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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

*****

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

*****

Thursday, January 18, 2001

8:30 **a.m.**

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Susan Leitman, M.D.

GUESTS

Richard Davey, M.D.
Louis Katz, M.D.

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PROCEEDINGS

DR. BROWN: Bill Freas, would you call the meeting to order, please?

DR. FREAS: Mr. Chairman, members of the committee, invited guests and public participants, I would like to welcome all of you to this, our eighth meeting of the Transmissible Spongiform Encephalopathies Advisory Committee. I am Bill Freas, the executive secretary for the committee. Both days of this meeting are open to the public.

At this time, I would like to introduce to the public members of this committee, seated at the head table. I would like to start on the right side of the room, the audience's right, and would the members please raise their hand as the name is called so that people in the audience can see who you are.

In the first chair, at the corner of the table, is Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago. Next to Dr. Roos is a temporary voting member for this meeting, Dr. Linda Detwiler, Senior Staff Veterinarian, U.S. Department of Agriculture. Next is a standing committee member, Dr. Bruce Ewenstein, Clinical Director, Hematology Division, Brigham and Women's Hospital. Next is a standing committee member, Dr. Donald Burke, Director, Center for Immunization Research, Johns Hopkins University.

Next is a temporary voting member for today and our consumer representative, Barbara Loe Fisher, Co-Founder and President, National Vaccine Information Center, Vienna, Virginia. Next is a temporary voting member, Dr. Paul McCurdy, consultant to the National Heart, Lung and Blood Institute, NIH. Next is a standing committee member, Dr. Pedro Piccardo, Assistant Professor, Indiana University Hospital.

In front of the podium is a temporary voting member, Dr. David Gaylor, statistician and consultant from Little Rock, Arkansas. Next is a temporary voting member and also the Chairman of FDA's Blood Products Advisory Committee, Dr. Kenrad Nelson, Professor, Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health. Next is a standing committee member, Dr. David Bolton, Head, Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is the Chairman of this committee, Dr. Paul Brown, Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Strokes. At the corner of the table is a standing committee member, Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention. Around the corner is a standing committee member, Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of

California, Davis.

The empty seat will shortly be filled by Dr. Peter Lurie, who is a medical researcher for Public Citizen's Health Research Group, Washington, DC. The next individual is a standing committee member, Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming. In the next chair is a standing committee member, Dr. Stan Prusiner, Professor of Neurology, University of California Institute for Neurodegenerative Diseases. Next is a non-voting consultant for today's meeting, Dr. Susan Leitman, Chief of Blood Services Section, Department of Transfusion Medicine, NIH.

Next are two guests of the committee, Dr. Richard Davey, who is here today as a representative from the Public Health Service Blood Safety and Availability Advisory Committee. Next is Dr. Louis Katz, Vice President for Medical Affairs and Medical Director for the Mississippi Valley Regional Blood Center, Davenport, Iowa. Drs. Lisa Ferguson and Jeffrey McCullough, standing members of this committee, will not be with us today.

I would like to thank everyone for coming. I now would like to read the conflict of interest statement into the official record.

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 Biologic Evaluation and Research, has appointed Drs. Linda Detwiler, David Gaylor, Paul McCurdy, Kenrad Nelson and Ms. Barbara Loe Fisher as temporary voting members. Based on the agenda made available, it has been determined that the agenda addresses general matters only. General matters waivers have been approved by the agency for all members and consultants of the TSE Advisory Committee. 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 imputed financial interests.

In regards to FDA's invited guests, the agency has determined that the services of these guests are essential. The following reported interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the participants. Dr. Richard Davey is a former chief medical officer of the American Red Cross. Dr. Dennis Confer is employed at the National Marrow Donor Program in Minneapolis. Dr. Jean-Philippe Deslys -- his employer, CEA in France, is involved in the development of a diagnostic kit for BSE. Dr. David Glasser is Chief of Ophthalmology at the Patuxent Medical Group. He was a paid consultant to the Lions Eye and Tissue Bank and Research Foundation. Dr. Louis Katz is employed by

ıe Mississippi Valley Regional Blood Center. Dr. Michael Miller's employer, the Colorado Division of Wildlife, has ɐgulatory authority of some deer and elk ranches in olorado. Dr. Alan Williams is currently employed by the merican Red Cross, J.H. Holland Laboratory. He is also cientific advisor to the American Association of Blood anks and the Canadian Blood Service. Dr. Glen Zebarth is he owner of an elk ranch. In addition, he provides medical rare for elk at his veterinary clinic.

In addition, Dr. Paul Brown has recused himself rom any votes involving cornea1 transplant risk during the iscussion of such risks because he is an unpaid consultant .nd co-author of the EBBA Risk Assessment Report.

In the event that discussions involve more specific products or specific firms for which FDA's ɔarticipants have a financial interest, the participants are ıware of the need to exclude themselves from such discussion ınd their exclusion will be noted in the public record.

A copy of the waivers will be available, upon written request, under the Freedom of Information Act. With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment on. So ends the reading of the conflict of interest statement. Dr. Brown, I turn the

meeting over to you.

DR. BROWN: Thank you very much, Bill. Welcome, everyone, to what will be for many members on the committee, myself included, our last meeting. We take it, I think, as a compliment from the FDA that they have loaded our plate today and tomorrow with every conceivable question they might have in the coming year. Therefore, we are operating on a short schedule and I brought this grotesque toy as a defense against prolixity of presentation --

[Laughter]

-- I never want to hear it again but, as a last resort, I will operate it if long-windedness gets out of hand. I think we should now start. I should tell the audience, in case they did not know, that this morning the topic will be a reconsideration of the same topic that we have considered several times in the past, namely, risk of acquiring CJD through exposure to a bovine spongiform encephalopathy. So, this is old territory, reevaluated.

This afternoon we will extend these considerations into new territory, namely, similar risk considerations to cell and tissue products. Tomorrow we will also address some new territory in the form of any potential risks for humans and specifically human donors, recipients of blood from people who might conceivably have come in contact with chronic wasting disease focused in northern Colorado to

southern Montana and, finally, a consideration at the end of the day tomorrow of any potential risks inherent in the consumption of nutritional supplements.

DR. FREAS: Dr. Brown, there is one official announcement, the Acting Deputy Commissioner for Food and Drugs has announcement that he has to make at this time, with your permission.

Presentation of Awards for Committee Service

DR. SCHWETZ: Thank you, Bill. Thank you, Dr. Brown. I will be brief to not incur the wrath of what you have sitting in front of you as your tool.

I just want to comment on advisory committees within the FDA. In the spirit of bringing experts in to advise us and in the spirit of transparency of the process of accumulating information for decisions and the decision-making process, the agency has a large number of advisory committees. I can assure you that this advisory committee for TSE -- 1 don't know of any of the other advisory committees that have a responsibility that is greater than yours. I don't know of one where the recommendations that you have made through the years are discussed in our meetings more often than the recommendations that have come out of this advisory committee. When you think of the effect on the health of people; when you think of the effect on the health of the economy, this is a major advisory committee

and the recommendations that you provide for us are extremely important.

In that spirit, it is a particular pleasure for me to bring special attention to three members who are coming off your advisory committee at this time. If the three of you would come and join me up here just for a second, Dr. Brown, Dr. Prusiner and Dr. Roos?

These three people have made major contributions to this field, obviously through a long period of time. They have had many, many awards that have been given to them, and it is a particular pleasure for me to be able to recognize the help and the years of service that you have given to us. The TSE had its first meeting in '97 and prior to that the committee was known as the Ad Hoc Special Advisory Committee on Creutzfeldt-Jakob Disease. These three scientists are the three remaining members of that original TSE committee. So, we are particularly happy that you have worked with us for all of this time and provided the helpful advice that you have given us, and we have a plaque for you and a letter from the Commissioner thanking you for your help.

[Applause]

I have asked Paul to stay on just for a second longer because of the special role that he has played in chairing this effort. Your skill in running meetings; your skill in being able to draw people out; and the skill of

allowing everybody to have an opportunity to speak and to be fair in getting information into the record, giving verybody the opportunity to express their opinions; and I link, importantly, pulling things together in the form of ecommendations that not only came to us but recommendations hat have stood up under a lot of fire through a number of ears -- 1 think that is a particular tribute to your skill nd your knowledge of the whole field and your ability to anage an advisory committee of this kind.

So, in special recognition we have another plaque o go with that. Thank you very much, Paul.

[Applause]

DR. BROWN: I thought perhaps I was going to get a itanium gavel but I still have wood. Now we have Dr. Asher rho will charge us for this morning's topic. Dr. Asher is irom the CBER,'which is in the FDA, and you are well iamiliar with him because he gives us our charge twice a rear.

Introduction, Charge and Questions

DR. ASHER: Thank you, Paul. Good morning.

[Slide]

This session will address once again a now Eamiliar and troubling topic, the suitability of blood and plasma donors who traveled or lived in BSE countries, and let me begin by reviewing briefly part of the history of

this issue.

[Slide]

For several years the FDA has recommended deferral of blood and plasma donors at increased risk of getting CJD and that blood and blood components, including plasma, from donors recognized to be at increased risk who actually get CJD be withdrawn.

Until 1998 FDA also recommended withdrawal of plasma derivatives, however, there is no demonstrated risk to recipients of CJD-implicated plasma derivatives. Processing greatly reduced infectivity, if not eliminates it, from Fractions IV and V, and CJD withdrawals do not substantially reduce the theoretical risk because at least 25 percent of the plasma pools used to produce derivatives are likely to contain a contribution from a donor who will ultimately get sporadic CJD and, of course, no screening question can defer; no laboratory test can detect those donors. Furthermore, withdrawal have failed to retrieve most CJD-implicated products and contributed significantly to shortages of some plasma derivatives.

[Slide]

Recognizing those facts, in September of 1998 the FDA revised its policy recommending continued deferral with CJD or increased risk of CJD, continued quarantine of blood and components, including plasma, from donors with CJD or at

increased risk of CJD but no withdrawal of plasma derivatives prepared from pools to which donors with classical CJD or at increased risk of classical CJD had contributed.

However, the FDA continues to recommend withdrawal of plasma derivatives and quarantine of intermediates prepared from pools to which any donor who develops new vCJD contributed which, fortunately, has never occurred.

[Slide]

But there remains a concern about donors who were potentially exposed to the BSE agent and who might be incubating new vCJD. The reasons for that increased concern or that new vCJD is an emerging infection not found in the U.S.A. Less is known about its pathogenesis than of sporadic CJD and the two different diseases may differ. For example, lyrnphoid tissues in new vCJD contain detectable protease-resistant prion protein while those in sporadic CJD do not.

In 1998, U.K. authorities decided not to source plasma for fractionation from U.K. donors, which implied some lack of confidence in the safety of the plasma on the part of another regulatory authority.

[Slide]

Aided by advice from this committee in December, 1998 and June, 1999, the FDA announced revised measures. Deferral of donors who had resided in the U.K. for at least

ix months cumulative between the first of January, 1980, when the BSE epidemic is thought to have most likely have egun or slightly thereafter, and December 31, 1996, a time fter which the U.K. was thought to be in good compliance ith several measures to reduce opportunities for human xposures to the BSE agent, that is, the ban on use of wheat nd bone in ruminant feeds specified risk materials removal nd the 30-month slaughter scheme. This deferral was stimated to reduce the number of donor days of exposure in he U.K. by almost 87 percent while losing a predicted 2.2 ercent of donors.

