U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE

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MEETING

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Thursday, June 3, 1999

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The meeting was held in the Ballroom, Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, at 8:30 a.m., Paul W. Brown, M.D., Chairman, presiding.

PRESENT:

PAUL W. BROWN, M.D., Chairman

WILLIAM FREAS, Ph.D., Executive Secretary

ERMIAS, D. BELAY, M.D., Member

DAVID C. BOLTON, Ph.D., Member

DEAN O. CLIVER, Ph.D., Member

LINDA D. DETWILER, M.V.M., Member

BRUCE M. EWENSTEIN, M.D., Ph.D., Member

BARBARA W. HARRELL, M.P.A., Member

PRESENT (Continued):

DAVID G. HOEL, Ph.D., Member

PETER G. LURIE, M.D., Member

J. JEFFREY McCULLOUGH, M.D., Member

STANLEY B. PRUSINER, M.D., Member

RAYMOND P. ROOS, M.D., Member

ELIZABETH S. WILLIAMS, D.V.M., Ph.D., Member

LAWRENCE B. SCHONBERGER, M.D., Temporary Voting Member

ROBERT G. ROHWER, Ph.D., Consultant

LISA FERGUSON, D.V.M., Speaker

JEFFREY ALMOND, Ph.D., Speaker

RICHARD RACE, D.V.M. (by teleconference), Speaker

DIANE SUTTON D.V.M., Speaker

CHARLES DURFOR, Ph.D., Speaker

DAVID ASHER, M.D., Speaker

JOHN HONSTEAD, D.V.M., Speaker

KIKI B. HELLMAN, Ph.D., Speaker

ALSO PRESENT:

DR. JAMES HOURRIGAN

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P R O C E E D I N G S

(8:34 a.m.)

DR. FREAS: We'll go ahead and get started.

Dr. Brown, before we officially begin, I would like to just go around and introduce to the members of the audience the new table arrangement. Those of you who were here yesterday can notice there are many changes between yesterday and today.

We have one temporary voting member. That's Dr. Lawrence Schonberger. He's on the right-hand side of the table standing up. Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, Centers for Disease Control.

Coming around the table is Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago.

Next is Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention.

Next is Dr. Peter Grant Lurie, Public Citizens Health Resource Group, Washington, D.C.

Sitting down right now is Dr. Stan Prusiner, Professor of Neurology, University of California School of Medicine.

Coming around the corner of the table in front of the podium is Dr. David Hoel, Professor and Chairman, Department of Biometry and Epidemiology, Medical University of South Carolina.

Next is Dr. David Bolton, head, Laboratory of Molecular Structure and Function, New York Institute for Basic Research.

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

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

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

Around the corner of the table, Dr. Linda Detwiler, senior staff veterinarian, U.S. Department of Agriculture.

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

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

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

Next is the consultant for today, Dr. Robert Rohwer, Director, Molecular and Neuro-virology Unit, VA Medical Center, Baltimore.

Dr. Piccardo will not be joining us today, and we should be joined very shortly by Dr. Donald Burke, Director, Center for Immunization Research at Johns Hopkins University.

Good morning and welcome to everybody.

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

CHAIRMAN BROWN: Thank you, Dr. Freas.

I've worn my happy shirt this morning to readjust the tone after yesterday's very difficult meeting, not because of personalities, I think, but because the topic was an extremely difficult one to deal with, and I'd like to reiterate my appreciation to the Committee for whacking away at it as best they could and arriving at some sort of recommendation that the FDA can now consider.

Today, on the other hand, I'm looking forward to a relatively easy deliberation, and before we start the main topic, which will be the safe sourcing of products derived from sheep and goat that

are used in the manufacture of FDA regulated products, we will very briefly look again at the topic of precautions in the processing of human dura mater, which the Committee considered in detail last year.

And for that, we have a presentation by Dr. Charles Durfor, Center for Devices and Radiological Health in the FDA.

Dr. Durfor.

DR. DURFOR: Good morning. Today I wish to give you a brief update on the status of revising the guidance for the preparation of a pre-market notification application for processed human dura mater. You can stay on the first slide, please.

This document has not been publicly released yet, and it is completing the final stages at this time of FDA review and sign-off. Hence, my comments today provide the agency's current thinking on this issue with the intent of updating this Advisory Committee and answering related questions.

Next overhead, please.

Before I discuss the key elements of the proposed revision of the guidance, I'd like to begin by defining the product under consideration. Then I will offer some brief regulatory history as to how we got where we are today.

First, the product under discussion is processed human dura mater. Dura mater substitutes are different products and are regulated as Class 2 medical devices.

Next slide.

A brief regulatory history starts with the understanding that processed human dura mater for implantation was commercially distributed before the medical device amendments to the FD&C Act were enacted in 1976. Thus, this product is regulated as a pre-amendments medical device.

The sensitivity to Creutzfeldt Jakob disease transmission, related to processed human dura mater implantation, was heightened after the report of the first case of CJD in the United States by the CDC, CJD related to dura mater implantation reported by the CDC in February of 1987.

In April of 1987, the FDA issued a "Dear Doctor" letter to alert physicians about the potential risk of transmitted Creutzfeldt Jakob disease through potentially contaminated batches of human dura mater. This alert specifically mentioned the product Lyadura packaged in 1982. It also requested that all CJD cases be reported to the FDA.

In June of 1987, FDA banned the

importation of Lyadura into the United States.

On February 2nd, 1990, the Neurological Devices Advisory Committee to the Center for Devices and Radiological Health recommended that processed human dura mater be regulated as a Class 2 medical device, that is, a device whose safety and effectiveness is maintained through compliance with special controls.

FDA did not finalize this classification recommendation, and hence today processed human dura mater remains an unclassified medical device. As such, commercial distribution requires FDA review and clearance of a pre-market notification application.

To provide guidance to FDA reviewers and product manufacturers, FDA published in June of 1990, a guide for the 510(k) review of processed human dura mater.

In 1996, a Japanese survey identified 43 cases of Creutzfeldt Jakob disease associated with the use of processed human dura mater. Most of these cases were associated with the use of Lyadura.

Next slide.

In March of 1997, the World Health Organization recommended that processed human dura mater grafts no longer be used, especially in

neurosurgery, unless no alternative was available.

The following day, an announcement from the Japanese Health and Welfare Ministry banned the use of dura mater in brain surgery. Because FDA had established safeguards and guidelines in 1990 to minimize the possibility of such infections, the agency at that time did not restrict the distribution of dura mater cleared for the United States markets.

While the U.S. distribution of processed human dura mater was not restricted, FDA did, however, feel that further evaluation of these issues and alternative practices was appropriate. Thus, in October of 1997 this Committee considered the risks and benefits of human dura mater implantation through the testimony of manufacturers, neurosurgeons, and other scientific personnel.

At the conclusion of this meeting, the Committee provided FDA with recommendations for improving the safety of processed human dura mater. Based on these recommendations and internal FDA discussions, FDA issued to the processed human dura mater providers regulatory correspondence in March of 1998. These letters offered recommendations for improving the safety of processed human dura mater.

Thank you.

The following month, FDA presented once again to this Committee proposed revisions in the recommendations for improving the safety of processed human dura mater. These FDA proposals were based on previous Committee recommendations, responses from the providers of processed human dura mater, and FDA discussions.

At the end of that April 1998 Committee meeting, additional guidance on these proposed recommendations was offered by this Committee.

Finally, in December of 1998, FDA issued a tracking order for processed human dura mater. This regulation insures the tracking of each device from the manufacturing facility to the patient.

In March of this year, Tutogen Medical Corporation initiated a recall of Tutoplast processed dura mater with expiration dates before April of 1999. This recall was based on a concern that patients may potentially contract CJD from an implanted piece of dura mater contaminated with CJD prions.

Another important in the regulation of human dura mater was the February 1997 publication of the proposed approach to the regulation of cellular and tissue based products. This document, in particular, states that FDA may in the future

redesignate human dura mater to the regulation under the human tissue regulation under the legal authority of Section 361 of the Public Health Service Act.

Currently, FDA still believes that human dura mater may be regulated under the human tissue regulation in Section 361 of the PHS Act. However, the transfer of regulatory authority for processed human dura mater may not occur until the rule for human tissue regulation is finalized. Until that time processed human dura mater will remain a medical device, and consistent with other medical products, FDA believes that all guidance documents should be updated as our scientific understanding of specific issues evolves. This is the basis upon which I come before you today.

Next slide.

Once again, the information I'm presenting reflects FDA's current thinking about issues that would be appropriate for a guidance document. The document has not been publicly released. However, when the guidance has completed FDA review and sign-off, a notice of availability will be published in the Federal Register, and the document will be posted on the FDA Web site.

With this caveat in mind, the next three

slides provide a general outline of what a proposed guidance could be. The final slide then provides additional information on specific topics.

It should be noted that this revision of the guidance document largely draws upon existing FDA guidance documents, as well as FDA experience in the regulation of human dura mater, communications with industry, recommendations of this Advisory Committee, and the published scientific literature.

Next slide.

The general outline of the document includes information or guidance on qualification for donors and device components, device manufacturing methods and manufacturing controls, product sterilization issues.

Next slide.

There is also guidance provided on product characterization, device packaging and labeling.

Next slide.

The new major guidance presented in this document, folks, is on the issues on this slide, and I'd like to go through them briefly with you. There is information and guidance provided to manufacturers with regards to donor suitability, with regard to serology testing for infectious disease, evaluating

risk factors for and clinical evidence of neurological and infectious diseases through both review of medical records and interviews with next of kin, and a physical assessment of the cadaver.

The guidance also recommends a full autopsy on each donor's brain. This would include gross examination of the entire brain, including multiple cross-sections. Histological examinations of multiple tissue samples from different parts of the brain is also recommended.

Regarding archiving of brain and dura mater tissue, FDA recommends that frozen and fixed samples of both donor brain and dura mater tissue should be archived. The donor brain samples would include at least five grams of the frontotemporal region.

