sequential unit operations having sequential effect. So if we get 2 logs reduction here we can add it to 4 logs reduction there.

The one thing that I was a little bothered by was the mass balance unit operation analysis using Western blot and logs. If the fraction of use has less than 10 percent of the contaminant, then you really can't compare that logarithmically to what you recovered in the precipitate, let's say, that you're not going to use or the other fraction if you have only one percent in your useful fraction, you'd better not be able to detect any loss from the discarded fraction because a 2 log in the useful fraction and 3 log in the other fraction doesn't add up again to where you started with. So mass balance in logarithms works in one direction but it doesn't perhaps work validly in the other.

DR. VEY: I guess I was the one who showed mass balance. First of all, it was the confirmation dependent immunoassay, not the Western blot. But I agree, mass balance does not mean that if you have one percent in the supernatant fraction that this one can be then further analyzed and if this disappears, that the mass balance that I showed for the first step is coping for the mass balance of a second step behind

that.

But you can see that when you do the mass balance that the major flow of the spike is into one direction and you don't lose it along the way. It's just for reassurance that you really know where the majority of the spike is going. If you didn't do this kind of mass balance, you would raise the question so where is it then. You only compare input and output. But I agree.

CHAIRMAN BOLTON: Yes, Colonel Fitzpatrick?

COLONEL FITZPATRICK: Two questions on the bioassays. On the primate study, first this looks like a really good opportunity to answer some questions about transfusion transmission. I wasn't clear, has the primate study begun, how long will it last and how many transfusions are you planning to extend this out toward?

DR. KREIL: Well, the primate study has been an issue that, as I said a couple of years ago, there were some logistic hurdles to come across which took us some while. So, we're now into roughly 22 months after inoculation of the animals. The positive controls, if you will, that is the ones that have been inoculated with brain material from variant or

classical CJD patients at a dilution of 1 to 10, they have already come down with disease, so we know the model works.

You were asking how long we intend to carry out the transfusions. We're basically intending to do that as long as the animals live. And then also we intend to keep these animals as long as the animals live, because there is a well known correlation between infectivity titers and incubation period animals so that the lower the infectivity, the longer you have to wait for the animal to come down.

As we expect plasma or buffy coat specifically to, if any bear either a low infectivity levels, we would have to carry the study out probably until the natural lifespan of the animals.

COLONEL FITZPATRICK: The second question is on the --

DR. VEY: Could I add something? So we are sitting up or we have set up infectivity bioassay in transgenic mice which don't have the species barrier versus, or a much lower species barrier towards variant CJD prions. And so we expect also data within the coming one or two years on petitioning and trituration in infectivity bioassays using highly susceptible transgenic mice.

DR. KAGAN: And then is that a whole blood study?

DR. VEY: Pardon me?

DR. KAGAN: Is that whole blood transfusions in the mice?

DR. VEY: It's the petitioning studies I was showing.

CHAIRMAN BOLTON: I just have a question relevant to that study also. Can you comment on why you choose to inoculate the source animal intracranially as opposed to a peripheral inoculation? It seems to me that if you're trying to model the contamination of blood in a new variant case, that intracranial inoculation is not the best way to do it.

DR. KREIL: Well, what we tried to do in that study is we had, obviously, to first have a donor animal which we know would develop the disease so that we could then take from this donor animal blood that we would transfuse into a naive recipient, the body.

CHAIRMAN BOLTON: Well, I must say I'm still surprised that you had so little confidence that it would be transmitted if you inoculated either intraperitoneally or intravenously or even fed orally. I mean, these diseases are transmissible almost without question. And I would have little doubt that

squirrel monkeys would be infected.

I realize that you're looking at a cost situation here where you might not wanted to take the risk. But is such a study contemplated?

DR. KREIL: Well, to investigate oral exposure?

CHAIRMAN BOLTON: That would be good, yes.

DR. KREIL: I know that currently in Europe there is two further studies ongoing in primates and one of which at least addresses oral transmission of prion diseases as well.

CHAIRMAN BOLTON: Ermias?

DR. BELAY: Would you be able to tell us how many animals were out to be inoculated for sporadic figured in also for the variant study?

DR. KREIL: The study in total is 80 animals. The positive control groups for sporadic as well as variant CJD have been inoculated in dilutions of 100 fold. It's been four animals per group. And I just couldn't really tell you how many groups we diluted it down. I think it was four dilutions down.

Then the bodies of the animals where we tried to transfuse and transmit if that is possible at all; that we have done for the animals which have been inoculation with a dilution 1 to 10, and then one

animal in that group transfuses into one animal in the recipient group. So there is four in the recipient group and four in the donors group.

And then there is four intracranial inoculation of human variant CJD or classical CJD buffy or plasma, also groups of four animals each.

DR. BELAY: A total of 17?

DR. KREIL: It's a total of eight, 80.

DR. BELAY: Eight-zero. Thanks.

CHAIRMAN BOLTON: Well, I'll make one more comment. I want to really commend you on looking at the question of the nature of the spike. I think that that is probably the most important aspect of these studies, and for two reasons. Obviously, it was something that we had seen years ago and feared might be true, and that is that the purified preparations, while they're very useful for analyzing the nature of the agent, they are possibly the worst thing to use in modeling this kind of natural contamination. And I'm very pleased to see that you looked at these different alternatives.

And the second part of that is that the reason that you're even investigating that is that there isn't really a source, a practical source of the natural contaminated product. Because these agents

really are almost undetectable in blood, even in the model system. So I want to bring that out, because as scientists we tend to focus on the little details of the science and whether or not you use IC inoculation or what have you, but an important fundamental fact is that the contamination of blood in this case is theoretical still in the human case and is still extremely low in the cases where it's known.

Additional questions or comments from the Committee?

DR. NELSON: Yes.

CHAIRMAN BOLTON: One more. Dr. Nelson.

DR. NELSON: Yes, I'm interested in the route intracranial versus let's say a transfusion, intravenous. And I know there's a great difference between the infectious inoculate by those routes, and I guess it must be a couple of laws.

I remember the Brown paper in *Transfusion* looking at this. But, you know, there are people that get a 100 units of blood, but I'm not sure that's equivalent. I think that the risk may not be additive, and it may be very difficult to quantitate what the differences are in these units. But there are people that get very large numbers of blood transfusion, but I'm not sure that that puts them at

that much of an increased risk. I wonder if you'd comment on that?

DR. VEY: So, first of all, the route of infection, IV intravenous versus IC is something like one log less efficient for IV inoculation. So you need ten times more of a contaminate on infectious agent to be infectious. That's all based on data of the TSE animal model in mice, GSS. So whether this applies for larger animals or humans which have more transfusions probably, it's not known yet. It could be even higher infectious doses necessary. That's not known at the moment, but the best guess so far is one log less efficient.

With regard to multiple doses, there epidemiology comes into play as well. I mean, it would be definitely adverse if a donor who was not yet diagnosed with CJD would donate 100 times and that would be donated to the same person so the risk increases. But since the epidemiology says that at the most 1 in 10,000 people is infected, so this risk is very, very low.

CHAIRMAN BOLTON: Other questions or comments? Yes.

DR. HOLLINGER: I don't think we should ever lose sight of the fact that at least at the

present we're dealing with a theoretical risk, that there's never been any documented transmission of variant CJD to our knowledge yet, at least in Britain or in other places where this epidemic is so high. So we should always keep that in mind in the background. It is maybe a theoretical risk.

I guess my question to the group up there would be are you confident enough in the processing that is being done with your spiked products that any of you would be willing to take a Factor VIII preparation that was spiked with one log of purified $PrP^{Sc}$ and take a Factor VIII preparation after that spiking process?

CHAIRMAN BOLTON: It sounds like an unfair question.

DR. HOLLINGER: Well, it's really, I mean it's not an unfair question, if that's what someone said. In essence because it is the issue if that is the question; that the confidence interval is such that if we're looking at something that's less than log or maybe perhaps not even there, one wants to know if the process is sufficient enough that one would be not concerned with any transmission of disease if it were present.

MR. HEALEY: With all due respect, I think

I'd have some larger problems if I knowingly were willing to take a product that had been intentionally infected with something and then put through a process for clearance. I think with that said, it's fair to say from a personal perspective I take great assurance in the data that's been presented here, and I trust the safety of the products. And if I were a product user, I'd rest assured that everything's being done and that the data support the safety of the products going forward, yes.

CHAIRMAN BOLTON: Colonel Fitzpatrick, one more question.

COLONEL FITZPATRICK: The ion exchange inclusion chromatography looks to be much more efficient and we know that not all fractionaters use that. Do you have an idea of what percentage of the industry uses ion exchange exclusion chromatography?

MR. HEALEY: I'm sorry, I didn't hear the question.

COLONEL FITZPATRICK: On ion exchange exclusion chromatography in the process, about how many fractionaters or what percentage of the industry uses that method?

DR. KREIL: Well, while I cannot comment on how many of us in the industry are using this

specific type, I think would I like to say as a comment to that is that while this one step may look efficient, there were also other steps which were efficient. And I think the major message was really the lines that are printed in bold for the different products. Because through the manufacturing processes, regardless now of whether they contain an ion exchange or its affinity chromatography, or it's one of these PEG-type precipitations, there is steps in every one of these individual manufacturing processes which finally provide the product with a safety margin. So it is not fair to say that there is only single steps which do that. There is steps within really every manufacturing processes, and that has been the information that I've provided in the bold line in summary.

CHAIRMAN BOLTON: Just when I thought we were safe. Dr. Petteway?

DR. PETTEWAY: Yes, just to make a comment so everyone's clear. Actually the most efficient processes, which is fortunate, are the precipitation processes which actually everybody has. So regardless of how they were investigated, where they were investigated, it's the nature of the prion itself that's lending to this removal by precipitation and

they are the most efficient, and everyone has those.

CHAIRMAN BOLTON: Dr. McCullough?

DR. McCULLOUGH: It's a very nice presentation. I think the group is to be applauded for doing this.

Just one small point, I'm not sure you intended it this way, but in comparing the one log reduction that would be achieved by the deferral policies with the logs of inactivation or depletion that you get in your process, it's not really additive.

I mean, the log reduction of risk has to do with 90 percent of the donors being eliminated, but that doesn't refer to reducing the infectivity of a particular donor by one log. So that really doesn't add into the extent of depletion that you're describing. A small point, and I don't know that you meant to do that anyway.

DR. KREIL: I was just trying to set that into perspective. Because basically both of the measures result in a reduction of risk. It's different, you know, mechanisms of actions, if you will. First you select for the right donors and then if you had a wrong donor in, you're taking care of that by the manufacturing procedures. So I'm not

saying that this is the same mechanism of action. It is both toward reduction of risk, and therefore I wanted to put in perspective what manufacturing processes really can achieve.

CHAIRMAN BOLTON: Okay. Let us conclude this part of the meeting.