The FDA also recommended deferral of donors who received injected U.K. bovine insulin, but no withdrawal of lasma derivatives for U.K. residents or exposure to injectable bovine products from BSE countries. The FDA made commitment to monitor effects of this revised policy on he blood supply and to reevaluate its policy frequently, nd the TSE Advisory Committee meeting of last June in this session were organized in partial fulfillment of that ommitment.

In June of last year the committee was asked to reevaluate the new donor deferral policy and to consider whether potential exposure to the BSE agent in France and other BSE countries justified recommending deferral of some donors resident there as well as the U.K. The committee

concluded that BSE was much less prevalent in other BSE countries compared with the U.K., at least at peak levels in the U.K. and that, while U.K. beef products had been consumed in some European countries, especially France and the Netherlands, that consumption was less than it had been in the U.K. In France both the fraction of beef products thought to have been from the U.K. and the number of new vCJD cases relative to those in the U.K. were about 5 percent by rough estimate. The exposure to BSE agent in French beef was considered small compared to that of U.K. beef.

[Slide]

The committee was concerned that the new policy for residents in the U.K. had just come into effect about six weeks earlier and that further deferrals might jeopardize supplies of blood and plasma. So, the members advised the FDA to make no change in donor deferral policy until effects of the new policy became apparent.

Since June of last year, of course, much has happened. Diagnosed cases of BSE in Britain, which peaked at more than 3000 a month in early 1993, have continued to fall and only about 100 a month recorded last year is still a substantial number. BSE cases may have peaked in Switzerland as well, but the situation is different in other European countries.

[Slide]

That came as no surprise to our Department of Agriculture which had become sufficiently concerned about the possible spread of BSE in European cattle to issue an interim regulation in December of 1997, prohibiting importation of live ruminants and most ruminant products from all countries of Europe, due to potential risk of BSE. The Scientific Steering Committee of the European Commission, in a report on geographic BSE risk published last year, also concluded that a number of European countries that have not recognized BSE in native cattle, nonetheless, probably had infected animals in their national herds.

[Slide]

Recently, concerns about BSE and new vCJD have increased. It has been recognized that substantial exports of U.K. cattle, beef and beef products, as well as meat and bone meal, to several European countries continued during high BSE years -- more about that later in the morning.

Rates of new diagnoses and deaths from new vCJD increased in the United Kingdom. Fortunately, that has not been found in France. Diagnosed BSE cases have increased in several European countries -- France, Belgium and new countries have recognized disease, most recently Germany, Italy and Austria.

These and other issues concerning Europe will be reviewed by two speakers. Robert Will is unable to attend due to family illness, but he will be represented in absentia by our Chairman, Paul Brown, who will present information about U.K. and other countries of Europe. Jean-Philippe Deslys will present information about France and other data of interest concerning BSE, and both will comment on the situation elsewhere in Europe as well. Johannes Loewer was to have reviewed TSE in Germany but the recent BSE related reorganization of their ministries of health and agriculture has prompted a reevaluation of biologics regulation and research in Germany requiring his urgent presence there.

Other information of concern, a preliminary report of TSE transmitted by transfusion of blood drawn during the asymptomatic incubation period of sheep experimentally infected with BSE agent to healthy sheep obtained from a BSE-free source -- if that finding reflects a higher level or more consistent infectivity in blood of animals with BSE than is found with other TSEs and if that property is also associated with blood-in new vCJD, the unfavorable implications for the safety of blood of persons incubating vCJD are obvious.

Health Canada has issued a precautionary directive for deferral of blood and plasma donors who spent extended

periods of time in France, and Tony Giulivi has kindly agreed to review the basis for that decision for us today.

The U.S. Department of Agriculture recognized that some U.S. military personnel and dependents in Europe consumed beef products obtained from the U.K., and Col. Mike Fitzpatrick and Col. Scott Severin will share information about that potential exposure with us.

[Slide]

Finally, Paul McCurdy will report on the current supply of blood in the U.S.A., and Allan Williams will attempt to estimate possible effects on supply to be expected if additional donors are deferred for residence in France and other BSE countries.

[Slide]

Let me close now by reading the charge and questions for the TSE Advisory Committee today. Please evaluate new information concerning new vCJD in the U.K. and France, and BSE in the U.K., France and other European countries where the disease has infected or may have infected cattle. Address the risk that donors resident in various countries, including overseas U.S. military personnel and dependents, might have been exposed to and infected with the BSE agent, and consider implications for the safety of the blood supply.

[Slide]

In the context of a risk-benefit estimate, please consider effects that FDA blood-donor policies may have already had on the blood supply in the U.S., as well as effects to be expected if additional deferrals of blood donors are recommended.

[Slide]

The questions -- are recent data on rates of new vCJD in the U.K. or the potential risk of transmitting vCJD by human blood or plasma sufficient to warrant a change in current FDA policies concerning deferrals of blood and plasma donors based on a history of travel or residence in the U.K.? Please comment.

Have recommendations of FDA concerning donor deferral for residence in the U.K. had an adverse effect on the blood supply sufficient to consider a change? Please comment.

[Slide]

Should the FDA recommend deferral of blood or plasma donations by persons with a history of travel or residence in France for an aggregate period of ten years or more after 1980? If not, which years and aggregate duration of residence, if any, should be of concern?

[Slide]

Should the FDA recommend deferral of blood or plasma donations by persons with a history of travel or

residence in other countries identified by the USDA as having BSE in cattle for an aggregate period of ten years or more after 1980? If not, which years and aggregate duration of residence, if **any**, should be of concern?

[Slide]

Should the FDA recommend deferral of blood or plasma donations based on a donor's history of travel or residence in more than one country identified by the USDA as having BSE in cattle for some combined aggregate period or time? If so, which years and aggregate duration of residence should be of concern?

[Slide]

Finally, should the FDA recommend deferral of blood or plasma donations based on a donor's history of potential exposure to beef or beef products from the U.K. while serving in the U.S. military or as a military dependent?

Those are the questions. We appreciate your deliberations. Thank you very much.

[Applause]

Updates on vCJD and Estimated Human Exposure to the BSE In the United Kingdom, France and Other BSE Countries

United Kingdom

DR. BROWN: Thank you, Dr. Asher. We are all disappointed and I am particularly disappointed that Bob

Will was unable to come at the last moment. His father became acutely ill and there was no question about a choice of coming or staying. He did, however, send to me a massive number of overheads which I have culled, and will present to you and, I hope, in a manner which he would approve.

[Slide]

This is the same chart that you saw from Dr. Asher, extended up through most of the year 2000. It is a classic epidemic. This is BSE in the United Kingdom. If it has not already entered textbooks of epidemiology as a model epidemic, it certainly will in years to come.

The epidemic in the U.K. was turned around basically by the feed ban which was introduced in 1988. The anticipation is that this will continue to trail off down to zero in the foreseeable future.

[Slide]

These are forecasts made by two different organizations. In 1999, the observed number of cases of BSE in the U.K. was close to 2000. The estimate was also close to 2000; slightly greater here.

In the year‘2000, the estimate was 1114. There actually were close to 1300, I believe but, again, the prediction based on modeling was quite good. In the year 2001, there is predicted to be a substantial reduction and further than that I have no information, but it is not

anticipated that this disease will continue to affect cattle.

[Slide]

A different type of predication, based on the previous models, is the number of BSE-infected cattle that might enter the human food chain under the age of 30 months -- that is, cattle under the age of 30 months during the last year of the BSE incubation period. Cattle infected earlier in life typically do not develop clinical BSE until about 36 months of age. So in that period of the year before they become ill, it is estimated that in 1998 there were about six animals that may, indeed, have entered still the human food chain in the United Kingdom. In 1999 it was halved. In the year 2000 it was down to about 1 and in 2001 about the same. But, again, it is going down. So this year, the prediction is that eight-tenths of a cow may yet enter the human food chain.

[Slide]

This is the human consequence. In 1994 the first case of vCJD occurred in the United Kingdom. These are years of onset of disease. As you see, over the past six years there has been a clear trend upward, nothing like you see in BSE which exploded but still a clear trend upward. These are unverified but almost certain cases, awaiting neuropathology. There will certainly be many more cases

reported in the year 2000. No one can predict exactly how many but it is certainly not going to be up on the ceiling; it is going to be in this range.

[Slide]

This is the quarterly onset, that is to say the number of cases with onsets on a quarterly basis, starting in 1984 and proceeding on up through probably -- well, this is 2000. They scatter around an average line which is significantly upward moving, and these are the confidence limits in dots. So, this is the picture at the moment, both BSE and variant Creutzfeldt-Jakob disease in the United Kingdom. As you know, neither disease is limited to the United Kingdom.

[Slide]

Here is not quite up to date because the numbers change every day but this BSE in Europe compared to BSE in the U.K. These are all U.K. You start in Continental Europe with Austria. So U.K., over 180,000 cases since 1987. I have highlighted the four countries which more cases of BSE have occurred than in any other country to date in Europe, and they are France with 243; Ireland w nearly 600; Portugal with nearly 500; and Switzerland with 365.

[Slide]

This overhead shows you examples of the yearly incidence of BSE in four of these countries. In Switzerland,

which has had an active surveillance program for some time, you can see that there appears to be a plateau, possibly even a decrease, over the last several years.

[Slide]

In Portugal -- we don't know what happens in 2000 yet but there was a clear increase in Portugal in the last few years of the decade.

[Slide]

In Ireland, similarly, there was an explosion in 1996 and that has continued to increase until the present time.

[Slide]

Then, finally France, in which there was very little recognized BSE in the early years, in the '90's, and now a very large increase in recognized cases in part, and perhaps a major part, by virtue of active surveillance.

In many countries in Europe BSE has not really been looked for, not really, and when it really is looked for with the support of immunocytochemical staining and a search for the prion protein, cases are being found and that is probably largely responsible for the apparent increase but not necessarily so. It is certainly contributing, and it is also contributing to those countries that did not earlier recognize BSE and now, in the past several weeks or months, have been reporting their first cases.

[Slide]

So, how did that happen? Well, it happened presumably because Britain exported contaminated material, and they did this in three different ways. They exported what are called flours, meals, meat offal and grieves, and grieves is approximately the same 'as meat and bone meal -- not quite but approximately. Bob split these into two half decades, '80 through '84 and then '85 through '90. Belgium and Luxembourg imported a substantial amount in both periods, that is throughout that decade. They must have had a fantastic salesman in France because is jumped from 2600 tons to almost 35,000 tons in the late 1980's, a period of greatest concern for BSE contamination peaking. The Irish Republic imported, as would be expected, a considerable amount and in the Netherlands, as in France, there was a very large increase in the importation of meat and bone meal. The significance of meat and bone meal, of course, is that this is fed as a nutritional supplement to cattle in these countries. So, presumably, a good deal of this material was going into cattle in the countries into which it was imported.

In this slide and the next slide there is an important caveat or two, and one thing that everybody who has ever dealt with international trade knows is that when a country says they exported X amount of things to another

ountry, the other country will tell you that they imported different figure. So, it is not known whether or not all these -- well, I think we can say with certainty that all these exports did not go to these countries and, if they id, some of them left and went to another country. witzerland may have, for example, gotten meat and bone meal rom Yugoslavia, which got it from Italy, which got it from he Netherlands, which got it from the United Kingdom. nternational trade in this kind of material is hopelessly ntraceable.

[Slide]

The U.K. also sent live cattle elsewhere. Here gain, France is the champion importer of live bovines from he United Kingdom; the Irish Republic somewhat less but still a very important number; Italy, of course, a lot in 980-84. The Netherlands again, like France, imported a great many live cattle.

