UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE

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MEETING

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THURSDAY,

JUNE 1, 2000

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The Advisory Committee met at 8:30 in the Ballroom of the Holiday Inn - Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland 20879, Dr. Paul W. Brown, Chairman, presiding.

MEMBERS PRESENT:

PAUL W. BROWN, M.D., Chairman
ERMIAS D. BELAY, M.D.
DAVID C. BOLTON, Ph.D.
DONALD S. BURKE, M.D.
DEAN O. CLIVER, Ph.D.
BRUCE M. EWENSTEIN, M.D., Ph.D.
LISA A. FERGUSON, D.V.M.
PETER G. LURIE, M.D.
J. JEFFREY McCULLOUGH, M.D.
PEDRO PICCARDO, M.D.
SHIRLEY JEAN WALKER
WILLIAM FREAS, Ph.D., Executive Secretary

TEMPORARY VOTING MEMBERS PRESENT:

LINDA A. DETWILER, D.V.M.
DAVID G. HOEL, M.D.
SUSAN F. LEITMAN, M.D.
LAWRENCE B. SCHONBERGER, M.D.
F. BLAINE HOLLINGER, M.D.
PAUL R. McCURDY, M.D.
EDMUND C. TRAMONT, M.D.

GUESTS PRESENT:

LOUIS KATZ, M.D.
ROBERT S. ROHWER, Ph.D.
MERLIN SAYERS, M.D., Ph.D.
ROBERT WILL, M.D.

INVITED SPEAKERS:

ANNICK ALPEROVITCH, M.D., MSc.
JoANNE CHIAVETTA, Ph.D.
CHRISTIAN DUCROT, D.V.M., Ph.D.
MARC GERMAIN, M.D., Ph.D.
ANTONIO GIULIVI, M.D., FRCPC
DAGMAR HEIM, D.V.M.
JOHANNES LOWER, M.D.
SOPHIE MOLLOY, M.D.
FABIO MONTRASIO, Ph.D.
MARIAN T. SULLIVAN, M.S., MPH
KEVIN WATANABE, M.S.

PUBLIC COMMENT:

KAY R. GREGORY, M.S.
CHRISTOPHER HEALEY
PAUL HOLLAND, M.D.

ALSO PRESENT:

DAVID ASHER, M.D.
JAY EPSTEIN, M.D.
MARY BETH JACOBS, Ph.D.
ERNARD SCHWETZ, D.V.M., Ph.D.

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P R O C E E D I N G S

(8:34 a.m.)

DR. FREAS: Good morning to everyone. My name is Bill Freas. I'm the Executive Service of this Advisory Committee and before we begin, I'd like to go around and introduce to the audience the members seated at the head table. We'll be starting on the right-hand side of the room.

In the first chair we have a temporary voting member, Dr. Lawrence Schonberger, Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention.

In the next chair we have a temporary voting member, Dr. Linda Detwiler, Senior Staff Veterinarian, U.S. Department of Agriculture.

Sitting in the next chair is a temporary voting member for today, Dr. Susan Leitman, Chief of Blood Services Section, Department of Transfusion Medicine, National Institute of Health.

In the next chair we have a standing Committee member, Dr. Peter Lurie, Medical Researcher for Public Citizen's Health Research Group, Washington, D.C.

Next is a standing Committee member, Dr.

Bruce Ewenstein, Clinical Director, Hematology Division, Brigham and Women's Hospital.

In the next chair we have a standing Committee member, Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention.

Around the corner of the table we have a temporary voting member for today, Dr. Edmund Tramont, Professor of Medicine, University of Maryland.

In the next chair we have a standing Committee member, Dr. David Bolton, Head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

In the next chair is the Chairman of FDA's Blood Products Advisory Committee who will be serving today as a temporary voting member of this Committee, that is Dr. Blaine Hollinger, Professor of Medicine, Virology & Epidemiology, Baylor College of Medicine.

In the next chair we have the Chairman of the TSE Advisory Committee, Dr. Paul Brown, who is the Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke.

In the next chair we have a new member. I would like to welcome our Consumer Representative, Ms. Shirley Jean Walker, Vice President of Health and Human Services, Dallas Urban League, Incorporated.

In the next chair we have a standing Committee member, Dr. Peter Piccardo, Assistant Professor, Indiana University Hospital.

At the corner of the table we have a temporary voting member, Dr. David Hoel, Distinguished University Professor, Department of Biometry and Epidemiology, Medical University of South Carolina.

Around the corner of the table we have a standing Committee member, Dr. Donald Burke, Director, Center for Immunization Research, Johns Hopkins University.

In the empty chair soon to join us will be Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of California at Davis.

In the next chair is Dr. Lisa Ferguson. She's another new member. I'd like to welcome both our new members. Dr. Ferguson is Senior Staff Veterinarian, U.S. Department of Agriculture.

In the next chair is a temporary voting

member, Dr. Paul McCurdy, Consultant to the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

In the next chair is Dr. Jeffrey McCullough, Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Hospital.

The next four chairs are guest. Our guest for today are Dr. Merlin Sayers, Director, Blood Bank, Carter Blood Care in Bedford, Texas.

Next is Dr. Louis Katz, Vice President for Medical Affairs and Medical Director for the Mississippi Valley Blood Center, Davenport, Iowa.

In the next chair is Dr. Robert Rohwer, Director of Molecular Neuro-virology Unit, VA Medical Center, Baltimore.

At the end of the table is Dr. Robert Will, Consultant, a neurologist, Department of Neurosciences, Western General Hospital in Edinburgh.

I'd like to welcome all of you for coming today.

Now I'd just like to quickly read the Conflict of Interest Statement into the official record for today.

"The following announcement is made part of a public record to include the appearance of a conflict of interest of this meeting. Pursuant to the authority granted under the Committee Charter, the Director, Center for Biologics Evaluation and Research has appointed Drs. Linda Detwiler, David Hoel, Blaine Hollinger, Susan Leitman, Paul McCurdy, Lawrence Schonberger and Edmund Tramont as temporary voting members.

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

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

In 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 participant.

Dr. Louis Katz is employed by the Mississippi Valley Regional Blood Center.

Dr. Robert Rohwer consults with the American Red Cross and Baxter Healthcare. He is the principal investigator on a contract awarded by the American Red Cross and is negotiating contracts with the American Red Cross and Baxter.

Dr. Merlin Sayers is employed by the Carter Blood Care Community Blood Center.

Ms. Marian Sullivan is employed by the National Blood Data Resource Center.

Dr. Robert Will collaborates on our research project funded by Baxter Health Care. He also receives a consulting fee from Centeon.

In the event the discussions involve specific products or firms for which the FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such discussions and their exclusions will be noted for the public

record. Copies of the waivers are available by written request under the Freedom of Information Act.

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

So ends the reading of the Conflict of Interest Statement.

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

DR. BROWN: Welcome from the Chairman to the Committee members. We have the largest representation on the Committee today of any of the meetings over which I have presided, and I think today's meeting is going to be both good and interesting.

It is the result of the fact that the FDA a year or so ago asked for guidance with respect to the potential for iatrogenic transmission of CJD via blood or blood products and amongst the subjects covered were or was the possibility of risks from visitors to countries in which new-variant CJD has

occurred, and a year ago, that was limited to Great Britain.

Since that time, there have occurred cases of new-variant CJD in the Republic of Ireland, a case, and some cases of variant CJD in France, and therefore the FDA has decided to again ask the Committee about its recommendations both with respect to the standing guidance concerning the United Kingdom and whether or not the Committee should enlarge its perspective of risk to include those other countries in which new-variant CJD has occurred and even those countries in which BSE has occurred without the occurrence of new-variant CJD.

That is the subject of today's meeting and I think we should begin, and the administrative remarks I guess have already been taken care of by Mr. Freas and we now have Bernard Schwetz who is the Acting Deputy Commissioner for Food and Drugs and a Senior Advisor for Science for the FDA. Dr. Schwetz.

DR. SCHWETZ: Thank you, Dr. Brown. Good morning to all of you. I certainly want to extend welcome from myself and from Dr. Henney, our Commissioner, to all of the members of the TSE Advisory Committee and the guests that we have here

today.

There certainly are issues that surround TSE that are still numerous and it seems like they don't get any less complex as we continue to work through these issues. These are issues that tend to go across multiple parts of the FDA which make it particularly critical for us to have a good communication mechanism within the agency, but in addition, these tend to be issues that go across numerous federal agencies within the U.S. and as you can tell by the speakers today and the membership of this Advisory Committee, they also extend to the Federal Health and Regulatory Agencies throughout the world.

I would just comment in addition that advisory committees are extremely important to us within the FDA. They not only bring us scientific expertise that goes beyond what we have within the Agency, but these open meetings of advisory committees help to make some of the decisions of the Agency a more transparent process, transparent to fellow scientists and clinical scientists but also to the public and these afford the opportunity to have public input on topics that are of great importance to us scientifically but are also of

concern to the public. So advisory committee meetings that are held in public sessions of this kind help to provide access for the public to some of the issues that we're dealing with. So advisory committees of which we have many are very important to the Agency.

This Advisory Committee has helped to provide specific advice on a number of important issues including gelatin and gelatin byproducts, the safety thereof, tallow and derivatives, blood and blood products, human implanted tissues such as processed human dura mater and a number of other important issues of that kind.

In addition, our Advisory Committee members have participated in public workshops to help gather information and bring more information to the attention of all of us. For example, there was a workshop on TSE risks that was held in June of '98, that was organized by our Joint Institute for Food Safety and Applied Nutrition, a joint institute between the Center for Food Safety and Applied Nutrition of the FDA and the University of Maryland.

There was an FDA international workshop on clearance of TSE agents from blood products and implanted tissues that was held in September of

1999, and I would remind you that in September of this year, there will be an FDA NIH International Workshop on Diagnostics for TSE agents, and it has been helpful to have members of our Advisory Committee involved in all of these meetings.

The recommendations of this Advisory Committee have been helpful in formulating a number of actions taken by the FDA to prevent exposures of the public to infectious TSE agents in products that we regulate. A couple of examples here, "Guidance for Industry on Sourcing and Processing of Gelatin." It was issued in September of 1997. Also "Guidance for Industry and FDA Staff on Processed Human Dura Mater" issued in October of 1999. These are important guidances that we've been able to put out with the help of your advice.

Dr. Brown has already indicated that the primary agenda items today and tomorrow have to do with blood safety and also an update on the regulatory status of processed human dura mater. I won't take anymore of your time except again to thank you all for serving in this important role and I'm sure this will be a good meeting. Thank you.