FDA recommends that these samples be retained for ten years. This recommendation is based upon the current state of scientific knowledge regarding the development of Creutzfeldt Jakob disease screening tests and our expectation that as science evolves, screening tests may become available within that time.

Regarding PrP testing, we recognize that this is currently a research and investigational use

tool. Because there is no approved or validated test that is marketed for screening of Creutzfeldt Jakob disease in the brain, the FDA is not recommending its use at this time.

However, when either a validated test does become available or evaluations of available data demonstrate the utility of PrP-RES testing, FDA will recommend the use of this test.

Regarding viral inactivation and disinfection, once again, FDA believes that careful control of donor selection and tissue collection procedures constitute critical safety practices for processed human dura mater.

In addition, histological examination of the brain may detect most infected tissues, but it may not identify all infected grafts. Therefore, FDA recommends treatment of each product with a generally accepted disinfection technique, and this will provide an additional level of device safety, assurance for device safety.

This particular Committee has recommended treating processed human dura mater with one normal sodium hydroxide. FDA recommends that sponsors supply information about methods for disinfection with sodium hydroxide or another procedure that has been validated

to significantly reduce CJD infectivity.

Such data would also demonstrate that subsequent rinsing steps are sufficient to reduce the concentration of residual disinfection to a noncytotoxic level.

Regarding dura mater processing, FDA recommends that processed human dura mater grafts from different donors not be commingled during tissue collection or product manufacture.

FDA also recommends that manufacturers take all appropriate efforts to eliminate any opportunity for cross-contamination during tissue collection and processing. For example, FDA recommends that manufacturers use only disposable processing material and surgical instruments during the recovery and processing of dura mater allografts.

Regarding record keeping and tissue tracking, this section -- issues of device tracking have already been discussed, but this section also provides guidance on the sort of documentation that should be kept by manufacturers on each donor, and it also requests in the product labeling that information be provided to a graft recipient in writing, that he or she has received a processed human dura mater graft implant.

In conclusion, I wish to thank the panel for their previous scientific input on this issue and also the time at this meeting to present FDA's current thinking on a revision of the guidance for the preparation of a pre-market notification application for processed human dura mater.

We also recognize that rapid scientific and medical advances in this field may require this to be a continually evolving guidance document.

Thank you very much.

CHAIRMAN BROWN: Thank you, Dr. Durfor.

Does the Committee have any questions for Dr. Durfor?

Bob.

DR. ROHWER: Dr. Durfor, it might be informative and enlightening to know why there was a withdrawal of the Tutoplast product since I thought there was no commingling in U.S. produced dura, and we were using sodium hydroxide.

DR. DURFOR: This sponsor initiated recall, was recalled because patients could potentially contract CJD from an implanted piece of dura mater, and the presence of the CJD could be due to inadequate donor screening or handling by the German manufacturer, Pfirmer-Vigo.

CHAIRMAN BROWN: Does that mean that in your interpretation of this, that is, the company voluntarily withdrew?

DR. DURFOR: Correct.

CHAIRMAN BROWN: On the basis not because of specific knowledge that that particular graft which had caused CJD had, in fact, been batch processed, but because they were concerned that other batches -- other dura processed at the same time, even though they didn't come in contact with this dura, might somehow have escaped adequate screening?

DR. DURFOR: Yes.

CHAIRMAN BROWN: Was there any -- Peter. I'm sorry. There was a question over here. Linda.

DR. DETWILER: I just had a question. In animals with TACs, mostly sheep and goats and deer, it's been established -- deer and elk -- it's been established that PrP-RES is there prior to clinical signs and histological lesions, and I can understand about this validation and whatnot that's commercially available. However, what would be the incentive in the human public health arena to have anybody validated if it's not mandated?

I mean if you don't mandate it, what other use, other than screening for things like this, would

you have to have anybody want? The demand would not be that great, right?

DR. DURFOR: That's why when I discussed this issue I suggested either a validated test or evaluation of current scientific data, and so it's a matter of keeping up with where the science is and how well the screen tests can work in the area of human dura.

DR. DETWILER: Well, I would ask then the Committee because, I mean, the human, is it not there yet for human for detection in the brain?

CHAIRMAN BROWN: We have -- we can answer that. We have two questions. Who wants to go first, Peter or Kiki?"

DR. LURIE: I was sort of back to the recall. So why don't I wait?

CHAIRMAN BROWN: Okay. Okay. Kiki.

I don't think the mic is on, Kiki. Is there anybody operating the microphones?

DR. HELLMAN: Hello? That's better.

CHAIRMAN BROWN: Yes.

DR. HELLMAN: Kiki Hellman, FDA.

I just wanted to follow up on Linda's comment and also a comment that Chuck made.

The PrP-RES testing, and we went into

quite a discussion of this with the Committee at our last meeting, we do require a validated test by the FDA, and it is for this reason that we have discussed within the FDA the holding of a workshop on diagnostics. We're hoping that we will convene this either later this year or early next year to look at the status of the different tests that are being developed, with the goal, I might say, to encourage the developers of tests to get their tests validated and to submit to the FDA for approval of that test.

So we are taking a proactive role in this regard.

DR. LURIE: Paul you hinted at this, but unfortunately the presentation did not make clear that the reason for the recall is because there was a case of CJD related to dura mater, and I think that the committee needs to know that, and in fact, the recall was made of a material described. It was a 39 year old woman who had been implanted in 1992 following a duraplasty during a neurosurgical procedure.

She developed CJD in June of 1998, and she died in September of 1998.

The company had been subject to a couple of inspections back in '92 and '93 which revealed problems in donor screening and processing, and in

1994 an import alert, but no recall was announced.

It's true evidently that there was not commingling in the sense of the Lyadura implant, and it also seems to be true that there has been an improvement in the processing of the dura mater in that one normal sodium hydroxide at least in the present version of the company's product is now used.

But for me, this emphasizes again that there is unnecessary risk there; that there are alternatives that have been suggested and alternatives that have been implemented in other countries, and I think that this case -- because that is what caused the recall -- is, again, concerning -- and I think that to me all of this, improvements in the guidance, are really just window dressing as far as I'm concerned. This product needs to be off the market.

CHAIRMAN BROWN: We can discuss that a little bit. I would take a different direction than you suggest. This was, of course, with you present, discussed at the meeting in which the dura was discussed, and one of the options was to recommend banning dura altogether. That was rejected, I think, fairly soundly by the Committee, and the alternative procedural option was taken, and I think that had this donor been subject to the regulations which were

recommended by the Committee, this never would have happened.

It's not just a question of sodium hydroxide disinfection. It's a question of non-commingling, which presumably did not occur. It is a question of adequate historical screening. It is a question of a complete neuropathology exam, and it is, finally, a question of, in addition to all of that, sodium hydroxide decontamination.

Had each of these steps been followed, this dura surely never would have been implanted, never would even have been -- well, it would have been collected, but it never would have been distributed.

Larry?

DR. SCHONBERGER: Yes. I'd like to concur with what you just said and point out that the actual selection of this particular dura for the case that Peter described was in the 1990 period, and then the questions that Peter raised about FDA questioning the adequacy of their screening was actually done in subsequent years and was, as I understood it, corrected by FDA regs and actions as of 1994.

So as Paul has said, the current regs, even since 1994, probably would have stopped this case, and the regs that we're talking about now are

even more conservative.

In investigating this case, I can give you an impression that there tended to be perhaps an over reliance, in my opinion, on the efficacy of the sodium hydroxide step, and an under appreciation, in my judgment, of the importance of screening. I think that that situation has now changed, and this case, I think, demonstrates the importance of screening.

CHAIRMAN BROWN: Yes, and in summary, this is history.

DR. SCHONBERGER: Exactly.

CHAIRMAN BROWN: And because of the long incubation period, you only find out about it now after the more recent regulations were put into place, which would certainly -- I think there is absolutely no question that this case never would have occurred under current regulations.

So I don't think we need to further revise what we recommended last year. I think those safeguards are very stringent and will be very effective. I don't expect ever again to see a case of dura mater CJD in this country as a result of having been done since last year. I just can't imagine it.

DR. SCHONBERGER: Just for the record, let me say because I know the company would object in

saying that this is not a proven relationship, and CDC would concur that it is not a proven relationship, although in our judgment the association certainly makes it, in our judgment, a probable etiologic relationship.

CHAIRMAN BROWN: The company has no case, period.

Ray.

DR. ROOS: There's a little bit of a stretch, but I just wonder whether these kinds of regulations should also be implemented for something like corneal transplants. Are we dealing with a different entity there or is it similar?

And if it's similar, would we be consistent about moving over towards comparable regulations?

DR. DURFOR: I think that was the intent of the proposed rule that I mentioned or the proposed approach to regulation of human tissue. The focus of Section 361 of the PHS Act is to provide safe, implantable material through maintaining appropriate storage and disinfection techniques. So yes.

CHAIRMAN BROWN: Kiki?

DR. HELLMAN: Yes, and I would just reiterate -- Kiki Hellman, FDA -- that the more we

learn about adventitious, potentially infectious agents from animal and human derived material, the more stringent we are becoming and the more attentive we are to these types of problems.

And I think that the dura mater issue is actually a case in point and provides a prototype for the types of things that we're going to be concerned about.

CHAIRMAN BROWN: Yes, it may be that the FDA will want to convene us at some time in the next year or two to consider precisely that question. That will raise a huge whoop and holler from the eye banks, and the situation is a little different and would have to be considered a little differently.

As opposed to more than 80 dura mater CJD cases, there are two certain and one probable corneal case, and I would guess that the number of corneas transplanted exceed by several-fold the number of duras. So it's certainly on the basis of that alone not as risky a matter and deserves separate consideration.

Are there any other questions before we go on to the sheep subject?

Larry.

DR. SCHONBERGER: I wanted to just put

this on the table. To our knowledge, there has not been a confirmed case of -- let's put it this way -- a confirmed relationship, etiologic relationship, between the product that has been used or made, fully processed in the United States that does not use the sodium hydroxide step, that has been very strongly concerned about screening and has been successful in tight screening, and the new regs, our guidelines are saying that they should use sodium hydroxide or something equivalent to it.

