many Americans for how long in various years.

The second thing is, I guess basically what you are talking about is some sort of risk estimate, for what year, how long and all this, versus what would this do in terms of cutting out the numbers in the blood supply.

DR. BROWN: Obviously, the shorter the period on both ends, the less impact it has on deferrals, period.

We are doing this exercise largely because we are trying to give the FDA an idea of where our thinking is going as a committee. Was there a comment over here, I think?

DR. KATZ: I was just going to say, it sounds like what we are getting to here is, if you can collect this data, and if it can be done in a quick, and I hope not a terribly dirty way, that that can be done between the Red Cross, the American Blood Centers and the AABB. That can be done.

What we are going to do is say, how bit a donor hit can we take versus how are we going to construct the bans. It strikes me as extraordinarily arbitrary.

DR. ROOS: It is hard to settle on a time interval, but maybe we could propose a time and see how it fits.

DR. BROWN: You are telling us that a question phrased as did you live in Great Britain in the period in the

late 1980s and early 1990s as opposed to just visiting, is not a question that you think could be a practical question to ask?

Do you think you need one year between 1987 and 1990, for example? That is what you said before. We need a number. We can't just say lived or resided, as opposed to just visited.

DR. LEITMAN: I think you need to take a six month period. Did you reside in the United Kingdom for a period of greater than six months between the years 1982 and 1996.

DR. BROWN: You still need the years and you still need the time. You need a number.

Well, I think it is fair to say that we will continue this discussion, but nobody at this table can provide with any kind of security the number. It has almost not even reached the level of informed guesses.

DR. EPSTEIN: I appreciate that. I think I am also hearing the sense of the committee that if the FDA goes forward with such a program, that it should be drawn very conservatively so that we don't unduly impact the donor pool. I am hearing that being crafted in here.

I think what you are saying is that, try to limit it in such a way that it is meaningful in regard to the risk period -- whatever we may end up deciding that is -- but not

undue impact on the donor base. I think that is fair.

DR. BROWN: I think you are absolutely right, and that is the sense I am getting, too. One could say, for example, ask the question, did you live for a year or longer in Great Britain between the years 1985 and 1995.

DR. PUSINER: I have to go. I am sorry. I would just like to incorporate in this questionnaire if there are people who have traveled there many times during that period. So, they didn't reside there for a year. What is the cumulative time.

I don't know exactly how you structure a questionnaire, but I think that is important in trying to acquire this data. It is not just a one-time estimate. It is the accumulated exposure or total exposure.

DR. BROWN: We are not talking about what to recommend. We are just talking now about getting more information.

DR. PUSINER: I think the question should be between period X and Y. How many months did you cumulatively spend.

DR. BROWN: What total time did you spend in Great Britain between 1985 and 1995.

DR. LURIE: And the other point we are missing here is, we are not only interested in a description of the distribution of residing times in Britain. We are interested

in the relationship between that and the risk factors, behavioral, for hepatitis B, HIV, et cetera, and do the blood tests.

If we want to get at the other part of the problem, then if the REDS is the basic mechanism that we are going to drop this into, then we have adequate measures. We need that analysis

If we want to get at the other part of the problem, then if the REDS is the basic mechanism that we are going to drop this into, then we have adequate measures. We need that analysis.

DR. BROWN: Alan, when this is constructed, the information we would like would be total time spent in Great Britain between, I guess the committee would be happy with 1985 to 1995, a decade.

DR. WILLIAMS: For each cut in the analysis -- if I understand correctly -- in the analysis, what impact would each analytic cut have on donor reduction and the amount of other infections that might be expected as a result of having to increase first time donors. Is that what you want?

DR. BROWN: What we want is, when you do the analysis, assuming you ever get it done, that you take cuts, and for each cut you tell us what the consequences are in terms of lost donors and the numbers of new first-time donors

that have to be recruited to replace them.

DR. LURIE: What is the impact on increased risk of other infections.

DR. BROWN: Yes, impact on additional infections.

DR. SCHONBERGER: I think I heard from Dr. Rohwer that he was thinking about even before 1985.

DR. BROWN: You can take it back to 1979 or 1980 and you can go up to the present day. I think this is something the committee ought to think about.

DR. BURKE: I am a bit concerned about this whole approach. It seems that the total risk to the American blood supply is going to be a function of the total person days spent by Americans in the United Kingdom.

What we may end up finding is that more than 50 percent of the person days in the United Kingdom will be by people who were there less than a month. I won't be surprised to find that out.

If that is the case, and we only choose a window which we say is greater than a month, even though these may be the high risk individuals, there may be so many more of these people who were there for a shorter period of time, that the total risk to the U.S. blood supply, a high percentage of it may be in this shorter window.

I am very uncomfortable with this notion of only

excluding long timers, because it doesn't measure the area under the curve, it doesn't give the total risk potential.

DR. SCHONBERGER: We were worried about the impact issue.

DR. BURKE: I understand that. I am worried that if you do this you may reduce the risk by 30 percent by introducing this particular intervention.

The other kind of data that I would like to know as well, before I make this, is not just the distribution, but what is the potential -- if you make that assumption that days in the United Kingdom is the risk to the blood supply, I would like to see that before I make that decision.

DR. BROWN: What you just asked for will not influence the questions and the raw data. It will simply modify the kind of analysis.

You can see the area under the curve. You can design all this.

In short, in order for us even to guess at an exclusion criterion of time spent, we need to see a curve, and we need to see what the impacts of cuts of that curve will be on the other side of the equation, the disadvantages.

DR. LEITMAN: I think you need to give the beginning year. I heard 1985 to 1995. Then Dr. Hueston had suggested we use 1981 or 1982.

DR. CLIVER: One year in residence in 1981 might be worth one month of residence in 1990.

DR. BROWN: Well, we will not know that for another 10 years, I am afraid. It is just one of those things.

I don't think, because of that, we ought to just throw up our hands and run out of the room. I think we are here and, to the extent that we can help, we should.

DR. ROHWER: My sense is that the exercises in risk minimization and risk elimination, as Dr. Metters defined it earlier, just a quick calculation here suggests that if you compare a population of donors which 90 percent of them are 10-day travelers, versus 10 percent of them being one-year residents, it still comes out very strongly in favor of residents, by about four to one, in terms of efficacy.

Now, if it turns out to be one percent of residents, it might be different. You get a lot of bang for your buck from people who have been there a long time.

DR. DETWEILER: Maybe with this time frame, maybe we can use kind of what the world has been using for risk, even if cattle doesn't apply. That would put some more credibility or at least some standardization to it.

Ninety days, in the beginning year, and then at the other end, by the end of 1996, in the United Kingdom, the ban as built in had the 30-month scheme. So, you had a lot of

different enforcement things that were in place and really in force.

Those would be some things that you would have some backing on, what you did in 1980 to 1996.

DR. BROWN: I can't argue with that. That is the whole ball of wax. It is two years since 1996, and nothing before 1980.

How do you feel about that? What we are doing is creating a questionnaire. We are not talking any more about the questions and what we are going to recommend to the FDA.

What we are now doing is saying what do we want, what information we want so they can make a decision.

DR. ROHWER: In terms of collecting data, why not collect as much as possible and start in 1975, whatever. You don't have to use that.

DR. BROWN: You don't have to ask just one question, is what you are saying. You can ask three, actually. You can start at 1970, 1975 --

DR. KATZ: I just once again want to remind people that this could be done on the donor room floor where we are attempting to process donors. We don't have to recapitulate the REDS study.

DR. BROWN: Yes, it can be short.

DR. BROWN: I think everybody is more or less moving

toward a longish period of inquiry, whether it is 1985 to 1995 or 1980 to 1996. Has the committee got a preference between those two or suggest a different period?