DR. BROWN: Thank you very much, Dr. Schwetz. And before we begin this group of

instructive presentations, I would simply like to express my thanks and applaud the collection which in my judgment is an all star cast of speakers and the work of Drs. Asher, Jacobs and Epstein in putting this panel together. And in fact, Dr. Asher is the first speaker.

DR. ASHER: Thank you, Paul. This will be a preview of coming attractions really rather than a star performance. I'd like to wish you all a good morning. Today the TSE Advisory Committee will consider the issue of blood donors traveling to or resident in BSE Countries besides the UK. Next please.

Just to remind you the risk of transmitting CJD by blood and blood products is entirely theoretical. There has been no convincing case report of CJD attributable to blood. Six case control studies have all been negative. Dr. Schonberger's CDC survey of national mortality report suggests no link to blood exposure. Next.

Recipients of blood components from CJD donors being followed by Marian Sullivan who will speak on another topic later today and others reveal no CJD in recipients. A survey of more than 12,000 hemophilia patients, very high exposure to blood, no

cases of CJD. Next please. Next.

And finally, no CJD has been attributable to exposure to vaccines containing excipient human albumin in more than 38 million recipients. Next slide please.

However, there are conflicting experimental studies concerning blood of humans and animals with TSE. Infectivity has never been convincingly demonstrated in blood of humans with CJD or sheep or goats with scrapie or cows with BSE. However, those studies have all been limited and assays have most often been performed in mice which have suboptimal sensitivity. Rodents with experimental TSE, however, have been consistently found to have infectivity in blood and it seems unreasonable to think that such a regular phenomenon in one species can never occur in another. Next slide.

And when very high doses of TSE infectivity are spiked into blood although clearance is very substantial as plasma is fractionated, still some infectivity enters all derivatives and minuscule amounts have even been detected in albumin. Next please.

Because of the potential risk, the FDA

as recently as the end of 1996 has recommended withdrawal not only of blood in components but also of plasma derivatives to which a donor who was later recognized to have CJD or to be at increased risk of CJD had donated, but there were serious problems with that policy. First, there is no demonstrated risk to recipients of CJD implicated plasma derivatives. The risk is only theoretical. CJD withdrawals do not substantially reduce that theoretical risk since at least 25 percent of large plasma pools used to produce derivatives are likely to contain contribution from a donor who will ultimately get sporadic CJD. No screening question can defer such a donor and there's no pre-morbid laboratory test to detect them. Withdrawals additionally fail to retrieve most CJD implicated product. It's already been distributed by the time the case is recognized and finally it was clear that CJD withdrawals were contributing to some significant degree to shortages of some plasma derivatives. Next slide please.

So in January 1998, the Public Health Service Advisory Committee on Blood Safety and Availability suggested that the FDA should work with industry and appropriate consumer groups to relax

current CJD guidelines on retrieval and withdrawal of blood products to the extent necessary to relieve shortages of affected plasma derivatives. Next slide.

In August of 1998, the Surgeon General, Dr. David Satcher, announced a new policy which was soon followed by revised FDA guidance for industry recommending continued deferral of donors with classical sporadic CJD or increased risk of CJD and continued quarantine of whole blood and blood components including plasma from such donors but no withdrawal of plasma derivatives prepared from pools to which the donors with classical CJD or at increased risk of classical CJD had contributed. However, withdrawal of plasma derivatives and quarantine of intermediates prepared from pools to which any donor who had developed new-variant CJD was stressed, and there's several reasons for that. And the next slide.

First much less is known about the pathogenesis of new-variant CJD than about sporadic CJD. New-variant CJD is an emerging infection exotic in the United States, never recognized here and lymphoid tissues in patients with new-variant CJD contained detectible amounts of protease-

resistant prion protein while those of patients with sporadic CJD do not although it's fair to say that lymphoid tissues of subjects with sporadic CJD have been found to contain infectivity, but not large amounts or not detectible amounts of protease-resistant PrP.

And finally, authorities in the United Kingdom themselves decided not to source plasma for fractionation from UK donors which implied a certain lack of confidence in the raw material. It was probably that decision as much as anything that prompted review by the TSE Advisory Committee as Dr. Brown has mentioned of donors which spent time in the United Kingdom during the years of greatest potential exposure to BSE and led to further revision of FDA guidance last November. Next slide please.

The new guidance recommended the deferral of donors who resided in the UK for a period of greater than six months cumulative between the 1st of January, 1980, and the end of December, 1996. This was expected to reduce the exposure to BSE agent estimated as donor days resident in the UK by some 87 percent at a cost of perhaps 2.2 percent of the blood supply. Deferral of donors who had

received UK bovine insulin was also recommended. Retrieval of blood and blood components including plasma from donors deferred because of UK residence but no withdrawal of plasma derivatives for UK residence or for exposure to injectable bovine products from BSE countries, and finally, the agency was committed to monitor the effects of the revised blood policy on the supply of blood and to reevaluate that policy frequently. Next slide please.

There is reason to think that human exposures to BSE in the United Kingdom have been greatly reduced after 1996. First compliance with the prohibition on feeding ruminant meat and bone meal to ruminants is high there followed by a dramatic fall in BSE cases although there were still more than 2,000 recognized there last year. The so-called 30-month slaughter scheme was well in place and removal of so-called specified risk materials, neural and lymphoid tissues, from the carcasses of ruminants was also well in place. Recently the news from the UK as I hope we'll hear in a minute has been guardedly good. The number of cases of new-variant CJD unfortunately continued to appear but their rate is not markedly increasing after a

troubling bout at the end of 1998 and recently interim results of a survey for protease-resistant prion protein in lymphoid tissues of young people was negative. Next slide please.

But it is fair to say that concern regarding potential exposure to BSE in other European countries is increasing. Since January 1998, our USDA has considered all European countries suspect and prohibited the importation of all live ruminants and most ruminant products from all countries of Europe due to the potential risk of BSE. Next slide.

Recently diagnosed cases of BSE in cattle have increased in several European countries and a new country has been recognized with BSE. It was recently realized that there were substantial exports of UK cattle, beef and beef products to several European countries that continued during high BSE years and perhaps most troubling there are now three cases of new-variant CJD that have been recognized in France.

If new-variant CJD was acquired by oral exposure which is generally considered to be a route of low efficiency and a cross of species barrier, should we not then be concerned about the

possibility of IV exposure to potentially infected human materials? Next slide.

Or should we? As most TSEs, sporadic CJD included, only neural tissues contain substantial amounts of infectivity. Other tissues are less often infected and the amounts of infectivity there appears to be less. Next slide.

And many tissues including blood may not be infected at all or at least not infected consistently at detectible levels. In new-variant CJD, of course, the presence of protease-resistant prion protein in lymphoid tissues is of great concern, but lymphoid tissues of sheep with scrapie also contain detectible amounts of protease-resistant prion protein and infectivity but infectivity has not been detected in their blood. So why this level of concern about blood in new-variant CJD? Next slide please.

The problem, of course, concerns the uncertainty, the general uncertainty about new-variant CJD and the situation has been I think well articulated in general terms by the European Commission recently as what they call the "Precautionary Principle". Let me hasten to add on the advice of our legal experts that the

Precautionary Principle is a strictly European concept with no status in the United States and U.S. law, but it does express an opinion concerning risk that is common to governments everywhere, and that is "Where there is uncertainty as to the existence or extent of risks to human health . . . then institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent." And that's a quotation from the EC Court concerning the prohibition on imports of British beef. Next slide please.

Essentially decisions based on the Precautionary Principles are attempts to manage a risk that cannot be accurately and confidently assessed. As such, such decisions on risk are political, and that's not necessarily in a pejorative sense, based both on limited available science and on a response to public concern. Next slide please. Next slide please.

As for any political decision, those based on the Precautionary Principle are highly subjective and as such are prone to abuse because one person's idea of a prudent precaution may be another person's pandering to irrational fear either

on the part of the public or the regulator or worse than that. It may even be a non-tariff trade barrier serving some economic interest of the country involved. The European Commission has recently attempted to address that problem directly suggesting that when fairly applied any risk management measure based on the Precautionary Principle should be non-discriminatory in its application, consistent with similar measures taken previously based on a risk benefit analysis subject to review when scientific information becomes available.

I must interject here that we wait with great anticipation the results of direct assay of the infectivity of blood from patients with new-variant CJD in a variety of experimental animals. Perhaps we'll hear some more about that today.

And finally such a decision must explicitly assign responsibility for producing new scientific information to improve the assessment of risk as time goes on, and some of those considerations may be relevant to today's discussion in addition to the information that's going to be presented for review. Next slide please.

So let me turn to today's charge to the

TSE Advisory Committee. We're asking them to evaluate new information concerning new-variant CJD and BSE in the United Kingdom, France and BSE in other European countries besides France and the United Kingdom. Recognizing remaining uncertainties about BSE and new-variant CJD, please consider the risk that donors traveling or resident in France and other BSE countries outside the UK might have been exposed to and infected by the BSE agent and that their blood, blood components and plasma derivatives might transmit infection to recipients, that risks should be compared with that for donors in the United Kingdom. Next slide please.

The Committee should also consider, in the context of a risk-benefit estimate, any effects that recent changes in blood-donor deferral policy may have had on the supply of blood and blood products in the United States as well as effects to be anticipated if additional deferrals of donors are recommended. Next slide.

To help the TSE Advisory Committee in its deliberations, we have arranged today a program beginning with a review of recent events concerning new-variant CJD and BSE in the United Kingdom by Bob Will who follows me; projections of potential

exposure to BSE agent and cases of vCJD recognized or expected in France, later the Republic of Ireland; CJD and BSE surveillance in Switzerland; USDA estimates of BSE in various countries; USDA policies intended to prevent the importation of materials contaminated with the BSE agent in the United States; next, estimates of possible human exposure to BSE agent throughout the European Union and BSE and CJD surveillance activities and policies of the European Commission and of European national authorities; assessment by Canadian authorities of new-variant CJD risk to Canadians traveling to the UK and France; and finally effects of recent deferral policies on the supply of blood and blood products in the USA and estimates of further reduction that might be expected if additional deferral policies are recommended. Next slide please.

And the questions to be addressed and answered if possible, do Committee members believe that available scientific data on the risk of transmitting CJD and new-variant CJD warrant a change in current FDA policy regarding deferrals of blood and plasma donors and product retrievals? Please comment. Next slide.