Because this is an area of some controversy about whether the sodium hydroxide step is absolutely necessary if one does use the severe screening test, including an autopsy on the donor, I was wondering whether there's any reports that anybody in the audience or others know about of any complications with the sodium hydroxide.

I've been contacted by a W. Guest, M.D., Executive Director of Transplantation Research Foundation, who said, "Dr. Schonberger, I want you to know that we have had at least the strong suspicion that residual sodium hydroxide," quote, "in Tutoplast has led to fulminant postoperative inflammatory reactions that resulted in cortical scarring, meningo cortical adhesions, and epileptic seizures in at least

two patients."

I told him that I would at least if I had the opportunity bring that up to the Committee, so at least put that on the table, and I don't think he has convincing evidence that these complications are, in fact, related to the sodium hydroxide step, but if there is evidence that others know about, that there's complications with the sodium hydroxide, I think that should be raised.

CHAIRMAN BROWN: Well, it's on the table. I don't think we have the expertise either in the Committee or in the room to know anything about that kind of reaction.

I haven't heard personally about any, and I imagine a solicitation of neurosurgeons in this country would answer that question very quickly.

Stan, did you have -- I'm anticipating your finger.

DR. PRUSINER: I, just for completeness, since we're having this discussion, will be very brief. I think that we get a false sense from the idea that an autopsy on these patients who are the donors necessarily exclude CJD. We can have people who have very few histologic changes. We've had several cases like that.

You can do PrP scrapie or PrP-RES, whatever you want to call it, determinations. In a big brain, you can find many areas where you see no protease resistant PrP.

So the idea of having a workshop and discussing this and trying to come up with some, I think, better procedures to try to screen for dura from donors who to all one's best information do not have prions in their brains contaminating the dura I think is a good idea because I really don't know a simple way to say this piece of dura does not contain prions.

And I'm not sure even that the sodium hydroxide method as it's used currently is absolutely the best that can be done.

CHAIRMAN BROWN: Yes, I don't think anybody on the Committee would disagree that no single step is adequate to insure total safety. I think most of the Committee would agree that the ensemble of steps, particularly if in the future it includes testing for PrP-RES, will virtually eliminate risk entirely.

But that is a subject for another conference.

Yes.

DR. ROHWER: I would like to be absolutely clear though about this withdrawal because as I understand the presentation here, the recommendations were made in '97, 10/97, and this case occurred in '98. When was the dura actually implanted?

CHAIRMAN BROWN: '92.

DR. ROHWER: Oh, '92. I see. Okay. That I had missed.

CHAIRMAN BROWN: Oh, and I forgot. For the purpose of the Congressional Record, it should be stated that Dr. Roos' absence yesterday was because of a phone call, not for any other reason.

(Laughter.)

DR. ROOS: Thank you, Paul.

CHAIRMAN BROWN: Thank you.

Safe sourcing of sheep derived and goat derived materials contained in or used to manufacturer FDA regulated products will be initiated, with a background and introduction presentation by Dr. David Asher, Center for Biologics Evaluation and Research of the FDA.

Dr. Asher.

DR. ASHER: Thank you, Dr. Brown.

Can you hear me? Can we have the slides, please?

Good morning. I'd like to introduce our next topic, which is safe sourcing of materials from sheep and goats in countries not free of ruminant TSEs.

Can we start the slides, please? Great. Thank you.

So I'll briefly address the issue, list some sheep derived and goat derived materials found in or used to make FDA regulated implantable and injectable products, and give the first reading, charge in question.

Then I'll begin a review of the risk to humans from TSE agents of animal origin, aspects of which will be covered in detail by our invited speakers.

BSE I will leave to Professor Almond, who has so kindly agreed to be here today.

Scrapie I'll address myself. I'll mention just in passing other animal TSEs. Then I'll note several uncertainties about the risk to humans, list some of the regulations, policies, and practices of the U.S. government intended to reduce the risk, and close by listing several discussion topics, that is, possible actions that might be considered in efforts to reduce still further the risk of human exposures to

TSE agents of goats and sheep.

There are two demonstrated sources of human infections with TSE agents, first from human material, as was discussed yesterday and in today's first topic, and from animal material, and I list here a third possible source just to be complete, though it remains hypothetical.

Of greatest interest today is the BSE agent because it is the presumptive cause of new variant CJD and must be considered a demonstrated risk to human health. The scrapie agent poses a theoretical risk to human health.

Today we ask you to consider the implications of two theoretical possibilities: the first, that sheep and goats in BSE countries theoretically might be infected with the BSE agent, and Professor Almond, who headed a subcommittee of the United Kingdom's Spongiform Encephalopathy Advisory Committee, has agreed to review that topic for us today.

Then scrapie, which theoretically might be a human pathogen, though there's no hard evidence for that, and of course, some number of sheep and goats in many countries, including the United States, are infected with the scrapie agent.

Now, let me say now that no U.S. government regulatory authority would ever knowingly permit humans or animals to be exposed to a product containing the scrapie agent, but considering the nature of the scrapie agent and the disease, we are not so naive as to think that such exposures have not already occurred.

We in the FDA and our colleagues in the USDA are well aware that there are other animal TSEs in the USA, specifically chronic wasting disease of deer and elk and transmissible mink encephalopathy and other animal TSEs have been postulated.

However, few FDA regulated projects, none injectable and implantable that I know of, are directly affected by the two known diseases. The extent of human exposure to those diseases remains uncertain, and the agents are not known pathogens for human beings.

We in the FDA's TSE working group agree that public health implications of those animal TSEs are an appropriate topic for discussion, but that will be on another day.

Sheep derived and goat derived materials are found in a variety of regulated, implantable, and injectable materials. Sutures and vascular grafts are

prepared from sheep materials. There are several injected enzymes of goat and sheep origin, a variety of therapeutic antibodies prepared in normal and transgenic animals and allergens are derived from sheep and goats, and some examples are listed here on the slide.

With the possible exception of sutures, these products are not widely used.

Sheep and goat derived materials are also used to prepare injectable biologics, as immunoaffinity purification reagents, bacteriological culture media, and some other materials. This is not an exhaustive list.

Although the products may not be widely used, the people treated with them and the FDA staff are concerned that all source materials be as safe as possible, especially injected in implanted products, routes where smaller amounts of TSE agents are needed to infect than by oral routes.

In our center, in response to concerns about theoretical risks from scrapie, some sponsors have concluded that it would be prudent to obtain sheep derived and goat derived material from countries free of both BSE and scrapie.

The FDA has never articulated specific

criteria sufficient to assure the agency that such materials are free of the agents when obtained from animals in countries with TSEs of ruminants, like the USA, and it would be desirable to have a consistent FDA policy on the issue.

The TSE Advisory Committee is, therefore, asked to consider whether current policies of the FDA, an agency which relies on import restrictions and other policies of the USDA, are adequate to protect humans and animals from potential exposure to the BSE agent in FDA regulated products containing or produced with materials derived from sheep and goats originating in BSE countries, or if additional precautions are needed.

The Committee is also requested to consider appropriate precautions including sourcing, selection of animals, veterinary scrutiny, monitoring of animals, feeding practices and other measures that might be adequate to assure the agency that materials obtained from sheep and goats from the USA or from other countries where scrapie occurs are free of the scrapie agent and can be used safely in FDA regulated products intended for injection or implantation.

After considering risks and benefits, we ask you to advise the FDA whether there are safeguards

that might be sufficient to insure that sheep and goats from BSE countries would nonetheless provide acceptable sources of materials for manufacture of regulated products intended for injection or implantation both as components of the products and as manufacturing process reagents.

And you'll hear in a few minutes that there are current precautions and policies of the FDA that are in place, and any relaxation of those policies would constitute a reduction in safeguards.

After considering possible risks and benefits, we finally ask you to suggest safeguards adequate to assure that sheep and goats originating from or residing in countries where scrapie occurs are scrapie free and acceptable sources of materials for manufacture of FDA regulated products intended for injection or implantation.

Most of what follows in my talk and those of the invited speakers address estimating the risk of the TSEs of sheep and goats for human health, that is, to assess potential exposures and the effects of those exposures.

As I mentioned, Professor Almond will address BSE, and I will begin our consideration of the theoretical risk of scrapie by reviewing attempts to

detect that risk.

Dr. Richard Race has agreed to speak with us here by telephone to review his classic studies with Carl Eklund and Bill Hadlow on the distribution of scrapie agent in tissues of sheep and goats, and share his thoughts on today's topic.

Diane Sutton -- has Diane come yet? Okay, good -- will speak with us about the prevalence of scrapie in U.S. animals and in other countries and then begin a discussion of efforts to mitigate risk by summarizing USDA regulations and programs.

John Honstead from our Center for Veterinary Medicine will discuss the FDA ruminant protein feed ban, our major effort to stop food borne spread of ruminant TSEs.

And then Lisa Ferguson will outline additional measures to consider.

Finally Kiki Hellman will summarize the day's events and deliver the final charge in question.

We in the FDA are aware of no convincing evidence that scrapie, unlike BSE where the evidence though incomplete is highly persuasive, has infected humans. Individual case reports of Creutzfeldt Jakob disease have been sufficiently dramatic to convince us that human pituitary hormones, corneas, contaminated

electrodes, dura mater were the sources of infection, but except for a few anecdotes, there have been no comparable case reports linking scrapie to Creutzfeldt Jakob disease, although people have kept, killed, and eaten sheep during the more than 200 years that scrapie has been known.

Through the 1960s, scrapie research facilities both in the United Kingdom and here observed very few precautions in handling infected materials, and there were no reported transmissions to staff. Scrapie appears very unlikely to be a major source of CJD.

Creutzfeldt Jakob disease has occurred in at least four lifelong vegetarians, and the incidence of CJD in scrapie free Australia, which is shown here for the year 1993, is no less -- actually in 1993 probably because their surveillance program for CJD began in that year, the incidence was substantially higher in Australia than it was in the five European Union countries listed here.