I have 10:28, let's round it to 10:30, which puts us 15 minutes behind schedule. But we'll go ahead and take a 15 minute break with the hope that we'll get back on schedule at some point later on.

So let's meet back here at 10:45. And have a nice break. Thank you.

(Whereupon, at 10:29 a.m. a recess until 10:50 a.m.)

CHAIRMAN BOLTON: Okay. We're going to begin the next session of the meeting. This will be Topic 1: Effectiveness of measures taken to protect humans from food-borne exposure to the BSE agent in countries with BSE: Implications for variant CJD risk and blood safety. And this will begin with Dr. David Asher who will provide the introduction, background and charge and the questions to the Committee.

Dr. Asher?

DR. ASHER: Okay. Thank you, Dr. Bolton.

I'm David Asher from CBER's Office of

Blood. And I'll introduce the decisional issue of the day, which is a consideration of the effectiveness of measures taken to protect humans from food-borne exposure to BSE agent and implications for risk of variant CJD disease in blood safety.

We seek advice from the Committees on whether food chain controls to prevent human exposure to BSE as implemented in the United Kingdom since 1996 provide a sufficient bases to obviate need to defer blood in plasma donors based on their subsequent travel or residence in a BSE country.

Let me add that we are not soliciting advice on importation of ruminant products into the USA from BSE countries. Most of those products are regulated by the USDA and we endorse their very strict control of such products.

We also are not discussing the topic of food safety in the USA, an issue that was discussed at some length by FDA Center for Food Safety and Applied Nutrition and USDA's Food Safety and Inspection Service in the TSE Advisory Committee meeting last October.

Before proceeding, let me try to place today's activity in context. For those of you new to the business of reaching precautionary decisions

concerning uncertain but presumably small risks, in this case the risk that blood or blood products might transmit the new variant CJD disease, when a theoretical risk has been identified for a life sustaining product that cannot be replaced there are choices to make. To accept the risk and to continue to use the product as is with disclosure, of course, or to attempt to reduce risk while maintaining as much benefit as possible. And there are several ways to do that.

One can limit the sources of raw materials to the safest possible, for example by deferring some blood donors, or use manufacturing processes that reduce the risk, for example, some of the steps in fractionation of plasma described earlier this morning, or one can restrict the use of the product.

For transmission of CJD by blood and blood products the risk is theoretical. We, of course, are aware of no anecdotal or epidemiological evidence for human infection with any TSE, including variant CJD via blood. However, studies have found TSE agents in blood of some experimentally infected animals, even during the incubation period, so there is a theoretical risk.

Encouraged by the Institute of Medicine,

the FDA long ago concluded that it was prudent to maintain an aggressive precautionary policy to ensure that blood and blood products in the USA remain as safe as possible. And that police has included recommending precautionary deferrals of some donors thought to be at increased risk of incubating TSEs.

In 1987 the FDA recommended deferral of recipients of human cadaveric pituitary growth hormone as blood donors.

In 1996 precautionary withdrawal of blood components and plasma derivatives from donors with CJD are at increased risk of getting CJD, that is iatrogenic or familial CJD and deferral of such donors.

In 1998 and 1999 faced with shortages of import in plasma derivatives and reassured by accumulating epidemiological evidence that exposure to blood products have not been identified as a risk factor for CJD, the FDA revised its guidance and no longer recommended withdrawal from the market of plasma derivatives from donors at increased risk of most forms of CJD. But because variant CJD was so new and so different in some respects from other better known forms of CJD, we retained the recommendation to withdraw derivatives prepared from any plasma pool to

which a donor subsequently recognized to have variant CJD had contributed; something that fortunately has not happened.

And donors at increased risk for variant CJD, that is donors with a history of substantial potential exposure to the BSE agent, remain a special concern.

In November 1999 following discussion by the TSE Advisory Committee, the FDA recommended precautionary deferral of blood donors who had spent 6 months or more in the UK between 1980, the estimated start of the BSE epidemic, and the end of 1996, a time when we were assured that the UK had fully implemented a variety of measures to control BSE and prevent human exposure to the BSE agent, the topic of today's discussion. That policy was estimated to reduce exposure risk as blood donor days spent in the UK by about 87 percent while deferring some 2.2 percent of blood donors.

Finally, following several discussions by the Advisory Committee, the FDA proposed the revised guidance published last week and summarized by Dr. Scott this morning. The policies articulated there are estimated to eliminate some 91 percent of total risk adjusted time exposure to BSE agent by donors

while deferring about 5 percent of otherwise suitable donors, a substantial but probably sustainable loss.

In that guidance the FDA once again recognizes the probable effectiveness of measures that the UK implemented after 1996 to reduce opportunities for food-borne exposure to the BSE agent and does not recommend considering time spent in the UK after 1996 in deciding the suitability of blood and plasma donors.

From the outset, both the FDA and the TSE Advisory Committee have acknowledged that in order to maintain an adequate supply of blood some theoretical risk must be accepted. For example, it is conceivable that some rare unlucky person might visit a BSE country for a very short time, consume a contaminated product and become infected with the BSE agent.

But had blood programs attempted to defer all donors who visited the UK for any length of time, however short, the estimated loss would have been 24 percent of donors. Had programs attempted to defer anyone who had ever spent anytime in any BSE country after 1979, then the predicted overall loss of donors would reach 35 percent, even higher in some cities because as a group committed blood donors travel a great deal. The cost to eliminate the theoretical

risk completely would be unsustainable.

So one risk that seemed acceptable was that of a short stay in the UK during the period of highest risk for exposure to the BSE agent. Another risk deemed acceptable was a stay of any duration after implementation by the UK of measures to protect humans against exposure, today's topic.

That position was taken despite the fact that far more cases of BSE have been reported in the UK than in any other BSE country, almost 700 last year, and that may be seen as paradoxical. But since other European BSE countries, countries identified by USDA as having BSE or substantial BSE risk in native cattle, since those countries introduced measures to protect human food much later than did the UK, if at all, but significant risk in those countries must be considered to pose an unknown but significant risk that was not mitigated after 1996. And, therefore, time spent there from 1980 until the present should be considered in determining suitability of blood donors.

We intend to reconsider frequently our recommendations to defer donors to spent time in various BSE countries as more information becomes available about the estimated numbers of people who might have been infected with the BSE agent and about

the potential of human blood to transmit variant CJD. We also expect to consider the effectiveness of measures taken by various countries to keep the BSE agent out of their food supply in deciding when the risk of human exposure has been sufficiently mitigated to warrant a change in blood donor deferral policy.

Our current policy acknowledges that by the end of 1996 efforts in the UK were sufficient to reduce the risk of further human exposures to a level presumably less than the risk in other BSE countries that, while recognizing smaller numbers of animals with BSE, have not fully implemented similar effective measures to protect the food supply. That FDA policy has not been universally endorsed and some blood programs recently elected to defer donors who spent three months or more in the UK from 1980 through the present time.

We continue to believe that current UK measures to protect human food from contamination with the BSE agent have markedly reduced opportunities for human exposure, and that the small additional reduction in theoretical risk afforded by deferring donors who spent time in the UK after 1996 does not justify the probable substantial loss of otherwise suitable donors. However, we appreciate ongoing

concern about the effectiveness of UK measures to protect human food and we believe it to be in the public interest to review those measures.

Several specific measures are generally considered likely to reduce markedly the opportunities for food borne exposures to the BSE agent. Effective programs to control BSE in ruminants, age-based slaughter schemes, separation of potentially high risk materials from edible meat products and control of imported meat products. We ask the Committees to consider those measures and any others you consider important in your discussions today.

First, control of BSE in ruminants, cattle and sheep is particularly important. If TSEs are eliminated from ruminants, then humans will be at no further risk from exposure to their meat products. To be considered protective of humans eating meat products, any program to control BSE in ruminants should include: An effective, active national surveillance system including examination of brains from animals at increased risk of BSE; feed bans adequate to prevent the intentional feeding of most mammalian proteins to ruminants as well as the accidental feeding of prohibited proteins; immediate removal of ruminants with provisional diagnoses of BSE

and safe destruction of their carcasses, and; preventive culling of ruminants at increased risk of BSE.

A second kind of protective measure, age-based slaughter, attempts to reduce risk by limiting the human consumption of meat products to those prepared from young animals slaughtered before the appearance of substantial amounts of BSE agent in tissues. An example of that is the United Kingdom's over-30-month scheme

A third kind of measure attempts to reduce the contamination of muscle, which is conceded to be a very low risk tissue in laboratory studies of TSEs with high risk materials like brain, spinal cord, dorsal root and trigeminal ganglia, intestines and lymphoid tissues.

Summarized here in slaughterhouse order are three examples. Prohibition of slaughtering techniques likely to embolize brain into low risk tissues; removal of specified risk materials from carcasses at the time of slaughter with careful segregation and sanitary disposal, and; the prohibition of special meat recovery systems likely to contaminate muscle meat with high risk materials.

Of course, since we should protect humans

against all potential food borne exposures to the BSE agent, it goes without saying that imports must be controlled by at least the same strict standards as our domestic meat products. In that regard, one reason why variant CJD cases were first recognized outside the UK and France was probably the substantial export to France of meat products from the UK during the years when BSE was common and before the implementation of protective measures.

Let me add here that we know that it is not realistic to expect perfect compliance with all protected measures. We are aware that in the UK some cows born after the fed ban have gotten BSE, that animals at increase BSE risk have been sold for meat and that carcasses with risk material still in place have been imported. But we continue to believe that taken together, the measures implemented in the UK are likely to afford humans substantial protection, the same kind of substantial protection already demonstrated for cattle in the UK where recognized cases have BSE have plummeted since the end of 1992.

Those food chain protections should markedly reduce opportunities for human exposure to the BSE agent and their adoption is to be encouraged by other BSE countries.

We're fortunate to have today three authorities with us to share their experience regarding these issues. First, Dr. Hester Ward, epidemiologist for the UK Creutzfeldt-Jakob disease Surveillance Unit in Edinburgh has graciously agreed to summarize for us the latest information concerning variant CJD, projections of various models concerning possible numbers of people who may have been infected with the BSE agent, as well as the current status of investigations of potential infectivity of their blood, the theoretical risk that prompts our concern.

Next, Dr. Peter Soul from the UK Department for Environment, Food and Rural Affairs, DEFRA, will discuss the actual measures implemented in the UK to protect humans and animals from exposure to the BSE agent.

Finally, Dr. Maura Ricketts will summarize recent efforts of the World Health Organization and other international organizations to address the need for global control of BSE and variant CJD in her view of the situation.

Following the break, there will be opportunity for public comment preceding the discussions of the Committees. Members will then be asked to vote one question and one contingent

question.

Now, the charge to the Committees. Please evaluate the probable effectiveness of those measures taken by the UK to protect humans from food-borne exposure to the BSE agent and their value in mitigating risk otherwise addressed through donor deferral.

And the questions do members of the Committee agree that the combination of measures implemented in the UK by the end of 1996 to protect the human food chain from BSE contamination are sufficient to obviate the need for donor deferrals based on subsequent travel or residence in the UK.