DR. BURKE: Yes, I am uncomfortable about the idea that there is a clear linkage between the cessation of the animal epidemic and the human epidemic.

I would like to believe that is the case, but I don't know that at the moment. I think a conservative position here would be to say that it is possible that the animal epidemic and the human epidemic are not directly linked, but that there is some common link, or there is some other unusual way that the epidemiology links -- that the human epidemiology is that it is at least flat and it may be going up.

If that is the case, I would say that the window should be extended to the presented. I don't see any logic in saying we know when the human risk stopped.

DR. DETWEILER: Mine was just on exposure to animal products, was 1996.

DR. BROWN: We don't know that, Don, but we do know, from experimental and human evidence that the incubation period after oral or peripheral exposures -- that is to say, non-intercellular exposures -- is likely to be in the range of 10 to 20 years.

DR. BURKE: With some arbitrary time as to when the

potential risk -- we are assuming that it is oral risk. Is everybody happy with that, that it is oral risk?

DR. BROWN: It is proven, I think, or there is an evolving consensus that that is the most logical route.

DR. BURKE: But it is a supposition.

DR. BROWN: Yes, it could be a supposition forever, like cigarettes cause lung cancer. It is still a supposition.

DR. ROHWER: The other point is, in terms of putting an upper limit on this, it is important to realize that the United Kingdom is not collecting blood from people --

DR. BROWN: That is an invitation instead of something that you are initiating yourself. Would you have any suggestions about a period, of what the British themselves, or what you might yourself consider a rational period for maximum risk, to the human population in Great Britain?

DR. METTERS: The single biggest fall in the risk to the human population occurred in 1989 with the removal of the specified bovine offals from the human food chain.

Before that date, they could in theory go into the human food chain. That was the position since the 1970s, was no restriction.

That was the biggest single reduction in risk for the human population, from that day forward until 1996 when it

was really policed, not in the sense that we had the constabulary around, but we did have the other inspections, including seeing that all the bits that had to be removed were removed. I would say that the big cut off point was in 1989.

DR. BROWN: There will be a tail, as you said.

DR. METTERS: There will be a tail.

DR. BROWN: But there is a big event that happened in 1989. So, it would be from that standpoint, one reasonable assumption, would be maximum risk the latter half of the 1980s, and another reasonable assignment would be the entire decade of the 1980s.

This would be -- in your judgement, this would probably be more sensible, to look at the period before 1990 than the period after, in terms of human risk.

DR. METTERS: I believe that would be a widely shared view in the United Kingdom.

DR. SAYERS: I have to leave, but I just wanted to make a couple of comments.

DR. BROWN: The nice thing about this durability is that the ones who stay the latest generally carry the day. People tend to disappear. Go ahead.

DR. SAYERS: Maybe those that stay behind are less encumbered. I just want to bring this up, not because these are excuses for not doing something, but just as a reminder,

that introducing a question like this will have very real consequences, even though the issue that is being dealt with is unrate-able as measured in terms of what the risk is.

Let's say this question is introduced. I can guarantee that donors who were regular donors will go home and inform their partners that they have just been deferred for a CJD risk.

This will induce in their partner anxieties to the extent that they worry whether this might be a sexually transmitted disease, whether they might have been exposed to it.

They will worry whether their partner is now going to have to be somebody that they are going to have to be looking after as an invalid. They are going to worry how they are going to afford a tonsillar biopsy. What are the consequences of those questions.

I mention the concern on the part of the patients. There are three million a year, a significant percentage of which group is now going to wonder, once this question gets added to the question, did I, in my last transfusion, get a transfusion from somebody who had resided in Britain during this period of time.

We will give credibility to this smoky risk of transfusion transmission of CJD.

Finally, I have to add that when the question is asked of the donor, there is no guarantee that even the earnest donor can answer that question truthfully and honestly at the time it is delivered.

Frequently, with complicated questions like that, the real answer comes back long after that donor has donated. His or her unit is accepted and the components are transfused.

The individual comes back 56 days later or two weeks later and says, gosh, I have just spoken to my partner. He or she has informed me that, in fact, I had been in Great Britain during that period of time.

This then provokes a whole host of activities on the part of the blood program to notify the recipients of those products.

Those patients, in turn, are then subjected to the anxiety that they may have gotten something from a donor who should have been deferred but, unfortunately, was not aware of exactly where he had been at the time he was asked the question during the interview.

It is not excuses for not doing something that is worthwhile. It is just a reminder that there are very real consequences to doing something that is very difficult to ascertain.

DR. BROWN: Dr. Metters would like to say something,

and before he does, I absolutely agree. I would also point out that in 1985, before the connection between human growth hormone and CJD was made with any convincing arguments, there was a huge hue and cry about even letting this out, because it would create such an incredible panic and anxiety on the part of the blood donor population.

It did, but it was still a valid action that was taken. In retrospect, now we know that the connection was a real one, so it is something that has to be balanced. Dr. Metters, I will let you say something now.

DR. METTERS: I just wanted to say, as the individual in the United Kingdom who had to make three of these announcements, that each time, based on earlier referral problems, that we went to great lengths to say to the donors, this does not mean there is any risk to you as a donor.

We emphasized that, and each time we saw a fall in donors, because there was this somehow misunderstanding that the actual donation was a risk to them.

I don't know whether the United States noticed a difference, but in the United Kingdom, that happened. It is inexplicable, but it is a reality, and I just lay it on the table for you.

DR. BROWN: The other thing I would ask before you leave -- and again, I re-emphasize that what we are talking

about now is not what is going to be our recommendations to the FDA at this meeting for deferrals.

What we are really talking about now is what kind of information we would like to have in order to make that kind of judgement six months down the road.

DR. EPSTEIN: I would just like to express a concern, that the hour is late. It seems less likely that we will get to all of our questions.

I would like to ask that if you could get your sense of the committee, whether it is willing to vote on question 1-E, whether there should be plasma derivative withdrawal.

A majority of the committee has advised us that we should institute some form of donor deferral criteria. I think that we have heard a lot of discussion about how one might craft that, what additional data we might like to look at, and I think we have heard that message.

At the end of the day, we are going to be dealing with the issue of, if we have these donor deferral criteria in place, what do we do when we obtain this post-donation information.

This is a concern that Dr. Sayers just explained, and I think you have heard from presentations earlier today that the impact on the availability of plasma derivatives could be quite large.

So, I think it would be important for FDA to get the sense of the committee on this issue if, indeed, the committee is prepared to address it.

DR. BROWN: I agree. However, these withdrawal recommendations are concluded in each case -- D and E -- with the phrase, based on these donor deferral criteria.

As we haven't established donor deferral criteria, I am not sure how we can answer D and E logically, as the questions are asked.

Perhaps we can wrap up, because it does look like we are getting mired in an undesirable issue at the moment.

Shall we wrap up questions A-C with any suggestion in terms of a time of exposure?

DR. LEITMAN: I suggested -- well, conservative would be as long as possible until we know more. To me, that would be a year, just as an opening statement, resided for a year or greater.

DR. BROWN: During any special year?

DR. LEITMAN: The year 1980 through 1996.

DR. BROWN: A year. Is that a motion?

DR. LEITMAN: It is a motion.

DR. BROWN: If that is a suggestion, is there a discussion of the motion? Are there any other suggestions?

DR. NELSON: I think it would probably not be so

difficult to put it into several categories, to have cumulative exposure. You can ask the question, were you ever in Great Britain for six months to a year.

DR. BROWN: I don't think it would take a long time, if we were all inclusive, 1970 to 1996, and then follow up with a question, oh, when.

DR. CLIVER: Why do these have to be done in sections, though. If have got a total time period of interest you could ask, during that period, what amount of time did you spend in the United Kingdom.