And note that many of the patients with CJD in Australia had never left the continent of Australia.

Epidemiological surveys and case control studies are sometimes invoked as supporting the

hypothesis that scrapie or some other TSE of animals may be a source of known infection. I reviewed six major case series and eight case control studies of CJD beginning with Dr. Roos' series in 1973 through this year, and if I missed some, I apologize.

For each series or case control study, I tried to summarize the conclusions about occupational exposures, other exposures to animals, dietary exposures, and surgery or trauma. A whole variety of intriguing associations were reported, and obviously we don't want to review them all this morning, except to remark that most of them were found in one study and then never seen in any of the other studies.

I'm going to rush through the next nine slides to show you a few of those associations and simply to demonstrate that none was observed consistently.

For example, in Dr. Brown's French survey, in the first approach, urban residence was an intriguing association noted, although it disappeared in a further study, and no association with exposure to sheep, goats or their products was noted, not only in that case series, but in any case series.

Case control series yielded the most associations. The earliest suggested some possible

link to pig brains, although oysters were even more impressive, a very puzzling association.

In a study in which I participated, Zored Davanipour found more than 20 significant associations between Creutzfeldt Jakob disease and a variety of exposures. There was a slight excess in the consumption of roast lamb, but that was no more than for a variety of other foods, and you'll notice that pork products were even more highly associated with patients with Creutzfeldt Jakob disease.

A similar case control study in the United Kingdom found no increase in exposures to meat, brain, or sheep in Creutzfeldt Jakob disease cases compared with controls, although a variety of other statistically significant associations were noted.

The authors of that study modestly concluded, and that presumably applies to the other case control series, that it is unlikely that the few positive findings are related in any way to the etiology of Creutzfeldt Jakob disease.

When over 100 factors are examined, some statistically significant results are to be expected by chance.

One study, the second one on this slide, pooled and reanalyzed the three previous studies that

I mentioned, found a slight increase in exposure to cows and sheep, but no association with eating raw meat or animal brains.

Last year a large, collaborative case control study in the European Union found no significant association with eating raw meat or brain or any food or occupation.

Finally, a carefully matched Australian case control study just published found associations with work and residence on farms or truck gardens and work in butcher shops, but there is no scrapie known in Australia.

So, in summary, these studies have really not revealed any consistent association. This presumably, the findings noted presumably resulted from biases, respondent bias, recall bias, because it's really not possible to match carefully the controls with the cases. The cases, of course, have died, and they're always surrogate respondents.

The studies also suffered from a low statistical power and from the multiple comparison effect that we noted for the U.K. study. When you ask so many questions from so few people, there's a high probability of getting significant differences by chance.

So general conclusions from the case series and case control studies are that there was no previously unknown risk factor for CJD common to any of the several studies, and that exposures to sheep and goats and their products were not identified as a risk factor.

A small number of experimental studies conducted by Joe Gibbs at the NIH may be relevant here. Four chimpanzees inoculated with two strains of scrapie many years ago are still alive more than 30 years after inoculation. Can we conclude from that that there is an anthropoid species barrier to infection with a scrapie agent? It would be comforting to think so, but there remained uncertainties concerning the theoretical risks to humans from exposure to scrapie.

Perhaps most troubling is that BSE is suspected to have originated from some strain of the sheep scrapie agent. Multiple strains of scrapie agent exist, and some of them might be transmissible to humans or they might become so after passage through animals.

The negative experimental studies with scrapie in chimpanzees were very small, and used only two strains of scrapie agent, while several species of

monkeys inoculated with scrapie agents by intracerebral and peripheral and oral routes developed a TSE 17 months to 20 years later.

So there cannot be an absolute primate species barrier to infection with all strains of the scrapie agent.

The weakness of the epidemiological studies I've mentioned, and human exposures to sheep-derived, goat-derived, injectable and implantable products have been much less frequent than exposures to food so that an association there would be even harder to detect by a case control study.

And it's hard to be sure of how an infection is not acquired when you don't know how it is acquired, at least in most cases.

There are regulations, policies, and practices of the U.S. government that should reduce opportunities for human exposure to TSEs in sheep and goats. In 1997, the Animal, Plant Health Inspection Service of the USDA issued an emergency amended regulation that restricted importation of ruminants, and that's ruminants, not just cows; that's all ruminants and meat products from ruminants, not only from BSE countries, but also from countries of unknown BSE status, and they also removed previous exceptions

that had allowed imports of some meat and meat products from BSE countries.

In November of 1992, the FDA sent a letter to manufacturers of dietary supplements recommending that they reformulate their products using neural or glandular tissues assured to be BSE or scrapie free.

Then in December of 1993 and in 1994, the FDA sent letters to manufacturers of drugs, biologicals, devices, animal products, and FDA regulated animal products, and manufacturers and importers of dietary supplements and cosmetics recommending that bovine-derived materials from BSE countries not be used. Scrapie was not specifically addressed.

FDA's most important action has been in the form of regulation, the ruminant feed ban of 1997 that John Honstead will discuss, and note that a successful ruminant feed ban would reduce food borne spread of scrapie as well as of accidentally introduced BSE.

Other U.S. government policies and practices are also intended to protect humans from exposure to animal TSE. The USDA has a voluntary scrapie flock certification program that we'll hear about. The Food Safety and Inspection Service has

inspections. Agricultural Research Service has diagnostic and research programs, and there are other activities.

Within the FDA, in product reviews, efforts are made to assure a source is free of all extraneous agents, including all TSE agents, regardless of whether the agents are known to be human pathogens or not, and at least in the Center for Biologics, there is a statutory requirement for that.

And let me close by suggesting possible actions that might be considered to reduce the theoretical risk to humans from scrapie in sheep and goats, and these, of course, are simply for discussion purposes. You may well think of others.

First, scrapie free regions might be determined in countries that otherwise have scrapie. New flocks might be derived from known scrapie free progenitors. For production of implantable, injectable materials, closed flocks might be maintained. Satisfactory feeding histories for sheep and goats might be presented; that is, certifying that they were never fed mammalian protein.

Sheep might be bred selectively either for susceptibility to reveal scrapie in a flock or for resistance to reduce the likelihood of infection.

Intensity of surveillance should almost certainly be introduced. Sentinel animals might be kept in flocks. There might be routine PrP testing in the brains of old animals, animals found dead, and all disabled animals. And of course, in general we think that the surveillance for TSEs in animals in the United States, including those in contact with sheep and goats, should be introduced.

But we feel that surely even in countries with ruminant TSEs, like this goat with scrapie, it should be possible to assure clean sources of sheep and goats to prevent transmission of human disease like this.

I thank you. I haven't used the 50 minutes allotted, and if there are any questions that I can answer, please feel free to ask.

CHAIRMAN BROWN: Thank you, Dr. Asher.

Questions for Dr. Asher?

All right. Then -- yes.

DR. PRUSINER: There's a page in here, and I'm worried that we come away with the wrong conclusion. I thought it was a very nice presentation. There was one point. Let me see if I can find it now. Here is it.

DR. ASHER: Which page, Stan?

DR. PRUSINER: It's on these slides that say uncertainties concerning theoretical -- twenty-eight. Thank you.

DR. ASHER: Yes.

DR. PRUSINER: I can't see that with my glasses.

DR. ASHER: Uncertainties concerning.

DR. PRUSINER: Right. So it says sources of infection and sporadic CJD are unknown. I mean I would argue all of these epidemiologic studies, I think, clearly argue that sporadic CJD are -- what people are now calling classical CJD -- don't come from infection. Would you agree with that?

I don't understand the Point 6.

DR. ASHER: Don't come from infection? No, I think that the whole issue is still open. They certainly are associated with an infectious agent, and when subsequent subjects are exposed to them, they become infected. I don't believe that the issue is settled at all.

I mentioned the possibility, which is certainly possible, but certainly not demonstrated, that the infection is of endogenous origin, but more than that I wouldn't be prepared to say.

I believe that rigorously the cause of

sporadic CJD has not been -- the source of sporadic CJD has not been determined.

DR. PRUSINER: Okay. I just want to make it very clear from my point of view that this is not a scientifically defensible point of view at this point. That's my --

DR. ASHER: I don't think any point of view at the moment is scientifically defensible. I think it's simply not known.

(Laughter.)

CHAIRMAN BROWN: Can we resolve the issue by noting that the source of infection can be the brain itself?

DR. PRUSINER: It's not going to be resolved. I just want to make the point --

CHAIRMAN BROWN: No, but I mean is that -- is that -- if we accept the fact that source of infection does not necessarily imply an external source --

DR. PRUSINER: That's fine.

CHAIRMAN BROWN: -- then, you know, then I think we're talking the same language.

DR. PRUSINER: That's fine.

DR. ASHER: I don't believe that an external source -- that the state of knowledge today

permits an external source to be excluded.

CHAIRMAN BROWN: Okay.

DR. ASHER: I don't think this is the place to have this kind of discussion, but it is important that these differences, I suppose, that these differences be aired.

DR. ROHWER: Paul.

CHAIRMAN BROWN: Bob.

DR. ROHWER: I don't want Dr. Asher to have to stand alone on this either, and I agree with him fully.

CHAIRMAN BROWN: Maybe we should have what, a seminar, two, three hours?

(Laughter.)

CHAIRMAN BROWN: We have time, don't we?

DR. ROHWER: No, we could have a vote.

(Laughter.)

CHAIRMAN BROWN: That'll take too much time.

Thanks, Dave.

We'll now proceed to the next speaker, who is Professor Almond from Pasteur-Marieux Connaught in France, whose title is "The Potential Risk of Introducing BSE Agent into Sheep and Goats in Europe."

DR. ALMOND: Ladies and gentlemen, it

looks like my computer has crashed. All of my slides are on my computer. So I'm going to have to ask you to bear with me for a few moments until I reboot it. I'm sorry about that.

I'm sorry. Everything was set up so I could just come up here and touch the buttons, and it's obviously crashed.