Second, considering the current scientific data on the risk of new-variant CJD and potential impact on the blood supply, should FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence in France? If so, what time period, that is years during which there was greatest potential exposure, and what aggregate duration of exposure should be considered as a basis for the deferral? If so, should deferral be based on the combined duration of travel or residence in the UK and France? Next slide.

Should the recommendations apply to whole blood and blood components? Should they apply to plasma for fractionation? Next slide.

Finally, should the FDA recommend deferral from blood or plasma donation for persons with a history of travel or residence to BSE countries other than the UK and France? If so, which countries, during what time period, what aggregate duration of exposure should the donor deferral be recommended? Should deferral be based on the combined duration of travel or residence in all BSE countries? Next slide.

Should the recommendation apply to all

blood and blood components? Should it apply to plasma for fractionation?

I'm sure we all look forward to today's presentation and to the discussions that follow. I thank you very much.

DR. BROWN: Thanks, Dr. Asher. We begin with a presentation by Dr. Robert Will from Scotland. Dr. Will's experience with CJD of all types stretches back 20 to 25 years, at first limited to the United Kingdom and over the past decade expanded to the entire European community. The European Surveillance Program on CJD which many of you know has been occurring or has been in existence has put Dr. Will at its helm, and it continues to run very efficiently indeed. Dr. Will.

DR. WILL: Well, good morning, and I'm very grateful for the invitation to give a talk today.

Dr. Asher has very clearly summarized the major issues and indeed much of what I've got to say, but I think my role is to add some detail to Dr. Asher's comments. I'm going to start off with a brief description of BSE in the UK, and this is a figure taken from a report from December 1999, BSE in Great Britain, and it shows the total number of

cases as of December were 176,023 cases. It also shows that the incidence of BSE peaked in the early 1990s and has declined subsequently. This figure of 1,982 cases in 1999 has been superseded. There are no more than 2,000 cases in that year.

It also shows the cattle that have been removed from the human food chain due to various legislative measures and the total is now more than 3,300,000, including a large number removed because of the over 30-month scheme which indicates that cattle over this age should not enter the human food chain. Could I have the next? Thank you.

A number of forecasts have been carried out to try and indicate what may happen to the BSE epidemic in the United Kingdom in future years and these are two of these models, the Veterinary Laboratory Agency Model and the Wellcome Trust Model. These are mathematical calculations of what may be expected in terms of numbers of BSE cases and as you can see the central estimate and the VLA is just over 2,000 for 1999, 2,500 the Wellcome Trust Model, with numbers of cases dropping to 470 in 2001, a central estimate with confidence intervals and 866 with confidence intervals here for the year 2001.

So it looks according to these predictions although the BSE epidemic will continue to decline. Although, of course, the exact observation of the epidemic is very important. This is an important issue in terms of public health also because it does tend to suggest the risks from BSE are declining. Could I have the next slide please?

Of particular importance is the over 30-month scheme. An analysis has been done by the Wellcome Trust Center in Oxford of the numbers of BSE infected cattle that may be entering the human food chain under the age of 30 months in the last year of the BSE incubation period, that is cattle that are most likely to pose a risk to human health and the estimate of the numbers of cattle in this particular category are 3.1 in 1999, 1.2 in 2000 and 0.8 in 2001, with confidence intervals over here. I must add that in addition to the over 30-month scheme, there is the ban on the entry of specified risk materials into the human food chain, materials that are likely to be infectious even from these cattle should not be entering the human food chain.

So in summary it looks from this type of work and from these calculations that the risk to human health in the United Kingdom from BSE is

clearly in a major decline. Could I have the next slide please?

Now I'd just like to just briefly stress that the original evidence that new-variant CJD might be caused by the BSE agent was based on epidemiological information and also on the novelty of the clinical and in particular, the pathological phenotype of this condition, and I think the epidemiological evidence continues to indicate that this is a condition predominantly occurring in the UK consistent with a link with BSE and also that the phenotype is indeed novel. But in addition, there's been a range of laboratory evidence supporting the hypothesis that the BSE agent is the cause of variant CJD and these are listed here including transmission studies in wild-type mice and transgenic mice and most recently worked by Dr. Prusiner's group published late last year. And overall, I think there is now very strong evidence in support of the hypothesis that variant CJD is caused by the BSE agent. Could I have the next slide please?

I now turn to the numbers of cases of variant CJD in the United Kingdom. This is the latest figure in terms of death from variant CJD, 57

cases, mean age of death, 29 years with a range of 15 to 54 years; mean age at onset 28 years, range 14 to 53 years; median duration of illness 14 months with some variation and 26 males, 31 females, 53 cases tested, methionine homozygotes occurred on 129 of the prion protein gene. In the other cases we may not ever get results because DNA was not available. Could I have the next slide please?

Earlier this month, well, actually last month, an article was published which is in the papers which proposes diagnostic criteria for variant CJD which we believe allow us to report now not only on mortality but also on surviving probable cases or probable cases not yet reported in which postmortem results are awaited and we believe that these criteria have sufficient sensitivity and specificity to justify doing this. We also believe it's important to report these cases. It gives a more timely idea of what's actually happening with the numbers of cases and these are the probable variant CJD cases, that's 13 of these cases in addition to the 57 in the previous overhead. Eleven are alive, two have died, one in 1999, one died in 2000, and both are awaiting postmortem results. In this group, the mean age at onset is 25 years with a

range of 12 years to 42 years, nine males, four females. Genetic analysis available on five of these cases and will be available in many more of these cases in the future, all on methionine homozygotes and to date we have not identified any case of variant CJD death or probable with an alternative codon 129 gene type. The onsets of these cases one in 1996 and this case was lost to follow up because the individual moved abroad and we may never find out what happened to this individual. As far as the others, four had onsets in 1998 and eight in 1999. Could I have the next overhead please?

Now the major hypothesis for the cause of variant CJD is that this was due to oral exposure to high titer bovine tissue in the human food chain and we believe the most likely hypothesis is through contamination of food products with mechanically recovered meat. The reason for this age distribution which is restricted as you can see from age from approximately 14 at death to approximately 54 at death is not understood, and one hypothesis is that this age distribution is because of an age related dietary exposure to particular foodstuffs, and I thought I'd show this slide. This is the 72

cases of death and probable vCJD which are listed according to date of birth, and the hypothesis is that this group, major group in the middle are more likely to have been exposed to particular foodstuffs resulting in this particular age distribution. I must say that that is one hypothesis that's favored by some epidemiologists but not by all and it's just possible that there are alternative explanations including biological explanations but this is speculative. The other reason I wanted to show this particular figure is that we have to consider any potential cause of variant CJD in relation to BSE exposure and one hypothesis that has been publicized in the United Kingdom is that these cases might be due to vaccine exposure, vaccines contaminated with the BSE agent in their production. A risk assessment of this was carried out many years ago and suggested that the relative risk from this was very low indeed, perhaps negligible, and all I wanted to show was that the dates of birth of these cases as you can see, really the great majority were born before 1980, and it is most unlikely that any vaccines, childhood vaccines could have been in any way contaminated with the BSE agent even if they were at all up until the mid-1980s, and this makes

it very unlikely that these cases are related to vaccine exposure, particularly childhood vaccines. May I have the next slide please?

What about the trends with time? And here are the 57 cases that have died according to deaths per year and as you can see, there was an upward trend. This figure from 1999 is nearly complete. We believe it is unlikely that this will exceed 13 or 14 cases. So the total for 1999 will not be greater than 1998 and, of course, the data for the year 2000 is still incomplete.

The problem with looking at deaths is that there are medical interventions that influence when patients die. Some patients are treated with peg feeding, others are not, and this may influence how long they survive. Could I have the next slide?

And so we've also plotted the vCJD cases according to disease onset, that is to see how this looks and this shows a fairly level pattern, perhaps a slight increase although I must say that the data, of course, for onsets in 1999 and perhaps 1998 are not yet complete. This sort of data has been analyzed to look for short term trends by the PHLS on a regular basis and as yet, there is no statistically significant trend in terms of either

an increase or decrease in the numbers of cases of variant CJD per quarter.

What about long term predictions of what may happen? And a number of mathematical groups have looked at this with varying results and the problem with these calculations is there's so many unknowns including the mean incubation period, exposure, species barrier, et cetera. Could I have the next overhead please?

However, this is one example of the calculations that have been done. This again is from the Oxford Group, from Donnelly and Ferguson, published in 1999, and shows the bounds of the variant CJD epidemic size according to a number of assumptions. This is the total numbers of cases in this particular calculation. R is the mean number of people infected by, one, the maximally infectious bovine. Of course, this is unknown. There are a whole range of possibilities and this is the numbers of cases and, of course, since the cases are smaller in number for 1999, it does restrict the potential future epidemic, but this depends very much on how infectious BSE is to humans.

As you'll see, four to 14, this column, we have observed, we think there will be 13 cases in

1999. The reason I put this up is to show that it is possible that the numbers of cases in the year 2000 and perhaps in 2001 may restrict future mathematical predictions of any epidemic. If there are 10 and 29, between 10 and 29 cases in the years 1999 and 2000 in this model, this would restrict any future epidemic significantly in relation to these very large numbers here, and so the observed number of cases in the years 1999 and 2000 may be very important.

The other thing I should state is that the upper estimates, these very large numbers, are reduced by five to 10 fold if the SBO ban was more than 90 percent effective. Could I have the next overhead please?

Dr. Asher has mentioned the possibility of doing screening studies of lympho-reticular tissues in order to try and determine the numbers of individuals in the UK who might be incubating variant CJD and this is another analysis by Donnelly and Ferguson looking at the bounds of the vCJD epidemic size based on unlinked, anonymous testing of tonsil and appendix tissue and a paper was recently published in the Lancet by Dr. Ironside and colleagues indicating that 3,000 approximately of

these specimens had been negative in the first stages of the study. The reason I wanted to put this up is just to show that although this is clearly not bad news, it's very difficult to interpret this interim finding as good news because even if the results are negative, it still does not restrict the size of any potential epidemic in a major way. So I think it's an important study because of any positives, particularly if significant numbers of positives were found, it might indicate that there may be a large epidemic. The problem with a negative study is that it does not really preclude that. Could I have the next overhead please?