So, live cattle are, in some cases and perhaps nany cases, slaughtered in the countries to which they have been exported, slaughtered and, therefore, able to be rendered in those countries and being rendered would then go into the nutritional supplements made in those particular countries. Hence, there would be a risk for BSE to develop apparently endogenously but, in fact, secondarily to their own recycling of material.

[Slide]

This is mainly for human use. Once again, France imported substantially more offals that would include such things as brain, thymus, spleen, liver, kidneys and intestines. Most of this material was destined for the human food chain, not for animals, although spleens sometimes find their way into animal feed an in particular pet feed.

[Slide]

This is a slide which I thought would be of particular interest. I got some extra information from Bob when I saw the slide. In the U.K. there have been some identified patients who subsequently died from vCJD, who had at some point, in the previous 10-15 years, donated blood. The number reported by the relatives was 12, of whom 7 were able to be traced through the National Blood Association. The number of recipients of blood from the above these 7 traced cases was 20. So, there were 20 people in the United Kingdom, as we speak, who received blood or a blood product from a patient that subsequently died from Creutzfeldt-Jakob disease, from variant disease. One of these died while asymptomatic but it is not known at the moment which one.

You can see the years of receipt, and they range from 1981 through 1999. They also include not only labile blood components, typically packed red cells, whole blood, plasma and in one case cryoprecipitate. Most of this plasma

is fresh-frozen plasma. As they also point out, or I would point out, 8 donors later developed vCJD and their plasma was used for plasma product manufacture. The products and recipients have not been identified. I doubt if they ever will because we are talking about thousands of donations in a given pool and, therefore, hundreds if not thousands of recipients. So it is a mixed bag of recipients but at least those who receive labile components are under surveillance, and obviously this will be a major point of interest as to what happens to these people. At the moment, all remain healthy.

[Slide]

Finally, these are the projections for the eventual total number of variant cases in the United Kingdom. If the mean incubation period -- and this is all mathematical modeling that appeared in Nature this past year -- if the mean incubation period, that is the lag period between the point of infection and the beginning of symptoms of vCJD is assumed to be less than 20 years -- and these columns don't differ in a great way, and if the number of cases last year were 10-14, 15-19 or 20, these are the predicted ranges of numbers of cases that will occur forever, total, finished. You see they range from somewhat less than 100 to somewhat less than 3000.

One of these two columns will probably in fact

turn out to be correct. My own view is that this incubation period will probably turn out to be correct. If it doesn't and if the mean incubation period extends to 20-30 years, the numbers go up somewhat -- I am sorry, I misread the previous one. It is under 100 to just a few hundred, 630. If the incubation period is somewhat 'longer, the low end of the scale is modeled to be not too much different but the upper limits would be closer to 3000 cases. These are similar figures over here.

I didn't highlight these because I think this is really quite unrealistic. I cannot imagine an average incubation period being greater than 30 years in this disease; certainly not greater than 60 years. What you want to notice particularly is that it is only if the incubation period is modeled as greater than 60 years on average that you get those horrendous figures that were and continue to be quoted, that is the upper limit of over 100,000 cases. Even if it is just 60 years in this grouping, the maximum predicted number of variant cases in the United Kingdom will not exceed 6000. That 6000 is not something that we would look forward to but it certainly beats 100,000 or 200,000 which are the upper limits that were being calculated until very recently.

So, I would think personally that we are probably talking about a maximum 20-30 year average incubation period

and, therefore, predicting that there will not be more than a few thousand, 3000 cases in the United Kingdom for all time. I think that is the substance of what Bob would have said. He would also have pointed out that the British BSE Inquiry, which was published a couple of months ago, pointed out that a popular misconception is that the British government really didn't do anything until their backs were against the wall in the mid-1990's after vCJD had been recognized, and that is a misconception. Very significant measures were taken well before anybody knew that BSE was, in fact, going to be transmitted to humans. That included measures both to break the cycle of infection in animals and to prevent contaminated material from entering the human food chain. They commended all of the scientists and agencies in Great Britain for doing that, and they also pointed out that there were some oversights and there was some perhaps unacceptable lag time between when the measures were first thought about and when they were put into practice. Thank you.

[Applause]

Returning to my function as chairman, we will now have an update on the BSE vCJD situation in France, given by Jean-Philippe Deslys. I did not mention something that most people in the room know, I think, that there are 91 cases of vCJD currently identified in the United Kingdom, one case in

Ireland in a patient who had lived in England for several years so, in a sense, doesn't count as an indigenous case. But, there are three cases in France in patients who never visited Great Britain. Dr. Deslys?

France

DR. DESLYS: Thank you very much.

[Slide]

Just to present the situation, unfortunately, as I am the last scientist who was able to reach this meeting due to different circumstances, Dr. Asher asked me to put this in perspective.

So, the problem in Europe is that an important number of BSE-contaminated cattle which are supposed to have entered into the food chain, about one million originated from United Kingdom and so many went in the United Kingdom food chain, a number of cases after the ban and that is the problem of the crisis that we are now in, in Europe because with the measures which were taken we were supposed to have no more cases. The fact that the BSE agent is transmissible to sheep and that sheep have been fed with the same contaminated meals, and that sheep have been exported in many countries, not only in Europe of course, and the fact that -- these numbers are wrong now because it is an old transparency, but the fact that BSE is transmissible to man.

[Slide]

This one is in French, but just to remind you that it is the same agent which contaminated cattle and which contaminated man. In fact, this is just to show that in man and the macaque model we have exactly the same signature and in France we have the same signature in the first new variant cases as in the cases that are seen in the U.K., and that with the lesion profile done in mice, in France we have exactly the same thing with BSE as what is seen in the U.K.

[Slide]

So, the same agent contaminated the cattle, all the cattle in Europe and man in the U.K. and in France. These are the results we obtained with the patients in France. This is a tonsil from a patient. In the previous slide you saw patient number 1 with a cerebral biopsy, and here is a tonsil in patient number 2, and here is a tonsil from patient number 3, who is still alive in France.

That is the main problem with new vCJD. New vCJD in man is detectable in peripheral tissues and in all reticular endothelial systems. Here you see it in tonsils but you can detect it in spleen, in Peyer's patches, in lymph nodes, while with the usual strength of CJD and with sporadic CJD you don't detect anything in peripheral tissues.

[Slide]

Here is a theoretical view which comes from work

from Kimerline showing that in scrapie, after peripheral contamination, you will first have replication of the agent in reticular endothelial system, and then very delayed you have neuron invasion until the death of the host. In the blood, in an experimental model, you can detect it. Much work, not including Paul Brown's work, really showed it. And, the level of infectivity in blood certainly is related to the level of replication in peripheral tissues. Everybody will understand easily that if this agent replicates in all the lymphoid tissues, then blood can be contaminated at a level which cannot be predicted easily because, in fact, you have very few infectivities in blood.

[Slide]

I can't give you details on that work which is still ongoing, which will be published in PNAs, but just to say that the intravenous route in primates -- and we used macaques here -- is very efficient. So, the general idea that the difference of efficiency between the intravenous route and direct intracerebral route is around 10 is certainly true for BSE, and perhaps it is more efficient.

[Slide]

To try to detect new variant in blood -- we are all hoping that new tests are going to be efficient. You have heard about tests developed by MaryJo Schmerr with capillary electrophoresis. Jerry Safar also developed a

beautiful test. James Hope has another technique. Prionics is developing a new one. We have a new test which is in development too. But for the moment none of these tests have been able, to my knowledge, to detect anything in blood from man. For the moment, I have not heard of other groups than the one of MaryJo Schmerr being able to detect it in blood in different models. So, for the moment, unfortunately, we have no tool to detect simply with a biochemical test new variant infection in blood.

[Slide]

This is to try to explain what is happening in Europe and more particularly in France. When a BSE case is detected in France, all the herd is killed. These cases were reported in October, and I know you know that we have more cases. But when you represent them depending on the date of birth, you see here the first peak which corresponds to the infections when meat and bone meal contaminated from the United Kingdom were massively imported to France. After that you have a drop when there is a ban on this meat and bone meal, and then a new increase here, more important than what we observed previously. And that is a problem, what happened exactly here. In fact, certainly things came into the alimentation of bovines. It is true that here there were holes in the epidemiological detection. You can see here that when you present the data depending on the year of

preparation -- here you have a hole, we were lacking some cases. But you see an increase here. You have something more or less exponential.

What is true too is that this phenomenon is increased by the fact that tests are being used. People are looking more carefully and, so, you are detecting cases that were not detected before. That is true. However, we are speaking of a very limited amount of cases compared to U.K. and I will show you that on further transparencies.

The other problem here is that you see abnormally young cases in bovines, here less than four years old, which is abnormal with cattle which is supposed to have been contaminated with low doses with the infectious agent.

[Slide]

Here is the latest data, I obtained yesterday, with the cases during last year. During last year we obtained more cases than during all previous years. One-third of them are linked to the active surveillance but one part of them in the passive surveillance is also linked to my point of view and to the point of view of other scientists, that people were more careful. They knew that there was an active surveillance, and the same phenomenon occurred also in Switzerland. When the program of active surveillance began a number of cases detected by passive surveillance increased too.

[Slide]

But, in fact, the main interest here is to know the exposure of man to the BSE agent. I have put on the same graphic cases from the U.K. and cases from France. As you can see, you don't see the cases from France because the number of cases from the U.K. are so important that the cases from other countries are completely ridiculous.

So, concerning the exposure of man in France, I have tried to make some calculations. About 10 percent of the human consumption of beef products in France were linked to beef imported from U.K. So, if you take these cases and you divide them by 10, you still see that here the problem comes from the U.K. From here, there was an embargo on cattle from U.K. and, second, you can't compare here this phenomenon with what is happening here because there is an enormous difference, especially for specified offals and notably on brain and on spinal cord which was used before in human food. It is not because people were not eating brain that they have not eaten these contaminated offals. They were using many things in sausages, in many sauces, in many things. They were banned in France but they were still used, for example, in other countries like Germany and it is a big problem now in Germany because they are discovering that there are now 14 cases and they think that they are going to find many cases with systematic screening.

The other problem is the increase in the exports rom the U.K. of offals, and these increased exports were efore the ban on offals. So, we suppose that a greater mount of contaminated brain and spinal cord could come into rance here.

So, we could separate these data into three parts. ere, before '96 and before the ban on offals and now where here are efficient measures, and now the systematic testing n all bovines over 30 months. So, now in Europe you have wo possibilities. Young bovines are tested or they do not nter into the food chain. This was a measure which was aken in U.K. since '96 concerning the ban on bovines over 0 months.

[Slide]

Concerning the tests which are used to evaluate ovines which can enter the food chain, you know that four ests were evaluated and three tests were selected by the European Union.

[Slide]

This one was eliminated. It was not sensitive enough and there was misdiagnosis of positive cases, and also false-positive for negative. But it has been corrected and now it will be reevaluated with the new corrections. It was the English test.

Here is the Prionics test and the test we

developed. This was the most sensitive one, 300 times more sensitive than the first one and 30 times more sensitive than the Western Blot. The more important thing is that this test, here, was as sensitive as the mouse bioassay.

[Slide]

I can't give details on that because it is work which is still undergoing and which will be published next week in Nature. So, you can consider it only as a hypothetical thing based on previous data that I gave you on the sensitivity versus bioassays.

The principle of this analysis is to say it is true that we don't know which is the minimal infectious dose, for mice, but what we know is that mice inoculated directly by the intracerebral route are more sensitive than bovine contaminated by the oral route. We know that the mouse model is then 100 times more sensitive than bovine contaminated by the oral route. It means that with one gram of brain titrating 10^3 infectious units per gram you are able to kill 1000 mice or ten cows. And we know that cows contaminated by the oral route are, we suppose, less sensitive than man contaminated by the oral route because you have a species barrier. Then, if with a sensitive test you are able to eliminate all that is dangerous for mice, then you will protect man.