CHAIRMAN BROWN: Jeff, this is not the first time, nor will it be the last time that computer programs have disappointed the speaker. Do you think we're talking, you know, a minute or two or a more extended rebooting?

DR. ALMOND: I hope we're talking about two minutes.

CHAIRMAN BROWN: Okay. We'll just wait then.

(Whereupon, the foregoing matter went off the record at 9:37 a.m. and went back on the record at 9:43 a.m.)

CHAIRMAN BROWN: The speaker is ready. Can we reconvene after this unscheduled break?

The podium is yours, Dr. Almond.

DR. ALMOND: Okay, Mr. Chairman. Thank you very much for your patience and understanding. I'm sorry that my computer let me down at the last

minute, but that's it with this new technology. It always does.

I would like to thank you for the invitation to speak to you, and I want to talk to you really about my least favorite subject. The reason I say it's my least favorite is because it has been an extremely sensitive subject, particularly in the United Kingdom where we, serving on this Spongiform Encephalopathies Advisory Committee of our government, felt obliged to raise the question simply as a question: Is there a danger, a possible danger from BSE having reentered the sheep population?

You can imagine that the farming communities were very sensitive to that question being raised even though, and I will stress at this point, there is absolutely no evidence there is any risk at all from BSE in sheep either in the U.K. or in any other country, and I want to make that position absolutely clear before I continue.

However, I feel it was important, and the committee felt it was important, to address this issue and actually to simply pose the questions and try and decide what further information was required to try and reassure ourselves that there was, indeed, no such risk.

So the SEAC Committee established a subcommittee of which I was chairman around about a year ago to look at this question, and we had meetings and several drafts of the report, and the report was eventually published, I think, in March or April of this year.

So let me take you through some of the issues that we talked about and some of the key points that I think may be relevant to your deliberations here today.

First of all, just to make the point about BSE in sheep or is it scrapie in sheep? Our previous speaker, Dr. Asher, has pointed out, and he did so in much more detail than my first sentence does here, that really there is no correlation between the geographical presence of CJD and the consumption of scrapie-infected ovine products. In other words, there's as much CJD in Australia as there is in Europe, where we have scrapie-infected sheep, and we eat a lot of sheep meat, and no difference again really statistically between Europe and Australia and the United States, where again you have scrapie, but you eat a lot less sheep meat certainly than we do in the U.K. and in England.

So there's a conclusion from that that

scrapie does not pose a significant human health risk that we can detect.

But the issue really of BSE is that it may be different, and I'll come to the points later on. There is evidence from Moira Bruce and colleagues and from John Collinge and colleagues working at St. Mary's, Bruce, at Edinburgh and Collinge at St. Mary's in London, that the characteristics of the BSE agent, what I've called here the BSE strain phenotype -- and I don't want to go into the scientific basis of this because I'm sure many of you are very familiar with it, but the BSE phenotype as defined by Moira Bruce is the incubation time of BSE in a panel of mice, of different breeds of mice, and on the pathology that develops in those mice. BSE gives a distinct pattern, a distinct incubation time, and a distinct pattern of lesions, which is characteristic.

And, indeed, all of the cattle that have so far been tested give more or less exactly the same phenotype, and indeed, she's shown that the TSEs that we've observed in our country in antelope species, like kudu and oryx, also in cats, have that same BSE phenotype.

And the important thing is that in experimental transmissions to a sheep and, indeed, to

a pig and, indeed, to a goat, that BSE phenotype as measured in mice was stable. So it looked like, in other words, the BSE characteristics were retained when BSE infected a sheep.

John Collinge provided similar data on some of those species in relation to glycotype in terms of its migration on gels.

So there is an issue then because of those studies that BSE may behave differently, if it was in sheep, than natural scrapie does.

Just again as background to give you what was our thinking on this SEAC Committee in relation to BSE and variant CJD, just to quickly review the evidence, the evidence as we saw it was, first of all, the space-time correlation.

New variant CJD emerged in the U.K. in 1984-85. Principally, apart from one case in France, it is a disease of the United Kingdom. The figures to date are 40 cases, with any real discernable increase in their rate of presentation, but nevertheless they are in the U.K.

They are also in this time era, that is, the time era in which we have had BSE in our country, and they are in the sort of time that you might have expected to see a new disease appearing in humans if

BSE were to transmit. In other words, the first cases of new variant were seen about eight or nine years after the first cases of BSE were seen.

So the first thing linking them together then is what I call the space-time link.

The second is the work of Domenic Dormont and colleagues that one of the characteristics of new variant CJD, that of the unusual pathology of the florid plaques, the extensive plaque deposition in the cerebrum, the cerebellum, and the spinal cord is reproducible in another primate species, and that was in his case macaques where Domenic Dormont showed that that unusual pathology was reproduced quite spectacularly in that primate species.

So BSE can cause that unusual type of pathology in a primate species.

The third piece of evidence was John Collinge's which said that the glycotypes, the migration pattern of the PrP-RES was, again, indistinguishable in variant CJD and cases of BSE from cattle, cases of BSE from cats, and indeed, the macaque that I've just referred to in the previous study, and that that glycoform profile, that glycotype was different in the variant CJD cases, identical among them all, of course, but different from other

sporadic CJD that we'd experienced up until then.

And then, of course, there was Moira Bruce's data, which I referred to already, but it was published in Nature about a year and a half ago, which is that the strain characteristics as defined in mice on pathology and incubation time of BSE and variant CJD are indistinguishable.

That sort of evidence says that the people who have got new variant CJD in Britain are highly likely to have got it through some contact with the BSE agent. At the present time, there is no data that I'm aware of that distinguishes the BSE agent from the new variant CJD agent. But we did not and have never concluded that, therefore, these people have got new variant CJD from eating contaminated beef or, indeed, that they've got it directly from cattle.

The obvious conclusion of saying that the BSE and the variant CJD agent are the same is, of course, to think of a causal relationship like this, that whatever caused in the first place the BSE outbreak did so, and that it's through human contact with that BSE outbreak that we've now seen the emergency of variant CJD.

But you could also, of course, have a relationship like this, that whatever was the original

cause, of course, may have infected cattle and caused the BSE outbreak there and may have independently, from some unknown route, infected the humans to cause the new variant CJD, and that there may not be a line connecting these two things.

Now, that remains a formal possibility on the basis of the evidence we have. You can also think of a third possibility, which is whatever it was that caused BSE did so, that BSE has then caused another spongiform encephalopathy, and we've of course seen it in cats and kudu and oryx, and that that has caused the variant CJD, and again, you can't formally rule out this possibility.

So although we think of it like this, these other two possibilities remain formally possible, and of course, there are other possibilities that you have something like this, Cause X causing BSE, but you may also have transmission to a third species, and that, too, as well as cattle can cause new variant CJD. It's imply impossible at this stage to know where these 40 victims have become infected from.

What we do know, however, is that we did have a huge BSE epidemic in the United Kingdom. The present figures, up until this month or actually up

until the end of May, just over 177,000 cases of clinical BSE, and they're still occurring at the rate of around about 250 to 300 a month in our older cattle.

That contrasts with the peak rate, which was over 4,000 cases a month, and the peak rate was actually February 1993.

This is BSE in cattle, but one of the things that I want to point out here is that the feed ban which, of course, removed the source of that BSE to a very large extent, was introduced fairly early on in this epidemic, and in fact, it was July 1988, just about 19 or 20 months after the first description, the first histopathological confirmation of BSE.

But the level of contamination of our meat and bone meal, of our animal feed at that time when it was used in this period was manifestly quite high because we had this huge epidemic. And of course, a lot of you are very aware that this represents only a small proportion of the number of infected animals. The estimates are that there were probably a million infected animals, and we ate about 800,000 of them before they had a chance to develop the BSE.

The point was that we introduced the ban in July 1988. It didn't stop the epidemic, but it

certainly has been a principal factor in the cause of its decline one incubation period further on from the introduction of the ban.

I mention this ban, and I mention the extent of the contamination of the meat and bone meal that is evident from this slide because of the fact that when we think about sheep, we have to bear in mind that sheep, too, were exposed to the meat and bone meal that were so contaminated.

So if I could just look at this slide for a moment and put the issues to you: Is BSE present in U.K. sheep? I'm talking now the BSE agent with BSE characteristics.

Well, in support of the possibility, Moira Bruce and Chris Bostock's work has shown that sheep are infectable orally by BSE, by cow brain. As little as .5 of a gram of infected cow brain has transmitted BSE to sheep, where then the analysis of the spongiform encephalopathy that develops in those sheep, using the mouse panel, strain typing, shows that it does retain the BSE characteristics.

Second, my point here, which is that sheep were fed contaminated meat and bone meal up to July 1988 when that ban came in, and it's important to remember when the ban came in, it was a ban not only

to stop the use of that meat and bone meal in cattle feed. It was to stop that meat and bone meal being used in ruminant feed. So it did cover sheep and goat food at that time.

But I think you're all aware that the ban was not 100 percent effective. We estimate probably 95 percent plus effective, but there was a little leakage after that date.

The other thing I should point out is that although sheep were exposed, the practice of using high concentrate feeds on sheep-to-sheep flocks and sheep farms is much, much less widespread than it was on dairy farms. Most sheep eat just grass, but there are a few high output farms which bring their lambs on very early, which do use concentrates from time to time, particularly during the winter months.

We estimate that there were several hundred thousand tons of meat and bone meal that went into sheep feed, but the proportion as compared to that that went into cattle feed was really quite small, probably of the order of five percent.

The other point to mention which supports the possibility -- and I want to put it no more than a possibility that the BSE was present in sheep -- is that scrapie does transmit readily from sheep to

sheep. We know it can become endemic.

So one point that has been raised is that if BSE got into sheep from the meat and bone meal, could it be sustained there by transmission mechanisms akin to those for scrapie in sheep.