If the answer to question one is yes, which measures should the FDA consider to be of greatest importance when it considers future revisions and recommendations for determining the suitability of donors who spend time in other BSE countries?

If the answer to question one is no, what other measures, if any, would the Committee members consider sufficient to obviate the need for donor deferrals based on subsequent travel or residence in a BSE endemic country?

Let me close by saying that we're very grateful to both Committees today, to our guest

speakers and to the interested public for coming to help the Food and Drug Administration and the American public.

Thank you very much.

CHAIRMAN BOLTON: Thank you, David.

I don't know, are there any questions for Dr. Asher before we move to our next speaker? Seeing none, our next speaker is Dr. Hester Ward from the CJD Surveillance Unit in Western General Hospital in Edinburgh, and she will inform on the variant CJD in the UK and updated review of recent epidemiological studies.

Dr. Ward?

DR. WARD: Thank you very much for inviting me here today. I'm an epidemiologist at the National CJD Surveillance Unit in Edinburgh in the UK.

What I'm going to do is spend about 30 minutes going through the epidemiology of variant CJD within the UK. I'll describe the basic demographic features, the geographic distribution within the UK, some investigations into risk factors into variant CJD.

I'll then talk a bit about some recent papers that have been published trying to predict the size of the variant CJD epidemic. And then I'll close

with an update on our ongoing transfusion medicine epidemiology review that we carry out within the unit in association with our national Blood Transfusion Service.

I'd just like to start just by showing the frequency of CJD in percentage terms. Before 1994 the most common type of CJD in the UK was classical or sporadic CJD compared with genetic or iatrogenic CJD. And since 1995 22 percent of our cases in the UK have been variant CJD.

To date we have 114 cases of definite and probable CJD. Eighty-nine of these are definite cases, that is they have been confirmed neuropathologically. Fourteen cases have died and haven't consented to have a post mortem, but I have to say that all probable cases that have gone on to have a post mortem have been confirmed neuropathologically. So we take a problem case as being a case of variant CJD. There's one probable case whose awaiting post mortem, and we have ten probable cases alive at this time in the UK.

In France, there's been 3 definite cases and there are two alive probable cases at present.

And the Republic of Ireland has had one definite case.

I'd just like to mention what was termed the Hong Kong case. The Kong Kong case actually has been classified as a United Kingdom case because they had the onset of symptoms while also living in the United Kingdom and, in fact, had resided in the United Kingdom two periods of significant time during the '80s.

So looking at the age of variant CJD, the median age onset is 26 years with a range from 12 to 74 years. And the median age at death is 28 years. This compares with sporadic CJD where the median age of onset is about 65 years. It's about 50/50 male to female split. And the duration of illness is 13 months with a range of 6 to 39 months. This is longer than sporadic CJD where the median duration of illness, that is from onset to death, is 4 months.

All those that have been tested, that's 97, are methionine homozygote codon 129. Up until last year our oldest case of variant CJD was in, I think, it was about 54. And since then we have had a 74 year old.

Although what should be noted about the age of variant CJD is that mainly the age is consistent within the relatively young people. And the median age hasn't changed with time. So what we

can conclude from this is that young people either have a reduced incubation period, they have either had increased exposure or they're more susceptible to variant CJD. And although models suggests that young people are more susceptible or have had an increased exposure, it hasn't been proven yet.

I'm sorry, you can't really read that very well. It's showing the age and sex-specific mortality rates from variant CJD in the UK up to January 2001. And basically the red triangles are males and the green circles are females. And it basically shows that the peak of the mortality rates is the 25 to 29 year age group.

This is showing variant CJD onsets by year of definite and probable cases, the number of cases by year. And you can see since 1994 the onsets have been increasing. Because of the duration of the illness, we'll be expecting onsets in 2000 and 2001 to be picked up in the future.

And this variant CJD deaths by year, definite and probable cases. 104 deaths to date. A slightly variable pattern in 28 deaths in 2000, and we've 20 deaths in 2001. I don't think at this stage you can say anything significant about the reduction there. We'll just have to see how many we have next

year or this year.

This is a figure carried out by the Public Health Laboratory Service Statistics Unit by Nick Andrews which shows the observed and expected quarterly incidence of variant CJD onsets. And the solid line is an underlying trend by quarter, by year. And the dotted line is the upper 95 percent confidence interval, and that's a lower 95 percent confidence interval.

And, obviously, this is carried out every quarter. And this shows that there's a statistically significant increasing incidence of variant CJD onsets at the rate of about 22 percent per year, and a doubling every 3.5 years. And this similar analysis is being carried out for deaths, and it shows a similar increasing incidence of 27 percent. So that's quite useful information to have, and it's recently been repeated. This was up to the end of September 2001. It's being repeated up to the end of December, and it shows a similar result.

I'd like now to move on to the geographical distribution of variant CJD within United Kingdom. This is a picture of Great Britain, Scotland, Northern Ireland, Wales and England. And these dots, targets are cases of variant CJD. Remember

we had 93 cases. And they're scattered throughout the whole country.

What I'd like to go on to describe is we were looking at cases of variant CJD by region in the country, and the regions here are in the north and going further south as you go down the slide. And this is the population of those regions. And these are the number of cases of variant CJD.

And we looked at rates, we just eye balled them and saw that the rates in the northern regions seemed to be greater than the rates in the southern regions. So when we arbitrarily grouped the four northern ones and the six southern ones, and you can see that the population in the south is double that of the north, but the number of cases were the same.

You can see that the rate per millions, cumulative rate per million in the north was about double that of the south. And we didn't have any prior hypothesis to suggest why this may be. So in true epidemiological fashion, we had looked at the first 51 cases; we wanted to see if we could repeat that over time, was this consistent.

And so we then looked at the subsequent 40 cases, and we got a similar result. The rate in the north was double that of the south and the total rates

of that are double in the north compared with the south. So what does this mean?

Is this ascertainment bias? Our unit is based in the north of the country, so were we just getting more referrals because people knew about us in the north? So we looked at sporadic CJD and divided it into the north and the south, and there was no difference in the rates of sporadic CJD in the north compared with the south.

And we also looked at cases that ere referred to the unit as suspect variant CJD but then turned out to have another illness. And, again, there was no difference between the rates of those cases in the north compared with the south. So we thought, well, this must be a real effect then. So what could it be do?

Could it be due to a difference in the urban/rural mix of the cases and social class, or was it a difference of diet or butchering practices? And this is sort of ongoing research.

We have looked at differences in the urban/rural mix and differences in the social class and it doesn't seem to explain when you allow for these in the analysis the increased rate in the north of the country.

To try and see if there was a difference in diets, we turned to surveys that have been carried out during the 1980s. The first is the Dietary and Nutritional Survey of British Adults that was quite a relatively small survey, about 2000 adults, where they weighed what they ate for a whole week.

The second was the Household Food Consumption and Expenditure Report, which was a larger survey of 20,000 households, but it wasn't necessarily so accurate. I think people kept a diary of the food that was coming into the house during a week.

And then what we wanted to do was look at the amounts people were eating of products that were likely to contain the BSE agent compared with different regions and variant CJD in the country.

This is data from the Nutritional Survey of British Adults, that's the one that has about 2,000 people and was fairly accurate measurements. Looking at this, this is Scotland going further south, burgers and kebabs seem to be eaten more in the southeast of the country than further north while meat pies and pastries seem to be eaten in the north of the country. There wasn't a correlation with variant CJD.

The second study, the Household Food Consumption and Expenditure we considered that

mechanically recovered meat would most likely be in other meat and meat products. And it seemed that in the north of the country was more of these consumed than in the south. More carcass meats and poultry consumed in the south than the north.

And when you process the cumulative instance of variant CJD by this other meat and meat products which we thought would have contained mechanically recovered meat, there was a significant correlation with variant CJD instance and the region. And this is Scotland and the northern region going sort of further south.

So what can we conclude from this? Well, I think you can conclude that the results were consistent. There was a post of correlation with one study and not with another study. There's always problems with correlation study because you can't really conclude to the individual from results made in a group level, because confounding factors haven't been measured in these studies. So basically we're seeing what happens in the future and we're going to carry on looking into this.

Now I'd like to move on to what we've termed in the UK geographically associated cases of variant CJD or you could call it sometimes clusters of

variant CJD.

We've got a definition for this which is fairly loose, which is two or more cases of definite or probable variant CJD where investigations show that there's been an association because of geographical proximity of residence at some time either now or in the past, or another link within the same geographical area. So cases of variant CJD who have attended the same school or the work place, or the same functions in the same area. And there are about 20 areas in the UK where we have two or more geographically associated cases of variant CJD. And there's a national protocol, and we are investigating these in turn.

The Leicester cluster was one that received a great deal of media interest, and I'll just run through the conclusions from that investigation.

There were 5 cases of variant CJD that lived in Leicestershire, which has a population of 870,000. And they lived there before 1992; 4 of them lived there during their whole lives and one moved away in the early '90s. The cumulative instance of variant CJD at the time was 1.5 per million, and in Leicestershire, it was 5.7 per million. Four of these came from a small area and gave a cumulative instance of 28.2 per million.

So when we looked to see whether this was a statistically significant result, we used the Kulldorff's methods, which is a spatial scan statistic which takes into account there was no prior hypothesis that we would expect a cluster in Leicester. And it looks at every varying size circles whether there is an increased rate of CJD within the circles compared with outside. And Leicester offers the most likely cluster, and there were no other significant clusters in the UK.

So in the investigation four out of five of the cases in Leicester were reported to have bought meat from butchers who process whole carcass beasts. Basically they split the heads, they remove the brains. These were removed for commercial purposes. Then they went on to dissect the rest of the animal for commercial purposes also.

The hypothesis was that cases bought meat from butchers that split heads and the theory was that they contaminated if there was a BSE infected carcass, once they removed the brain, it then contaminated the rest of the meat as they dissected the animal. This was tested in a local case control study matching each case to six community controls. Basically although the confidence intervals are wide so it's inpercise,

it would appear that cases were more likely to have bought meat from butchers who carried out this practice than not.

What does this study show us? Well, it's interesting in itself. Does this explain other cases in the UK and other countries? Up to now it's been thought that mechanically recovered meat was maybe the main way but the BSE agent was spread throughout the food that was eaten in the UK. Maybe more traditional butchering practices can explain some of the cases.

Also interesting was that one of the butchers actually died in 1982 so we can work out quite accurately the minimum incubation period which is between 10 and 16 years which is quite long for a minimum incubation period so it might have implications for the size of the epidemic.

But my feeling is there were some epidemiological problems with the study that we call bias in the cases that were interviewed multiple times where the controls were only interviewed once. There was interview bias. They knew which were cases and controls. The interviews with butchers weren't blinded. They knew which butchers were related to cases and which were related to controls.