DR. BROWN: That is just what I said, a follow-up question.

DR. CLIVER: Just one question. During the period 1980 to 1996, how much time did you personally spend in the United Kingdom.

DR. BROWN: Then you have to ask when.

DR. CLIVER: It would be easier to categorize seven days or three weeks.

DR. BROWN: Why don't we leave the details up to the people who are actually going to do the questions and just express our desire that the period investigated be inclusive, between 1970 and 1996 -- excuse me, 1980 to 1996.

We had a motion. This is just discussion. Your motion is --

DR. LEITMAN: 1980 to 1996, were you in residence greater than one year during that time period.

DR. BROWN: Any further discussion about that?

DR. ROHWER: It seems to me that another way to approach this is on the basis of your questionnaire. Once the data come in, and realizing that this is going to be an imperfect measure, that you could divide it into the amount of risk you want to remove and say, we want to remove 95 percent of the exposure.

That would be based on the results of your survey and it will be balanced against the amount of time that balances the greater economies of using people who have lived there longer versus people who have had transient exposures. Hopefully that will work out so that you can do that.

DR. CLIVER: If you just ask about one year during that period, then one or more is black, less than one is white.

You will never get that 95 percent distribution unless gratuitously they follow it up with years. If you have got a curve, like how long were you there during this period - the motion is for one year.

DR. LEITMAN: I guess it is two separate issues. One is what the REDS questionnaire should have. We are not trying to get anything right now. We are just trying to get

some feeling in our minds. It has nothing to do with the study, which should provide a continuum of data as you suggested.

DR. BROWN: Right. Again, this is a suggestion and a question. In doing or obtaining this extra information, wouldn't it be possible to say, have you lived in Great Britain between 1980 and 1996, yes or no.

If it is yes, when, and how long. I mean, that would give us all the information that we need.

DR. ROHWER: Except, I would strongly urge that it be worded 1980 to the present.

DR. BROWN: Okay, 1980 to the present. That is another discussion.

MS. HARRELL: I want to make another suggestion that would probably exclude the casual visitor on vacation or holiday, to substitute one year for one month or longer, and using the same time period that she has suggested.

That would be one question. We could make it several in terms of, did you live in the United Kingdom for one month or more during the period of 1980 to 1996.

DR. BROWN: I understand what you are saying and I understand what Dr. Leitman says. I am suggesting that we can do better than that.

We have a motion on the floor. We are going to have

maybe a second, maybe not, and then we are going to vote on it.

My alternative is to say 1980 to the present and then ask, not a specified time, but an open-ended question of when and how long.

MS. HARRELL: Are they going to tell the blood bank

--

DR. BROWN: This is just for the survey. We are strictly talking survey. So, these are the possibilities. Does anyone want to second Dr. Leitman's motion?

DR. HOEL: I second.

DR. BROWN: All right, all in favor of Dr. Leitman's motion, raise your hands, unless you want to withdraw in favor of the alternative.

DR. LEITMAN: I don't think we should be voting on the survey question. We are advising the FDA, not helping them write their survey. They know how to do that.

DR. BROWN: That is what we have been doing for the last 15 minutes. We are not telling the FDA now. For the last 15 minutes, we have not been concerned with what we are recommending the FDA ask their blood donors to exclude them.

We have been talking about how to get additional data so that in the future, as quickly as possible, we can provide the FDA with the answers to the questions they have

asked us.

DR. LEITMAN: Can I ask Dr. Williams, do you need this or do you know how to do it?

DR. WILLIAMS: I think we certainly wouldn't want to go down the survey route and not meet the wishes of the committee. So, I think this is certainly very useful.

I guess I would also like to say that I see the importance of the question. I can't speak on behalf of the other participants, speaking for REDS, as to how much we can put into this.

I think it is certainly worth doing and hopefully we can get information to meet your needs in the time frame that you need.

DR. BROWN: Dr. Leitman, do you now understand what we are talking about in terms of what we are doing?

DR. LEITMAN: I think we should get the most information possible from the survey.

DR. BROWN: Do you withdraw your motion?

DR. LEITMAN: Maybe. My motion was to get at D and B.

DR. BROWN: I am going to make a motion, which as I understand it, the committee would agree to, which is, suggest that a survey be conducted as quickly as possible by REDS, Red Cross, whoever can do it best, quickest.

The survey be asked to include the following three questions. One, have you lived in Great Britain at any time between 1980 and the present. Two, if so, when, and how long. Discussion? A hand vote on that motion, yea or nay. All in favor?

[12 hands in favor.]

DR. BROWN: Opposed?

DR. ROOS: I abstain.

DR. BROWN: One abstention.

Now it seems to me that we can wrap up questions A, B and C by simply saying, that we prefer not to advise the FDA on criteria for donor exclusion until we have this information.

DR. ROHWER: I think we could be more generous than that, in terms of, as I suggested before, what kind of risk we are trying to eliminate.

Admitting that whatever measure that we put in place here is going to be an imperfect measure, and that the gist of these questions is -- especially question E, the one that Jay brought up -- is about withdrawals. I think the committee could express the sense that they don't want withdrawals, regardless.

DR. BROWN: We haven't yet considered D and E.

DR. ROHWER: Oh, I thought you were.

DR. BROWN: We are now. A through C is finished. Now we are talking about withdrawal.

DR. ROHWER: Yes, I am also talking about withdrawals. I thought you said there was nothing we could say about them.

I think we could say something about it and we could say we don't want withdrawals, regardless of what the policy is.

DR. BROWN: We could do that. Is there some thought about withdrawals?

DR. KATZ: I just have a question. When my daughter comes in next month and we ask this question, and this recovered plasma has been given by our corporation for the last five years, or the commercial plasma donor comes into a plasma center and says, oh, yes, how are we rationally going to avoid -- looking at REDS data in particular, about the number of people who would fall out of this question, how we are rationally going to justify a position on what we do with everything that is "contaminated" for the last 10 years.

DR. ROHWER: I think you rationalize it by the fact that you admit up front that this is a risk minimization process. Our goal here is reducing our sources of risk.

To have withdrawals on the basis of occasionally identified lapses in that policy would not make sense, because

obviously there are a lot of cases we are going to miss, in the partial imposition of a plan like this in the first place.

We are admitting that it is leaky, and it is a stop gap measure and you do it because hopefully it is something that can be done efficiently without having a huge impact and still increase the safety and decrease our exposure somewhat.

DR. BROWN: You are talking historical versus future risk, and that is a reasonable and logical difference, particularly since we have no solid evidence that there is any risk at all

We are admitting that it is leaky, and it is a stop gap measure and you do it because hopefully it is something that can be done efficiently without having a huge impact and still increase the safety and decrease our exposure somewhat.

DR. BROWN: You are talking historical versus future risk, and that is a reasonable and logical difference, particularly since we have no solid evidence that there is any risk at all.

DR. ROOS: Once you have decided -- I mean, that is one of the reasons I voted no initially -- once you have decided that there is a risk, then I think it would be wrong, then, not to do withdrawal.

I think that is where you are in trouble, if you have someone coming in and you don't have the plasma

available. I think you are setting yourself up for a real problem.

DR. BROWN: My sense is that what the committee has decided so far is that we don't know that there is a risk. It is not that we know there is a risk. We don't know that there is a risk.

Not knowing that there is a risk, we would prefer to kind of cut our losses, if there is a risk, in the sense that we would like to prevent future risk.

If we had no known risk to begin with, it seems ineffective to effect withdrawals on the basis of no known risk.

DR. ROOS: What we are talking about is killing a pool from 60,000 people because one person traveled or stayed in the United Kingdom for a year or two.