I'd now like to turn to the possibility of secondary transmission of variant CJD and there has been concern expressed that there might be a theoretical risk of transmission of variant CJD through blood or blood products as mentioned by Dr. Asher. We have been carrying out a look back study which is termed the Transfusion Medicine Epidemiology Review. This is results as of last November. At that stage, there were 51 variant CJD cases and six of these individuals were confirmed to have been blood donors. Thirty-one components were

donated and the component fate 14 were not transfused. Some of them discarded and not issued, some of them sent for plasma fractionation, some were not traced, but 12 were transfused. None of these transfusion recipients have been determined to have variant CJD as of yet. They do not appear in our register. The reverse TMER is to look at individuals with variant CJD with a transfusion history. There is one of these individuals to identify the blood components that have been transfused. Of this individual, there were 103 and 103 of the donor names were traced. None of these individuals appear on the register of variant CJD cases. Could I have the next overhead please?

Of course, it's an important study, the look back study, but it has limitations which I'm sure you're aware of. If you look at the year of blood transfusion, you can see that many of these blood transfusions were carried fairly recently and therefore if there was a significant incubation period, one would not expect that these individuals would have appeared with variant CJD as yet even if there were a risk and I must stress, this is a theoretical risk. However, we have a couple of individuals who in fact received a blood transfusion

many years ago. The other issue is what is the year of clinical onset in the variant CJD donor in relation to the year of the blood transfusion, and this is relevant because it is possible that the changes of infectivity being present in blood may vary according to where you are in the incubation period, perhaps more likely to be significant if at all the closer the blood donation was to the time of clinical onset and you can see that in some of these individuals the blood was donated actually relatively shortly before clinical onset. So no conclusions can be reached from this study as yet and we will continue it likely for the long term.

Dr. Asher had mentioned the various experimental studies that have been set up to try and determine whether there is infectivity in blood in variant CJD. A number of studies are ongoing and as far as I'm aware, there is no results from any of these studies as yet. Could I have the next overhead please?

The other thing I was asked to talk about was the European Surveillance System and also speculation about exposures to BSE in other European countries.

Since 1993, a system for harmonized

surveillance of CJD has been funded by the European Union. This originally included France, Germany, Italy, the Netherlands, Slovakia and the UK, but has been extended to other countries including Australia and Canada and since 1998, the European Union has also funded a separate system although it's linked and we have common meetings of other countries in Europe that were not at that stage carrying out systematic surveillance and these systems are also harmonized now. So we believe that if variant CJD cases are occurring in other countries in Europe, that it is likely that they would be identified. Could I have the next slide please?

What is the relative risk of BSE exposure in countries other than the UK? I'm sure this will be commented on later in this meeting and this is data supplied to me recently by John Wilesmith which shows the numbers of reported cases of BSE in France, Ireland, Portugal and Switzerland, showing that in all of these countries there seems to have been some increase although I think the Swiss data will be discussed in more detail later, the reasons for that. And although, of course, this does show an increase for example in Portugal, I must stress that the number of cases here are still

orders of magnitude less than in the United Kingdom and I think one could argue that the risks to the human population from indigenous BSE in Europe on current evidence are very much less than they are in the UK. However, a question does arise as to whether a risk to the human population could have been exported inadvertently from the UK during the 1980s. Could I have the next slide please?

What I'm going to do now is to show a series of slides just to finish off with of data supplied by the UK Customs and Excise of exports from the UK to other countries in Europe and elsewhere. The major caveat to this data is that the information supplied has not been validated by the importing countries, and I think it's very important to stress that.

Here's export of carcass beef from the UK during 1982 to 1985 and 1986 to 1990. Now I personally do not believe that carcass beef is likely to have been a risk factor in itself for variant CJD, but if one assumes, and I must admit it's a big assumption, that carcass beef could be used as a surrogate marker for imports of meat products that might be contaminated with BSE if possible, this gives some indication that the risk

could been exported through food products, and as you can see, fairly large amounts of carcass beef were exported to France for example, also to the Netherlands and the Irish Republic. Could I have the next slide please?

What about the export of meat and bone meal, the means by which BSE is thought to have been transmitted in the UK. There's another caveat to this data is that there is no available information on bovine meat and bone meal as such. All that we have available is all animal foodstuffs some of which might have been meat and bone meal. So again this is a major caveat but again fairly large quantities of feed potentially contaminated with BSE were exposed to the Irish Republic and France in particular, also the Netherlands. Could I have the next slide please?

Just to finish off with in my last two minutes, there has also been export of live bovines to various countries in Europe as well as the feed stuffs and meat and this data has not been validated but large numbers of cattle were exported from the UK to a range of countries in Europe and one of the caveats to this data is that many of these cattle may have been slaughtered at a very young age for

veal production and therefore are most unlikely to have posed a significant risk because they would have been culled at a stage at which they're unlikely to have contained significant infectivity. However, for example, one of the figures here in France is over 800,000 cattle exported from the UK between 1986 and '90, 109,000 to the Irish Republic and 670,000 to the Netherlands. It is possible that some of these cattle were allowed to reach adult life at which stage they might have a greater risk of BSE because of exposures in the UK. Could I have the last slide please?

Just for comparison I thought I'd show you some of the exports from the UK of live bovines to other countries including the United States. I don't know if this has been validated in the USA, very small numbers in comparison to the many very large numbers I just mentioned regarding some other countries in Europe, hundreds rather than tens or hundreds of thousands of cattle, and it is of note that in the Falkland Islands one of these cattle developed BSE and in Oman, two of these cattle developed BSE. Thank you for your attention.

DR. BROWN: Thank you very much, Dr. Will. I think rather than take questions of

individual presentations in order to keep on our time line, if you have members of the Committee have specific questions that they'd like to address to any of the speakers today, if they'd just make a little note and at the time of our discussions, we can interrogate any of the speakers.

The next presentation will be by Monsieur Ducrot concerning bovine spongiform encephalopathy in France.

DR. DUCROT: Thank you, Mr. Chairman. Dr. Dominique Dormont who is the Chairman of the French TSE Advisory Committee couldn't join you today. So he asked me to present the French situation concerning BSE and veterinary epidemiologists working on scrapie and BSE at the National Institute for Agronomic Research. Next slide please.

So I will address three questions. First, how is organized the surveillance and control of BSE in France? Second question, how efficient are these measures? And the third question, the data, what is the current epidemiological situation concerning BSE? Next please.

So first, surveillance and control. We will see the surveillance, then control of

transmission and then the identification of cattle which is a complementary and necessary aspect to control the disease.

Concerning surveillance, next please, a mandatory reporting system has been implemented in '90 in France based on clinical signs on cattle, cattle more than two years old and it is organized with local veterinary services and in each county, a specialized veterinary practitioner is trained and is looking at all of the suspicions seen by other vets and farmers and is sent for diagnosis of those suspicions that meet the criteria for inclusion.

Compensation of slaughtered animal has been improved in '94 and it is based on the real value and losses evaluated by a farmer committee. Then next please.

Since last year, the surveillance system has been reinforced in several ways. First, special attention is done on emergency slaughtering especially when there are neurological symptoms. Also special attention on animals imported from other countries like Switzerland and Portugal and also since December, a complementary control on the sample of old and poor conditioned cows at the ordinary culling. Finally, a test survey based on

rapid test is going to start in the very near future. I will come back to it further.

Now let's move to the control. First in yellow, the first point is the stamping out of the affected herds, the entire herd as well as all animals of the same age cohort, same age generation as the case, even if they were sold to other farms and also the progeny of the case. So these started at the same time as the mandatory reporting system.

Now in blue, the control of transmission via food through a meat and bone meal ban for cattle has been implemented in '90, and for all ruminants in '94. That's a few years later, we saw the first born cases, that means the cases born after the ban and it proved that the ban was not 100 percent efficient. So very strong measures have been taken in '96, complementary measures and they are the following: first, all dead animals from any specials are removed from the meat and bone meal process. Also tissues at risk from cattle and sheep are removed from the MBM. Also I didn't write it on the slide, but it was important to introduce every animal product in compound feed for ruminants in order to allow the controls.

Then MBM has been decided to be treated

133 degrees 3 bars 20 minutes in '98. In order to complete all these measures, in green, other measures have been taken to avoid introduction of BSE from United Kingdom. So in '89, MBM and cattle import was prohibited from United Kingdom but calves to be slaughtered by six month of age and this has been widened to all cattle in '96. Next please.

Now to sum up, surveillance and control of BSE started in '90 in France and have been improved regularly based on scientific knowledge and field data. But there are also benefits from the mandatory and individual identification of the cows. It started in France in the seventies and it has been computerized in several databases but can be connected with each other in order to allow the tracing of animals and they will be merged in a unique database this year. Next please.

Now let's move to efficiency of the surveillance and control. It's a very difficult question and I'm going to give you a few elements to answer the question. These will concern the negative clinical suspicions, the controls and the test survey. Next please.

So we do not have perfect criteria to evaluate the efficiency of a mandatory surveillance

system based on the voluntary declaration from the farmer. One method is to look at the number of negative clinical suspicions every year and I plotted that on the figure and I have to remember you that every suspicion is firstly seen by a specialized veterinary practitioner and he removes all the suspicions that do not fit the criteria. So all the removed suspicions are not plotted in the figures. Only animals that were sent for diagnosis. So what you can see is a general increasing in the number of clinical negative suspicions sent for diagnosis since '90 up to this year. We've a small peak in '96 which is the year of the BSE crisis and I think we can interpret that as an increase in the awareness of the farmers and veterinarians and, of course, are not plotted in these figures which is related to mandatory reporting system, are not plotted the cases sent for diagnosis in the complementary surveillance system last year, and if we had this data, we should add in '99 and 2000, more than 200 animals tested negative. Next please.

So the controls on compound feed for ruminants and MBM processing, they started in '97 and they are made by the Ministry of Agriculture and the Consumer Protection Office. Concerning compound

feed for ruminants, they look the MBM incorporation through the analysis of bone fragments and fish scale and there are also controls on the compound feed process and labelling. Concerning MBM, there are regular visits in all the factories several times a year and the process of the MBM is checked, is tested through protein transformation with an Elisa method. Next please.

The results of the control tests concerning compound feed for ruminants, 1,372 samples have been tested since 1997 to test the MBM incorporation and we saw a decrease in non-compliance situations from 3.3 percent in '97 to 0 percent this year. Concerning MBM, 55 samples have been used to test the MBM process and two did not comply with the recommendations. Next please.

Now the rapid test survey. It should be an important and practical way to evaluation both the surveillance and control of BSE and it is based on the same ground as the survey carried out by the Swiss. The goal is to estimate the prevalence of BSE infection on a population at risk. So which target population? These are all dead cattle and emergency slaughtering of cattle over two years old in the West of France. Why the West of France?