There is another point, which is the evidence to date -- and the next speaker, I think, will deal with this in more detail -- but the evidence to date from Moira Bruce and colleagues, and some of this is unpublished, and I'm unable to development it fully, but the evidence to date is that BSE in sheep, unlike BSE in cattle, is more lymphoreticular. It involves lymph nodes and spleen, more lymphyoreticular than BSE in cattle, and this sort of lends support to the notion that it may therefore more readily transmit animal to animal than BSE seems to do in cattle, where there is no evidence, no firm evidence at all, for transmission of BSE from cow to cow.

Okay. So these concerns then were in the backs of our mind when we considered the question of is or was BSE present in U.K. sheep. Arguments against that possibility were as follows.

Certainly when we consider the U.K. sheep flock today, we have to bear in mind that feeding of meat and bone meal really did stop to certainly 95

percent, and in sheep feed probably higher than that, and almost all sheep that will have received meat and bone meal in the period up to July 1988 will by now have been slaughtered.

The demographics of the sheep flocks in our country are such that most animals don't live beyond about five or six years of age, and we're talking now more than a decade since this ban. So it's highly unlikely that there are any sheep left in our country that would have been exposed to the feeds that were contaminated before this date.

Secondly, the point I've already made, that the quantity of meat and bone meal in sheep feed was much less than that in cattle actually in several ways. One was the practice was much less widespread to feed concentrates, but secondly also, sheep are a little bit more discerning in their diets, and they don't like it. So if you put the meat and bone meal in there at more than two or three percent, the sheep don't eat it.

Cattle will tolerate meat and bone meal at a higher proportion than that. So the sheep, in fact, have good noses on them, and they knew when to say no. So the amount of meat and bone meal for that reason, too, was less in sheep feed.

The other point, and this is a little bit flimsy because we don't have good evidence on this, but there is some evidence to suggest that only certain PrP genotypes in sheep would be susceptible to BSE. I say this is limited data, and it's difficult to get firm data on this when some of the genotypes that one would want to look at in the U.K. have endemic scrapie.

And the final point in the points against the possibility is that there has really been no evidence at all for a large scale epidemic in sheep of a spongiform encephalopathy, although there are some flocks which have a high incidence of scrapie like disease or scrapie. Generally speaking, throughout the country as a whole, there is no evidence of anything going on that is anywhere near approaching the scale of that that we've seen in our cattle.

But bear in mind there is endemic scrapie. The surveillance of that epidemic scrapie is rather difficult and incomplete. So there is the possibility, the faint possibility, I think, that the presence of scrapie might mask BSE if it were present in sheep. I'll come back to that point in a moment.

CHAIRMAN BROWN: Let me interrupt you for just a second because a question occurs to me that may

occur to other people. In the animal or animals that were infected with BSE orally, were they in any way clinically distinguishable from scrapie infected sheep?

DR. ALMOND: That is on my next slide. So I'll deal with it in just a moment.

Before I get there, the question that was put in the context of this meeting was what about European sheep as well, and my first point is very strong: no evidence at all that there has been any BSE in European sheep, but some meat and bone meal was exported to Europe and some may have been used in high production sheep-milking flocks, although I hesitate to say this because I am aware that the vast, vast majority of meat and bone meal that was exported went into pig and poultry feed, but it's difficult to exclude.

Second, there is a recent report of an epidemic of a TSE in sheep and goats in Italy, but this is being investigated as apparently not the Type 4 pattern. So the evidence at the moment says that it's not BSE.

But we should also bear in mind that scrapie is endemic in several European countries. Surveillance is limited. So, again, you have the

possibility that very small numbers of BSE affected sheep could be effectively masked by the presence of that endemic scrapie.

It's two slides ahead.

Just a few words about the levels of TSEs or scrapie in sheep in the U.K. We've decided on the committee that we need to know more about this. The data that we have are incomplete. There isn't a routine analysis of sheep that die on the farms. They're not routinely tested for spongiform change in the brain, and it's absolutely the case that in many sheep flocks, farmers accept a certain proportion of their ewes dying every year from illnesses which are poorly defined, and it's just part of the turnover of their sheep population. It may range from anything of sort of two or three up to ten percent of the ewes might die during a lambing season where there's particular stress.

Most of those cases, the vast, vast majority of those cases are never investigated, certainly not at the level of post mortem. So it's difficult to know how much endemic scrapie might be out there.

We're trying to address this question now with a postal survey which guarantees anonymity,

asking farmers to be honest about observing in sheep diseases that could be TSE-like, scrapie or anything else, but that will not tell you that it's BSE.

We've also considered and, indeed, put in place the random sampling of brains of sheep from abattoirs, but there is a real issue here, and I know Linda Detwiler is here, and she may have some comments on this. There is a real difficulty about how to diagnose that.

So if you take a sheep brain from an abattoir or lymph nodes and tonsils, you can also look at the criteria for deciding whether those are definitely positive for TSE in the absence of any clinical signs in the sheep are not well defined.

What do you do if you get a positive Western and negative immunocytochemistry, for example, or a positive SAF and a negative Western? What does that mean? What if you get a positive tonsil and a negative brain or a negative brain and a negative tonsil, but you get a positive lymph node?

At the moment we don't have good criteria for allowing us to decide firmly whether a preclinical animal has definitely got a TSE. So random sampling of brains in sheep from abattoirs is a little bit tricky to interpret at the present time.

Now, bear in mind that it's difficult to get information on TSEs generally. It's even more difficult to get any information as to whether any of that, a very small proportion of it perhaps, could be BSE. There are ways of doing it. For example, you could focus on high incidence flocks and ask by glycotyping -- that's the John Collinge method -- do we see any Type 4 patterns, and that is an approach that has been suggested, but it's not yet validated. We don't know how many different glycotypes there are in the sheep population. We don't know what significance it would be if we saw something that was indistinguishable from the Type 4 glycotype that has been associated with BSE in cattle and new variant CJD.

If we saw that in a sheep at this point in time, we couldn't be certain that, therefore, it meant that sheep had BSE. It could be a different scrapie strain that happened to look similar.

The strain typing of Moira Bruce, one could make a similar criticism about it, but I think at the moment this is the test which has defined the characteristics of the BSE phenotype. So if one looked at sheep and found by the strain phenotype a BSE-like phenotype, I think that would be probably

taken as a strong indication that that sheep had BSE.

However, it's important to bear in mind that this type of test is very time consuming, takes two or three years; very expensive, we estimate in the region of 20,000 pounds per sheep; and to date only nine such tests or nine sheep with scrapie have been tested by that method. All of them were scrapie. They were not BSE, but it's obviously a very small number.

Coming to the point about whether you could tell the difference between BSE and scrapie clinically, the observations on those infected animals to date, both ones which were orally infected and ones which were intracerebally inoculated, there is no good data to say that you could distinguish clinically BSE in a sheep from regular scrapie in a sheep.

But I have to say that the observation of the animals through the illness period was perhaps not as robust as one would want to make it if one was really posing that question, nor is the number of animals that have been infected been good enough yet to see any particular patterns emerging.

But at the moment, I think we would conclude that it's probably indistinguishable from scrapie clinically, certainly at the level of asking

a veterinarian or a farmer to distinguish between the two.

The same is true histopathologically. There is nothing remarkable as far as I'm aware about BSE in terms of its histopathology in a sheep brain as compared with scrapie, and again, you have a range of levels of spongiform change and amyloid plaque depending on breed and so on.

So this just reinforces the point that BSE would be difficult to detect in sheep and could possibly be masked by epidemic scrapie; histologically and clinically, probably indistinguishable; and the fact that scrapie is endemic in some of our sheep flocks.

The next point, of course, to bear in mind, which again, the previous speaker alluded to, is the question, well, if you found BSE in sheep, what does it mean anyway. If you had excellent surveillance and you found a case out there in the sheep population, what would it mean?

And bear in mind that we don't know the origin of BSE for certain, but the most likely explanation for the origin of BSE was that, in fact, it came from sheep. So if you go out and look for it in sheep and you suspect that's what cause the BSE in

the cattle, you might simply conclude, well, okay, there it is. It's been there for hundreds of years. It's never posed a problem when it was in the sheep, but it caused then the BSE epidemic in cattle and, of course, since then the scare and the worry and, of course, the big outbreak in cattle.

But the point I'm making is finding it in sheep could indicate one of two things. One is that you found the origin of the BSE epidemic in cattle. The second is that you found BSE which may never have been in sheep, but it's gone back there via the meat and bone meal that was fed up until July 1988.

I wouldn't like to distinguish between those two interpretations if I found a single case of BSE in sheep. So it's very difficult.

The next point is that if BSE has gone back into sheep or established itself in sheep, does it retain or will it retain all of the characteristics of the BSE phenotype, including this apparent potential to transmit to other species, including humans, and it could be that once BSE goes from sheep to sheep to sheep, it actually becomes scrapie again and, therefore, poses no risk to humans whatsoever.

So there are a lot of imponderables, a lot of unknowns in this, and even if BSE was there, you

wouldn't necessarily conclude that it posed a substantial risk to the human population.

This little chart which is in, I think, the pre-read papers that were circulated just makes the point that finding a low level of BSE among scrapie would be very, very difficult. This table relates to the number of samples that would need to be strain typed using either the Moira Bruce test or a validated glycotyping. That would need to strain typed to be 95 percent certain of detecting at least one BSE case within a population of 5,000 suspected scrapie cases, and that's when the proportion of those cases that were BSE would be ten percent. You'd need to look at 29 animals, and I go back to the point that so far only nine have been looked at by the strain typing method.

If it's five percent of those, you'd need to look at 59. If it's one percent, you'd need to look at 290; 0.5 percent, 554; and 0.1 percent, you're into the thousands. Actually doing this number of sheep analyses by the classical strain typing test of Moira Bruce which, as I said, involves inoculating into several panels of mice and then analysis of the histopathology, is actually unrealistic. It's extremely expensive, demands large numbers of animals,

and the time scale would be awful.

Indeed, we'd have a hard time collecting anything like this number of samples of brains from around the country from suspected scrapie cases. There certainly aren't that many out there, and even the ones that you see it, it's sometimes difficult to get them in an uncontaminated state that you'd be happy with to carry out such strain analysis.