I am certain that it increases the risk of this pool of 60,000, but I don't think it is worth shooting ourselves in the foot.

On the other hand, if we can avoid using that individual as a donor up front, clearly that might be advisable.

Anyway, we have this already, and that is that we have donor deferral for growth hormone, for dura mater, and for family members.

Presumably, we are worried about these people being in the incubation period of time.

On the other hand, we don't -- if somebody is identified as having Creutzfeldt-Jakob and contributed to a plasma pool, we have let that plasma pool go through; you don't withdraw it, even though this person might have contributed at the time of this incubation period.

In a way we have, I think, a very similar situation in which we are deferring donors that are at an increased risk, but not killing a plasma source with a similar situation.

DR. HOLLINGER: You just made a comment, that we are not withdrawing the CJD blood from the donors who are found to be infected?

DR. ROOS: If there is a plasma pool in which a donor is identified as having had Creutzfeldt-Jakob after that plasma is contributed, that plasma is not withdrawn as of what, September 1998?

DR. HOLLINGER: Then I would ask Bayer, then, why they have just withdrawn the factor --

DR. BROWN: Can I just interrupt? Ray is correct now, as we speak. This is the FDA position. That is a very recent position. In fact, it is like two months recent. It is very recent.

DR. EPSTEIN: September 8, 1998.

DR. BROWN: Three months ago, the FDA followed the advice of their blood advisory committee and Dr. Satcher and revised and relaxed what had been their previous position, which was, at least at minimum, a case-by-case examination of situations in which someone who had later gotten CJD had contributed to a pool. For the last three months, that has not been required.

DR. HOLLINGER: That is right, but do you know that Bayer just yesterday --

DR. BROWN: I do, and I think we shouldn't get into that situation, frankly, because it is a very special situation.

It involves regular donations and other matters which really take it out of the generality. Trust me.

DR. HOLLINGER: I am aware of all the situations you are talking about.

DR. BROWN: That is an even further wrinkle to the whole question of what to do about withdrawal instructions and quarantines and all the rest of it.

DR. ROOS: Maybe I should just forget the FDA policy and just think conceptually of the idea of killing a pool of 60,000 people because somebody lived in the United Kingdom for two years.

I don't know. I have a feeling that when we voted initially on question number one, all of us said we didn't want to jeopardize the important blood products. We should be reminded of that.

DR. BROWN: It is one step further, isn't it. If we were acting on the fact that a known CJD donor had contributed to a pool and we acted on that, which was done fairly recently, now the FDA prefers not to do that.

That is to say, a known CJD donor, who donated blood that went into the plasma pool, that is now all right.

What we are being asked to do here, is to consider - - I am not saying do it or don't do it -- consider withdrawal, that kind of a policy for pools of blood for someone who might have CJD has donated.

It gets into an improbability that is a magnitude order even less than what is now on the board.

DR. ROOS: Part of the reason for that decision resulted from our experience with withdrawals. We know about many negative public health consequences from those withdrawals.

I wonder if a motion might be in order that we recommend that FDA not withdraw blood from a plasma group based on the donor deferral criteria.

DR. BROWN: Do you make a motion?

DR. ROOS: I will make a motion.

DR. BROWN: A global motion for both D and E.

DR. SCHONBERGER: Just a point of definition, blood components are --

DR. ROOS: Red cells, plasma, white cells. If what we are talking about is somebody donated blood and there is limited blood and it is on the shelf there, I don't have a problem with the FDA not withdrawing it.

DR. SCHONBERGER: The negative public health consequences are primarily with the derivatives.

DR. BROWN: There is a motion -- Susan?

DR. LEITMAN: This exact conversation, almost word for word, occurred before the blood product advisory committee in 1994, the exact same discussion.

The initial thinking on should we do something that we can actually do, and then later on it forced an inconsistency. It was an illogical partition into supply considerations versus a theoretical increase in risk. It brought about an inconsistent approach to this, no in one case and yes in another case.

I don't think we can go for withdrawal of plasma derivatives. There won't be enough to meet patient needs.

DR. ROOS: One way around that is that you could defer the UK resident for contributing to the plasma pool.

DR. BROWN: I am going to make a motion that we vote on E. The question is, should the FDA recommend withdrawal for plasma derivatives based on these donor deferral criteria. Yes or no? Barbara?

MS. HARRELL: Yes.

DR. LEITMAN: No.

DR. SCHONBERGER: No.

DR. ROOS: No.

DR. HOLLINGER: No.

DR. HOEL: No.

DR. LURIE: No.

DR. BURKE: No.

DR. BROWN: No.

DR. CLIVER: No.

DR. DETWEILER: No.

DR. HUESTON: No.

DR. BROWN: It is unanimous. The noes have it. So, Jay has E taken care of. Does the committee even wish to consider D?

DR. FREAS: My understanding of the count was one yes vote and a lot of no votes.

DR. BROWN: That is correct. Does the committee wish to consider 1-D?

DR. DETWEILER: I wish to consider it. I think the

committee should be consistent. If it voted no, whatever was voted on E, it should be considered as it applies to D.

These are components that are in what is called active inventory. If they are red cells, they are in a refrigerator. If they are cryoprecipitated plasmas, they are in a freezer. They are accessible to the blood service, so they can be withdrawn.

Their impact on the blood supply is certainly much less than withdrawal of plasma derivatives.

DR. BROWN: What is the shelf life of the longest components, and cryoprecipitates, I understand, is not a component.

DR. HUESTON: Ten years for frozen red cells.

DR. DETWEILER: So, this is 10 years.

DR. LEITMAN: That is extremely rare.

DR. BROWN: In general, the components are used up fairly quickly. Platelets go in about five or six days and buffy coat in less than a month?

DR. LEITMAN: It would be red cells for 42 days, frozen plasma for one year, cryoprecipitate for one year, frozen red cells for 10 years, platelets for five days.

DR. BROWN: Any comments on what they would like to do about D?

DR. ROHWER: I think you can make a clear

distinction between these two types of products in terms of risk. One type is pooled and the other one isn't. Right now, I don't see that there is a big consistency. I think you can justify it the same way that the UK folks have justified it.

DR. KATZ: I want people, as they work on this question, to understand that if these components are going to be subject to withdrawal, then we have to deal with the question of, must we notify recipients of prior donations from those donors.

We can slice it any way we want, but that is the way things have worked in the recent past history of blood banking.

Whether at the time when a decision like this was made or some time later under pressure from the Congress, the public, other public health authorities, FDA, we do need to deal with does this have implications for something we are going to tell recipients down the line.

LT. FITZPATRICK: I just wanted to clarify one point. We do have fresh frozen plasma licensed for seven years that the DOD stores, and we also have about 85,000 units of frozen red cells in storage.

DR. BROWN: Further discussion about components?

DR. LEITMAN: I just wondered, to emphasize what Dr. Katz just said, trying to inform the recipients in a lookback

notification, that they have taken a component off the shelf that they have received and already transfused, a component from the same donor, and trying to explain what the risk of CJD is because the donor spent a couple of years in England. I can't imagine how you could unduly upset an individual. That is just something we should consider.

DR. NELSON: It would seem to me that until there is a real risk, that is totally unnecessary.

DR. ROOS: This is the wrong issue, though, because those have already been dispensed, those units; right?

In other words, the answer to D has nothing to do with telling people or not. In other words, it is the remaining units.

DR. KATZ: I understand exactly the point. However, we have been on this slippery slope many, many times in the last 10 years.

DR. ROOS: I think we are going beyond the slippery slope more if we give these units, and we are having to inform people, telling them this is potentially contaminated, because that is the slippery slope we have to worry about now.

DR. BROWN: No, we haven't condemned these units.