[Slide]

It is possible to confirm these kinds of results with Western Blot because you have a purification step.

[Slide]

We will not discuss this because we have not published it, but just to tell you that it works very well in scrapie, as I presented in September.

[Slide]

Even if we don't know the exact nature of the agent, you know that many people think that it is protein but, whatever, with the level of sensitivity we have now, from my point of view, we are able to protect people from contamination in food but we are not, unfortunately, able to say that there are not healthy carriers and that the blood is safe. Thank you for your attention.

[Applause]

DR. BROWN: Thank you very much, Jean-Philippe. I think, you know, we have heard a fair amount already and possibly there might be questions that committee members would want to ask at this point. Yes?

DR. LURIE: Dr. Deslys, you had that striking slide of the trends and the number of **cases** in France compared to in the U.K., but do you have any comparable information where you have corrected for the number of cows in those countries? In other words, what is the rate of detection of cow cases in Britain compared to France, not

just the numbers?

DR. DESLYS: No, I do not have many details. What we know for the moment is that the cases observed in France clearly come from the U.K., from contaminated cattle from the U.K. That is in evidence in France. We have only three cases for the moment versus 88, if I understood well the last numbers from Bob Will. So, the estimations done by Anica Perovich were that if we have a maximum of 3000 cases in the U.K. we would have a maximum of 300 in France, but these are very rough estimations. In fact, when we discussed with Bob Will he said I prefer to say that we don't know. So, here is a very imprecise point of view. I admit it. But I am not a specialist of modelization.

DR. BROWN: Your question actually had to do with cows.

DR. DESLYS: Oh, sorry.

DR. BROWN: That is okay. Is it not true that France actually has more cattle than Great Britain even before BSE?

DR. DESLYS: Of course.

DR. BROWN: The number of cattle in France exceeds by a significant amount the number of cattle in the United Kingdom.

DR. DESLYS: Sorry, I omitted --

DR. BROWN: That is okay.

DR. DESLYS: Yes, the cattle of France -- I don't know if it is three times more than in the U.K. Let me see, we have 20 million of cattle, I think, in France --

DR. BROWN: I think that is right. I think France has about twice the number of cattle that the U.K. had before BSE. Yes, you had a questidn?

DR. CLIVER: Another frame of reference thing, I am assuming that the U.K. is still experiencing sporadic CJD at a one in one million rate approximately. I am too lazy to look up their population but by way of frame of reference, compared to the new vCJD, how many classic CJD cases are there?

DR. BROWN: Yes, the population of Great Britain is approximately 60 million.

DR. CLIVER: So, they should have about 60 per year.

DR. BROWN: And they have about 60 per year.

DR. CLIVER: Okay. So, we are looking at something approaching but nowhere near yet the sporadic CJD --

DR. BROWN: That is correct. What we are looking at now is something approaching a third of the sporadic incidence. Stan?

DR. PRUSINER: Two things, I wonder if we can get copies of the overheads that have been shown in the first two presentations? Unless they are in here and I can't find

them. It would be very useful.

DR. BROWN: I will have to ask Bob. I don't think any of it is classified. It is certainly not classified anymore.

DR. PRUSINER: That is what I mean. I have a comment on the second presentation. I presume you were at this meeting -- in honesty, I can't remember; there were a lot of people there in November.

DR. DESLYS: No, I was not there.

DR. PRUSINER: Okay. It is now very clear, by three different methods, that the R3 mice underestimate the titer of BSE prions by a factor of 1000 to 10,000.

DR. DESLYS: Yes.

DR. PRUSINER: So, I think to stand there and say that that is the standard on which you then relate your immunoassays really is not informative at this point because we know in cattle and titration done in Great Britain, we now know in bovinized, meaning transgenic mice expressing bovine PRP genes where the mouse PRP gene is knocked out, both from Martin Groship in Germany and our own data, that the titers are, as I said, between 1000 and 10,000 times greater than with R3 mice. I think it is a very important point that needs to be made and I don't think that the R3 nice are a good standard on which you then compare your immunoassays.

DR. DESLYS: You are perfectly correct concerning the sensitivity. Cattle inoculated by intracerebral route are about 1000 times more sensitive than R3 mice. We all hope that it will be confirmed that transgenic mice will be at least as sensitive as cattle contaminated by R3 mice.

But the point was not this one. The point was if you take the new mice, transgenic mice, then my demonstration will be not a difference from 100 between R3 mice and cattle contaminated by the oral route, but 100,000 between transgenic mice and cattle contaminated by the oral route, but it will not change the demonstration. Do you see what I mean? Am I clear enough?

DR. PRUSINER: No, I don't understand.

DR. DESLYS: Oh, sorry.

DR. BROWN: You know, Philippe, this is an interesting point and I tend to side, unusually, with Stan on this issue but it is really not too relevant to the focus of the committee, that is, the diagnostics of BSE in cattle, the details, and what tests are best and what tests aren't is a little peripheral to what the committee wants to address. So, I think I will snuff this discussion.

Laura, you may have had a question. This is Laura Manuelidis. Laura, you are going to have to use the mike.

DR. MANUELIDIS: I think one of my concerns about the tests and also about perhaps some of what may be low

estimates, Paul, as far as I am concerned about potential human cases is the fact that most of these tests are done on brain at end-stage of disease and we really have no idea of any test, at a preclinical stage, how sensitive it is. so, really products from animals that are preclinical are going back into the food chain and also people's own times of materials are going back possibly through instrument contamination, etc. So, in fact, that might lead to an increased incidence of some of the things that you have been proposing. That is a concern that I think we have to address unless there is some kind of preclinical test that really can be done.

DR. BROWN: I think Jean-Philippe makes this point in his article actually. Nobody yet knows whether any test currently available is sensitive enough to make the diagnosis of BSE at the preclinical stage, but this is work in progress, isn't it, Jean-Philippe?

DR. DESLYS: Yes. I am going to try to respond without saying things which are under embargo. We know different things from literature. First, I am sorry but it will be once more with the R3 model because it is the reference one for the moment. What we know from BSE is that we don't find anything outside the central nervous system in naturally contaminated cattle. You only find something in Peyer's patches in the ilium when you contaminate cattle

with heavy amounts of contaminated brain, 100 grams of brains. It doesn't mean that it is not infectious; it means that it is not within the limits of detection. I agree with you.

Now, concerning the preclinical samples, we know also from a pathogenesis study from Gerald Weiss that always with this model of mice, conventional models, they'are able to detect it from 32 months, and that is why there is a limit of 30 months for the elimination of cattle. So, that is a point for new invasion but I have a small correction. In this study, unfortunately, there were not enough animals at each point; only one at point 26. So, I am not so sure that 30 months is perfect. To give you an example, it seems that in Germany they have just found with our test cattle naturally contaminated which was 28 months old, and confirmed by Western Blot.

DR. MAFJUELIDIS: That is fine but that is a brain after the animal has died so there is not an effective preventive measure, and that is the problem. You can't stop it going into the food chain --

DR. DESLYS: Concerning the preventive measures, you ask for elimination of specified offals. You know that the intestine is eliminated, the spleen and many peripheral tissues. Second, I was putting my finger on this level of sensitivity of mice versus man because if you are not able

to detect anything in mice outside the central nervous system in naturally contaminated cattle, then it implies that the infectivity is at a low level. I agree with you that there is infectivity but at a low level and so not dangerous for man, as it is not dangerous for mice. But we are dealing not only by the fact that there is no infectious agent but that you are under the limit that is dangerous for man. And, if you go further in this way of thinking you can see that scrapie is very dangerous for man because scrapie, when inoculated to primates by the intracerebral route, will kill the animal but in the natural way of life we don't inoculate contaminated brain of sheep in man's brain and, so, by the oral route there has been no problem for centuries, or I would say not a detectable problem.

DR. BROWN: Dr. Belay?

DR. BELAY: Dr. Deslys, I have heard reports that beef from BSE-infected animals have actually ended up in the grocery stores in France. Were you able to determine or assess how often this actually occurs or was this an isolated incident?

DR. BROWN: This grocery store incident, animals from a herd that got into the food chain --

DR. DESLYS: Yes --

DR. BROWN: -- about three months ago.

DR. DESLYS: Yes, that is the beginning of the

crisis in fact.

DR. BELAY: The question is whether or not this was an isolated incident or were you able to determine how often this actually occurred?

DR. DESLYS: To my knowledge, it was the first time that it occurred and that is 'why it got such publicity. But you are dealing with the fact that in France we are eliminating systematically the whole herd when we find one contaminated animal, even if we know perfectly well that we will not find anything else in this herd because there are a very limited number of cases per herd.

DR. BROWN: In that situation, Jean-Philippe, was the animal that was diagnosed, did it die? Was the animal sick? Was it a clinical case of BSE?

DR. DESLYS: Yes, in fact the details of the story are that at the slaughter house they received an animal which was not well clinically so the veterinarian blocked it. They diagnosed the disease and then they understood that there was a problem because this animal was coming from a herd which had been sent to the slaughter house one week or two weeks before. It was an agriculturist responsible for the sale who took off the diseased animal officially to allow it to have feed him better, but he went to jail.

DR. BROWN: So, the answer is without a good veterinarian there wouldn't have been any detection; there

wouldn't have been any publicity. It would have been a non-event. So, these things have happened and may happen again. We have a long-waiting question or comment. All right, Jay.

DR. EPSTEIN: Jay Epstein, FDA. Dr. Deslys, I know that you didn't want to comment about the human epidemiology vCJD in France but I would like to press you on the point with the following observation. It strikes me as odd that the first two cases in France were reported very early on in recognition of the human epidemic, around '96, early '97.

DR. BROWN: The first case.

DR. EPSTEIN: The first case.

DR. BROWN: Not the first two; the first.

DR. EPSTEIN: Do you actually know the dates of the cases? Because the question I want to ask is whether the apparent lack of any increase is notable, and how that might correlate with estimates of the time period during which there were intensive infectious exposures in France. In other words, have you looked at the question of how long and in what magnitude there were potentially infectious meat products coming from U.K., and at what level has been the apparent persistence in France and does that correlate in any way with the apparent lack of a rising epidemic curve in France?

Also, I would like to focus on the apparent third case in France. It seems as if that individual has survived

a particularly long time. Is that true? And, does that, you know, negate that that is a real case, and is there any other supporting evidence, such as from MRI or tonsil biopsy or anything else, to establish that that is a case? And, are you reporting probable cases the way the U.K. is? In other words, do we have three but do we have some additional number surviving now who are probable that should be added to the total?

So, if you could just clarify a little bit better what we think is going on with human surveillance and whether there is any correlation with intensivity of BSE risk in France?

DR. BROWN: Did you get all that? Even I can't remember all, that but fundamentally he wants to know is there any correlation between BSE exposure and the frequency with which CJD occurs -- impossible answer because you only have three cases.

The second is about the diagnosis of disease in the third case, who is living a long time, and probable cases.

DR. DESLYS: I am going to try to respond to all of these points. First, the first case occurred in France -- I was personally anxious because it occurred in the region of Lyons which is very well known for cooking of brain and spinal cord. If we had had a guess for a case it would have

been there because of the culinary tradition. But, in fact, with only a few cases you can't do any statistics and it is only a gamble.