DR. LURIE: Can I just ask a question for comparative purposes?

DR. ALMOND: Yes.

DR. LURIE: At its peak, what was the prevalence of BSE in British cattle?

DR. ALMOND: I can't give you a figure for the population as a whole. The size of our cattle population was around 12 million at the beginning of the BSE epidemic. It's around ten million now. So it declined during the period.

In the high incidence affected herds, there were some herds that got up to eight to ten percent, but the cohorts within those herds which were exposed, it was even higher, and there's occasionally a very high level percentage cases in particular cohorts within a herd, both cohorts I'm talking about.

But as for the population as a whole in

the cattle, it was probably -- probably of the order of .5 to one percent because the average within herd incidence was around 2.5 percent. That's those herds that were affected. About 60 percent of our dairy herds were so affected, and about 15 percent of our beef suckler herds, and I think that represents about something, 35 percent of our total number of herds were affected. Average within herd incidence, 2.5. So if you divide that by three or somewhere there for the average incidence of BSE during the peak in the U.K. cattle. Okay?

This is not really relevant to the Committee, but it just illustrates the sort of difficulty that we were faced with when considering this. If you find BSE in sheep, what would you do? The answer would be it's very difficult to know what to do. An offals ban, such as we introduced in cattle, would probably not be sufficient because of the lymphoreticular nature of the spread of BSE in sheep, the much greater involvement of the spleen and the lymph nodes and the tonsils and so on.

Targeted culls would be difficult. We know that it would be difficult to distinguish BSE from scrapie. You wouldn't want to conclude that certain flocks had scrapie and that was all. So culls

would be also very difficult.

And clearly, policy, if you found BSE in sheep, would be extremely difficult to recommend on. It depends how widespread it is, whether we really do perceive a risk to humans. It will also depends if it ever happens on what the current state of the variant CJD situation is.

If that begins to turn down, if the variant cases dry up over the next few years, I think we can breathe a big sigh of relief, and our concern about whether BSE has been in sheep or is in sheep will, of course, diminish substantially from that point onwards.

The SEAC Subcommittee did, of course, pose a number of questions and recommended research be done on these questions. We don't know how readily BSE transmits to sheep as compared with cattle. There are further experiments ongoing that look at the effective dose, the amount of cow brain you need for an LD50 in cattle. We don't have a good figure for that at the present time, and we certainly don't have it for sheep at all.

If sheep are, in fact, 1,000 or 100 or tenfold less infectable orally than cattle, again, that would imply that the level of meat and bone meal

that they receive prior to July '88 posed a very small risk of developing BSE as compared with that of the cattle population, but at the moment we don't have a comparable figure for how readily BSE transmits to sheep versus cattle.

This has been the big question. Has it transmitted and would it be maintained there. Of course, my whole talk has been about that, and the answer is we don't know, but we think the likelihood is quite small, but it's extremely difficult to make a certain no to that question.

Is the BSE strain phenotype stable in sheep? I've raised this a few moments ago. The answer is, again, we don't know. Only passage to passage within the sheep population will allow us to address that, but that, again, may depend on the breed of sheep, the genotype of the sheep, and so on.

And how can any risk to humans from BSE in sheep versus BSE in cattle be assessed? Again, quite difficult. There are transgenic models now which might enable you to titrate into a human PrP transgene, cow brain infected with BSE versus sheep brain infected with BSE. If those transmit to the transgenic mice with different efficiency, that may allow you to draw some conclusions about what might

any possible risks be if BSE was found in sheep, and indeed, the same question can be posed about whether BSE in sheep poses a risk to other species through natural transmission.

Okay. So our recommendations to our government in relation to the sheep issue, which were published in the report, as I mentioned, which was published in March-April of this year, was that we do need to improve ascertainment and diagnosis of TSEs in sheep. We do need to improve the methods and the speed of differential diagnosis which might distinguish BSE from scrapie in sheep.

We do need to identify which tissues in sheep that are experimentally infected with BSE carry infectivity, therefore, defined properly any risk tissues that may exist.

And we also eventually want to support the development of disease control programs of scrapie as well as any other TSE, with the ultimate aim of eradication of scrapie in the U.K. If scrapie was, indeed, the cause of the BSE epidemic, then it does become public enemy number one as we get rid of BSE because we sure as hell don't want another adventure in our country comparable to the BSE that we've had over the last ten to 15 years.

Another recommendation was that we need to perform a detailed clinical analysis of BSE, clinical signs and pathology in sheep in relation to our Chairman's question. There is a question of whether carrier states of TSEs exist in sheep, and we recommended that some work be initiated to investigate that possibility and then to assess what implications that might have for scrapie control.

And then as I mentioned -- well, the last point I dealt with on the previous slide.

Okay. I think I'll stop at that point, and I'm happy to answer our questions, and I'd just like to reiterate, as I did at the start, this whole talk has been about a "what if" question. There is no evidence at all that there is BSE or has been BSE in U.K. sheep or sheep from any other country, and the farming community very sensitive to the implication that it might be there.

Indeed, the fact that I raised the question at one point had me branded in the newspapers, indeed, in the Times in the U.K. as a scientific terrorist because I was suggesting that this might have happened and, therefore, the farming community would have to bear the consequence of another food scare.

I don't want to suggest that that has happened. I don't want to in any way give the impression that there is evidence that BSE is there, but I think it's fair that we raise the question and think carefully about what it would take to reassure ourselves that BSE was not there and also in the meantime to consider what best public health measures we should put in place applying the precautionary principle. What would be reasonable to put in place just to safeguard against any possible risk that might have existed?

Thank you very much.

(Applause.)

CHAIRMAN BROWN: Thanks very much, Jeff. That was a very thorough and lucid presentation.

I have a comment, I guess, and maybe you can correct me. The more I think about scrapie, the more puzzled I am. Mainly why scrapie doesn't infect humans is just a very peculiar matter.

The question I have is that it seems to me that of all of the recommendations and experiments that you outlined, one is of overarching importance, and that is what happens to the glycotypes and the biological panel behavior on passage.

DR. ALMOND: Absolutely.

CHAIRMAN BROWN: Because on initial reintroduction into sheep, BSE already takes a scrapie phenotype, clinically and neuropathologically indistinguishable from scrapie so far as one knows, with certain limited data.

Yes?

DR. ALMOND: Well, let me make several points.

First, on your first point, why doesn't scrapie transmit to humans? I don't know the answer.

CHAIRMAN BROWN: No, of course not.

DR. ALMOND: But I would just point out that BSE from what we know about it is more promiscuous in terms of its potential to transmit to other species than any known scrapie strains hitherto.

Bear in mind we've had a spongiform encephalopathy in cats, an FSE epidemic in the U.K. on top of the BSE. There was no evidence in the past that cats got TSE from scrapie. They do appear to have got a TSE during that BSE era, and the Moira Bruce analysis says that that is a strain which is indistinguishable from BSE.

The same is true of the kudu and the oryx, the ocelot, and the other species that we've seen in our zoos, the big cats, the tigers, the cheetahs.

So --

CHAIRMAN BROWN: Let me interrupt, Jeff. I didn't actually ask the question. That was the background.

DR. ALMOND: Yes.

CHAIRMAN BROWN: The question is since on first passage to sheep BSE is essentially indistinguishable clinically and neuropathologically from scrapie, therefore the only markers that you've dealt with that you've got at transmission that is, in fact, BSE is the glycotype and the mouse panel --

DR. ALMOND: Correct, correct.

CHAIRMAN BROWN: -- if they disappear --

DR. ALMOND: Correct.

CHAIRMAN BROWN: -- on passage, you might as well fold up your tent because you'll never find out whether BSE is present in sheep at the present point or not. So there's really nothing to do because there's nothing to detect.

DR. ALMOND: Absolutely, and those experiments are, of course, in progress. They are difficult in that you know the example in mice. If you pass BSE in VM mice, you get a change in the phenotype in the Moira Bruce type analysis of BSE, whereas if you passage BSE in these other species that

I just referred to, you apparently do not.

There is, therefore, the possibility that passing BSE through different genotypes of sheep may affect those profiles differently. So it's difficult to prove that the BSE phenotype is never stable on sheep-to-sheep passage. So it's very difficult.

But I take your point absolutely. The only markers that we've got of BSE in sheep is BSE, as opposed to scrapie, is the Moira Bruce type test, but then that's the only marker that we've got -- and the glycoform as well, of course -- that has been the only marker we've had in relation to these other species, including humans and new variant CJD.

It's been on the basis of the Moira Bruce type strain analysis and the glycoforms that we've concluded the strains are indistinguishable.

CHAIRMAN BROWN: Yes, we have -- who was first? Let me ask Linda because I rarely look over at this side of the table. Linda.

DR. DETWILER: I just wanted to add a comment about scrapie as far as phenotypes. I don't even know if you can define scrapie as a typical phenotype because there's such a variation in clinical presentation, and I think we've had to broaden our definition to capture more, and we've seen even almost

a movement some, even within the Suffolks breed, from an intense itching to hardly that sign, and see, owners wouldn't report it if they didn't itch, to more of the motor, the incoordination and the motor signs.

And histologically we've even observed in different breeds different patterns where if you used a certain criteria, that we found that it was difficult to diagnose in other breeds. With the inclusion of PrP-RES detection, we've been able to capture those now. So that's just my addition on scrapie.

But I had one comment on Europe. I guess that I would add for Europe per say is that I totally agree with you that there's been no evidence of a case of BSE in sheep, but I think in all fairness and not to have this total false sense of security, the continent is behind in the U.K. in detection and looking and into discern it's scrapie or BSE and even some of the practices and the enforcement of controls with the feed bans to they're not where the U.K. is.

CHAIRMAN BROWN: Ray?

DR. ROOS: I wondered whether you could comment on surveillance of scrapie in U.K. because one might at least at first glance wonder whether there might be an increased incidence of scrapie if, in

fact, it was related to contamination of feed or are animals slaughtered before you might see the clinical disease, which might make that not as informative as one might hope.