DR. ROOS: I think, Paul, when this person comes back and says, I made a mistake, and I was in Britain for two years, and we have some deferral practice, it is going to go

to the hospital ethics group, and it is going to bring in the neurologist and the hematologist and the ethicist, and they are going to say, what should we do about these units; should we give these units or shouldn't we.

Whether you have condemned them or not, I think it is an issue for them at the moment. I think if it has little impact, then we should get rid of them.

DR. BROWN: I think we can solve the problem. We haven't made recommendations for deferral to the FDA, first. We have deferred recommending deferrals.

It would be possible, and consistent today to say also, no, to question D and ask the FDA to put that on the agenda again in the future, when we decide whether or not we want to recommend deferrals and have the question come up.

Then we could logically consider it in the future. For the moment, since we haven't made a recommendation on referrals, we could logically talk about withdrawals yea or nay.

DR. GILCHER: I think there really are two questions. You have to draw a line in the sand and you go forward and you go backward.

Going forward is withdraw the product, as Dr. Leitman said, that is in inventory. Going backward is a monumental problem, as Dr. Katz has pointed out, because the

recipients, I believe, will have to be notified, unless the FDA is willing to, in fact, not to go backward.

There are two separate problems. I think it is a dangerous game.

DR. BROWN: On the other hand, it is possible that the FDA will follow its traditions and act sufficiently slowly on our guidance that we will have an opportunity to revise it before anyone has any problems with it.

DR. EPSTEIN: We are very good at that. I think this will take time to work through anyway. I don't think the guidance will hit the street any time soon.

I just want to clarify that FDA does not see the issue of recipient notification or the retrospective, as you put it, as linked to the question of taking an in-date component off the shelf.

We are really only asking about the latter. I understand Dr. Katz' point, that those problems do come to the fore.

We have lived since 1995 with a policy where we withdraw components and we are not notifying prior recipients.

That has not led to an outcry that we are somehow neglecting health and safety or public information and communication issues.

I do think we can separate those. It is not

accidental that we have only asked the committee about withdrawing the in-date component.

We are asking it because we felt that we needed to be quite up front, visible and public, on the question of how the policy would affect components versus derivatives from the pools of plasma.

DR. BROWN: If the committee is ready, we will vote on D. The question is, should the FDA recommend withdrawal for blood components based on the donor deferral criteria. Barbara, do you want me to start in the other direction for a change?

DR. HARRELL: Yes. I mean, the answer is yes.

DR. BROWN: Yes, it is a straightforward yes. The answer is yes.

DR. LEITMAN: I should vote consistently. I vote no.

DR. SCHONBERGER: I vote yes.

DR. TRAMANT: I vote no.

DR. ROOS: Yes.

DR. LURIE: Yes.

DR. BURKE: No.

DR. FREAS: Dr. Roos, was it yes?

DR. BROWN: Let's start again. Barbara?

MS. HARRELL: Yes.

DR. LEITMAN: No.

DR. SCHONBERGER: Yes, using Jay's limitation.

DR. TRAMANT: No.

DR. ROOS: Yes.

DR. LURIE: Yes.

DR. BURKE: No.

DR. BROWN: No.

DR. CLIVER: No.

DR. NELSON: Yes, based on a yes to the first question.

DR. BROWN: But your answer to the first question was no.

DR. NELSON: The first question won by a nine to five vote.

DR. BROWN: Should the FDA --

DR. NELSON: The first question.

DR. FREAS: The general point.

DR. DETWEILER: Yes.

DR. HUESTON: Yes.

DR. FREAS: I count six noes, I count seven yeses. For the yeses I marked Harrell, Schonberger, Dr. Roos, Dr. Lurie, Dr. Nelson, Dr. Detweiler and Dr. Hueston, six yeses -- seven yeses.

The noes I have Dr. Leitman, Dr. Tramant, Dr. Burke,

Dr. Brown, Dr. Cliver.

DR. BROWN: Let's move on to question two, which I think we can deal with fairly quickly. Again, we are talking about the withdrawal policy.

Question two has two parts. Should the recommend precautionary quarantine or withdrawal for plasma derivatives to which a possible nvCJD donor contributed pending confirmation of the clinical diagnosis?

Rephrased or simplified, should the FDA recommend quarantine or withdrawal for plasma derivatives to which a possible nvCJD donor contributed.

I guess we didn't get an answer to the question I hoped we would get immediately, so let's have the committee decide what they want to consider possible.

Is possible going to be a probable, a clinically probable, or is possible going to be a case of CJD that is 30 years old and someone says, oh, that might be new variant. Any discussion about that?

We heard from Dr. Will that what they call suspect cases outnumber the probable cases five to one.

A probable case is one that meets quite specific criteria; a neuropsychiatric --

DR. TRAMANT: If we vote yes for one, how can you vote no to two? Isn't CJD, not even new variant CJD now not

used? They are excluded.

DR. KATZ: There wouldn't be any withdrawal policy with classical Creutzfeldt-Jakob, since September. The point of this question is that this individual must be a relatively young person, perhaps with some sensory abnormalities, raising questions that this is new variant CJD.

When that occurs, and the individual is identified as a donor and you have a pool that includes this individual who becomes a suspicious case of new variant, what are you going to get.

DR. BROWN: This is a whole different ball game than the first question which was somebody who has been living in Great Britain.

DR. KATZ: This is somebody who is sick. Unfortunately, it can get a little complicated in the sense that you might not have immunohistochemical and histological confirmation. In other words, this person may not want a biopsy, or the neurosurgeons may not want to biopsy the individual.

So, essentially you have one scenario that you have a sick patient in which the diagnosis of new variant CJD is entertained.

The other possibility is that this individual is going to be biopsied in a short time, or already was, in which

case I think you could get the immunohistochemical data without too much difficulty.

The possible new variant case is already sick. He ain't going to be alive too much longer, 14 months average.

DR. ROOS: But we have a duration of 38 months on the outside.

DR. BROWN: The point is it is not going to be forever, and he will have confirmation sometime within a period when there are probably still products on the shelf.

In most cases the average duration is 14 months. They are not going to even be a suspicious case until they have been sick for a month or two. These are sort of details.

We are talking now about someone who is sick, who might have new variant on the basis of his clinical presentation, but he has no biopsy evidence one way or the other.

DR. ROOS: I think what is important here is that we haven't had any new variants in this country. At least before I believe in the new variant, I want to see some data about it.

Even in England there are a lot of false positives. I am concerned that if we say, boy, if we see a new variant or anybody who looks like a new variant, we are going to blow the whistle and not use this large pool in the face of essentially

this disease not occurring yet in the United States.

I would be cautious about condemning lots on the basis of clinical suspicion.

DR. BROWN: I suggest to this committee that we substitute the use probable for the word possible, and use the criteria that have been established in Great Britain.

DR. ROOS: I agree.

DR. BURKE: Could one of the blood bank experts tell me what the word quarantine means here?

DR. LEITMAN: Take all plasma derivatives that are in date and could be used off the shelf, which means you send letters out to pharmacies to withdraw them from the pharmacy shelves and return them to the manufacturer.

DR. EPSTEIN: I think that FDA's concept here of a quarantine could best be described as ceasing distribution.

It is not actually a legal term in our lexicon, but we have worked toward a model where we request voluntary cooperation in situations of uncertainty and ask the manufacturer to discontinue distributing what is in the current inventory, to inform the consignees, even down to the product user level, not to use the product for now.

It is an action short of declaring that the product unsuitable and should be removed. So, they don't actually call for retrieval or non-use, nor do they make any kind of

field correction or labeling change. They simply say, hold distribution and use for now.

DR. BROWN: Until further notice.

DR. EPSTEIN: Until further notice. I am afraid that we may have muddied the waters here, because there are two different concepts going on in this question.