Because it is the part of France which is the most affected with BSE. The sample, all eligible animals will be tested up to 40,000 animals and it should allow us to evaluate a prevalence rate as low as 0.1 per thousand cows. It should be done by December of this year, and the analysis with one of the rapid tests positively evaluated by the EU. And the survey should start in the coming days. Next please.

We're going to move to the last questions, the epidemiological situation of BSE in France. We will see the cases up to May 15, the temporal variation and the incidence rate. Next please.

BSE cases up to May 15, we had 97 cases in France, BSE, the first one in '91 and among those one imported case from Switzerland. The detection method, 92 of these cases were found through the clinical suspicion, four through the reinforced surveillance since one year, and one through the complementary surveillance on old and poor conditioned cows since December. From these 97 cases, 90 were dairy cows and 7 beef cows. In all cases, we always had doubts about a possible cross-contamination of the compound feed given to the cow

with pig or poultry food. Next please.

Now the temporal variation of the cases. It is plotted in red on the figure and I put also the number of negative suspicions in green for each year. So a general pattern is an increase in the number of cases in the last few years and especially in 1999, we had 13 negative cases, but you can see at the same time that these increase is not proportional, but follows also the same kind of pattern as the number of negative clinical suspicions and I think we could incorporate part of the increase as an increase in the surveillance efficiency. Next please.

Let's look on the birth date of the BSE cases in France. If we make the hypothesis that most of the cases were contaminated during the first year of life which is not true for all cases, but could be true for the most part of them, it can give an idea in which periods, what were the important periods for contamination, and we can see two peaks on these figure. The first one is second semester of '88 and the year '89 and the second peak started in '93. Concerning the first peak, it just started with the feed ban in United Kingdom and finished with a feed ban in France and we know about at that

time MBM was imported from United Kingdom.

Concerning the second peak, it proves that the feed ban in France was not 100 percent efficient and it tends to be related to the fact that there were cross-contaminations of compound feed for ruminants and food for pig and poultry, but why these MBM introduced in pig and poultry food were contaminated with BSE, there can be two explanations. These are interpretations, of course. The first one is small recycling of BSE in France. The second one is import of contaminated MBM. Concerning the second one, we know that in '93, the European market became opened more largely, and it improved the import of MBM from different countries.

Concerning the recycling of BSE in France, we know also that it can be recycling from animals that were dead in France and recycled in the MBM or animals imported as Dr. Will said before, and at that time, the MBM process was not efficient as it was after '96 and '98. So tissues were not removed and also the process was not so strong for sterilization. Next please.

Let's finish by the BSE incidence rate in France and other European countries. I just gave a few numbers for '98 and '99 which are the years

with the most important number of cases in France and you can see that compared to the overall population, there are a million cattle over two years old, you can see that the BSE incidence rate in France is one of the lowest in Europe with Belgium and Netherlands, and this is due to the fact that France has the largest cattle population among these countries, about 11 million cattle. Next please.

In order to summarize and conclude, what do we expect for the near future? The number of observed cases depends of the combined effects of both the efficiency of the surveillance and the efficiency of the control measures. And the improvement in surveillance like in '90 or '99 was followed immediately by an increase in the number of cases, but the improvement in the control measures is delayed four years. It is efficient in the beginning, but we can see the effects four years later. So we expect for next year, the effect of the strong measures taken in '96 and '98, so we expect a decrease in the number of cases in 2001. At the same time, the test campaign that is going to start now and will be finished at the end of the year will give us much more detailed information on

the real prevalence value of BSE prevalence in France. Thank you for your attention.

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

We'll conclude the French story now and shift to humans from cattle, Dr. Alperovitch has headed the surveillance of Cruetzfeldt-Jakob disease in France for some years. She's part of the biomed CJD surveillance program and she will the data on the epidemiology modeling and predictions about variant CJD in France. Dr. Alperovitch.

DR. ALPEROVITCH: Thank you, Mr. Chairman, for you invitation to present the future situation about variant CJD in France.

Before presenting that, I will first summarize the organization of the surveillance of CJD in France. Data are centralized by a research unit of the National Institute of Medical Research which receive data about CJD suspicions from different sources, from medical clinics, medical and neurological clinics, from laboratory which are responsible for detection of protein 14-3-3 in CSF and this is the main sources of notification in France because for your information, during the year 1999, there has been more than 500 requests for

14-3-3 examination in CSF for possible CJD in France, and you have also received that data from the National Center from Iatrogenicity, many from gross hormone treatment and also from other sources. All these data are centralized by the unit and this unit produced official national statistic about CJD in France. Next please.

This system works since 1992 and during the period 1992 to 1999, the annual incidence rate of CJD, sporadic CJD, has increased from 0.7 to 1.4 per million and this is most probably the result of target surveillance. Postmortem examination is performed in about 65 percent of the cases. About 70 percent of case of prion protein gene examination and during the period of 1992 to 1999, about four percent of sporadic case were under the age of 50 years. Next please.

The first new-variant CJD case was notified to our unit in '95. This was a male patient, age 77 years. The date of death was '96. The profession of the patient was not exposed to BSE. He was a mechanic, at no interval traveled in UK and the only possible waste factor was the use of tonic for body building, but it was never possible to determine what was the exact compound of these

products. He has a medical history of congenital glaucoma but with surgery at six years old and this was methionine-methionine as Codon 129 of the prion protein gene. Next please.

The second definite variant CJD was a female, age 36 or 35 at date of the onset, dying in February this year. Also no professional exposed to BSE. She was a bookkeeper. No travel in UK and she was also methionine-methionine of the prion protein gene.

There is now in France a third case which is a probable case with criteria proposed by the UK Group. This case is very young. He's 18 years old and also has no history of travel in UK. He's still living. It's still a probable case and not a definite one. Next please.

So as Dr. Will point out, it is still very difficult to predict the epidemic of CJD in the UK and it is really easy to understand that it is more difficult to predict the CJD epidemic in France, and the only way to try to predict this number is to bear with our prediction about the predicted number of vCJD in UK and then to compare the exposure of the two population in UK and France to the BSE agent. Next please.

So there are four potential sources of exposure to the BSE agent for the France population. First is BSE cases in France; second, travel in Switzerland and Portugal; third, travel in United Kingdom or Ireland; and fourth, exposure to contaminated bovine material imported from UK. At the present time, we consider the two first sources of exposure as negligible and we consider only these two last possible sources. Next please.

To ourselves, the exposure to the French population who traveled in United Kingdom, the Agence Francaise de Securite Sanitaire conduct recently as to date in blood donor very similar to those which have been conducting in USA and in Canada. The study was conducted in 10 blood transfusion centers throughout France. It was a one week survey, October 18-24, '99, which include all persons who came to the selected centers to donate blood during this survey. So it was representative of the blood donor population. And the question that was very similar to that used in USA for the 1999 survey. Next please.

This is a comparison of the survey population to the general population, not the general population of blood donors, but the general

population of France, and as you can see, there is no major difference in men between the population of the survey and the general population, but the population of women is more diferent with an excess of young women in the survey compared to the general population of France. Next please.

This survey shows that between '80 and '89, 20 percent of the French population shad traveled in UK, between 1990 and '96, 25 percent and for the period '80 to '96, about 35 percent of the French population had traveled in UK compared to 23 in U.S. The prevalence of travel in UK was not surprisingly lower in older donors than in the younger ones. There was no gender difference and there was a lot of difference between center located in large urban area of area prevalence of people traveling in UK than in rural area. This was surprising. Next please.

The duration of stay, this is a cumulative duration of stay, is not surprisingly different in between USA and France, and in particular the numbers, the prevalence of very short stay is higher in France than it was in U.S. and actually in countries is a prevalence of longer stay, was higher in U.S. than the French population

is very low. Next please.

So the result of this survey is that about one-third of the blood donor population reported travel/residence in UK/Republic of Ireland, between '80 and '96, that short stay, that is stays less than two weeks cumulative, between '80 and '96, account for 10 percent of the total person-days of exposure and if this data from this survey can be applied to the French population as a rule, residents in France in person-days account for most of the exposure of the population, of the exposure to the BSE agent. Next please.

So in order to predict the risk in France compared to the risk in UK, the main assumption is that the risk or incidence ration between UK and France is proportional to the BSE exposure ration between UK and France. And this main assumption implies also the basic assumption which have been detailed in the report of the French Agence which has been distributed to every member of the Committee I think. Next please.

I will just emphasize two of these hypothesis, that is the risk of exposure to BSE linked to consumption of British bovine products in the United Kingdom and the risk linked to the

consumption of Brit bovine products in France are considered equivalent. This hypothesis does not take into account possible differences in the nature of products, especially some types of offal, entering the food chain or other possibly as for example the age distribution of the animals. Next please.

And there was also a very crucial hypothesis, that is the ration of exposure in France and UK was constant throughout the period, '80 and '96, and this hypothesis implies as a risk of infection by the BSE for a given period was also, the ratio of the of the risk was also constant during the period. Next please.

So on these hypotheses, there is a number of parameters which must be taken into account. The parameters are listed here. It's the total number of days for the period '80 to '96; the number of days spent in UK by French people; the total French population aged 18-65 presently at the time of the modeling; the proportion of French people who travelled in UK between '80 and '96; and the level of exposure for one day of stay in the two countries. Next please.

So the general computation, I will not

enter into the detail of the computation, but it's very similar to the model which has been used in Canada or for example to assess the exposure of the population to the BSE agent. The model takes into account all this parameter in the person being multiplied by risk of exposure evaluation. Next please.

So the number of CJD in France in this model is expressed as the number of CJD in UK multiplied by this quantity. There are two parts in this quantity. The first part is a ration of exposure between for one day spent in France and in UK, exposure to the BSE agent. The other part taken into account, the stay and residence of the French population in UK but it's clear, just a point, the total population of French and UK are very similar, about the same number of population. In this quantity, the numerator is very, very small compared to the denominator. So this can be summarized that the number of vCJD in France will be, if all the assumptions are correct, the number of CJD in UK multiplied by this factor travel in UK of the French population are negligible compared to this quantity. Next please.

So the question is what is the value of

this ratio? And to estimate these first two, there is data from France, from different institution in France and also from United Kingdom as pointed to by Dr. Will previously, and it's possible to compare this data from France, that is importation of bovine material from UK and this one, exportation from UK and they are very, very similar. We compared these two sources and it gives us almost the same results. So this data suggests that this ratio is comprised between 0.05 and .01. Next.