Also, where did the brain go? It went

into the food chain. Apparently it went into brain pate and there was a local restaurant that might have used some of this brain. One would have thought there would have been cases related to this brain directly.

Moving on to risk factors of variant CJD we are carrying out an ongoing case control study in the UK looking at risk factors of sporadic and variant CJD. To date there has been no evidence of increased risk associated with diet, surgery, or occupation, although there has been some differences seen in diet between cases in controls. These aren't consistent between different groups of controls and they are not significant.

The study does have problems. It's a very rare disease. There is recall bias. Cases are more likely to recall meats in the controls. We have to rely on surrogate witnesses. The cases themselves are often demented and we can't rely on them to tell us what they've eaten in the 1980s so we have to rely on a relatively small number. We have experienced some problems with control recruitment which we are trying to rectify.

I'm just now going to move on to the sizes of variant CJD epidemic and predictions. I would just like to say this isn't my work and I'm reporting back

-- summarizing other people's work.

In 1997 Cousens, et al., did some back calculations where they predicted from 14 cases of variant CJD, the size of the epidemic to be in the upper limit of 80,000. Ghani, et al. in 2000, which was with 55 variant cases, this is Roy Anderson's group, predicted an upper limit of 136,000 of the variant CJD epidemic in the UK. This was a scenario analysis using over 5 million combinations of parameters. Both are restricted to the MM genotype. Interesting they predicted there would be less than two cases of variant CJD per infection bovine.

Recently in science there's been a couple of papers published. One by Huillard (d'Aignaux), et al. This was a back calculation method where they were looking at the number of affected cases based on assumptions of when they were infected and the incubation period.

Basically if you say that the incubation period can be any length, then the number of cases we've seen to date of variant CJD are compatible with any numbers of infected people from a few hundred to a millions in the UK.

However, if you take the worse case scenario, which is there are millions of infected

people in UK, then the incubation period must be very long and most people will die from other diseases such as heart disease and cancer before they develop CJD. You have clinical cases of a few hundred to a few thousand so the upper limits sort of come down. Infected individuals could be hundreds to millions but the mean incubation period would be long.

Also they predicted that we are close to the peak of the epidemic. This was based on exposure cut-off in 1996 and the MM genotype. This is not necessarily reassuring when you're regarding potential secondary spread because obviously the people who are affected could potentially still pass on CJD through surgery through blood transfusion, although the absolute number of clinical cases has come down.

The second study that was published recently in science, Valleron, et al., was based on the age of diagnosis which basically is the age of infection plus the incubation time. They were looking at the fact that the mean age hasn't increased over time. They predict that there was a total number of cases of 205 with an upper limit of 403 with a mean incubation period of 16.7 years and a peak at the end of the year 2000/2001, so we just passed the peak.

Interestingly they came up with a bimodal

age distribution so in the future we'll see increasingly older cases. They had an exposure cutoff of 1990 which I'm not quite sure why they chose 1990. And an exponential decrease in susceptibility after the age of 15 which they said in the paper was arbitrarily picked and I'm not sure again how this can be explained.

Then just last week in Nature Online Ferguson, et al., Roy Anderson's group, published further predictions on the site of the epidemic and was mainly based on -- it was predictions using BSE infection of British sheep.

Two notable things that should be noted about experimental BSE in sheep. One is that compared with cattle the distributions of the prion protein is increased throughout the sheep so that prion protein has been found in the central nervous system, some of the peripheral nervous system, the lymphoreticular system including gastrointestinal track. Whereas in cattle it's mainly restricted, I understand, to the central nervous system.

Also, if BSE in sheep is like scrapie in sheep there is potential for horizontal transmission, i.e., transmission from mother to lamb. They considered three scenarios. One was BSE in sheep was

self-sustaining in the UK within flocks.

The second scenario was it was self-sustaining within flocks and between flocks and that gave the worse case scenario which became BSE endemic in the national flock. The third scenario, which was the best case scenario, was that it wasn't self-sustaining within or between flocks.

The results were that for bovine BSE only the upper 90 percent intervals for variant CJD bases were between 50,000 and 100,000 so the upper limits have come down from their previous study from 136,000 to 50 to 100,000. When they added on the ovine BSE the upper confidence interval was 150,000 cases of variant CJD. This was the worse case scenario where BSE was endemic in the national flock.

They suggested that past exposure to BSE in the UK, the majority was from cattle but future exposure the sheep will be greater than cattle. Also they predicted that you could reduce the risk by up to 90 percent if you reduce the age of slaughter of sheep for food and increase the specified risk material controls. This work is based on many assumptions some of which -- a lot of which are unknown.

I think what I would like to say about all these studies being published recently is they are

based on a lot of assumptions and there are a lot of unknowns. In fact, I think the epidemic can be a small number of cases with a short incubation period or large number of cases with a long incubation period.

In fact, the incubation period is vital to all of these studies and we just don't know the incubation period. There are still a lot of unknowns. What we need to do to try and reduce the unknowns is know more about risk, about diet, and about exposure which we are trying to do at the CJD surveillance unit.

The studies are based only on the methionine homozygote genotypes which account for 40 percent of the population. In the worse case scenario you would have to -- if you say the other genotypes are susceptible to variant CJD, you would have to multiply the figures by 2.5, although in other TSE illnesses the other genotypes have been less susceptible.

Again, there is the question of secondary spread. The upper limit of the case numbers have come down but there might be a large number of infected people within the UK.

I would just like to finish off with a

summary of where we are with our transfusion medicine and epidemiology review, the TMER study in the UK. This is a joint project between the UK National Blood Service and the National CJD Surveillance Unit. The aim is to investigate whether there is any evidence CJD, including variant CJD, may be transmitted by the blood supply.

All definite and probable cases of variant CJD are reported to the transfusion service of the relevant countries, England, Wales, Scotland, and Northern Ireland so we look at the residential history of cases of variant CJD and inform the relevant country if they have lived there.

If the transfusion service determines whether they are a donor and traces the fate of all donations and passes on the recipient details to us at the CJD surveillance unit so we will then be able to determine if any of these recipients develop variant CJD.

We are also flagging the recipients with the Office of National Statistics so if they die from another disease, we'll know that as well.

The reverse TMER is looking at variant cases who have received blood transfusions. We passed the details to the Blood Transfusion Service and they

determined who donated the blood that variant CJD cases received and passed the detail of the donor again back to us at the CJD surveillance unit. In addition, these donors are flagged also.

The results up to April of last year we had 87 cases of variant CJD at that stage. Eight cases of variant CJD have been blood donors, 22 recipients of products from these blood donations between '81 and 1999. Interestingly one case donated blood within a few months of onset of variant CJD, another six months before onset, and seven a year before onset of CJD.

None of the recipients to date have developed CJD and, in fact, this number if now 12. Twelve have died from other causes and none have been registered as blood donors.

The reverse TMER there were actually eight cases of variant CJD who have reported they have reported they had received blood transfusion but only four were recorded by the Blood Transfusion Service. There were 117 components that were received. One case who had a liver transplant received 103 of these. There were 111 donors and none had developed CJD to date.

I would just like to conclude by thanking

and acknowledging all my colleagues at the national CJD surveillance unit. Thank you.

CHAIRMAN BOLTON: Thank you, Dr. Ward. Questions for Dr. Ward.

DR. NELSON: Did you say all of the cases so far have had MM genotype?

DR. WARD: No. I think it was about 97. All that have been tested are the MM which is about 97 out of 114.

DR. NELSON: So there have been no longer incubation cases with a non-MM genotype at the present?

DR. WARD: No.

CHAIRMAN BOLTON: Dr. Belay.

DR. BELAY: I'm interested about the clinical manifestation of the most recent cases of variant CJD. It's been reported that the clinical manifestation has been different from the classic form of CJD. Have you observed this in the most recent cases also of variant CJD?

DR. WARD: Are you referring to variant CJD or sporadic CJD?

DR. BELAY: The clinical manifestations of patients with variant CJD compared with the classic form of CJD.

DR. WARD: Variant CJD cases do present -- do have a different clinical presentation. Sporadic CJD will present often with dementia and that's how they present. Well, variant CJD present often with psychiatric symptoms and atypical sensory symptoms. They have pain in their arms and their legs which is not seen in sporadic CJD. Then they go on to develop dementia later.

DR. BELAY: So that has been consistent in all the cases of variant CJD?

DR. WARD: Yes.

DR. BELAY: And, specifically, some of the patients presented with psychiatric manifestations and there was a delay in the onset of neurologic signs. Has that been consistent over the years in all the cases of variant CJD?

DR. WARD: Yes. There is a psychiatric component to the onset of variant CJD. In the early stages there were some delay in picking up the diagnosis because they were often referred to psychiatrists.

Now in the UK we are getting better at psychiatrists realizing this may be an atypical psychiatric disease and so then referring to a neurologist and questioning whether it's variant CJD.

Yes, they do often still present at onset with psychiatric symptoms.

DR. BELAY: In the absence of neurologic signs?

DR. WARD: It might have sensory signs as well but not the frank dementia which sporadic CJD has at that stage.

DR. BELAY: The other question I had was the difference in the BNC data in the north and in the south. One factor that should be considered obviously the age. Should I assume that the way that you presented was age adjusted?

DR. WARD: Once we adjust for age and sex there is no difference.

CHAIRMAN BOLTON: Pedro and then Steve.

DR. PICCARDO: You said that 22 patients received blood from variant CJD patients. Do you know the general type of the recipients?

DR. WARD: I'm afraid I don't have that data with me. Professor Will, who has been involved in this work, he wants me to present what I presented and so that's what I have.

DR. PICCARDO: And then to follow up on that, you said that the number of the recipients died already. How many years after the transfusion did

they die?

DR. WARD: We have got that data. Interestingly I don't know the exact proportion but I know quite a few died within the first year after receiving the transfusion.

DR. PICCARDO: So actually that is not valid because, I mean, the creation time is 10 years and most of them died in the first year.

DR. WARD: Yes.

DR. PICCARDO: Autopsies were done?

DR. WARD: Post mortems weren't necessarily done on these people. It depends. Professor Will is in the process of writing it up and that's why he doesn't want me to show all the results.

CHAIRMAN BOLTON: Steve and then Pierluigi.

DR. DeARMOND: The north south difference in incidence, or the portion of the population that gets the disease, you have some data that correlates with traditional old fashioned butcher type techniques. How strong was that? Is there really a difference between the north and the south in the way a butcher would process?

DR. WARD: That's a good question we are trying to answer but we haven't answered yet. The

traditional practices that were carried out in Leicestershire were I am told unusual in the 1980s but we just don't know. It's a very sensitive issue to start asking butchers what they were doing in the 1980s.

We don't have data that says in the north that was a traditional practice and in the south it wasn't. We don't have that data yet. What we're trying to do is through the upper areas where we have geographically associated cases try to determine whether those can be explained by traditional butchering practices.