One concept is if there is a possible case, perhaps not yet meeting the threshold of probable, should we do a precautionary quarantine anyway.

A different question is, if you have a case and it reaches the threshold of probable, should we go ahead and do withdrawals at that level, not waiting for certainty. I am afraid that we have muddied the waters a little bit.

DR. BROWN: Yes, I suggested that you had at the outset, and you have. Possible we have to have a definition of.

DR. ROOS: Is it possible that we could review on a case by case basis some of these individuals, which I guess probably happens at the moment, in the sense that cases that are identified as Creutzfeldt-Jakob go in to the CDC and distribution blood distribution centers are notified and they are looked at very carefully.

I would hate to lock us into this because in a way, what is probable in the United Kingdom for a diagnosis of new

variant CJD may not be probable here, in the sense that we haven't seen any of those cases yet.

So, I am not certain that we should, or that we won't see them until they become probable.

DR. BROWN: I think that the diagnosis of probable new variant CJD is going to be universal. If they turn up in Thailand or if they turn up here. I mean, they have got a good set of diagnostic criteria for probable CJD.

They include age, they include clinical presentation, they include an EEG and they include magnetic resonance imaging which is suggestive of hyper-signaling. There are excellent criteria.

They have been very good predictive criteria for new variant. Everything short of that is very dicey. I am not sure whether we can agree on what is a possible case.

I mean, is a possible case somebody who gets dementia under the age of 30? Is it someone who has a neuropsychiatric sensory disease at the age of 45?

These are all possible introductions to new variant CJD. As we have just heard, only one in five of such patients has ever turned out even to be probable.

DR. METTERS: Before I make my own comments, it strikes me that we have been dealing with this situation for some time.

I think the committee on proprietary medicine products is responsible for introducing the word possible, and it is encountered in all EU countries, not just the United Kingdom.

Countries were then left with the difficult task of deciding what possible was, and you have heard from a lot of them this morning what is used.

The reason that they chose that was the eventuality that somebody was referred as a possible case.

The profusion service nevertheless allowed those components to be issued whilst the diagnosis was being made.

The CPMP was very clear that there should be quarantine while making certain whether this was going on from possible to probable or whether it was an extraneous case of something else. That was the motivation.

DR. BROWN: Do you know what the criteria were, Dr. Metters, for considering a case as possible?

DR. METTERS: I can only refer you to what Bob Will said this morning.

DR. ROOS: I have copies of the categories. He had three categories. Possible was one, and four out of the five criteria were two. The criteria of one was progressive neuropsychiatric disease, duration of illness greater than six months, no history of iatrogenic exposure.

II was early psychiatric symptoms, persistent sensory symptoms, ataxia, myoclonus or corneal distemnia(?) and then dementia. That was possible. Probable throws in --

DR. BROWN: Probable I know about. Dr. Metters, was Bob Will's ratio of five to one established on the transition, that is, on these two groups, possible and probable?

He told me in private conversation that that five to one ratio was suspect -- another word -- to probable, and suspect was anybody that was referred as a possible case of new variant CJD.

DR. METTERS: You have got it right. The five to one is all the cases referred to date.

DR. BROWN: So, possible, the ratio was much lower. Once they have achieved possible, they were well on their way to becoming probable.

All right, in that case, I withdraw the notion of changing the word to probable, and we can use, if you like, Bob Will's criteria for possible, which are less secure, but they are much closer.

DR. ROOS: I wanted to ask Larry just to comment. Maybe you get notified about a lot of these cases, and how many of them would fit into possible or probable, and what kind of impact do you think it would have.

I worry whether there may be some patients

identified by MRI and ending up in a nursing home, and they can't be put into probable. How many patients are you talking about, that have been identified.

DR. SCHONBERGER: I suspect that our numbers would be very similar to the United Kingdom, in terms of what duration would be, except that we would have zero to 14.

Probably you will have more than that out there, but what is usually reported to us from the donor's perspective is from the blood banks, who tell us that they have a donor who is sick.

We had one similar --

DR. BROWN: We are talking about new variant, now.

DR. SCHONBERGER: I am talking about new variant. We had one that was described to us as a suspect new variant. Clinically, we could tell right away that it wasn't consistent with one of the criteria.

I think FDA was wondering whether that one symptom, that they didn't seem to have more criteria, that it would be enough to rule that out. We would still want to get a more definitive study done, which would be the tissue.

In the United States, my assumption would be that it would better to probably wait until we at least had one example of new variant CJD here.

We will get cases here that will fit the new variant

diagnosis. We had one in Minnesota, which I showed it to Will and he said, this is the new variant CJD.

Then we went and took the tissue and looked at it and said, no, it is not. So, you can have a clinical case of regular CJD that is really indistinguishable from the new variant, number one.

If we could add the criteria that they met this exposure in England, then I think we would be on much better grounds.

That is, if part of the history was living in England for whatever years we decide, plus they had these other criteria of new variant CJD, I think that would be much more what we are concerned with.

DR. BROWN: Yes, I agree, they would be much more concerned if that were in England, but I don't think we ought to make that, personally, as part of the diagnosis or criteria.

I would make a motion that we accept the British criteria for possible CJD, and vote this question using those criteria.

DR. ROOS: What about the EEG?

DR. BROWN: It is always positive.

DR. ROOS: It is always positive?

DR. BROWN: It has always been positive. In new

variant, it is the reverse, it is always negative.

DR. ROOS: So, if you saw someone with a typical EEG, then they wouldn't fall into possible or probable.

If we have already got a set of criteria, why fiddle with it. I just want to make sure about the details.

DR. BROWN: I don't want to evaluate his set of criteria. It is a set of criteria that works in Great Britain. It works. Their experience is that it is an excellent categorization of possible new variant versus probable new variant versus definite new variant. I don't want to fiddle with it.

DR. SCHONBERGER: I think the criteria there are fine. It is just that that is being used in a clinic where you have new variant CJD. We haven't had new variant CJD, so it may not --

DR. BROWN: I guarantee, if you have the same criteria here, you also have the same suspicion, as you did in the Minnesota case.

DR. SCHONBERGER: Correct.

DR. BROWN: So, the question is, do you quarantine.

DR. LURIE: The question is, what is the positive predictive value of a particular set of diagnostic criteria.

The answer is, it depends upon the prevalence. Here the prevalence is perhaps zero, there the prevalence is

something greater than zero. You are going to get many more false positives.

DR. BROWN: Okay, we have got a guy out west who eats squirrel brains and venison brains every week for the last year.

He comes down with symptoms that are clinically possible new variant. Are you going to tell me you are going to distribute his blood donation that he made the week before?

DR. ROOS: I am going to vote that we should look at this on a case by case basis.

DR. BROWN: There are so few cases that are going to qualify anyway, that it is going to be part of it anyway.

DR. LURIE: I think that is what is going to happen. I am just hesitant to lock ourselves in, especially because there is such ambiguity about what is possible and what is probable here.

DR. SCHONBERGER: I think Peter's point is correct, that the prevalence of disease has a big impact on the benefit of your criteria.

At the present time, we now we are going to have cases that are going to look like new variant CJD. So far, none of those have turned out to be. That is not the case in the United Kingdom.

So, using the criteria that works for them and

applying it to us may not be totally appropriate, if the negative consequences of identifying such a case are withdrawal.

DR. ROOS: I think all of us agree that in this new variant CJD, that we would be interested in quarantining the plasma derivatives.

The only issue is what is your index of suspicion. What I would say is, I would kind of leave it in the hands of the FDA and their consultants. They can actually review the case with Bob Will or something.