And this is the last one. So despite limitations about accuracy of data, all this data is not very precise and all hypotheses have to be discussed very, very carefully but despite this limitation about accuracy of underlying assumptions, reliability of data about French importations of bovine materials and reliability about data about travel and residence in UK, we think this study provides a rough estimate of the vCJD risk ration between France and the United Kingdom. Thank you for your attention.

DR. BROWN: Thank you, Dr. Alperovitch. Now we have a parallel presentation about first BSE and second CJD for the country of switzerland and the first presentation will be Dr. Heim of the Swiss

Veterinary Authority on BSE in Switzerland, history, surveillance, control, agricultural policies. Dr. Heim.

DR. HEIM: Good morning. I will tell you not only the 10 year old story of BSE in Switzerland, I will tell you about the surveillance, the control efforts and agricultural policies. Next please.

I will show you the evolution of the epidemiology, how it goes on, the BSE in Switzerland, the measures we have implemented and at the end I want to concentrate a little more on the active target surveillance we have implemented in '99 in Switzerland. Next please.

The situation before the first BSE case in Switzerland, in '86, the first case was diagnosed in UK. In '89, the first imported case was diagnosed outside UK. Then in '89, the first native case outside UK in Ireland and then in '90, we had to think about are we really free? What risk factors do we have? Do we have to implement prophylactic measures? Next please.

We looked at the risk factors known at that time for Switzerland and we saw that we had a very small ratio of sheep/cattle, scrapie is very

rare. We have only seven cases up to now. Then we had at this time thought generally sufficient sterilization of MBM. We had hardly any import of live cattle and MBM from UK, but we used MBM in cattle feed, but we thought we had more or less no risk. Next please.

So we started in '89. We wanted to have the proof that we have no BSE. So we installed a reference lab and they were trained in UK for diagnosis of BSE. We started early in '89 with an information campaign for veterinarians which are the most important science for BSE. Then in mid of 1990, we began intensive surveillance. We screened the brains of animals found with neurological symptoms and then in November 1990, we detected the first BSE case and so we could not prove that we were BSE free. We found the first case. Next please.

So we had the advantage that we could look at the measures implemented in UK and we implemented similar measures for the interruption of the infection cow-cow and first thing is the ban of importation of MBM from UK. We had no imports but we implemented a formal ban for MBM from UK in early '90. Then in December 1990, we implemented

restrictions for MBM from other countries than UK. Then we had a feed ban for MBM for ruminants in '90. We decided to incinerate all the BSE cases and in '93, we implemented the processing of MBM at 133 degrees, 3 bar, 20 minutes, in the batch processing system. Next please.

The measures implemented in 1990 for the interruption of potential infection bovine-human, the BSE cases had to be incinerated. The antemortem inspection for animals at slaughter is the next level. Then we had already in November 1990, we decided to eliminate the so-called SRMs and later on we had as well restrictions for import of meat products from other countries with SRM. Next please.

That was the situation in '96. You can see here the blue ones born before the feed ban, the red ones born after the feed ban. We had to wait five years until we saw results of the measures implemented in '90. A strong increase until '94, then the increase between '94 and '95 was not as strong and then in '96, finally the decrease but we had BAB cases. We had already in '93, one BAB case but later on when we have immunohistochemistry, we saw that it was not a BSE case, it was a

histologically doubtful case, but we had mistook it with BSE, but in '95, it began that we had BAB cases and in '96, we saw that it would go on and so we had to look what we do with these BAB cases. Next please.

And so we thought about is it vertical transmission? There were studies from UK, it may be vertical transmission. Are they food borne or can we find something else? Next please.

On the vertical transmission, we found no evidence in Switzerland. We examined all the living mothers of the BAB cases but we found no mother with neurological symptoms, and we examined all the killed offspring. We decided in September '96, to kill all the offspring of the BSE cows and we examined them clinically and histologically and we could not find indications of BSE. Next please.

And so we said we found out that the only explanation we have is the cross-contamination. Before '96, we had an SRM ban for the human food chain, but not for the feed chain and so infectious brain was used as raw material for MBM. It was treated with 133 degrees, 3 bar, 20 minutes, but you know that's not 100 percent perfect, and we imported material with the same conditions and so therefore

we had most probably infective MBM. It was forbidden for ruminant feed but not for pig and poultry and because it is produced in the same lines in the feed mills, they could be cross-contamination and we have as now we know two cases where cross-feeding was done on the farm. The farmers fed feed for pigs and poultry to ruminants. Next please.

So we decided in '96, we have to have the next level. We said we have to have two lines, one line carcasses, all the dead animals and brain, eyes, spinal cord of cows goes in one rendering plant and this MBM from this rendering plant is used as fuel in the cement industry. All the other materials not intended for human consumption is treated in another rendering plant. So we have a complete separation and that's the advantage in Switzerland, that we have only one plant for SRMs and cadavers. Next please.

So we hope that after '96, there should be no more cases born with BSE because the infectious material is not in the raw material anymore. We treated with the known conditions. The import is as well restricted only for MBM with the same conditions in Switzerland and so hopefully there won't be no cases born after '96. We are on

the way maybe to separate lines in the feed mills for pig and poultry and ruminant feed on the other part but it's still not decided. Next please.

So the situation in '98, we had a decrease until '98 and in '98, most people in Switzerland said the epidemic is nearly on the end. They calculated already '99, maybe 10 cases, 2000, it's more or less finished, but then we decided to do something with the Western Blot available and we decided to examine first BSE-herdmates and later on slaughter animals, normal slaughter animals. Next please.

So in '98 first, we checked herdmates of BSE infected animals because in the beginning of '97, we began to slaughter the whole herds of BSE infected animals in Switzerland as well retrospective, and we checked the brains of these herdmates and we found five positives. And then we thought there's maybe a risk population but what with the normal routinely slaughter of adult cattle and we started end of '98 to check 3,000 routinely slaughtered adult cattle and we found one positive. This one positive we were, of course, very interested what was with this animal. This was an animal without symptoms and by asking the

veterinarian and the farmer, we found out that this was an animal with severe mastitis. It was very painful for the animal and after the treatment of the mastitis, the animal began to kick during milking and didn't want to go back in the stable, and everybody thought it's because of this mastitis and kicking during milking is a typical sign of BSE more or less, but everybody had a reason or thought there was a reason why it is doing it. Next please.

So we looked again at our surveillance system and thought what are the factors influencing past surveillance system. We have mandatory notification since '90. The disease awareness is quite good. The information is distributed regularly. Veterinarians are not bad educated. The willingness to notify cases, that's another point. I told you we had since '97 a herds lot policy that's not very motivating for a farmer to notify a case. We decided on our result of the herds lot animals because all the doubles, the secondary cases we found, were born in a certain time period in one year before and one year after that BSE born. And so we decided only to do cow herd slaughtering in the last year and that helps a lot to notify the farmers. Then the compensation was in Switzerland

the whole time quite good. There were no problems and the laboratory competence was also good. Next please.

By then we began to think about what's the population we will most probably find animals with BSE in. We have dairy cattle population. We became more concentrate on this. We can concentrate on older animals. We have no problems with these animals, with the clear symptoms which are recognized, but we have problems to find animals with weak and atypical symptoms. We have problems with animals where the symptoms are not recognized as BSE like this animal with the mastitis. With the preclinical cases we have as well problems but we have no solution how to find it, but we decided to find the weak and atypical animals and symptoms not recognized. We could test the fallen stock and emergency slaughter. Next please.

So we decided in the beginning of '99 that we test all dead and killed cows and all emergency slaughtered cows. We didn't consider the normal slaughter cows and the routinely slaughter cows as a risk population but we decided to do a random sample of it because when the farmer and the veterinarians know that the line of the dead/killed

animals is blocked, all is tested, emergency slaughter line is blocked, all is tested, and farmers are human beings and they want to find a way out and so maybe they could go in the normal slaughter chain and we decided we have to check there a random sample. Next please.

These are the results from '99 and 2000. In the fallen stock, the dead/killed cows we examined nearly 9,000 animals. We found in 1999, 16; and in 2000, two animals. The emergency slaughter animals we tested 4,700. Up to now we found in 1999, six, and 2000, five. And we found last year as well in the regular slaughter three positive cases. Next please.

The tested animals, they are all first tested with the Western Blot from prionics and then for the confirmation we tested the immunohistochemistry and histology. We had seven cases where the Western Blot and the immunohistochemistry was positive, but the histology was completely negative. We had nine cases where the histology could not be done because the material was utilized. It was more or less a soup mixed with some flux and immunohistochemistry was possible but not histology. And we had 16 cases where all three

methods were positive.

Then to the clinical signs, there's always rumor around that the animals we find have no signs. That's not true. A third of the animals have clear typical BSE signs. Another third have weak typical signs. It's a bit more difficult to diagnose, but the symptoms were there. We were sometimes a little bit puzzled like this animal with the mastitis, and then we had a third with no typical signs of BSE but they all had something else. Nearly all of them had reduced milk yield and chronic wasting. Quite often they had claw problems and so they had movement disorders but because they had claw problems, people thought it was because of the claw problems. Quite often they had mastitis and some animals, well, we only know at the end through recumbency and nothing else. Next please.

So that's the situation today. How you can see in '99, we had an increase not only because we have this new surveillance program, that's the column in yellow, as well, the clinically suspect cases found positive, we have an increase. Of course, because of the disease awareness, it's much better now. The people know they will be caught when they go in the yellow lines and so they know

they have to notify us. The other one is that in '99, we implemented the cow herd slaughtering and that helps as well. And this year in 2000, we have more cases now found by -- as clinical suspects than by the actual surveillance. You can see it switched to the other side. The people know more now and they notify much more cases.

Here you can see the number of BSE cases according to the year of birth. You can see 1990, the feed ban. It worked but not perfect. Then we had cases now born until '95. We have until now no cases born in '96, but we expect them but hopefully we will have nothing born after '97. You can see an increase until '94. '95 is a bit less, but we cannot say really there is already a decrease. It's a bit too early. Next please.

You can see here the number of clinical suspects as well the negative cases, clinical suspect cases. We have an increase. In 2000, this year; we have nearly the same amount already like in the whole year last year and we will have quite a lot of more cases. So the active targeted surveillance helps to make the positive surveillance as well better.

So the question is, the true prevalence

and the conclusions from our targeted active surveillance we can say the passive surveillance system is quite subjective. It depends on quite a lot of factors and therefore variable. It's quite difficult to interpret and compare between countries when one country is making a positive surveillance more or less good or not good, and the other country makes an active targeted surveillance and we conclude that surveillance based on clinical signs is not sufficient and to be a bit nearer the reality, an active targeted surveillance helps a lot. Thanks.