Also I'm carrying out an ongoing survey of previous cases and future cases of in families where relatives with CJD would have likely purchased beef. The problem with that is that most bought from butchers and supermarkets and you say that butchers might have carried out the more traditional methods but supermarkets wouldn't have. That is still ongoing at present.

DR. DeARMOND: A second question related to that is geographic factors. I was asked once to speculate on why young people and why the tonsils are involved and I made the mistake of speculating. The question relates to the possibility that the northern

climates have a different incidence of certain viral infections, influenza, that is different than the south that would make the immune system more ready to accept any protein that seems to be passing by it. Is there any difference north and south in Great Britain that might correlate?

DR. WARD: None that I know of, although we don't actually know the distribution of the codon 129 genotype throughout the UK. That is something that could explain it but that's something we don't know.

DR. DeARMOND: But infectious diseases that would generally affect young people, upper respiratory infections, influenza, are they the same distribution north and south?

DR. WARD: I'm afraid I can't answer that.

CHAIRMAN BOLTON: Dr. Gambetti.

DR. GAMBETTI: Perhaps I should ask this question to Professor Ironside, but can you give us a feeling of the variability in the pathology of these 90 cases that have been examined? More specifically, whether the Leicester cluster had any feature, both clinically or pathologically, that could differentiate in any way than from all the others?

DR. WARD: Your first question I think you

should ask Professor Ironside because I can't say. I know from what I've heard Professor Ironside say is that variant CJD is distinct from sporadic CJD. I don't know about the variability within that. I wouldn't like the wants of that at this meeting.

The Leicester cases were very typical variance variant CJD cases. To my knowledge there was no difference in Europe pathology, the clinical signs, the age. There was no differences between them. They were just what we call typical variant CJD cases.

CHAIRMAN BOLTON: Dr. Boyle.

DR. BOYLE: Were there plasma product donors among those new variant CJD?

DR. WARD: I'm afraid I don't know actually.

DR. BOYLE: A second question. Has the rate of classic or sporadic CJD remained the same over the past five years or has it increased?

DR. WARD: It has increased, especially in the older age groups. We think this is ascertainment bias. It has increased throughout the whole of Europe, particularly in the older age groups. Also in the younger age groups as well but, again, we think that is the result of variant CJD and it has been seen throughout the whole of Europe.

CHAIRMAN BOLTON: Steve, let me ask one question first. I'm particularly interested in those cases where the donations were made near the onset of variant CJD. Can you comment on those cases? For example, do you know how long it's been since those transfusions were given and are those recipients still alive?

DR. WARD: I'm afraid I don't know the answers to those questions.

CHAIRMAN BOLTON: Steve.

DR. DeARMOND: This may have already been answered and my jet lag from California may have gotten to me. Tell me more about the 74-year-old. Has that patient passed away and has an autopsy been done and where did that patient reside?

DR. WARD: The patient was in the north of the country. Basically it was a case of dementia who was being looked after by a care-of-the-elderly specialist who, with all respect to the doctor involved, saw that it was actually an atypical case of dementia and referred the patient to a neurologist. An MRI scan wasn't done but the patient died and had a post mortem which confirmed variant CJD.

We were concerned in the unit that we might be missing other cases of variant CJD in the

elderly so we are trying to -- the post mortem rate in the elderly is very low in the UK. Also cases of dementia in the elderly aren't referred for MRI scanning which is another way of diagnosing variant CJD because of the cost. The two ways that we would have to diagnose this disease in a pool of people with dementia are not -- we don't have much access to them.

However, we are trying to set up dementia registers with other various centers throughout the UK whereby cases would be referred and they would be looked through by specialists to see whether there were atypical features that might suggest variant CJD and then we would try and either get them to have an MRI scan or ask the family for permission for post mortem after death. It's an area where we know it needs further work.

DR. DeARMOND: Was there abnormal protein? I presumed there were no tonsils in that older person. They should have been very atrophied, but was there protein in the tonsillar region or around the GI track?

DR. WARD: I'm afraid I can't remember.

CHAIRMAN BOLTON: First, Dr. Mitchell.

DR. MITCHELL: You had mentioned before that there were a few recipients who had died of other

causes and I wasn't clear whether you had talked about the post mortems. Were there any post mortems and did they look for variant CJD?

DR. WARD: The cases that died -- we've learned about the cases that died through the flagging mechanism whereby we received the death certificate that is filled out on those cases. I don't know whether -- I'm not party at this stage as to whether they've had post mortems or not.

DR. NELSON: You mentioned that the MM genotype was present in 40 percent of the population. Is the distribution different by age, particularly by older people? Do they have a lower frequency of MM genotype?

DR. WARD: It's a good question. I don't think we know enough about the distribution of the codon 129 genotype throughout different populations, throughout the world, throughout the UK, throughout different age groups and it's work that we need to do but we don't know that.

CHAIRMAN BOLTON: Suzette.

DR. PRIOLA: What percentage of sporadic CJD patients present with MV genotype 129? Is there any concern that you would miss variant CJD patient in that genotype because they would present differently

pathologically?

DR. WARD: About 13 percent of sporadic CJD have the MV genotype. There has been, as I alluded to earlier, an increase in cases of sporadic CJD picked up in the younger age group and that has normally been a VV genotype so they are atypical for sporadic CJD.

However, Professor Ironside has looked at the ones who've had neuropathology and neuropathology has been typical for sporadic CJD. He's also looked to see whether they've had prion protein within other organs of the body which would be consistent with variant CJD and he hasn't been able to.

There are ongoing studies to see whether there is infectivity of the BSE pattern where they have injected material into R3 mice. I think their studies are ongoing but there haven't been any positive results to date.

Although atypical cases of sporadic CJD have increased since the variant CJD epidemic, it is not statistically significant result and the differences are the same throughout the whole of Europe which we take to mean isn't sort of UK specific.

CHAIRMAN BOLTON: Okay. Very good. Thank

you very much, Dr. Ward. That was most informative.

DR. BELAY: Just one question.

CHAIRMAN BOLTON: Just one more question.

DR. BELAY: I know you have been answering a lot of questions but I should ask this one. The MRI pulvinar sign, is it pretty much established to be a specific for variant CJD or has there been any evaluation of the specificity of that test?

DR. WARD: Yes. It has to be done -- hang on. Actually I've got -- these are the diagnostic criteria for variant CJD that were agreed in the WHO meeting we had in May of 2001. Basically for a definite case of variant CJD -- let me get this right -- you need to have a progressive neuropsychiatric order and neuropathological diagnosis of variant CJD.

For probable case you need to have all of I, four out of five, of II, any four out of five. You have to have both of these. A positive MRI scan has to be taken in the correct context because I understand that you can have a positive MRI in other conditions but it is very specific if you have all of these and four or five out of these. I can't remember but I think it's in the 90s for specificity.

DR. DeARMOND: Just a comment on that. We have a case of sporadic CJD from north or South

Carolina that had this reverse hockey stick sign on the MRI scan but it had none of the features of variant CJD. It doesn't seem to be 100 percent specific, that MRI pattern.

DR. WARD: I'm sure my colleagues in radiology would like to see that scan. That would be interesting.

DR. DeARMOND: It will be in publication fairly soon.

DR. WARD: Okay.

CHAIRMAN BOLTON: Once again, thank you, Dr. Ward.

Our next presentation is by Dr. Peter Soul from DEFRA. Perhaps he will explain to me what DEFRA. And he will be speaking on BSE and human food chain protective measures in the UK.

Dr. Soul, you have the floor.

For the committee, I think we will take this presentation and then we'll break for lunch. This presentation and its discussion and then we'll break for lunch and come back for Dr. Ricketts, if that's okay, Maura. Where are you?

Dr. Ward, while we are waiting for this presentation, can I ask a favor of you? If you would try to round up that information on those cases that

donated blood closest to the incubation -- I mean, closest to the onset of disease and whatever information you have forward it to Dr. Asher and to myself. I think the committee would be most interested in whatever you have on those.

DR. WARD: I'm sorry I didn't bring it today. We only just received it last week and it hasn't really been collated but I'm sure I could forward it if Professor Will allows me to.

CHAIRMAN BOLTON: That would be great. Obviously the committee and the FDA are very interested in any of that data has it develops going forward. That is a crucial piece of information that we would like to have.

Dr. Soul.

DR. SOUL: Thank you for the invitation to address the committee today. DEFRA is described up there. I won't go into it in any great detail.

I'm going to be talking about food chain protection in the UK with respect to TSE. I'll mostly be talking about BSE but I would like to touch on scrapie. Of course, I can't avoid mentioning the European dimension.

So, what are the overarching objectives that we have for food chain protection? I would argue

that they are those, too, to eliminate or, at least I suppose, to reduce the disease in cattle with a view ultimately to irradiating it. Meanwhile, while you are doing that, then taking adequate measures to ensure that the good supply itself is safe and is protected.

If we start off with eliminating the disease in food animal, there's been a great deal of interest, I guess, in the source of BSE. The two most likely contenders are that it came from scrapie in sheep or that it was spontaneous mutation in cattle.

Whatever the source, what we do know is that it was being recycled through the food chain by slaughter houses, meat and bone meal, and then back into livestock feed. The first key action to take is to prevent infection in the feed via the feed. I'll come onto that later on.

We also need to take action on clinical cases because let's remember that they are the reservoir of the greatest weight of infectivity. We need to consider maternal and horizontal transmission. Just on horizontal transmission, unlike scrapie there doesn't seem to be any strong evidence for horizontal transmission in the case of BSE.

But, of course, we are very interested in

that and we are particularly interested in it in respect to those cattle born after August 1996, a date you've already heard quite a lot about and no doubt will hear more about.

Those cases shouldn't be as a result of feed transmission if measures are 100 percent effective. They possibly be maternal transmission but there may be some other source of infection so we need to investigate that very thoroughly indeed.

How about breeding for resistance? That seems to be a good bet as far as sheep are concerned, but for cattle and goats, certainly at the moment there doesn't seem to be anything on the horizon. Surveillance, of course, is absolutely essential so basically we know what's going on out there.

That first point then, to prevent infection by feed. At the moment there is a pretty comprehensive band on the feeding of PAP, processed animal protein to food animals. That's all animals which are kept fattened or breed for the production of food and that's an EU-wide band.

Our national feed survey we have a pretty comprehensive survey which I would argue is an essential monitoring and enforcement tool to ensure that there is effective compliance with the feed band.

Sorry. I seem to have gotten out of order here. Back in July of 1988 we introduced the first measure. We prevented the feeding of ruminant protein to ruminants.

In the light of emerging evidence and new evidence on the epidemiology and new scientific data, we've had to put in place a great deal -- a very large number of additional measures over and above that one simple measure which on the face of it if that had been 100 percent effective would have stopped the disease in its tracks. So the disease cycle is really much more complex than that.

I put up this next slide not to go through it in any detail but simply just to use it as an illustration of how complicated the disease cycle is as we've learned over the years and how it's necessary to put a very large number of control measures in place.