DR. BROWN: Would it be different, Jay -- what would be the impact if we left the two words, or withdrawal, out, if we just went with quarantine, which basically says hold them until we can have a better look at it. Would that be a much less bothersome thing?

DR. EPSTEIN: I think the problem, as it presents itself to us, we have no cases of new variant CJD in this country.

If we need criteria, it is very helpful to clarify that the sense of the committee is the UK criteria.

If we meet criteria for possible new variant, knowing that there are no cases in the United States, do we treat it as classic or do we treat it as new variant.

I think that there are a lot of reasons that people

might vote yes and vote noes. Individual votes may be for different reasons. It is always worth hearing why people vote the way they vote.

That is the problem as it presents itself to us. We do get reports of suspect new variant. So far, they have all panned out negative.

Some subset of them have been a plasma donor. So, what should we do.

DR. HUESTON: As this point they are suspect, though, not possible and probable in the terminology.

DR. BROWN: That is what I wanted to state, and I am going to make a motion and we can discuss it afterwards.

I am going to make a motion that we accept the word possible in the sense that is has been used in Great Britain, the criteria that have been established in Great Britain for possible new variant CJD.

We accept that, and that the motion implies that explicitly.

I suggest that -- I make a motion that we vote on question A, using the United Kingdom criteria for a possible case of new variant CJD.

DR. ROOS: With history of exposure?

DR. BROWN: No.

DR. ROOS: Without any exposure?

DR. BROWN: This is irrespective of where they have been and anything else about them. It is based strictly on clinical criteria.

That is the motion. Is there discussion?

DR. DETWEILER: I second the motion.

DR. BROWN: Okay, then we can vote on it. The question is, again, with the explicit set of clinical criteria that have been established for cases in the United Kingdom, that is what possible new variant means.

Should the FDA recommend precautionary quarantine, or withdrawal of plasma derivatives to which a possible new variant donor contributed, pending the establishment of a definite diagnosis. That is the question. Barbara?

MS. HARRELL: Yes.

DR. SCHONBERGER: No.

DR. TRAMANT: Yes.

DR. ROOS: I am going to abstain, just because I am concerned about some of the details here. I am also very alert to the possibility of new variant CJD and I have no problem if there is an index of suspicion that is sufficient to quarantine or withdraw the plasma derivatives.

My only hesitation is what satisfies that index of suspicion.

DR. BROWN: I might just interject here that the one

case in France has not had any action taken, because they have never visited England, if you are worried about the setting.

DR. LURIE: Yes.

DR. BURKE: I vote yes, but I would like to see a proportionality that is somehow built into this, that it is related to quarantine, that possible is quarantine and then probable or proven is withdrawal.

DR. BROWN: You want to vote yes and suggest that the FDA consider that division?

DR. LURIE: I have voted yes and I have given my caveat to Jay. I vote yes.

DR. BURKE: I vote yes.

DR. DETWEILER: Yes.

DR. HUESTON: Yes, and I agree with Don's statement.

DR. FREAS: I have eight yeses, one no and one abstain.

DR. BROWN: All right, the home stretch, question B. Is a tonsil biopsy negative for PrP sufficient to make product withdrawals unnecessary, or to reinstate products in which a donor with a possible diagnosis of nvCJD contributed.

What this question means is that if a person in A has a tonsil biopsy and there is no demonstrable PrP, does that mean the patient is okay.

DR. DETWEILER: May I make a comment?

DR. BROWN: Sure.

DR. DETWEILER: I am just thinking about sheep, which we have done a lot of tonsil biopsies on, I would say a negative does not necessarily mean the animal is not infected, especially the tonsil, if you don't get a decent biopsy, that that doesn't mean a correlation.

I hope we will have some specific numbers for false positives and negatives coming out.

DR. BROWN: The committee have all the data on which this kind of question is based. It is based on autopsy examination of the tonsil in a handful of patients with new variant, all of whom had positive staining, and a handful of patients with sporadic, none of whom had staining.

The same thing applies to living patients. There were, according to Dr. Will, five or six living patients with tonsillar biopsies that were positive. These patients ultimately turned out to have new variant CJD. A single, I think, patient with sporadic CJD did not stain.

Such as the numbers are, they are consistent in both the living and the autopsy patients, very small numbers of patients. Those are the only solid data that we have.

DR. TRAMANT: So, negative, vote no on B. It means that a yes on A means that any time someone says it is

possible, we are recommending that the product be quarantined. That is what a yes would mean.

What would be a test that could be done that would convince them that the person is not infected.

DR. BROWN: The question is, is the tonsil biopsy a good enough indicator of the diagnosis, or the absence of the diagnosis of CJD, to make an impact on decision A. Ray?

DR. ROOS: We know some brain biopsies are not supportive of a diagnosis of CJD in autopsied patients. I think that the negative tonsil maybe is supportive that it is not new variant, but I am not convinced completely.

DR. BROWN: I entirely agree. I don't think there is enough hard data to be able to say that if you have a positive tonsil, you have got new variant, and a negative tonsil you haven't. That is basically what the question is asking.

I would give the question up to a vote and vote no, that the tonsil biopsy is not adequate to make the diagnosis.

DR. TRAMANT: If you are willing to say possible, that that donation should be quarantined.

DR. BROWN: Yes, until such time as the diagnosis is established by either autopsy or brain biopsy. I would need to have a better handle on tissue diagnosis.

DR. TRAMANT: You would have to wait to see the

autopsy.

DR. BROWN: Or biopsy.

DR. TRAMANT: Ray said you could biopsy the brain and it could be negative and you could still have it.

DR. BROWN: Are you talking about new variant or are you talking about sporadic. I think Ray is also correct, though, that if you have a negative biopsy, you can't absolutely say it is not new variant, even with a brain biopsy. Wait for the autopsy.

DR. BURKE: Where the person's level of comfort is, how many places are there in the United States that would be considered competent to do a graham protein with any level of certainty. Are there places in every state?

DR. BROWN: No, there are not places in every state. First, we are not talking about thousands of cases. We would probably be talking about a handful, at most, in a year.

Any one of a half a dozen labs in this country, that is just nickels and dimes.

DR. BURKE: There are not laboratory problems, then.

DR. BROWN: No.

DR. SCHONBERGER: We have a referral lab that we use at Case Western Reserve. That is how we did it in this last case. Was there an age criteria? I didn't hear you say that.

DR. BROWN: I don't know that there was an age

criteria.

DR. SCHONBERGER: I think because they are in a different situation, you might want to leave it open and give us a chance for the criteria to be fairly strict here that would apply more to the United States.

DR. BROWN: Jay, did you want information only on the question of the tonsil biopsy?

DR. EPSTEIN: We are looking for anything that might be helpful, recognizing that there has yet to be a documented case of new variant.

We are trying to figure out what is our threshold for acting against product, and whether there is any useful information that would be mitigating. If we could be generally advised, we would appreciate it.

DR. BROWN: This opens an entire discussion about ethics. Whether or not a patient has got new variant or sporadic, it is not going to do him any good or make any difference at all, for his remaining life.

The only good that can possibly come out of this would be if the diagnosis is, in fact, new variant, then society benefits because of the possibility of a contaminated pool of plasma is taken off the shelf.

Therefore, tonsillar biopsies open the door to a certain amount of misuse. For example, you have got a donor

that is a suspected new variant.

You test him and you say, well, you have got to get a tonsillar biopsy, or it has got to be a brain biopsy. That is not nice to a patient.

DR. SCHONBERGER: I wonder if the committee would be willing to let us develop our criteria, rather than just adopting the UK criteria.

We would probably have in there something that they wouldn't have, which would be travel to Europe or travel to the United Kingdom. That would increase our concern.

We would probably also add an age criteria, possibly under 30 or under 35 or something like that. Because they have an ongoing epidemic, they might not put it that way.