Second, concerning the apparent absence of correlation between the occurrence of cases and the explosion of BSE, in fact, even with the well-known reported situation'with human growth hormone in France we have seen variations. So we have to know that with this disease there are variations that we don't know how to explain.

Third, concerning the diagnosis, we are the reference laboratory to make a diagnosis by Western Blot in France. So, we have studied all the samples. To my knowledge, there is no other suspect case but perhaps we will be wrong in one week. I don't know. For the moment, there is no notion that another case is occurring.

Concerning the length of the disease, it is a common pattern with what we have observed with growth hormone but you have to note that people are abnormally young and so more resistant; second, they go back to their family and they are nursed very carefully. So, I think that is the interpretation that pediatrics gave me but we think that it goes through a longer evolution but, in fact, we don't know.

DR. BROWN: Jay, to expound on that, a diagnosis is a lock once the biopsy is positive and, two, all over

Europe, not just France and the U.K., cases are being referred as possible vCJD and 90-odd cases that exist now in Europe are culled from over 600 patients in Europe over the past few years that have been referred as possible vCJD. The European surveillance system is a beautiful thing.

DR. EPSTEIN: (Not at microphone; inaudible) . . . in France.

DR. BROWN: The notion is that exposure to BSE in France is probably less than a twentieth of what it would be in the U.K. The numbers, in simple-minded arithmetic, aren't bad when the U.K. had 60 cases, France had 3. That is about a twentieth. And, the exposure in other parts of Europe is at least in order of magnitude less than it was in France, judging by imported materials, and so forth, and so it is no surprise that even one case of vCJD hasn't turned up elsewhere yet. It may but they haven't checked.

Jean-Philippe, thank you very much. I think we will conclude the questions now. Ray, you have one and then we have to move on. All right?

DR. ROOS: One quick one, Paul. On one of Bob Will's slides you had the transfusion history of the vCJD patients. Was that figure high? In other words, were there a surprisingly large number of individuals who had received blood? It went by quickly.

DR. BROWN: No, probably low -- well, perhaps

neither low nor high. Perhaps one of the blood people here can tell you, but 7 donors, 20 recipients. That is to say, there were 7 donors who provided blood and some of the recipients got packed cells. If supplies were not thrown away that could be fresh-frozen plasma given to somebody else. So, the same donor could donate blood that would go into two labile components, or the plasma could be used for plasma protein production.

DR. LEITMAN: Can I clarify? None of those patients had ever received transfusions. They had been healthy enough to be blood donors in the past. So, 7 were known donors, of which 10 recipients had been transfused. Is that correct?

DR. BROWN: Twenty.

DR. LEITMAN: I am sorry, 20 recipients.

DR. BROWN: Those donors subsequently died from vCJD but it has nothing to do with whether they themselves had received blood. The answer to your question is -- and I admitted it from the slide because I thought it was confusing -- of the 91 patients in the U.K. that have died from vCJD, only one had ever received blood in his life -- not surprising in view of the youth of the patients. Usually you would expect, you know, ten or so.

The next presentation is going to be made by Tony Giulivi, from Canada, and he is going to give us the

Canadian viewpoint. Tony?

Canadian Assessments and Policies Concerning Deferral of Blood Donors who Resided or Traveled in Countries with BSE and vCJD

DR. GIULIVI: Thank you, Paul. Thank you for inviting me and I thank also the FDA.

[Slide]

What I want to do is to review what we have done in the policies, and we started to look at this question since 1998, post Kreever, and then realized that we had to change completely our structures in Health Canada and with hospitals and with blood systems because this is just one part of problems that we are going to hit in the blood system all the time and, therefore, we changed the way we worked. I want to explain that because the way that we work now is how we developed the policies.

[Slide]

So, what we did is develop in the blood-borne pathogens -- Health Canada is divided really in two in this area. One is the regulatory field and the other one is a public health risk assessment field, and we worked together to give information to our regulators so they could do policies. So, my division has centered everything on risk assessment.

So, what we have done in the last two years, we

had received funding, and so on, to develop these types of outreach into the hospitals and into the public health field to look at different populations and to get information so that way, when we put in a policy, we know what is happening. This is what is important here because now we have a central site in Canada so when we put in a policy for CJD we know what is happening to the patients; we know what is happening with the blood supply, plus, we get information from our two blood suppliers, which are CBS and HemaQuebec. That is important, the blood supply and what is happening at the level of the hospitals.

[Slide]

We also have developed in the last three years, and work together with the European centralized system for CJD surveillance. With that we connect with our food regulation people and we have a risk assessment group there. Then we have centralized labs, and so on, to do autopsies and genetics. And, we work very closely with the blood system on that.

[Slide]

What else we have done is we have made a division to work as a risk assessment for CJD and for other blood problems. This division will get information from different areas within government and outside. So, this works as a centralized risk assessment center to help to give

information to the regulators. It also works as an early warning system.

[Slide]

We knew that we had to look at the question of CJD in other countries. We focused on France but, in the meantime, we did risk assessments for other countries that had BSE. When we did this we looked at different models and different ways of doing it, but it is a total risk assessment so we looked at the internal risk, ourselves, how much we imported meats; how much byproduct meats we got from different countries. We looked at what is happening in different countries, in U.K. and France in that respect, and we made connections with these through the surveillance group, the CJD surveillance group, and they got the information for us.

Then we looked at external risks of us importing meats from other countries that could have gone from U.K. to France, to France, to Belgium, to Canada, and we got that type of information. It is very unconfirmed information because it is very hard to trace. But because we have a close relationship with United States, most of our imports come from the United States. We are 90 percent self-sufficient; 90 percent we get our meats from Canada, and the rest, 9.9 percent comes from the United States and 0.1 comes from elsewhere.

[Slide]

Then when we do a policy we always have to look at he blood supply risk, and we work with the blood people, he blood suppliers. The regulators will tell them to do a onor assessment, which they have done in the last three ears and they are still continuing to do that. Both emaQuebec and CBS are always looking at whom they'are ecruiting, where they come from, and so on, and they are eveloping a nice system there. We get that information hrough our regulators. They ask for the information from he suppliers and we get it through the regulators.

[Slide]

When we looked at how to do analysis and modeling, ve came out with four or five different models and when we applied it to France and then to the U.K., the model on that 3ob Will's slide, the model that Paul showed you, is the node1 that we preferred -- not preferred but we did a model that said let's look at proxies. Let's look at the number of cases of BSE and the number of cases of cases of vCJD and use that as a proxy; ignore the incubation period and come out with numbers.

The numbers we got for the U.K., and that is where we came with the six-months policy, they were between 200-something to about 10,000. The number that we got for France is about 50-300 people who have come down, total, with vCJD.

We are going to be publishing this data. A lot of journals have asked us to publish this so we are just thinking of which journal. But that is the model. And, we looked at two important models, one, case history-l, the proxy system, and that is how we developed the options for the regulators.

[Slide]

The background for the regulators -- apart from the fact that we do something and we give it to the regulators, they do their own background, their own information. So, for CJD is the theoretical risk. We had done precautionary measurements in the U.K. in August, 1999. Donor deferral, withdrawal of components and derivatives because of that policy.

[Slide]

The donor deferral basis was the basis of residence in the U.K. -- this is our first policy -- in the period of time between 1980 and 1996, and then cumulative resistance for six months or longer and this was done by modeling that we gave to TTP of the number of people that will come down with the disease with time. Just a model.

[Slide]

What we knew at that time was that in France there were three cases, and we used that information and with our first model we predicted, at that time, that we should see about three to five cases in France. That was last year. Now

we should have seen about five to six cases. But there are only three cases in France, as far as I know.

So, we are reevaluating the models again but that does not change the policy. It is just the science part where we are reevaluating the models and because of our lack of knowledge of the pathology and 'the lack of knowledge of the disease itself.

[Slide]

We are considering now occurrence of BSE, consumption of U.K. beef, occurrence of vCJD for countries of Europe, and what is important is this, these two factors: When we did the risk analysis for France the occurrence of BSE in that country, and if you project with our models to the number of vCJD it came to almost 0.001 cases. And, with the models that we saw in U.K., we related that back to the U.K. and the U.K. had 1000 cases per month, and going down, and that is how we did the model.

So, now we are relying on saying that the numbers of BSE, if they are small in that country and if the surveillance system is excellent -- we watch it very closely but we don't change the policy yet. We wait until this happens or there is a probability of this happening in that country.

[Slide]

Option of risk is the withdrawal of products based

on ten years. So, when we did the model it was either based on ten years because of that "20 percent factor." The other option was to reduce the U.K. further down to the corresponding period of France and the "20 factor" that we came out with, or reducing aggressively U.K. from six months down and not even touching France.' So, those are the options we had at that time.

[Slide]

What we did at that time -- there is a slide missing -- we had data from the blood services, and knowing that this was a theoretical risk that we were dealing with, we wanted to know what we were going to introduce as a true risk -- blood supply, introduction of new viruses or other viruses in the system. With that data, we did an analysis and came out saying, fine, the cut-off point of a new risk versus theoretical risk in our model was 2 percent loss of donors. When we got the information back from CBS and HemaQuebec, that six-month deferral corresponded to two-three percent of loss of donors. So, that made sense for us; maybe we should just extend that policy.

[Slide]

The other thing we had to do is consider another major problem because we get immunoglobulins -- 50 percent of immunoglobulins come from elsewhere, mostly from the United States. We are self-sufficient in other things like

albumin which comes from Canadian plasma which is manufacture in the States. Most of our Factor deficiency is all recombinant even though there might be an albumin portion to it but Factor VII, Factor IX is 100 percent recombinant in Canada. So, our problem was with immunoglobulins. What do we do with immunoglobulins if we import and have a policy that is not existent in another country like the United States or France? What are we going to do with our product?

The true risk of not giving that product to a patient versus the risk of spreading that disease was outweighed and that is why we said that Canada applies the same deferral for fresh components, but will not mandate, you know, the people in the United States that they follow our deferral. We prefer it but we don't mandate that.

[Slide]

This is because of this 70 percent -- it is really 50 but at that time it was 70 percent. What we have done though is make a recommendation to the regulators and to the blood services to look and go for plasma sufficiency and now they are coming up with plans for that.

[Slide]

So, in conclusion, for us it is still a theoretical risk even though some animal studies have shown the true risk is the blood supply availability. So, we have

o weigh other relative risk with the true risk. It has to e balanced. And, how do we manage this hypothetical risk? f we put a policy in, what are we going to do about it? hat is why we have these central sites in the hospitals now o assess what type of medical changes are going on if there s a reduction of blood.

[Slide]

This is just an overview of what is happening. ;ike I said, there is now this unit that not only works for :JD risk but for other blood problems. They get information irom all our central sites, communities, public health ;ites. We have a surveillance system for the hemophiliacs, :or the bone marrow transplants, and we have an active ;urveillance system for new viruses. We have about a :housand samples of unknown viruses from transfusions that ve analyzing now with history. So, that is all put in :entrally. That is going to help us to see what is going to ıappen with CJD, and also will help us see what is happening at the level of the hospital blood supply. One thing is supply that CBS and HemaQuebec know they have, but what is nappening at the hospital level and in the ordinary practices. Thank you.

[Applause]

DR. BROWN: Does the committee have any questions for Tony?

DR. EWENSTEIN: I was wondering if you have considered some of the data on fractionation of TSE activity in Fractions IV and V? You are worried about albumin a little bit and more about immunoglobulins where infectivity seems to partition away from that.