DR. BROWN: Thank you very much, Dr. Heim. The last presentation before the break will be from Dr. Montrasio of the University Hospital in Zurich who will present his information on the surveillance and public-health policy on CJD in Switzerland.

DR. MONTRASIO: So first of all, thank you very much for the invitation to speak here. And may I have the first slide please.

So what I'm going to present to you today is our CJD surveillance in Switzerland and afterwards some public-health measurement that we took to reduce the risk of transmission to human

beings. So next slide please.

So in the first slide I want to present you how our surveillance system is built. So the central part is our Swiss National Reference Center for Prion Diseases which was started in 1995 and all the samples or the referral samples are sent to us to be analyzed and the major important service in Switzerland is the Swiss Health Department which is the regulatory authority in healthcare, maintaining the statistical analysis of CJD incidence and regulate biosafety for both hospital and laboratory practice. So all our cases are normally detected in the hospital where they normally analyze the CJD clinical diagnosis by different methods. So they just analyze the progression of the neuropsychiatric disorder and they perform EEG analysis and MRI and sometimes they collect probes which are then sent to us to be analyzed and they took sometimes, brain biopsy they call it CSF probe for 14-3-3 protein analyses and in case of death, sometimes they perform autopsy and if not, they send the patient to us where we perform the autopsies. And CJD and other prion disease in human and signs, 1988 mandatory notification.

So in our center what we do normally is

we collect patient and then we analyze brains and we do two type of analysis. The first is the histochemical examination and then we do biochemical examination and the third issue in our analysis, DNA analysis is where we want to check possible point mutation within the PRNP chain.

We put very high importance to collection of human tissues to establish a bank where we have different tissues from patient and from controlled patients. And third, we also help to produce statistical analysis of CJD incidence. Please next slide.

So some more details about our work in the Institute of Neuropathology and Disease Center for Prion Diseases, so the first what we perform is normally the autopsy of patient and of collection of tissue probe and we took always two type of probes, the frozen tissue to perform analysis and the Western Blot and then we took always a formalin-fixed tissue for histological examination. What we perform at the level of immunohistological examination is hematoxylin and eosin staining just to have a look at the tissue, whether it's damaged or not. Then we produce Alcian blue, silver staining, GFAP staining, beta alpha 4 protein, tau

protein, alphasynoclene and PrP. So that means that we are not just looking at possible PrP protein by having a look at the PrP staining in those tissue, but we want also to see if there are other differential diagnosis possible as Alzheimer's disease or Parkinson's disease.

The third level is the biochemical examination. We perform two type of analysis. The first one is to look whether we can find there pathological is a form of the PrP protein in brain extract and the second type of analysis is the 14-3-3 in immunoblot to see whether in the CNF there is augmentation of this protein.

And the last analysis we perform in collaboration with the Department of Neurogenetics in London is the sequencing of the PrP gene to see which type of amino acid is present at the site 129 and also to verify if we have point mutation which are linked to human in a familiar form of the disease. Next slide please.

So this is just a table summarize all kinds of probes we collect when performing autopsy. So we collect about 13 to 14 brain region and all of them we collect tissue, frozen tissues and some of them we collect formalin tissue and then we collect

also other organs as muscle, skin, spleen, small intestine, peripheral nerve, tonsils and lymph node, and since the appearance of the new-variant CJD form we are now taking also appendix to verify if we have PrP staining in the appendix. So next slide please.

So in this slide, just to summarize our standard diagnosis of PrP in brain slices of patient, so what we perform is EH staining to verify the presence of vacoule and neuronal loss. Then we perform a GFAP staining to detect astrogliosis and our final demonstration of CJD is the accumulation of the pathological form of PrP protein. Next slide please.

So the biochemical characterization is always done at two levels. So the first is the detection of the pathological PrP scrapie form and we perform always the analysis before proteinase K digestion and after proteinase K digestion. In this blot, you can see that we have two confirmed CJD cases where we can detect after proteinase K digestion, PrP scrapie. Then with normal -- we can find PrPC before proteinase K digestion and after digestion with proteinase K, PrP is completely degraded. So there is no PrP scrapie left and this was one case which was sent to us as probably CJD

but in our case we confirmed by Western Blot and also by histopathological analysis that this was not a real CJD case. For the 14-3-3 immunoblot we received CSF probes and then we just searched for the protein by immunoblot and you can see that in CJD patient we can detect the CSF, the 14-3-3 protein in the CNF whereas in the normal control patient we don't find it. Next slide please.

So just to go to some data analysis of all the cases we received starting 1996, so here are the referral case we receive every year. Here are the number of cases which we receive as already CJD by clinical diagnosis and here is our final determination of the disease and as you can see, we receive always much more suspected cases than what we really found and confirmed as CJD cases. And there are a lot of cases which are found to be caused by other diseases, Alzheimer or other CNS diseases. And as you can see the number of cases during the last five years maintain constantly. So we don't have any increase of CJD cases in Switzerland and what is good science in the appearance of new-variant CJD and also all the cases analyzed until last year, we did not find any case of new-variant CJD. So next slide please.

So here is the panel with the number of cases per year with the incidence of CJD per year. As you can see that in the last around 10 years, the number of CJD cases in Switzerland per year remain quite constant. We have a slight increase in this year, but it is not really significant and also the incidence of CJD cases per million inhabitants remain quite constant. Next slide please.

Here is the analysis of all CJD cases will receive in regard to the age of the patient and what results are important in this case is to analyze whether we have cases of new-variant where the onset of the disease are in the early stages. So what we have here is that the distribution is mainly like normal spread CJD cases where the main group is around between 16 and 17-years-old patient. We have very small number of patient which are between 40 and 49 years old. So next slide please.

So what we doing to check CJD and also to reduce the possible risk of transmission of CJD to other human be. So the first thing is really our surveillance of prion diseases. This is the major point where we can check every suspect case and then we have really to find out whether we have new cases of the new-variant CJD and then to look whether the

incidence of the disease in human has increased during the last times. And the other what we implement in the last year is the blood donor policy. So we want to avoid possible transmission of CJD or new-variant CJD to patient who receive blood or blood products. So what we did in the last time was to defer potential blood donors that received either dura mater or corneal transplantation and also people who receive treatment with human hormones where deferred from blood donation. And to increase the safety of the blood and blood products, we didn't use anymore breach plasma and then since last year we introduced leukoreduction not only to reduce the risk of transmission of CJD and new-variant CJD, but also to reduce the possibility of transmission of other viral diseases. So the next slide please and the last.

I have to thank the collaborator which are involved in our work, prion disease surveillance and, of course, my boss, Prof. Adriano Aguzzi and other people involved. Thank you very much for your attention.

DR. BROWN: Thank you. We are in the unusual position of running ahead of schedule and we

therefore have about 10 minutes during which the members of the Committee if they have questions of any of the speakers so far, we can entertain them. And before I do, if the presenters do not have microphone in front of them which most of them would not, when you answer the question, there is a microphone over here to the left. If you could go to that microphone and answer the question from it. Larry. Oh, I'm sorry. There is a roving microphone here. Okay.

DR. SCHONBERGER: I was wondering if each of the speakers would comment --

DR. BROWN: Each of the speakers?

DR. SCHONBERGER: What's that?

DR. BROWN: Each one?

DR. SCHONBERGER: Yeah. With regard to the block between the animals and the humans. I'm not sure I heard -- I know Will mentioned because he talked about whether there will be a few cases maybe in the next couple of years, but at least they have a specified risk material ban that he thought would reduce the risk of the material getting to the human food chain, but I don't recall that from France or I think maybe I did hear a little bit from Switzerland that they instituted something, what was it, if they

could review that issue. That's what I was trying to focus on.

DR. BROWN: So you'd like each of the speakers to specify what measures were taken in their respective countries to prevent high risk materials from reaching the human food chain.

DR. SCHONBERGER: Correct. Yes.

DR. BROWN: Okay. Bob, you want to summarize that?

DR. WILL: Yeah. In the UK, the specified bovine offals ban as it was called at that time was introduced in England and Wales in November 1989, and as I recall in February 1990 in Scotland and Northern Ireland. I believe that it is possible that that ban was not fully implemented but I think that in 1995 there was a ban on the use of vertebral column from cattle in mechanically recovered meat and I think in 1996 there was a ban, the 30-month scheme was introduced. So I think that the measures that were introduced in the UK in the late 1990s will have significantly reduced any exposure and I think from '95, '96, the measures will have in my view led to a negligible exposure of the human population to the BSE agent.

DR. BROWN: Yeah. And in the UK, the

specified risk ban also applied to nutritional supplements aimed at pigs and chickens and so forth?

DR. WILL: A ban on the feeding of ruminant protein to ruminants --

DR. BROWN: Yeah.

DR. WILL: -- was introduced in July 1998 --

DR. BROWN: Right.

DR. WILL: -- and in 1990, that was extended to other species including pigs and poultry because of experimental transmission --

DR. BROWN: Right.

DR. WILL: -- of BSE to pigs by intracellular inoculation.

DR. BROWN: Okay. Would there be a choice between the French representatives. Annick, you want to take France?

DR. ALPEROVITCH: We compared -- for human food, we compared the measure taken by United Kingdom in France in order to make predictions of modeling of variant CJD and the measure have been taken almost at the same time in France and UK, is the reason why it was possible to make the assumption that the ratio reached was similar in the country because the measure was similar.

DR. BROWN: So the same measures were taken in France at about the same time.

DR. ALPEROVITCH: Almost at the same time, within a few weeks.

DR. BROWN: Okay.

DR. ALPEROVITCH: For human food. I'm not sure for animals.

DR. BROWN: And in Switzerland.

DR. HEIM: In Switzerland, we have implemented an SRM ban in November '90.

DR. BROWN: I'm sorry. I didn't catch that.

DR. HEIM: In Switzerland we have implemented the SRM ban in November 1990.

DR. BROWN: Right. Yes, Susan. Excuse me, Susan, before you do, I think Mary Beth, you had a question earlier.

DR. JACOBS: I had a question for Dr. Alperovitch. Your French documents specifically addressed the role that UK travel might play in blood safety and risk compared to the risk from exposure from UK beef within France, and I think it would be helpful to have you address that point.

DR. ALPEROVITCH: Could you repeat your question?