This next slide I provided simply to give you a chronological list of the various meat and bone meal and feed related measures that have been put in place over the years. You might ask why on earth didn't we do all this right at the start?

I think the key factors that have come to our attention as time as gone on are, one, the very,

very small dose that you require to cause infection. Certainly I don't think that anybody thought at the start that you could infect animals with such a tiny amount of infectious agent.

The second key factor is the ease and the frequency with which cross-contamination can occur in the feed industry. There are so many points in the livestock feed production system, in the mills, in transports, on the farms, etc., where cross-contamination can occur and we are jolly sure did, occur prior to August 1996, at any rate.

Now, the second point was action on clinical cases. Obviously you need to have notification for the disease. You've got to know what's out there and deal with it. Once the animals are reported, then they are investigated, restricted, sorted, carcasses destroyed, and heads send for diagnosis. The key point is that you are removing that infected animal from the animal food chain and from supply for human consumption as well.

So compulsory slaughter with compensation, that was implemented from August 1988. I want to make a point on this which is that you must strike the right balance between providing an adequate incentive for notifying disease and not introducing a strong

disincentive to reporting disease. I think we are firmly convinced that you need to provide 100 percent of the market value in terms of compensation.

One of the measures which other people have introduced is whole herd slaughter. I think we are strongly opposed to that because our view would be that whole herd slaughter provides such a strong disincentive that you are likely to drive the disease underground.

We require isolation of clinical cases during carving and we destroyed a percent fundamentally to try and minimize any risk of natural or horizontal spread.

We have precautionary controls on milk. Not that there's any evidence that the disease is transmittable through the milk but as a human health safeguard that's in place. Milk can only be feed to the animal's own calf.

Total destruction and incineration of the carcass is an important measure to remove the infective agent from the environment and heads are sent for diagnosis in order to confirm the disease. You can't confirm on clinical grounds, only on laboratory tests.

I mentioned maternal transmission.

Although the trials that have been done on maternal transmission are equivocal and can be interpreted in different ways. There may be maternal transmission at the low level up to a maximum of 10 percent.

I'm told that would be insufficient to sustain the epidemic. Nevertheless, we do have an offspring cull in place to remove the offspring born after August 1996 and to destroy those and remove them from the food chain. Obviously those offspring are the animals most likely to be at risk of maternal transmission if it occurs.

We have recently introduced a measure to test the offspring as well. We test the brains of animals over 30 months of age to see if there is any evidence of the infectious agent in them.

Passive surveillance, which is reporting of the disease, it's essential that you've got an adequate level of awareness out there amongst all the various groups that are involved in order to ensure that you are getting a good level of notification.

I think we are pretty confident, in the UK at any rate, we have achieved that. I think we are reassured by the negative rate which has been increasing over the years and is now up to 30 percent for 2001.

In other words, you're getting lots of suspect animals reported even though quite a large proportion of those haven't actually got the disease so that's what you want to achieve with passive surveillance. I have already talked about incentives and disincentives and how important that is in passive surveillance.

On active surveillance, we are targeting -- the whole of Europe is targeting various high risk subpopulations such as cattle that die on the farm, fallen stock, casualty cattle, what's known as special emergency slaughter animals. Those are animals which are slaughtered on the farm but can still go to a slaughter house or an abattoir to produce meat for human consumption.

Ante mortem rejects. In other words, an animal that gets to the slaughter house without showing clinical signs but develops them on the way, if you like. As a result of the stress the signs may become more apparent, will be picked up at the slaughter house, and rejected for sale for human consumption.

I've mentioned the 1996 cohort. That is the group of animals that were born between the first of August 1996 and the end of July 1997. That's

obviously a very important group of animals for us because they are the animals which we believe should not have been exposed to infection following the reinforced feed band which was firmly established by the beginning of August 1996. It's very important that we look very closely at that group of animals to provide the evidence that they haven't acquired disease.

We are also doing surve.llance on sheep and goats. You are aware that there is a great deal of concern that BSE may have passed to sheep and goats so there is quite a high level of surveillance now going on in those populations to look for TSEs.

Moving on then to the second overarching objective which we must have which is to prevent contamination of the food supply. Clinical cases cannot enter the food chain that are diagnosed on the farm and destroyed as I have described.

Ante mortem inspection, again we want to ensure that the animals aren't getting through into the food chain in the very early stages of the infection -- sorry, early stages of clinical disease so we would aim to pick that up at the ante mortem inspection carried out by a veterinary surgeon.

The SRM controls are designed -- specified

risk material controls are designed to remove from the food chain those tissues most likely to harbor infectivity and I'll come onto that. MRM is mechanically recovered meat, mention the over-30-month rule and TSE testing.

A bullet point I should have put up there that I omitted because it's not particularly relevant in the UK which is the band that we now have on pithing. The reason that it's not particularly relevant in the UK is because of our over-30-month rule. Certainly in older animals there's a good case to be made for banning pithing.

Just listed there the SRMs as they are at the moment in both cattle and sheep and goats. These you recall are the tissues. Certainly at the time when the controls are first introduced, from what we knew about the disease in sheep, were believed to be most likely to harbor infectivity.

The first controls were specified bovine offal controls which were banned from human food in November 1999. And from September 1990 they were also excluded from all animal feed. The intention there was to reduce the risk of cross-contamination into ruminant feed. You will recall that we already had a ruminant feed ban in place.

The SRMs have to be removed, stained, stored separately, dispatched under controls, and rendered -- have to undergo a high-pressure rendering process and destroyed by incineration or burial in a licensed landfill site.

Mechanically recovered meat. I think you probably refer to that here as mechanically separated meat. It's different, again, from advanced meat recovery systems. The first ban for MRM was on ruminant vertical column in December '95. Currently there's a ban on the use of all ruminant bones in the production of MRM. That is related to the single finding of infectivity in bone marrow.

I would argue, and I think it has been mentioned earlier, that MRM was probably a major risk factor early on because of the risk of small pieces of spinal cord getting into that product, but also the spinal cord that gets spread onto the vertical column when it's split. During the splitting process there will be some spinal cord left behind and if that thing goes into MRM production, it's going to get into the product.

Perhaps I should also mention the head meat is also probably a major risk factor. It was in the early days. Again, we introduced it ban on head

meat. Not just because of the brains and the nerves in the head, but also because during the process of removal of the head meat and transporting the heads, then there was a good chance that central nervous tissue would get onto the head meat and be in that product when it was used for human consumption.

So moving onto the over-30-month rule. This, of course, has been successful in removing a very large number of preclinical cases from human food. There's a very low risk from UTM over 30 months cattle. The calculations that were carried out suggested that there was probably less than half an animal in 2001 that was within 12 months of developing clinical disease going into the food chain last year, 2001.

Of course, it's been carried out at enormous expense. Well over 5 million cattle have now been removed through the OTMS, the over-30-month scheme. The same rule applies to imported meat and I've put up a query there. Take time to review it. We certainly need to review it at some stage and decide whether it needs to continue.

Our Food Standards Agency looked at this very carefully and said that now is the time when we might start thinking about reviewing it based on the

information from the data that we were getting from the surveillance of the 1996/97 cohort.

You remember I mentioned that as being a very important group of animals first to look at to satisfy ourselves that the August '96 ban had been truly effective.

I thought I should just mention TSE testing because so much of this is now going on throughout the European union. It will have some benefits in detecting some preclinical cases. In other words, some animals which are going for human consumption but haven't yet developed any clinical signs. That will only be animals that are pretty close. Probably about within three months of developing clinical disease.

It's a valuable surveillance tool for those countries which are still -- those countries in Europe which are still using over-30-month animals for human consumption but which with a very few exceptions we're not doing in the UK so it has less value for us in the UK. Certainly less value in terms of consumer reassurance which I think is quite a strong motivating factor behind its use in other member states in Europe.

Can I just quickly run through what we see

as being the major factors in regulatory control. I know this has already been mentioned but education and training is so very important so that you've got that level of awareness amongst all the key stakeholders that are involved. We think we really have a very good record of that in the UK. Partly, of course, that is because BSE is such a high profile disease in the UK, whereas in those countries where it's not a high profile disease and where the incidence is very low, then it's very, very much more difficult to get a satisfactory level of reporting of suspicision of disease so you do need really effective education and training campaigns.

The legislation, of course, you must have a sound statutory basis for regulatory control. It must be clear and readily understood and, above all, enforceable. Very importantly, it must be supported by stakeholders.

We had a pretty embarrassing set of circumstances in the UK when we banned the sale of beef on the bone which wasn't supported by consumers generally speaking. After some difficulty we were able to repeal that particular piece of legislation. We didn't believe that it was necessary in terms of the risk involved, the risk to human health.

Monitoring, of course, to demonstrate effective control and to give you the data you need to elucidate the epidemiology and to provide the assurances you need that regulatory control is effective.

Enforcement obviously to ensure compliance with your controls. We certainly found that in the case of SRM controls that we needed to adopt a very, very rigorous approach to enforcement. In effect, it was a zero tolerance approach in slaughter houses. You must have an effective level of audit to provide the assurance you need that you have achieved effective control.

Another point I perhaps should have put up is the maintenance of good records. Just on audit and enforcement, the slaughter houses receive very frequent visits by the State Veterinary Service to check on the level of compliance with the SRM controls and with the enforcement effort that is put in by the Meat Hygiene Service in the slaughter houses.

After a pretty shaky start in early 1995, which is where, as I mentioned, we came in with really a very rigorous level of enforcement. Then we got up to a very, very high levels of compliance and we have maintained those subsequently. There should be copies

of that in the pack. It doesn't show up very well on here, does it?

The control of the epidemic, how are we doing? I think quite useful indicators for that are around about 40 percent reduction in the number of confirmed clinical cases in 2001 compared with 2000. The negative rate which I mentioned is increasing. It's now up to around 30 percent. In other words, 30 percent of the suspect cases that are notified to us prove not to have BSE.

And for the post August 1996 cases, then the negative rate is 98 percent. We are still getting quite a number of suspect cattle reported to us born after August '96 but the vast majority of those are negative.

The average age of clinical cases is also increasing. I think that is indicative of a waning epidemic, if you like. BARBs is "born after the reinforced ban." The reinforced ban was what happened in August 1996. it's not what the Europeans call it which is "born after the real ban." There will of course be more and we are carrying out very thorough investigations to try and find out where the diseases come from.

I mean, the immediate assumption would be

it's maternal transmission but in the majority of those cases, maternal transmission would seem to be very, very unlikely because the dams are still alive in some cases, or were still alive for a long time after the case was born. We think that if maternal transmission does occur, then the most likely risk period is close to carving.

So that is a pretty typical epidemic curve. Confirmed cases by clinical onset. You can't see it on there but it peaked in 1992, 1993. I've shown on there when the first feed ban was introduced.

So you may ask why did it carry on like that afterwards? Well, it indicates that these animals were already infected before the feed ban was introduced and due to long incubation period we continue to get clinical cases.