DR. GIULIVI: That is right, yes. We had data from different companies on this and when we looked at the data on TSE, the amount that is there, going through all the fractions, albumin came to be number one, but because of the problem that we see in Canada, that 90 or 100 percent of albumin comes from Canada, we didn't have to worry about it. It is not from another country. Since we put a policy in, it is our albumin. So, we were fortunate in that way. That is why we had to focus on the issue of immunoglobulins.

DR. EWENSTEIN: What I meant was that the immunoglobulin fraction also appears to benefit from the purification --

DR. GIULIVI: Yes, that is right. That is why we said we did not impose anything for manufacturing to comply with our policies, you know, from outside.

DR. BROWN: There was a question over here. Go ahead.

DR. LURIE: I would just like to ask you to enlarge a little bit more on what the thinking was in Canada when you extended the ban to amount certain amount of

residence in France. There is so much talk about that. Tell us what you thought about it; what the elements were; why you came down the way you did.

DR. GIULIVI: Yes. Remember, in Canada it is post-treever. Okay? So, that is one thing. The other thing is the precautionary principle that has been used for the U.K. So, we had that policy already, an official policy. So,' when TTP Looked at it, you know, they said they had a policy for one country; what are they going to do with another country? That is why they asked us to do the risk assessment and get the information. Our risk assessment pointed the probability of a person going to France and coming back and carrying that disease came, I think, to 0.01 of a Canadian traveling to U.K. coming back. Then we calculated the time and saw that if you spread that out in time it came to three years before you would have a person coming back, carrying that disease.

Now, because there was a policy already and because the policy stated that in countries with vCJD the TTP acted. Given the fact that the true problem would be blood supply and if the suppliers were able to supply blood in Canada, given the fact that the theoretical risk is so low, we went ahead with the policy. That is the thinking there and that is what happened. Right now, even though when we put the U.K. policy in we predicted a 4 percent decrease,

there was a 1.4 percent decrease. A lot of people self-deferred. But CBS and HemaQuebec did an aggressive campaign of bringing back donors. They did an excellent job. Then, when we thought about France the same thing happened. There was a little dip down and then the aggressive campaign brought it up.

DR. BROWN: We have two final questions. Ray has a question.

DR. ROOS: If I read some documents correctly, you separate residents in France from residents in U.K.

DR. GIULIVI: Yes, we don't combine them.

DR. ROOS: And, I wondered whether you would comment as to your rationale for that.

DR. GIULIVI: Yes, the rationale was simple. It was a logistic nightmare in the sense of how could you do four months plus two months in different countries? How would you get that information to the donors? There was a problem with the system, blood supply system, since the risk is the blood supply. That is number one.

Number two, the risk in U.K. is much, much higher than the risk in France. So, the policies don't add up. They are different. There is six months in one country or six months in another country.

DR. BROWN: Remember, Ray, that Tony earlier in his talk said that they were only reevaluating the science.

It would have no effect on the policy.

DR. GIULIVI: That is right, yes.

DR. BROWN: A question here?

DR. NELSON: I am not clear what the policy is. Exclusion in Canada for donors is six months either in France or U.K.?

DR. GIULIVI: Yes.

DR. BROWN: And a final question, Dr. Belay?

DR. BELAY: If you isolate HemaQuebec, what was the impact on the blood supply in Quebec of adding residence in France as part of the donor deferral policy? And, were you able to compensate?

DR. GIULIVI: Yes, HemaQuebec compensated very fast. HemaQuebec did their analysis. When they did their risk assessments for six months, three months, one month and so on, and looked at six months, they saw they would lose about 3.2 percent donors. The TTP, not us but the TTP asked what is your plan in place to recover those donors? And, they came out with a plan by which they have recovered -- in three weeks they recovered, right away.

DR. BROWN: Thank you. This is the first session of the morning. We are running a little bit behind so we are going to have a stretch break of ten minutes and then we will reconvene. Ten minutes.

[Brief recess]

DR. BROWN: We have two topics before the public hearing and the committee subject. The first subject is a very interesting one that has been brought up before the committee before and will continue, I think, to be of major interest. That is the potential dietary exposures of U.S. service personnel and dependents to the BSE agent. For this topic we have two colonels, Col. Severin from the Department of Defense, Vet Service Activity. Following him will be Col. Fitzpatrick from the Armed Services Blood Program Office. Col. Severin?

Potential Dietary Exposures of U.S. Service Personnel and Dependents to BSE Agent

COL. SEVERIN: Thank you.

[Slide]

Following the initial blood donor deferral policy for individuals who had spent six months or more in the U.K., DOD asked the FDA if they had considered service members and their families who had been in Europe during the same time period. We were aware that beef procurement contracts had included purchase of U.K. beef with delivery to Continental Europe. The FDA requested further information which was provided by the Army Surgeon General on 23 October, 2000. This memorandum is the basis for today's briefing.

[Slide]

Service members had four sources of beef while stationed in Europe. Obviously, the military dining facilities is one source; the commissary stores, which are DOD's version of a grocery store; the exchange outlets which would include convenience stores, snack bars, concession operations and cafeterias; and then, obviously, eating on the local economy. Since eating on the local economy is an individual choice, we have no information on the source of beef they bought for personal use or the frequency of the consumption of this type of beef item.

The contracting agencies were contacted for their procurement data, and this was compiled by the Office of the Army Surgeon General. Based upon the dollar value of these contracts, those records were kept from one to five years and then destroyed. Since we had to look back twenty years, the agencies had to provide us estimates instead of actual hard data numbers for the pounds of beef procured during this time frame. For carcass beef and box beef the procurement specification did require that beef shall be free of portions of spinal cord. However, this does not mean that if a spinal cord. is present the carcass would be rejected. All it means is that it would be considered as part of the veterinary inspection procedure for that offered lot by the meat packer and, depending upon how frequently this occurred, there may have been a price modification on

the contract but the carcass would not have been rejected.

[Slide]

Obviously, troop feeding, soldiers eating in the military dining facilities, were eating beef from the United States. The same is true for operational rations which would have included your MREs, your tray packs which are a hermetically sealed, institutional-packed type meal, or the hot meals that would have been prepared in the field.

[Slide]

The Commissary Agency does not do its own contracting. The Defense Logistics Agency provided contract support for all European procurement. During the 1980-1989 time frame beef procurement averaged 2.5 million pounds a month, and 35 percent of this amount came from the U.K. and 65 percent came from other European countries, which would primarily be Germany, Hungary, Yugoslavia, Denmark and Italy. Of the U.K. product, approximately 300,000 lbs monthly was delivered to commissary stores north of the Alps and 575,000 lbs went to the stores south of the Alps. These contracts were written on a monthly basis. Thus, the source of supply to a specific store could change monthly. The 112 commissary stores would distribute between 21 delivery routes, and contracts were bid as routes, not as individual stores. These contracts were for carcass beef which was split into forequarters and hindquarters at the packing

house, and further processed into retail cuts at the meat markets of the commissary stores.

[Slide]

In 1990 the Beef to Europe Program was initiated for commissary stores north of the Alps. This program entailed shipment of box beef of U.S. origin to Europe. This was a congressionally mandated program, not related to the issue of BSE. On the occasion of supply failure emergency purchase was done within Europe and 99 percent of this product came from German meat packers. All commissary stores within the U.K. participated in the Beef to Europe Program with the exception of the Edsel Commissary in Scotland. Shipments to the Edsel Commissary and to areas south of the Alps continued to be U.K. carcass beef up until 1994. In 1994 this was converted over to box beef and the annual amounts of beef shipped south of the Alps is shown on this slide.

[Slide]

AAFES, the Army and Air Force Exchange Service, was not able to provide estimates of total pounds of beef procured. They did use similar carcass meat cuts and distribution patterns as were described for the Commissary Agency. Records of beef purchase from the U.K. for 1980-1995 are not available. There are no records of U.K. carcass beef purchases after 1995. However, they did purchase primal and

sub-primal cuts through March of 1996 from the U.K. European beef was used by AAFES food service outlets and approximately 20 percent of this did come from the U.K.

Prior to the reduction of troop strength in Europe there were 54 hamburger franchises which operated as concessions. These operations used preformed patties which came from the U.K. through 1989, and in 1990 this was switched to either beef from the U.S. or beef that was ground in an AAFES operation in Germany which used a combination of U.S. and non-U.K. beef product.

This information answers the basic questions USDA posed back to the Office of the Army Surgeon General. I would like to point out, however, that the possibility exists that U.K. beef could have been consumed in areas outside of Europe. For example, it may have been purchased by naval ships resupplying in the Mediterranean Sea, or could have been provided to service members in southwest Asia at the time frame following Operations Desert Shield and Desert Storm.

Thank you. Col. Fitzpatrick will be doing presentations on the blood and dependent populations.

DR. BROWN: Col. Severin, I have a question.

COL. SEVERIN: Yes?

DR. BROWN: What kind of proportions would have been beef products rather than beef itself? Because beef

But any cooked meat product can be assumed to have been possibly contaminated by mechanically removed meat, which would have included nervous tissue.

COL. SEVERIN: From that standpoint, canned meat type products that we would have been purchasing would have been the same products that would have been shipped to the U.S. directly for importation, but I have no actual numbers for that.

DR. BROWN: Yes, Dave?

DR. BOLTON: I would like to ask do you have any idea of what other components, other than ground beef, would have been in the preformed patties from the U.K.?

COL. SEVERIN: I have no idea.

DR. BROWN: Laura?

DR. MANUELIDIS: I would just like to make a clarification or correction, as far as I understand it. When I was in England in 1989, we were informed that beef patties were 10 percent grain by weight up to the period of 1989. That was one of our discussion points. So, in fact, uncooked beef patties did have significant amounts of contamination.

DR. BROWN: Unfortunately, we don't have with us Ray Bradley or other experts because that is flat out in contradiction to what he has publicly said on numerous occasions. I don't know which of you is right. But I don't think we are in a massive government conspiracy mode here,

and I really don't know which is correct. It could be that you are wrong and it could be that Ray is wrong. In any case, at the least, in cooked beef products there would have been a high likelihood of spinal cord and ganglia included in it. That is, shall we say, a minimum level of risk.

Now, Col. Fitzpatrick?

COL. FITZPATRICK: Thank you, Dr. Brown. 'I am the Director of the Armed Services Blood Program Office and I will be providing you data on the numbers of active duty and dependents or family personnel stationed in Europe from 1980 to 1996. These numbers were provided by the Military Manpower Center at the Pentagon and do not include reservists who may have been stationed on active duty for training or extended active duty for training in Europe. They do not include government employees, in other words civil service employees of the United States Government stationed in Europe, or contractors to the Department of Defense stationed in Europe. I also need to point out that the reservists activated in support of Desert Shield/Desert Storm who were deployed to Europe, many to the United Kingdom and to Germany, to Italy and to Turkey are not included in these figures either.

I will be providing a very gross, rough estimate on the number of personnel dependents that may be affected if the committee accepts the suggestion published yesterday

by the American Red Cross and expands the donor deferral to the present and includes all of Europe.

[Slide]

In 1980 to 1989 -- and the figures are broken down this way to correspond to what Col. Severin has just told you about beef procurement in Europe, and we have also broken it down into numbers north of the Alps and south of the Alps so that you can see the differentiation given that he has provided you figures on the amount of beef available for consumption in those two areas.

During this time period, you can see that there was a total of a little over three million individuals who were stationed in Europe from 1980-'89; 1,400,000 were the active duty service members and 1,776,000 were their family members.

[Slide]

If we go to the next time frame where the area south of the Alps was receiving U.K. beef and the area north of the Alps was receiving the beef from the U.S. program, you can see that the numbers change drastically. The Cold War was over and we were reducing our numbers in Europe. There is about 125,000 affected from the active duty population, with 719,000 family members, for a total of 1,245,000.