DR. JACOBS: The question was that your report which the members of the Committee got and we put on our website, specifically looked at the risk of exposure to the BSE agent within France compared to the risk of your blood donors who are going to the UK and drew some conclusions about whether or not deferral based on travel would reduce your risk and could you discuss that?

DR. ALPEROVITCH: Yes, it is the opposite of my analysis. The analysis at present shows that travel in UK play a very, very small role in the exposure of the rural French population. Most of the exposure comes from importation from UK. So it is true for the UK population is also true for the blood donor population. So the importance of exposure due to travel in UK is very small compared to exposure by food import from UK and by all the French population. I answered.

DR. BROWN: Yes, thank you, Annick. So in other words, Annick has presented the French perspective, that is to say risk to the French citizens traveling to the UK versus French citizens not traveling to the UK but living in France. That's quite a different matter than the U.S. perspective and in fact would be the reverse of the

U.S. perspective. Yes, Susan, you had a question.

DR. LEITMAN: I think my question is a continuation of Dr. Schonberger's question. It's directed to Dr. Will. You quoted in your literature that you've given us quotes about 2,000 per year cattle in UK still developing BSE, 1900, but then there's a reduction to two to three animals potentially entering the human food chain. I don't understand that reduction since MRM and MBM are legally and you think completely interdicted from entering the human chain. So are those accidents where MBM enters or are those better cuts, those carcass cuts of meat that enter that you think are infectious?

DR. WILL: I'm not sure if entirely understand or whether I have caused some confusion. I think in relation to the BSE numbers which are derived from the report from December 1999, there were about 2,000 cases of BSE in the UK in that year. An analysis, a mathematical analysis by Professor Anderson's group suggested that in the under 30-month cattle which are at very low risk of getting BSE clinically, that the numbers of cattle that might be entering the human food chain in the last year of the incubation period were very small

indeed, and where I need to draw year on year to single, you know, one or less than one in the next two years. That is a mathematical analysis and it's not directly related to the number of total cattle with BSE that are observed because the great majority of those, all of them really are over 30 months.

with two different opinions.

The next slide shows the name of the first, the title of the first opinion on risk identification for CJD transmission by a substance issued or adopted in October 1998, and then we have developed recently an updated opinion, next slide, which was issued in February this year. You can get these opinions from the Internet.

I would like to review shortly the older opinion too before I go to the latest one. Next slide. I just want to go through the main elements of the first opinion and this opinion deals with the question of the probability of CJD being or could be transmitted by blood and this is just to remind you that there are a number of epidemiological studies looking whether there's a higher risk for blood transfusion for example in CJD cases and none of these studies showed an increase risk for blood or blood products.

The next slide shows you the outline of many experiments which have been performed to check experimentally sensitivity in

So I'm not sure if I've confused two things. There are two calculations. One is the prediction of the total numbers of cattle with

clinical BSE and there was a second calculation that has been done, the one that's relevant to human health which is what numbers of cattle in the final year of the incubation period could enter the human food chain in the under 30-month rule, and they're quite different calculations. I'm not sure if that's clarified it.

DR. BROWN: Susan, clarified? Not entirely.

DR. LEITMAN: Well, there are adult cattle which still -- greater than 30 months which enter the food chain yet aren't symptomatic?

DR. WILL: No cattle over the age of 30 months enter the human food chain in the UK. That is the law.

DR. LEITMAN: All right. I missed that. Sorry.

DR. BROWN: Bob.

DR. ROHWER: So, Bob, could you tell us what proportion of the 2,000 cases seen in 1999 were over 30 months of age that were actually confirmed cases?

DR. WILL: I derived this from, the age incidence of BSE indicates that the incidence under the age of 30 months is exceedingly low and Linda

Detwiler may know the exact details more than I do. There have been tiny numbers of cattle under the age of 30 months clinically and so the enormous majority of cattle are over 30 months, but it is because of this issue of the possibility of incubating cattle near the end of the incubation period that might still pose a risk even with the over 30-month scheme. That is why it is so important to calculate those numbers to estimate the numbers of such cattle that could be entering the human food chain.

But I stress that even if such cattle were entering the human food chain in tiny numbers, there is still the SRM ban that would provide a degree of security that even in those cattle should there be a risk that those risky tissues are not entering the human food chain anyway or should not.

DR. ROHWER: But the 2,000 animals that are identified are animals that will never enter the human food chain. That's what you're saying.

DR. BROWN: Dr. Burke.

DR. BURKE: Continuing along the same line for Dr. Will, it seems that probably the best measure of hypothesized risk is the number of ingested animals that are less that are infected animals over the course of the epidemic from 1981

on. Has there been any attempt to try to draw that curve of the number of ingested animals as the measure of human risk over the entire course of the epidemic and is there a similar attempt to provide that information in other countries other than the UK as some sort of way of getting a measure of the attributable risks or some sort of risk like that.

DR. WILL: Yes, that has been attempted and it looks like a whole range of variables including the age structure of the cattle population, the number of cattle that are likely to be in the last year of incubation period, et cetera, et cetera, and also looks at the various tissues, and I think my recollection of that assessment is that the human exposure to the BSE agent, significant exposure probably started in the early 1980s and probably peaked around 1990 or 1991 and then declined and, of course, the decline in exposure will have been influenced many of the measures that were taken around that time. So, yes, some modeling of that has been done in the UK suggesting a period of exposure that may be most relevant to the human population.

DR. BURKE: Right. And do we have a measure of that peak in the UK compared to what

we're currently seeing in France and in Switzerland? That's a question, and I'm not sure who should answer it.

DR. BROWN: Well, I think that's the problem.

DR. BURKE: Does that mean that it doesn't exist?

DR. BROWN: Well, I have no idea myself, but what you're asking is given these calculations for the United Kingdom --

DR. BURKE: Right.

DR. BROWN: -- are there comparable calculations for the other countries in Europe?

DR. BURKE: Yes.

DR. BROWN: Bob.

DR. WILL: I think just to be perhaps to give my personal opinion about that, of course, the calculations in the United Kingdom were based on an observed epidemic of BSE which was presumed to be the major source of risk in the United Kingdom, not from imports from other countries. I think the calculations that would be done in Switzerland and France as Annick Alperovitch has already indicated is that the assumption is there that the major risk comes from imports rather than from indigenous BSE.

So there's a different risk calculation and has to make all sorts of assumptions about what proportion of cattle are allowed to reach adult life, what proportion of British foodstuffs actually contained BSE agent, all the rest of it, and I think my own feeling about that is that there are so many unknowns about the actual exposures in the UK that it would probably be a formidable task to do such calculations in other countries, but I think it would be more appropriate for other people to comment to see whether they think that that is accurate.

DR. BROWN: Annick.

DR. ALPEROVITCH: I confirm what Dr. Will was saying. In France in '91, '92, there were only one or two cases of androgen BSE and most of the exposure came from importation from UK which increased in this period. So it's not possible to make this kind of calculation in France.

DR. BROWN: Annick, while you're still at the microphone, could I ask you just a quick unrelated question? Several months ago, the third possible new-variant CJD case I think had a tonsil biopsy and I think Dr. Dormont was in the process of having a look at the glycotype. Do you know what it

was?

DR. ALPEROVITCH: I think it's Type 4 Prp.

DR. BROWN: Right.

DR. ALPEROVITCH: So it's appropriate with --

DR. BROWN: It's consistent.

DR. ALPEROVITCH: Yes.

DR. BROWN: Larry, the last question.

DR. SCHONBERGER: Dr. Alperovitch just clarified to me on the side that in her previous answer she said the same measures were taken to protect the humans as was done in the UK, but what she was referring to specifically I guess was the specified risk material ban that didn't include this 30 month rule that the UK has developed. So what I guess I'd like to get maybe Dr. Will's perspective on how important he would regard the 30 month rule ban relative to the original specified risk material ban? Does that produce in his mind a significant degree of extra protection that is important or would the, you know, give me some sense of the relative balance there since France does not have that rule but has basically the specified risk material ban? Is that possible or is that just

totally --

DR. WILL: I think I need a bit of time to consider that question in a bit more detail. I'll try and answer perhaps later when I have had a chance to think about it. It's quite a difficult question to answer because the assumptions that you have to make and all the rest.

DR. SCHONBERGER: Okay.

DR. BROWN: Linda, were you going to deal with that at all?

DR. DETWILER: A little bit.

DR. BROWN: Okay. Maybe --

DR. SCHONBERGER: Okay. Good.

DR. BROWN: -- Bob, you can keep thinking, but Linda may answer it. Okay. Susan.

DR. LEITMAN: One last clarification please from Dr. Will again. There are several differences in legislative restrictions imposed on the UK and imposed in the other European countries. One is the 30-month rule as just stated. The other is is there an absolute ban on the meat and recovered meal to enter any mammalian food chain including pig and poultry regardless of any sort of treatment? It's an absolute ban whereas in the other countries one can treat that material. Is

that the case? I'm not really clear.

DR. WILL: (Nods head yes.)

DR. LEITMAN: That is the case. It's an absolute restriction in UK.

DR. BROWN: Very well. We now have a 15 minute break and we will reconvene for the first presentation after the break at 10 minutes past 11:00.

(Whereupon, the foregoing matter went off the record at 10:55 a.m. and went back on the record at 11:14 a.m.)

DR. FREAS: If you'll take your seats please, we'll resume.

DR. BROWN: We have two further presentations this morning before we begin an extended period of questions and discussion amongst the members of the committee and they expand the perspective from the national to the European community and in some cases the globe.

The first of the two presentations will be presented by Dr. Linda Detwiler of the U.S. Department of Agriculture who will talk to us about the worldwide occurrence of BSE and USDA policies and reactions to recent EC assessments and actions. Linda.

DR. DETWILER: Thank you very much. Next slide please.

Okay. Just to kind of give you an overview of the U.S. Department of Agriculture's prevention measures, they primarily involve import restrictions and then the Food and Drug Administration's feed ban, but USDA put on the import restriction first on countries having BSE. July of 1989, we prohibited all live ruminants from any country that diagnosed BSE. In November 1989, ruminant products or most ruminant products from countries known to have BSE went on the list. These were not done by formal regulation. They were done when we do what we consider almost like an emergency action with the halting of the issuance of permits.

In 1991, formal regulations were published. In 1997, December 1997, these restrictions were extended to the entirety of Europe and then to follow up again, that was done more of kind of like an emergency action and followed up with an interim rule in 1998. Again this prohibits all live ruminants and most ruminant products from the entirety of Europe. Next please.

The last probably year and a half we have realized Canada and Mexico and the United