If you look at this one, which is plotted by month of birth, then it's much clearer that after the feed ban, that shows just how timely and effective the feed ban was because without that, then this curve would have gone off exponentially, I would guess.

If you are wondering about the cyclical pattern, that is a consequence of our traditional carving season in the UK. I conclude on that and say that we have imposed some very, very strict and, to

some extent, draconian measures in the UK in order to achieve the necessary control of BSE.

We have certainly done that, not without enormous cost but I hope now that we are very well on the way to getting rid of this awful disease and find out means of protecting the food chain.

CHAIRMAN BOLTON: Thank you, Dr. Soul.

Peter, I was going to call on you if you didn't raise your hand so I'm glad you did.

DR. LURIE: I'm touched. I want to anticipate the discussion this afternoon and then ask a question for you, Dr. Soul. Really a series, I suppose.

As far as I can see this, and I'm sure other people on the committee might enlighten me, there are basically two questions or two elements to the question before us today. One is what is the degree of compliance with the UK ban. The second is what is the impact of extending the upper limit of the UK travel ban from 1996 to 2000 upon the rate of donor deferral. I think those are basically the questions. It's relatively simple, I think.

Now, I don't so far see any data about the second of those questions. I certainly would not have expected it in this presentation. If FDA could give

some thought to some sort of estimate over lunchtime over what that extension from '96 to 2000 might actually mean, we really can't make any kind of rational decision without that information, even an estimate.

Getting back to the first part then is a matter of compliance with the British ban. I think probably all of us would agree with your assertion that the existent ban is, however late they might have come into effect, and many people, of course, believe they were not as expeditious as they might have been, now presently if properly enforced would act as you assert, probably to prevent almost all transmission.

The question really then is compliance. In your presentation I see really only one slide that gets to that question and that, to me, is the nub of what's before us here. I don't know if you have this with you but I need to be more enlightened in any way you possibly can about the matter of compliance.

The data that you present, for example, are these inspections or are they reinspections? What does it mean to be compliant? Does 100 compliance mean 100 percent compliance with everything that was inspected? What exactly did they inspect?

I'm left with many, many questions about

what these data mean. I don't know if you have them right before you but anything you can tell us that expands an effect on that slide will be very helpful.

DR. SOUL: Yes. That was specifically about compliance with the SRM controls.

DR. LURIE: Only the SRM part, right? Not OTM, is that correct?

DR. SOUL: That slide was just on SRMs, yes.

DR. LURIE: So there's nothing in your presentation that goes to the OTM compliance whatsoever. Is that right?

DR. SOUL: That's correct, yes. I didn't really address that.

DR. LURIE: Do you have data on it?

DR. SOUL: Not really, no. On SRM compliance what happens there is the State Veterinary Service visits slaughter houses once a month and checks on all the rules surrounding SRM in a slaughter house. That is everything to do with removal, staining, storage, separation, dispatch, and so on and so forth.

Also the way at which that is enforced by the Meat Hygiene Service who have a full-time presence in the slaughter houses. If you like, there are two

tiers of enforcement there.

There's the on-the-ground enforcement authority and then there's an level of audit coming in every month to check that they are doing the job. As I say, after a somewhat shaky start, that got up to about 98 percent compliance and has stuck at around that level ever since.

The key aspect of it, of course, the most important aspect of it, is removal of the spinal cord. From memory there has only been one failure of that since that early difficult period. After about December of '95 there has been only one finding of spinal cord at those audit inspections.

Now, those results are all reported in what is called the BSE Bulletin which is a joint publication by the Food Standards Agency and my department. That is on the Food Standards Agency website. The details on those inspections, what they look for and so on, is there and available.

DR. LURIE: When you say there is at present 98 percent compliance, that means that of the monthly audits, not the underground part because that's what you present here. Of the monthly audits, 98 percent are compliant with all the dimensions of things that you look for.

DR. SOUL: That's correct. Sorry. What was the other point? I've lost it.

DR. LURIE: No. That's it.

CHAIRMAN BOLTON: Steve, then Dr. Mitchell, then Dean.

DR. DeARMOND: I would like to follow up on Peter's question because auditing and inspecting compliance seems to be very complicated because 1,000 cattle could be slaughtered in a day and over every day I don't know how many go through your slaughter houses but it's enormous numbers.

How does one determine through a compliance audit of the quality control of that? There's many rooms and many places for mistakes to be made with that massive number of animals being slaughtered each day.

DR. SOUL: Yes. Don't forget that each of those animals receives an individual inspection by a qualified meat inspector. One of the things that they have to do is to check that the spinal cord, for example, has been totally removed from the carcass before the carcass is health marked.

Then there is actually a secondary check after the initial inspection check because this is part of the sort of rigorous level of enforcement that

we had to put in place in order to achieve this extremely high level of compliance.

When the auditors go in, they have got several chillers full of beef sides and they go and look at them all again so this is a triple check, if you like, to ensure that that spinal cord has all been removed. Out of all the thousands and thousands and thousands of carcasses that have been inspected in that audit, there's only been this one failure since the end of 1995.

We are confident that in that particular respect, in respect to the SRM controls. It was very difficult initially and it was very painful but having got there, we have managed to maintain it.

Now, I could compare that with other member states who are going through the learning phase, if you like, now and we have found quite a number of failures on imported meat coming in where spinal cord is still being present. I think they are going through that difficult period that we went through back in '95 but fortunately we got there.

DR. DeARMOND: The other question related to that is how big of a problem -- how many individual cattle ranchers, or whatever you call them, over there do their own slaughtering and then they don't get

inspected? Does the individual small group get inspected also and how many of those are there compared to your big slaughter houses?

DR. SOUL: It's illegal to sell meat that hasn't been produced in a licensed slaughter house. Only a very small number of farmers would kill cattle for their own family's consumption.

CHAIRMAN BOLTON: I just want to clarify this point. When you say there is one instance post '95 of spinal cord not being removed, that's one carcass or one inspection?

DR. SOUL: One carcass.

CHAIRMAN BOLTON: One carcass. Okay.

Dr. Mitchell.

DR. MITCHELL: Yes. Our question is about the protection since 1996. Presumably the only source of variant CJD is from the food supply, then I think that this slide that you have up here is very, very important and are looking at the current amount of infected cattle.

I look and I see there that it only goes up until 1996 or '97 and I'm presuming that there hasn't been any other BSE confirmed since then but I wanted to find out if that was true.

DR. SOUL: I'm sorry?

DR. MITCHELL: This only goes up to 1996 or '97. If you were to bring it up to 2002 would you see other cattle that are born after '97 that would be infected with BSE?

DR. SOUL: Well, there haven't been any confirmed cases born after 1997. I showed you that there have been seven cases born after August 1996. It just doesn't show on here. The scale is just too small to show it. There are seven confirmed cases so far born after August 1996.

CHAIRMAN BOLTON: You have to keep in mind that the minimum incubation time after '97 is something like 36 months or something, right? I think that's right. About three years so you're looking at a starting point from there.

There were some incubation times below 30 months in animals that were born much earlier but they were in the height of the epidemic and probably received a much higher dose, exposure. At this point from -- well, you might expect to see some cases born in '97 or possibly '98 but those born in '99/2000 have not reached the sufficient length of incubation time to be seen yet.

DR. NELSON: Yes. I think we're concerned about the human exposure which certainly is related to

the cattle epidemic. My sense is that if a cow were slaughtered, that the likelihood that it would be consumed within a year or so is probably pretty high. Certainly that would be true for milk.

I mean, they have the thing expires after a month from now and goes sour or what have you. Are there any data on how long meat from an infected cow -- I mean, it could be frozen somewhere and it could be present maybe years later.

Are there any systematic data on the human consumption of meat after it's been -- after cattle have been slaughtered and it's converted into human food? I'm sure those data are very difficult and probably inaccurate but there may be some estimates.

DR. SOUL: No. I agree with you that beef can be in the store for some years before it is consumed. I'm certainly not aware of any data that regards infectivity surviving in frozen beef. The work just hasn't been done to my knowledge.

CHAIRMAN BOLTON: Dr. Cliver.

DR. CLIVER: Yes. A question that's been on my mind for a very long time might be based on the curves that we're seeing here. The UK, it seems to me, is in a unique situation to be able to give us some baseline data eventually on the sporadic

incidence of BSE by analogy to the sporadic incidence of CJD.

One might say why not look at Australia or New Zealand or even the United States, but clearly the level of surveillance is nowhere near what is going on now in the UK.

To what extent could present observations be brought to address that question? Is there a background level below which this cannot go with the present level of observation?

DR. SOUL: I don't really know how you would set about addressing that question really. We certainly looked to try and see if there are different strains of BSE in the current epidemic and the evidence to date suggest that it would appear to be a single strain.

Whether a sporadic case would show some strain differences, then you might pick that up through that work. I don't know. It seems to me that certainly with the number of cases we've got we couldn't begin to test the theory of sporadic BSE occurring.

DR. CLIVER: Well, I'm just thinking in terms of people -- we had a figure that we dealt with on the CJD incidents. Mind you, people tend to die

natural deaths or unprovoked deaths much more frequently or commonly than cattle do.

Having said that, we have animals living out their life span as producers in dairies and so on and maybe were never at risk. Nothing that we could ever identify would say that they were at risk of coming down with BSE. Yet, at some point one per year, one per million cattle of age or whatever are still going to show that BSE is out there.

Nothing at that point that one could do in a preventive way is going to preclude that. We will never know what that number is for the United States but just possibly it may be a derivable statistic in the case of the UK.

CHAIRMAN BOLTON: I would disagree with that actually. I think that for many theoretical reasons the best way to do that experiment to determine what that background rate of spontaneous generation, if you will, if BSE would be to do it in Australia or New Zealand with increased surveillance of the type that you have now in the UK because you have no endemic scrapie and you have no other, at least, known endemic transmissible spongiform encephalopathy in that location and you have plenty of cattle.

Whereas here you would always have the concern of residual infectious BSE residing somewhere that you would never -- you are looking at probably an incidence rate of one per million animals per year. It's a very -- you're looking at a few cases over a decade maybe against a background of 1,200 BSE cases last year alone in the UK.

DR. CLIVER: David, I can't argue that for a moment. The point is that in the grand scheme of public health and food safety and so on, there are only so many resources available. Tell the Australians that they need to be testing for something that might be occurring at a one in a million level at their expense.

Now, if NIH wants to fund a study there on a nationwide basis, I'm sure they would be thrilled to take the money. We do have more pressing concerns about what people are dying of in the United States, for example, and the money is not going to go into a study like that. They are already testing in the UK with good reason.

CHAIRMAN BOLTON: I understand your point. My point is that you cannot interpret the data. Should one try to undertake a study like that in the UK, the data would essentially be uninterpretable.

Yes, Dr. Gambetti.

DR. GAMBETTI: Just a quick question. How are animals, cattle tested in the UK for BSE? The same way as in continental Europe that virtually all the animals over 30 months of age are tested, or is it different?