[Slide]

So by combining those figures, we can see that there is a total of 4.4 million people who may be affected by a deferral policy involving the consumption of beef from the U.K. in these areas during these time frames.

[Slide]

I have broken that down and we asked the Military Manpower Center how many of these people are still actually on active duty because that is my major interest as the head of the Armed Services Blood Program. We currently operate 21 FDA-licensed blood donor centers to collect about 110,000 units of blood annually, or about 1 percent of the blood collected in the United States. We collect primarily from the active duty population so really the 215,000 figure here is the one I have used. We don't recruit heavily from the family member population.

[Slide]

Just so that the civilian collection agencies would have some numbers to work with, the numbers that are no longer on active duty or are no longer family members of active duty personnel that were stationed in Europe during that time frame of 1980-1996 total about 3.9 million individuals.

[Slide]

So the impact on our program would be that out of the current active duty population of 1,400,000, about

215,000 would be ineligible because of an expanded deferral. We have already deferred individuals who lived six months or longer in the U.K. when the FDA guidance was established that we should make that deferral. Using a gross estimate that Allan can refine, that is 15.3 percent of the entire active duty population. We know that the entire population of 1.4 million is not eligible to donate for other reasons and I have not adjusted those figures to make allowances for that. So, 15 percent of the active duty population will become ineligible should this deferral be expanded. And, the percentages work out about the same for the dependent population. That turns out to be about 16 percent.

[Slide]

We currently recruit about 130,000 donors annually in order to collect that 110,000 units of blood. Another rough estimate, that means we are recruiting about 9.2 percent of our total population. That is a little high. It doesn't account for repeat donors and it doesn't account for the civilians that donate to our program. A rough correction factor would probably reduce that to about 7 percent but we are still recruiting at a higher percentage rate than the 3-5 percent reported by civilian blood collection agencies.

If we have a ban enacted that denies us that extra 15 percent we will, of course, have to increase this recruitment number. That is probably doable within our

rganization. If, on the other hand, as the American Red ross suggested, we defer everyone who has been in western urope for over six months, again by gross, rough estimates hat could make as much as 47 percent of the active duty opulation ineligible to donate.

A very optimistic estimate which assumes that all hose individuals who are left would be able to donate says hat we would have to increase our recruitment to 17 ercent. Using a rough calculation that Dr. Epstein has entioned in the past that about 30 percent of the opulation is eligible to donate, and adjusting for that his 17 percent would have to increase to almost 57 percent of the available population. So, the impact of a deferral such as suggested by the Red Cross would be significant to our program. And, during Desert Shield/Desert Storm the military collected about 80 percent of the blood that was shipped to southwest Asia and we relied on civilian collection agencies for the other 20 percent.

So, my goal here was to make the committee aware of the impact of their decisions on our program and ask that they weigh the scientific and the hypothetical risk values accordingly and make a balance decision and we will, of course, comply with the recommendations and guidance of the FDA regarding collection of blood from individuals who had been stationed in Europe. Thank you.

[Applause]

DR. BROWN: Thank you, Col. Fitzpatrick. On the same topic, I think we will proceed directly to two brief comments, one by Dr. McCurdy and one by Dr. Williams, both on the topic of the possible effects of recent changes in the FDA blood-donor deferral policies on the U.S. blood supply. Dr. McCurdy?

Possible Effects of Recent Changes in FDA Blood-Donor Deferral Policies on U.S. Blood Supply

[Slide]

DR. MCCURDY: When the decision was in the process of being made to defer blood donors who had spent six or more months in the U.K., one of the requests that was made from the Office of the Assistant Secretary for Health was that we make an attempt to monitor the blood supply and see what effect this deferral rate would have on the availability of blood. The National Heart, Lung and Blood Institute began to do this as promptly as we could.

[Slide]

To refresh your memory, what we did was start out with a sample of blood centers. A sample of blood centers was selected from data available to the National Blood Resource Data Center of the AABB and was selected to be fairly representative of blood centers in the United States. We selected 27. There was a little bit of weighting to the

[Applause]

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Larger cities because we wanted to be a bit more sensitive to shortage than a truly random sample. We had one late dropout. There were six substitutes for dropouts, and the final sample was 26.

[Slide]

You will recall from a previous presentation that the various different centers took a while to get on line and, indeed, we didn't have a complete sample, I believe, until sometime in the summer or fall of the year 2000.

[Slide]

We, therefore, felt it necessary in making a time series comparison to correct the data for missing centers. We started out by doing a simple number correction, that is, dividing the data supplied by N centers and multiplying by the total sample. That is, if we got 20 centers we would divide by 20 and multiply by 26.

We also had data from previous surveys of the National Blood Data Resource Center that gave us the percent contribution to the total supply of individual centers, and after a while we began to do what I think is a bit more sophisticated correction but it, nevertheless, is a correction and one can ask questions as to whether that was reasonable or not.

[Slide]

We also decided to look at the blood released

rather than collected because we wanted to have information on what was available for distribution. On this slide we have the sample, the corrected sample actually. This is the percent correction so it is a bit more sophisticated than our initial one. These are the dates. We got 19 centers in January. We did get some data for the preceding three months retrospectively collected, but there were too few centers and I got the impression after looking at this with that information, that they probably weren't very reliable.

You can see the number of centers down here. We had data for October and November and those had a complete sample. The rest of them required some correction. This is, as you can see, an absolutely flat curve. The U.K. deferral had to be brought into play by all because centers by April. Some implemented it before that, but at least all of them had it implemented by April and there was no discernable change in the amount of blood released for distribution.

[Slide]

This shows the inventory during the same period of time. We collected inventory information on the first and third Wednesdays of each month, and there is some fluctuation here. Obviously, this is a regression line, a calculated regression line. As you can see, the slope is not significantly different from zero.

Again, here is the number of centers that

participated. We had a complete sample beginning with the first Wednesday in September, and have had a complete sample since that time.

I do want to point out that these data here do not speak to the issue of whether there is or is not a shortage. This is only the supply side. We had planned from the very beginning, and are still planning in the near future, to begin collecting data on the utilization of blood and transfusion services. That, of course, will give us the other side of the coin. Thank you.

[Applause]

DR. BROWN: Thank you, Paul. Now Dr. Allan Williams, who comes to us from the American Red Cross.

DR. WILLIAMS: Good morning.

[Slide]

I was asked to address three topics this morning related to donor related to U.K. travel. The first is the impact of the travel deferral from the perspective of documented deferrals observed to date. Second, based on the donor travel survey conducted in early 1999 to predict donor loss in relation to potentially expanded deferral criteria. Third, to address, to the extent possible, special populations of donors such a military dependents, tissue and cell donors and individuals who may have had exposure to animals that could potentially host TSEs.

Two preliminary notes, there are copies of my talk istributed to the committee. Anyone else who would like a opy is welcome to see me. I understand it will also be on he CBER web site. There is a handout which provides a onversion for the many percentages that you will hear in my alk to actual numbers of altruistic blood donors. I think t is important to remind ourselves that when we talk about ven low percentages we are talking about hundreds and housands of good people who donate blood for the good of thers, and. I think it is good to keep that in mind.

Because of time constraints, when there is nformation presented that has been presented at a prior eeting, I will go through that very rapidly.

[Slide]

Just a very brief overview of the survey which ill also support some of the data which will be presented oday.

[Slide]

The survey was conducted on a random sample of December, '98 or January '99 donors at 12 blood center sites. These included the five Reds sites plus three additional, extension REDS sites used for other surveys, plus the Red Cross ARCNET program. The total distribution was 19,000 optically read surveys with a single mailing and a cover letter from which we got 9500 responses, for about a

50 percent response rate.

Some of the other data collected was details about donor travel to the U.K. and Europe and some demographics, including sex, age, first time repeat donor status, and education.

[Slide]

Specific to the U.K., the question was, did you live in the United Kingdom or the Republic of Ireland bet 1980-1989 or, a separate question, 1990-1996. In fact, we ended up pooling these data and using the entire 16-year period. The intervals that we used to describe travel are shown here, and I think most of you are familiar with these.

[Slide]

Summarizing the data related to U.K. travel, crave1 by donors any time between 1980 to 1996, 22.8 percent of the donors and there was a wide range by blood centers, from 10.2 percent to 31.7 percent, particularly higher on the coastal areas, as you might expect. Travel was higher in relation to higher education, older age and repeat donor status.

I think one comment in relating the survey estimates to actual experience, we know we had higher survey return rates from repeat donors. That was corrected in the original estimate. We also recognize that there were more returns from older donors and from more educated donors. We

couldn't make that correction because not all of the centers had the demographics available for the sampling frame. In addition, these groups also donate more frequently so you don't really know how to make that correction, Per year travel to the U.K., 1.3 percent.

[Slide]

This, you will recall, is a comparison of donor loss for different periods of U.K. travel to the amount of person days in the U.K. that would be eliminated, and the figure ultimately chosen was a six-month deferral eliminating 2.2 percent of donors, with elimination of approximately 86 percent of the person day theoretical risk.

[Slide]

As far as what has happened since implementation of the deferral, we have some observations but there are a couple of points I want to make before showing those numbers.

[Slide]

Deferral occurs at several different levels, and we use the concept of self-deferral of the donor being aware through education of something that makes the donor ineligible for donation. This occurs before a blood drive and I think, particularly in the case of this travel deferral, there was a lot of immediate attention about the deferral. Some blood centers sent letters to their entire

donor base. I know Canada did and several Red Cross centers did. Several blood centers at the time of recruitment asked the question about travel so as to prevent these folks from coming in, and there were numerous telephone inquiries to the blood centers. Self-deferral can also occur at the blood drive prior to registration, based on donor educational material and, in some cases, the questionnaire itself is self-administered to the donor.

Then there is interview-based deferral. This is where the questionnaire is actually reviewed and/or administered by an individual. If that deferral then results, that is recorded as a U.K. travel deferral. Finally, a tough quantity to get at are individuals who may fail to defer appropriately. This could be not paying attention to the information, misunderstanding of the information, not heeding the travel deferral. These would be false-negative responses and we know from post-donation information, error and accident reports to the FDA these are fairly high for this particular deferral. We haven't examined specifically the causes behind that yet.

[Slide]

I say this as a preamble to the data that actually resulted from the on-site deferrals. The numbers are really very low compared to the estimate. For this deferral, within the American Red Cross system deferral is 3.1 percent. And,

61 percent of those donors deferred are repeat donors. From data shared by Marian Sullivan, National Blood Data Resource Center, based on the same 26-center sample described by Dr. McCurdy, deferral is 0.33 percent. This is probably the most representative estimate for the country because that is a good representative sample. Of that group, 75 percent were repeat donors. The difference between these two, I'would guess, is probably due to the fact that the Red Cross has fewer coastal areas represented and they use, for the most part, a self-deferral interview process which may facilitate donors leaving before they actually meet up with an interviewer. Some of the coastal sites that were high in the survey -- New York Blood Center has experienced 0.6 percent; blood centers of the Pacific and San Francisco, 1 percent.

An interesting comparison is with Canadian Blood Services deferrals. They ran a survey before ours and actually reached very similar deferral data, around 2, 2.3 percent. Their on-site deferral is 0.22 percent countrywide, but they also track data related to pre-site deferrals that had been administered through telephone interviews or recruitment prescreens by their blood centers and that added another 0.6 percent to the observed data. So, you can see there is some validation to the fact that there is pre-interview deferral happening.