DR. BROWN: I think that is a good idea. Why don't we vote on this one way or the other, and then add a recommendation that a set of diagnostic criteria for possible, probable and definite new variant CJD be constructed for use, that would be for patients in the United States.

DR. SCHONBERGER: I think there are cases where we, ourselves, have been concerned, such as the one in Minnesota. I am not sure that if we used -- we used a lot of the criteria that the had in the United Kingdom, but it might not be exactly the same. Again, exposure would increase our index of suspicion.

DR. BROWN: With that in mind as something that we could suggest, shall we vote on B? The question is, is a tonsil biopsy that is negative sufficient essentially to make product withdrawal unnecessary, or reinstate product with a probable diagnosis of new variant CJD?

Does everybody understand the question? We are saying, given A, that there is a negative tonsil biopsy, do we reverse ourselves and say it is not new variant? Is that true? Larry?

DR. SCHONBERGER: I am going to pass.

DR. TRAMANT: I abstain.

DR. ROOS: No.

DR. LURIE: No.

DR. BURKE: I abstain. I haven't seen enough data to make a decision.

DR. BROWN: No.

DR. NELSON: No.

DR. DETWEILER: Absolutely not.

DR. HUESTON: No.

DR. FREAS: I have six noes and two abstentions and one pass.

DR. SCHONBERGER: I will change that to abstention.

DR. BROWN: We have lost another. Now, shall we formally recommend as our final suggestion to the FDA that a

competent committee of clinicians establish diagnostic criteria for new variant CJD in the United States, and the criteria would be for possible, probable and definite.

These will be the diagnostic groupings, just as they are in Great Britain.

DR. SCHONBERGER: The criteria might be made in such a way that they either turn on this recommendation or do not.

DR. BROWN: Yes, we are defining the possible on which we are voting. Our vote is contingent on a set of criteria applicable to this recommendation.

Jay, is that clear?

DR. EPSTEIN: I think so, yes.

DR. BROWN: That, ladies and gentlemen, concludes our vote. Would you still like to have a dura mater allograft update?

Okay, let's move on to that. This is Celia Ann Witten. Dr. Witten is from the Center for Radiologic Devices and Health, FDA.

AGENDA ITEM: Dura Mater Allograft: Update.

DR. WITTEN: Thank you. I am Celia Witten, division director, the Division of General and Restorative Devices, at the Center for Devices and Radiological Health. I will be providing a brief update of the dura mater repair and replacement guidance.

I would first like to acknowledge the time and effort that this committee has put forth on the subject in the past.

Dura mater allografts for use in dura mater repair have been the subject of discussions of the panel on two previous occasions.

On October 5, 1997, this committee convened in the FDA's reevaluation of dura mater allografts used with respect to CJD transmission.

The committee at that time reviewed information provided by the FDA, industry, Centers for Disease Control, NIH, neurology and medical community, and other internationally recommended experts in the field, and provided recommendations to FDA.

In consideration of these recommendations, on March 6 of this year, FDA sent letters to dura providers on the FDA's limited recommendations.

At the April 16 meeting of the TSE advisory committee, the FDA presented its proposed course of action, taking into consideration the sponsor's responses to our letter. The committee, at that time, provided additional guidance and comments.

The purpose of my comments at today's meeting is to provide you with an update of our activities in the regulation

of these products.

As you may know, dura mater, when used for dura mater repair or replacement, is currently regulated by the Center for Devices and Radiologic Health.

As such, it has the regulatory status of a pre-amendment unclassified device. I will assume that people are not familiar with our device regulations, that medical devices are classified into three classes, based in part on risk of the device and/or whether there are controls available to minimize the risk for the class of devices as a whole.

Medical devices that were on the market prior to 1976 are termed preamendment devices, and all these devices need classification.

In 1990, we sought advice from our neurologic advisory panel on classification of human dura mater allograft materials. The panel recommended class II.

I will briefly highlight some of the considerations mentioned by the panel and the subsequent classification of the device.

What I first want to note is that the FDA plan is ultimately for dura mater to be regulated as a tissue, and the Center for Biologics is in the process of putting together regulations that articulate the principles noted in the proposed framework for regulation of human tissue. However, at

the present time it is regulated as a device.

These are the steps needed for device classification. After receiving a recommendation from the advisory panel, the FDA publishes a proposed rule regarding intent to classify.

This rule can incorporate special controls thought necessary to control the risk. Some examples of special controls are guidance documents, which as you know, we have been working on tracking and processing standards. These are the types of recommendations that have been discussed by this committee in past meetings.

Following the publication of the proposed rule there is a comment period. The comments are reviewed and assessed and the final rule is accomplished can incorporate special controls thought necessary to control the risk. Some examples of special controls are guidance documents, which as you know, we have been working on tracking and processing standards. These are the types of recommendations that have been discussed by this committee in past meetings.

Following the publication of the proposed rule there is a comment period. The comments are reviewed and assessed and the final rule is accomplished.

As I mentioned, the first step in device classification is obtaining a recommendation for the

classification, which we have already done and received a class II recommendation.

This classification means that the panel felt that this risks were understood and that controls could be established to minimize the risks.

Specific risk to health at that time included infection, CSF reagents, tissue reaction. At the time, they recommended performance standards and special controls.

Our plans, in brief, are to move forward with a guidance document, that has been formally based on recommendations of this committee as a classified product.

Tracking the dura mater will be required, and tracking is an issue. We continue to be in communication with sponsors.

If you have seen this in the past with me, the guidance document, the key points covered by the document will relate to the points that have been covered by the panel in the past, and I have listed them here.

I will just mentioned that the guidance document will take into account panel comments and other input, as well as the current regulatory environment and will be available for public comment. We will also be sending the panel a copy at that time, for comment by interested members.

The guidance document, after it is formalized, is

still an evolving document, that will evolve as science evolves.

I mentioned that I am not going to go into the recommendations in the guidance document on each of the points listed on the previous slide, but I do want to note that tracking orders have been issued for these products.

The tracking will include identification of recipients for receipt of the product, tissue source and information, patient medical record, for the sponsor to track the consignees.

The sponsors will also be required to track the recipients, so that there is the ability to notify the recipient in the event that it becomes necessary.

I would like to conclude by thanking the panel for their advice, and we look forward to working with you again. Thank you.

DR. BROWN: Thanks very much. Has anybody got any further comments before this day's business is adjourned?

DR. SCHONBERGER: You had mentioned to me some reviews on some of the risks of albumen. I wondered if maybe for the record you could clarify your position on albumen use as an excipient.

DR. BROWN: I have always, from the beginning, on the basis of our own work in the mouse model, and in human

blood, and now further supported by Dr. Rohwer's studies on hamsters, considered albumen to be essentially risk free, even if it were inoculated into the brain, undiluted, without further processing.

When you throw in the fact that albumen used as an excipient is not always, but often, at a much lower dose than it would be if it were used as albumen as a therapeutic product per se, when it is given intravenously, which is a far less effective way to transmit the disease, that based on these observations, and the fact that there is no case of CJD in any known recipient of a product using albumen, that albumen is essentially risk free.

The point was made at a previous meeting that, in spite of this scientific position, that the question of albumen use in vaccines was a sensitive one because vaccines, by their nature, require sensitivity, and particularly because the vaccines are frequently -- almost always -- given to children.

For what I would call political reasons -- political use interventions, is the word, that vaccines probably ought to be considered in the same boat that everything else that albumen went into.

I would answer you by clarifying that scientifically there seems to me to be no foundation for considering albumen

any other way than essentially risk free, no matter what it is in.

Thank you very much, members of the committee. We stand adjourned.

[Whereupon, at 5:46 p.m., the meeting was adjourned.]