DR. SOUL: Yes, it's different. In the UK we're testing all the 96/97 cohort and we're testing 50,000 other over-30-months animals. We are also testing all of the fallen stock over 24 months and all the casualty animals over 24 months. Plus animals rejected at ante mortem inspection at a slaughter house and what is known as special emergency slaughter animals.

CHAIRMAN BOLTON: Pedro and then --

DR. PICCARDO: In one of your slides it says surveillance of sheep and goals. How stringent is the surveillance in sheep?

DR. SOUL: We think there's an awful lot of under-reporting in the UK. We only get about 500 reported cases a year. We did a postal survey which suggest that is probably only about 10 percent of the true level.

DR. PICCARDO: Obviously my question refers to the well-known fact that if the BSE strain

went into sheep, the sheep might get another form of scrapie so I want to know if there is a very active surveillance in sheep looking for this unusual thing.

DR. SOUL: We just started an active surveillance program for sheep going through slaughter houses and we are going to be testing 20,000 of those this year. We are also testing a small number, about 60,000 of fallen sheep, sheep that die on the farm.

CHAIRMAN BOLTON: Dr. Chamberland.

DR. CHAMBERLAND: Yes. I wanted to follow up on Dr. Lurie's previous comment. The committee members were supplied with a large document called Review of BSE Controls. I think the author would be the Food Standards Agency and it's dated December 2000.

In just quickly re-reviewing this, there does seem to be in this document information current through December of last year that does relate to compliance with some of these various control measures.

For example, an audit that has been ongoing apparently since February of 1996 to look at evidence of ruminant protein and concentrated feed indicated that -- I guess this is an aggregated compliance rate that since that time about 99.7

percent of the fee that was tested was negative for protein.

There also was some mention of this over-30-month rule and it indicated that this rule is enforced by another group within the UK called the Meat Hygiene Service and at least current through December of 2000 it said records of cattle rejected under the rule are kept at individual abattoirs. They are not centrally collated by the Meat Hygiene Service and this group recommended that such a measure be enacted.

I guess a couple questions. One is, as Dr. Lurie stated, I think it will be really very helpful for the committee to have some sense of overall compliance or trends over time for these various measures. Are such data available and could these be made available to the committee?

I'm presuming it would have to be at some future time. Would it be a group other than yourself from where you come, the Department of Environmental Food and Rural Affairs. I apologize. I don't know how all of you are organized and how you relate to one another.

It may be that most of the information we need is here embedded in the document. Again, quickly

I could pull out a couple of what seem to be pertinent facts and figures. Are compliance data something that would be available that we could get?

DR. SOUL: Yeah. I mentioned the BSE Enforcement Bulletin which is published on the Food Standards Agency's website. It's www.foodstandards.gov.uk. That contains all the available enforcement and compliance information. We were talking earlier about SRM controls, but it also contains the data on the national feed survey, which I mentioned.

You are right to say that the compliance with the OTMS rule isn't centrally collated and, to the best of my knowledge, is not centrally collated. But if it is, that will also be published in that publication. There's a wealth of compliance information going back many, many years.

CHAIRMAN BOLTON: Blaine.

DR. HOLLINGER: I presume that the rise and fall that occurs every year there is because of the birthing rate at a particular time of year. Within those particular years, though, are the proportion of confirmed cases the same pretty much across the board based upon the number of births that occur in that particular year or are there differences

that occur?

DR. SOUL: Yeah. That doesn't really fluctuate across the course of a year.

CHAIRMAN BOLTON: Dr. Boyle.

DR. BOYLE: Could you please clarify is it correct to say that your seven BARBs came out of a census of all cattle in 1996 and then since that time you do samples of 50,000 per annum?

DR. SOUL: The seven BARBs, four of them were discovered as part of the active surveillance program. I think a couple of them were casualties and a couple of them were foreign stock. The other three were clinical cases.

DR. BOYLE: What's the size -- what was the size of the census in '96 from which the four BARBs came from?

DR. SOUL: I haven't got that.

DR. BOYLE: I'm just trying to understand whether you're going to pick up with samples of 50,000 the same rates that you were seeing in 1996.

DR. SOUL: We haven't really done enough at the 1996/97 cohort yet because that didn't start until the backend of last year to give you significant figures on that.

CHAIRMAN BOLTON: Other questions? Peter.

DR. LURIE: I just want to add a little bit to what Dr. Chamberlane said. Referring to the same document that she refers to, I see probably three points in this document that had information relevant to us. One is in paragraph 40 where it is indicated 99.9 percent compliance with the OTM rule, but that's at present. Of course, we are rather more interested in what was happening in 1996/97 than we are at present. That's paragraph 40.

On paragraph 52 there's discussion of the SRM ban, presumably the same data that you have provided for us. Here it said 99.4 percent compliance rate for the year ended September 2000 with no information provided about data prior to 1996. As far as I can see, those are the data that we have.

CHAIRMAN BOLTON: Steve.

DR. DeARMOND: We're going to be asked to discuss or give an answer to some of these questions. Are the combination of measures implemented in the UK by the end of 1996 to protect humans adequate essentially? Are they doing the job? I would like to ask you do you think they are doing the job and, if no, what would you add to the current measures?

DR. SOUL: Well, I'm quite content to eat our beef so I think from a personal point of view

then, yes, I do think the measures are now highly effective and are doing a very effective job.

I'm obviously concerned about the seven BARBs and I want to know if that's not maternal transmission, and I personally don't really think it is, then what is it? Is it just that there are a few bits and pieces of contaminated feed still out there in UK farms? Is there contamination of feed ingredients that are coming into the country? I mean, those are sort of issues which we want to investigate very, very thoroughly to satisfy ourselves. Don't forget it's all belt and braces stuff, you know. I showed you that complex slide with all the different measures that are in place. The truth of the matter is, and somebody mentioned it, that no measure can be 100 percent effective. You've got to acknowledge that. You've got to accept it. The raft of measures is such that I am very confident that we have got a very tight grip on the disease now.

CHAIRMAN BOLTON: I would like to ask in the control measures how closely linked are monitoring and enforcement and how are they linked if they are linked at all?

DR. SOUL: Generally speaking we try and have sort of two tiers, if you like. We try and have

the enforcement authority which for SRM controls, for example, is the Meat Hygiene Service present in the slaughter house. Then for audits we bring in an outside body, a separate body, to check that is taking place. It's quite complex because you asked about enforcement as well. The Meat Hygiene Service are also the enforcement authority in the slaughter houses. For the National Feed Survey the State Veterinary Service is doing the survey but the enforcement authority is actually the local authorities. There's not a simple picture I can give you.

CHAIRMAN BOLTON: I am assuming that in most countries that will be the case and if such controls are put into place, I'm sure it would be here as well, and that is that you have multiple agencies involved and not necessarily always good communications between them. How has the government in the UK worked to try to improve the communications between, for example, local agencies and the broader agencies?

DR. SOUL: There is a coordinating body and that sort of takes the lead on making sure that the central messages, if you would like, are getting out to the enforcement authorities. Also, in a way,

more importantly is the local link, the link between the divisional State Veterinary Service who may be doing the monitoring, for example, and their liaison with the enforcement authority. Those local arrangements are usually very good indeed.

CHAIRMAN BOLTON: They are good but how are they maintained? I mean, it's important, I think, to have an understanding of a process that keeps those links going because they are in many respects links of individuals to each other which are subject to he vagaries of individual personal relationships.

DR. SOUL: I think perhaps the key to it is the audit that you put in because we are all subject to very intensive levels of audit now in this area. I think everybody is alert to that and recognizes that if they are not doing the job that they are required to do, then they are going to be found out. That was one of the key lessons about the Phillips inquiry into BSE.

We're saying, look, it's not good enough just to put legislation in place and then assume that it's going to be enforced. You've got to enforce it, on one hand, but also you've got to check that it is being enforced.

CHAIRMAN BOLTON: Other questions? Very

good. I sense that people are getting hungry.

Thank you, Dr. Soul.

We will break for lunch now. I have 12:54. This time I'm not rounding off. I paid a dear price last time. We have an hour for lunch so let us meet back here at 1:54. Thank you. We stand temporarily adjourned.

(Whereupon, at 12:54 p.m. the meeting was adjourned for lunch to reconvene at 1:54 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:58 p.m.)

CHAIRMAN BOLTON: Okay. Let us resume. We are still on topic No. 1 which is the effectiveness of measures taken to protect humans from food-borne exposure to the BSE agent in countries with BSE, implications for variant CJD risk and blood safety. We will now have a presentation from Dr. Maura Ricketts from the WHO. Maura will inform us on the efforts and needs for global control of BSE and variant CJD, a view from the WHO.

Maura, thank you very much for coming.

DR. RICKETTS: Thank you very much for the invitation. I really appreciate the opportunity to come to the meeting and I'm glad there's a chance for WHO to share with the committee its perspective on this particular subject area.

You have in your handouts a copy of my slides. Actually, when I had a chance to read the charge to the committee, I thought I should alter my presentation a little bit. In fact, there are three slides that have been added to my presentation that are different than are in your material. I can provide this to somebody by Monday when I'm back in Geneva.

In addition, you'll see on this slide presentation some maps that are -- well, you'll see them. I won't provide those to you. I'm afraid I cannot. It's my experience that the misuse of this geographically based information without adding to it other relevant information is such that as a person from WHO I could not provide this to you directly but you'll be able to see them here. I can certainly provide the raw data to anybody who asked for it, although I don't want to receive, you don't mind, 30 requests for the information. If it is wanted by the committee, I am happy to provide the raw data.

Okay. I think that I have to start by telling you a few of the things that WHO is assuming when we do our analysis of the situation. First off, we are assuming that BSE and variant CJD are caused by the same agent. We believe that the BSE epidemic in cattle was caused by BSE contaminated meat and bone meal supplements in cattle feed. We think that the principal source of exposure for humans is food. There's not a lot of proof behind that but it seems both practical and pragmatic to operate from that assumption. Certainly our concerns will become human to human transmission as a possible secondary route in the future if the number of cases becomes of any size.

Lastly, at this point in time there is actually no test that can detect the agent in food or in living asymptomatic animals. That's living asymptomatic animals. So this epidemic curve is now familiar to you. There are a couple of points on it that I want to draw to your attention immediately.

The first is the institution of the feed ban in the United Kingdom. As has already been explained to you, the feed ban is a very important means of preventing the transmission of the disease, possibly the most important means of preventing the transmission of the disease.

However, its effects will not be seen for some five or six years after its implementation if BSE is already in the population. That is graphically demonstrated by this particular picture here. Secondly, that the specified Bovine's offal ban was introduced a couple of years after the beginning of the epidemic.

It was introduced, my understanding is, principally for the protection of human populations. The SBOs were not destroyed. They were returned actually into the animal feed for a period of time. Towards the end of this epidemic curve at the far end the sale of meat and bone meal from the United Kingdom