[Slide]

I would like to now cover some of the data that we have relating to travel to France and other countries in Europe. The questions on the survey that dealt with this -- the first one is did you travel or live elsewhere in Europe between the period 1980-1996 with the same time intervals concerned? This is important because this provides the cumulative time interval spent in Europe, similar to what we had for the U.K.

A more limited question, because of space on the survey instrument itself, is individual travel to countries within Europe, particularly the BSE countries. For that, we asked, please indicate if you traveled to or have lived in any of the countries listed below. While we can't tie this specifically to intervals, it does provide prevalence of any visits to a BSE country during that time period.

[Slide]

So, data for this particular question related to the U.K. overall travel, travel to BSE countries other than the U.K., 29.2 percent overall and any BSE country at all, 35.5 percent -- again, a large range among blood centers up to the highest range of 47.7 percent for travel to any BSE country at a single blood center. There is overlap in this figure which is why they are not additive.

[Slide]

Now, using these data to predict what the impact

of a France deferral would be, one needs to make an assumption that there is similar duration of travel within countries, given the overall prevalence of travel to a country. So, the observation made for France is that 15.6 percent of the donors had been in France ever within that time period. This is compared to i2.8 percent in the U.K. Therefore, relating that to 2.2 percent U.K. deferral for six months, one would estimate a 1.5 percentage for six-month deferral to France or 0.7 as a factor to convert between those two.

In fact, Canadian Blood Services collected those data, once again, and actually experienced a 1.7 increase in deferrals for the addition of the independent six-month cumulative France deferral.

[Slide]

Shown here are the actual data from Canadian Blood Services. Figures are per 10,000 so 35 per 10,000 would be 0.35 percent that they experienced at the start of the U.K. deferral. You see this downward trend, a little lower in the summer time when the demographics change, and then back up to 1.8 percent in October. Between October and November they implemented the France deferral and the rate went up to 3.2, almost exactly a 1.7-fold increase in deferrals. I think that validates to a certain extent that estimate.

[Slide]

Shown here, without going through them specifically, is the prevalence of any travel to countries that had experienced BSE at the time we ran the survey, and these conversion factors could be used to compare them to the U.K. travel estimates that are more specific.

[Slide]

Shown here also for reference are bar graphs representing travel to the U.K., to Europe exclusive of the U.K. and any BSE country between 1980 and 1996. Two-thirds of this graph was shown to you at a previous meeting. What was added in was the graph for travel to Europe not including the U.K., and these numbers are included for your reference. Eurotravel not including the U.K. runs from a high, it looks like, 29.2 down to a low of 0.7.

[Slide]

This is a similar graph. This was actually presented at a prior meeting and it included a U.K./France figure. I would actually prefer that you use the conversion that I introduced a couple of slides ago because this actually, I believe, uses the figure for travel only to France plus Britain and I think the other one is probably more accurate.

[Slide]

What I did was follow up some of the analysis that we had pursued in the first discussion of this talking about

risk in terms of person days. So, among travel survey respondents -- and this gets a little theoretical so shout out if you don't understand it -- total U.K. BSE exposure, the travel to the U.K. experienced by survey respondents, 252,000 person days. Travel to non-U.K. Europe, a total of 516,000 person days.

Now, we used semi-arbitrarily a factor of one-tenth the risk in other parts of Europe -- and I should say that France is included here -- related to U.K. exposure. So I cut the non-U.K. BSE exposure to 51,602 person days, for total BSE exposure of 304,000.

[Slide]

Now, looking at the U.K. deferral of six months already in place, the U.K. person days of theoretical risk removed 217,000 over the 252,000, the 86 percent figure that you have seen before. Total person days of theoretical risk removed -- this is U.K. plus the rest of Europe, 217,411 over 304,000 or 71 percent. The residual total risk not removed, given these assumptions, is about 87,000 against the donor loss of 2.2 percent. Just to create an index here for comparison, I am using percent person days removed over percent donor loss, and the figure for this calculation is 32.5.

[Slide]

Doing the same thing, but here considering that we

have a six-month deferral already in place, what would happen if the U.K. deferral is reduced to three months? The residual person days removed would be 21.2 percent. The total person days removed would be 77.5 percent; additional donor loss, 1.2 percent, and the index here 17.6 percent, so a little lower efficiency for increasing that deferral.

[Slide]

The same thing for one month. I won't go through all the numbers but you can see the index is 7.8, again continuing to go down.

[Slide]

Now, to look at it a little differently, I am using here travel to Europe. Those of you who are holding printouts of the talk, please either change the numbers or cross out the next three slides because I made an error in the numbers that are there. The numbers shown on the screen here were corrected.

So, for consideration of deferral for a period in Europe of over five years, and this includes France, on top of the U.K. deferral of six months the residual person days removed is 2414. The error that I think I made was removing specific risk person days instead of overall person days. I think right now this is correct. You actually have less efficiency than I had originally calculated. So, 2400 person days removed, 2.7 percent residual removed, and overall an

index of 3.9 for Europe greater than five years.

[Slide]

Following the same train, a lower figure, three to five years -- think in terms of the mid-point -- 2.4.

[Slide]

Finally, Europe one to two years, 1.7. So, in summary, the numbers for these indices -- what was gained by the original six months deferral had an index of 32.5; three months U.K., 17.6; and one month, 7.8. The numbers for Europe are considerably lower, so just as a factor of efficiency.

[Slide]

Special donor populations.

[Slide]

I was asked to consider the 4.4 million dependent military donors who had been on bases and possibly exposed to U.K. beef, and asked to convert these two likely current donors in the nation's blood supply. Based on U.S. census data, the typical family is 3.1 individuals. Trying to get a reduction in this figure for underage individuals who would not be potential donors, we were able to reduce this to 3.7 million. Based on national health interview survey data, the percentage of all adults in the country who donate, i.e., 6.4 percent per year. So, estimated current donors, 236,800 or about 3 percent of U.S. donors per year. That assumes

equal donation rates by military versus general population, and there are no data but I suspect they may actually be higher in that population.

[Slide]

This is data presented before that I won't go through in detail. In the general donor 1198 REDS survey we had a question about ingestion of mammalian brain in foods. This was stimulated by a couple of Lancet letters talking about squirrel brain ingestion and CJD. So, we asked the question. In summary, about 8.7 percent had eaten knowingly mammalian brain at some point, and it boils down to 3.7 percent beef, 2 percent pig, 0.8 percent lamb, 0.3 percent squirrel and the rest of the numbers are lower.

[Slide]

Hunting of deer and elk was also presented previously, 13.3 percent of our donors are hunters; 6.8 percent overall have field-dressed an animal; 62.6 percent have known that they ate deer or elk, 40 percent of that killed in the wild; 5 percent don't know; and 0.2 percent know that they ate brain or spinal cord from the animal.

[Slide]

Tissue and cell donors -- it is very tough to estimate deferrals for these populations. There is certainly no travel information readily available. Surveys would be different to conduct. I think probably the only way that we

can attack this is to look at the populations, trying to get some basic demographic characterizations of them and otherwise assume that a screened tissue donor may resemble a screened blood donor if you correct for the demographics. So what I am going to put in for the record is just the demographics of the donors that we had traveling in the survey.

[Slide]

Distribution by sex was fairly even. We found that the females tended to travel a little more as they got older, and we have done regression on these which were represented at the first meeting. So, you can actually see the corrected values for these demographics. These are the univariate analyses.

First time versus repeat donors, 13.8 percent of first time donors traveled to the U.K. -- these are all U.K. data; 23 percent of the repeat donors, for an overall of 22.8 percent. A major difference there.

[Slide]

Age -- you also see a substantial difference, from 16.4 percent in the youngest **age** group up to a high of 30.8 percent in the greater than 65 group.

[Slide]

Education -- even a more remarked change, with the under high school level generally under 1 percent; high

school graduates 5 percent; college and college graduates up in the 30-35 percent range. So, clearly, this is correctable if you know educational data for the population of interest.

[Slide]

I was also asked to briefly address what sort of data systems would be appropriate'to readily make data such as this available for future policy considerations; As most of you know, we have a program called the Retrovirus Epidemiology Donor Study that is sponsored by the National Heart, Lung and Blood Institute. We have a somewhat similar program, ARCNET, within the Red Cross, and we have the National Blood Data Resource Center, also funded partially by the Heart, Lung and Blood Institute. All of these have established systems to collect research and/or blood adequacy data and all of them do the job very well. But for an integrated rapid response network we need a little larger representation than is provided by REDS. We need capable data systems at each of the participating centers so that we can do things like define highly representative sampling frames. We need a rapid survey capability, which means ad hoc staffing availability, IRBs available and, most importantly, the ability to not lose ten months to a year by having OMB review of federally funded surveys that are deemed to be of great importance. Such a network could also participate in the blood adequacy measurements in the

future.

So, I just wanted to put that on the table. We were able to conduct a travel survey. It was only by tremendous cooperation by our colleagues and a fortuitous circumstance of being able to use some systems that were already in place that we were able to collect those data.

[Slide]

Limitations of survey data -- survey risk estimates are reproducible. That has been our experience. But they are based upon self-report and the accuracy has not been validated by other independent measures.

[Slide]

I would really like to acknowledge everyone who has helped with all of the presentations to this committee. I won't list all the prior ones but, particular to this talk, Dr. Joanne Chiavetta from CBS, Marian Sullivan representing the National Blood Data Resource Center, Debbie Kessler from New York Blood Center, BaOguang Want and Steve Schweinfurth from Westat and Ed Notari from our ARCNET program who is our data manager and cruncher, and Mike Busch from Blood Centers of the Pacific.

I am sorry if I have exceeded my time but thank you very much.

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

[Applause]

Rather than take questions for Dr. Williams, I am sure that the committee from time to time, in its deliberations before lunch and its multiple voting, will undoubtedly ask for some of those slides to be put back up or at least for your interpretations.

I am now going to turn over the meeting to Bill Freas who will handle five presentations requested from the general public. I remind each of them that there is a strict five-minute time limit on each presentation. Bill?

Open **Public Hearing**

DR. FREAS: Thank you, Dr. Brown. The purpose of this is to give members of the audience a chance to comment on committee matters that are relevant to today's discussions. Based on our FR notice, I have received two written requests. They are from Jerry Singettary and B. Sachan. They have been put in the committee's blue folders and will be made available to the public on our web site.

In addition to that notice, I have received four requests to speak today during the open public hearing. The first request is by Dr. Robert Jones, President of the New York Blood Center. Will you come forward and make your presentation?

DR. JONES: Thank you for the opportunity to address the committee.

I am Dr. Bob Jones, President of the New York

Blood Center. I am here to express some serious concern about possible recommendations regarding the risk of transmission of spongiform encephalopathies via blood transfusion. We strongly support FDA's vigorous and continuing efforts to reduce all risks associated with transfusions. As such, it is my obligation to inform you of the serious medical impact of any further reduction in availability of red blood cells for transfusion in the New York Metropolitan area.

We are a major supplier of blood products for the entire New York-New Jersey metropolitan are, serving 200 hospitals and major academic medical centers. We distribute nearly one million components a year, which is remarkably high due to the transfusion needs of our tertiary care centers that provide care to patients from all over the world. Our most precious and scarce component is packed red blood cells, derived from volunteer whole blood donations. Of 600,000 RBC units distributed annually in our area, 420,000 units come from donations made at NYBC; 30,000 units are purchased from U.S. blood programs as surplus; and over 150,000 units, or 25 percent, are imported under our Euroblood program.

Last April, we experienced immediate drops in our collections when we introduced the U.K. deferral. We currently, as previously mentioned, defer up to one percent