DR. ALMOND: I think people within the Ministry of Agriculture accept that the data we have on scrapie is poor. It's incomplete. The reasons we say that is that scrapie sort of bumps along. It's a few hundred cases per year. Then something happens like there is a collection effort where we pay or the ministry paid for brains to be used in a rendering experiment, and suddenly the number of declared cases of scrapie shoots up. It doubles sort of overnight because the farmers can get something for their dead sheep.

Then scrapie becomes notifiable because we decide it's important to know which of the flocks that have this disease, and the incidence plummets, goes down to half of what it had been before or even less.

So it's difficult to know what's going on. Hence, the need for increased surveillance, and as I said, we're doing it through abattoir survey, with all of the difficulty that that poses. Linda may comment again on this. It's not easy to make a firm diagnosis.

Well, it is easy to make a firm diagnosis where everything's positive, but when you get mixtures of positives and negatives, what does it mean?

And the postal survey, we believe, is a good way forward because it asks farmers to be honest. We know that not all of them will be. It makes it anonymous so that they're not going to get their knuckles rapped if they hide things, and it puts it to them that this is actually for the good of their industry to help us with scrapie eradication and surveillance so that, you know, they really should play ball.

And we can do estimates on the proportion of farmers that really do play ball and report honestly by sort of follow-up questionnaires and so on. So the postal survey, I don't know if it's yet got started, but there has been a pilot survey and the main survey will go ahead, and I think that will probably be the best way of giving us some data, but it won't be hugely reliable.

Over the BSE era, it's difficult to know whether there's anything been going on. There are a few flocks which have been really quite high incidence, up to ten percent of the animals dying of scrapie each year, and some of those had meat and bone

meal. Some of them became high incidence flocks during the BSE era, but, again, it's difficult to conclude that they are BSE as opposed to scrapie.

One or two of the sheep from such flocks were included in the nine that were looked at, and they were not BSE by the Moira Bruce type strain typing analysis.

CHAIRMAN BROWN: Larry, you had a question.

I may interrupt momentarily because we have Richard Race not quite on the phone, but when he comes on the phone, we'll stop things.

Larry.

DR. SCHONBERGER: Jeff, a great talk, and I just wondered if you could clarify the issue of is not the leading hypothesis for the origin of BSE in cattle the presence of scrapie in sheep, and if so, why would you be charged with scientific terror to do what you've done in looking for BSE agent in sheep?

And second, your talk started with saying, I thought, that 0.5 infectious gram of brain of cattle when orally given to sheep led to the sheep coming down, but then you said you weren't sure about the sensitivity of sheep --

DR. ALMOND: Versus cattle.

DR. SCHONBERGER: -- to -- versus cattle. Does that means that cattle are even much more sensitive than 0.5 grams?

DR. ALMOND: Yes. I perhaps should have put some more scientific background in slides.

The attack rate study, which was carried out by the Ministry of Agriculture attempted several years ago to estimate an LD50 for cattle via the oral route, and cattle were given 300 grams, 100 grams, ten grams, and one gram, ten cattle in each group.

All of those cattle seven years later became infected. So the experiment failed to define the LD50, but it's clearly less than a gram for cattle.

A new experiment is in progress which goes down, I think, to .1 of a milligram, but it will be several years before we have an outcome to that experiment. So it will be several years before we know what the LD50 is for cattle. That's cow brain infecting cattle via the oral route.

You would want to do the same experiment in sheep to make the comparison, and all we have in sheep at the moment is that the Bruce and colleagues experiments, which were published in Veterinary Record, 1st of June 1996, was that one out of three

animals that were fed 0.5 grams of infected cow brain came down with disease.

Since that time other animals have been infected orally, but they've received five grams. So they've received more. So they don't help in relation to defining what the oral LD50 is for sheep that are fed cow brain. So that's where we are.

CHAIRMAN BROWN: Thank you very much.

We now have the next speaker on the speaker phone, and that is Dr. Richard Race, who I imagine is talking to us from the Rocky Mountain Lab, is he not?

DR. RACE: Right.

CHAIRMAN BROWN: And he's going to tell us a little bit about tissue infectivity in scrapie infected sheep and goats.

Dr. Race, welcome.

DR. RACE: Can you hear me?

DR. FREAS: We can hear you, I believe.

DR. RACE: Okay. I guess I can tell you just a little bit about some of the earlier work that we did and then some more recent work that we've done looking for infectivity in sheep tissues, sometimes from a diagnostic point of view and other times trying to understand a little bit more about the pathogenesis

of scrapie in sheep, and then you know, if you have questions may be you can target where you want to go with the discussion from that.

I believe you have available at least one of the papers. Do you have both papers?

DR. FREAS: We have received both papers. One paper they received this morning, and the other is in their blue folders.

DR. RACE: Okay. So the papers basically summarize what we've done in terms of looking for infectivity in various tissues, and the first paper, that was basically Bill Hadlow's paper from 1982, showed that infectivity, high levels of infectivity are present in the central nervous system, relatively high levels, but much lower than PNS tissue present in lymphoid tissues and infectivity, either very, very low or nondetectable in the other tissues that were examined. The other tissues, the negative tissues that were looked at are indicated in the note at the bottom of Table 2.

In the second paper, we looked at essentially the same kinds -- we looked only really at central nervous system lymphoid, and we added placenta because we were interested in knowing more about placenta, whether or not that might be a major source

of pasture contamination.

There was some indication that it could be, but really no follow-up in recent years to really look at that. So with newer techniques, with our ability to look at PrP-RES and disease associated protein and infectivity, we thought we'd look at that again, and so that paper actually adds placenta, but it in all other respects is similar to the first paper in terms of what we found, and that is that central nervous system tissue is highly infected lymphoid tissue, and we looked only at spleen and a couple of selected lymph nodes, and also infected in about 80 percent of the animals, and placenta was infected in about 60 percent of the animals if the animals were scrapie positive, and we did not screen animals that had not been non-clinical.

So that the placenta aspect of that paper is a little bit biased in that we looked only at animals we already knew were scrapie positive when we were looking at those placentas.

In terms of transmission, I don't think our attitude has changed any from 1982. We still think that it's primarily via the oral route. We really don't know, and I don't think anybody else knows what part feces and urine, milk, colostrum,

semen, tissues that might be ordinarily expected to be excreted to the environment plays other than that we've found them to be negative, but I don't know of anyone who has gone to heroic measures to try to concentrate agent that might be present in those tissues, and we actually now have techniques available where, you know, hopefully somebody might decide to do that using purification techniques where we can concentrate disease associated protein and thereby then associate infectivity and look at that.

I think there are some people that are thinking about doing those kinds of things, but for lymphoid tissue and central nervous system tissues of sheep are infected by -- very highly infected if one considers that we're crossing a species barrier and going from sheep to the bioassay animal, which what we have used is mice, and we've used these rml mice, our titration mouse, and it's a very sensitive strain. It's worked better for me than a number of inbred strains, and I've utilized those.

I think that the data is pretty accurate at least to this point.

Would there be questions or kinds of other information would you like to hear about?

CHAIRMAN BROWN: If anybody on the panel

would like to ask Dr. Race a question now, please do so. Otherwise we'll have Dr. Race continue.

I don't see any hands, Dr. Race.

DR. RACE: Okay.

CHAIRMAN BROWN: Oh, wait. There's one hand in the back row. Actually he's a "back bencher." Dr. Asher.

Mic, mic.

DR. ASHER: Can you hear me here?

DR. RACE: Yes.

DR. ASHER: This is David Asher.

I'm just wondering how sensitive the rml mice are relative to sheep. Is there any estimate of that?

DR. RACE: We've never done an estimate of that. In the later study, the 1998 study where we were actually looking at placenta, where the amounts of agent looked to be fairly low, if we had a very, very low PrP-RES signal by immunoblot, we actually did find some infectivity. The two seemed to correlate pretty well and, you know, suggested to me that the mice were actually in this situation doing a fairly good job of detecting agent that might be there.

Usually if we get a PrP-RES signal, we usually get -- definitely get a titer in the mice, and

that seemed to correlate even in placenta in these studies where the amount of infectivity seemed to be fairly low.

CHAIRMAN BROWN: Dr. -- do you have another question?

Dr. Almond, did you have a question or a comment for Dr. Race?

DR. ALMOND: It was just a comment on that last point. The experiments carried out by MAFF looked at the relative susceptibility of cattle and R3 mice to BSE by IC inoculation, and the difference in sensitivity is about 1,000-fold. Cattle are 1,000 times more sensitive. So the species barrier there, if you like to put it in those terms, is 1,000.

Orally it's not clear whether that 1,000 difference will be maintained when one compares oral transmission of cow brain to cows versus cow brain to mice.

DR. RACE: Yes, I think generally, you know, we also would agree with that. I think, you know, most of our PrP-RES infectivity correlations where we've used tissue culture cells or mouse hamster systems, we think that the infectivity assay is about 1,000 times, 1,000-fold better as well.

I was a little bit surprised by the study

with the placenta, you know, that it turned out to be as sensitive as it did.

If you take the amount of infectivity in the placenta, if you look at it, the incubation periods are generally longer, and in two of the animals we found nothing. In two other animals we only killed one out of eight or nine assay mice. The others were a little bit stronger, and so we're really on the borderline, I think, on about four of those animals as far as placenta goes.

You know, as far as infecting animals, I think that whatever the source of the infectivity is, whether it's placenta or some tissue, to me it seems like it might be a very low grade exposure over a prolonged period of time that actually accounts for infectivity. So to really rule out some of the tissues that have not been positive in the past is going to require a little bit more in terms of trying to concentrate agent that might potentially be there.

The tissues that are positive are ones that, you know, it's a little bit difficult to envision getting fairly large amounts of infectivity into the environment unless it's prolonged, very low grade kinds of exposures or contamination.

CHAIRMAN BROWN: Stan.

DR. PRUSINER: Rick.

CHAIRMAN BROWN: This is Stan Prusiner.

DR. PRUSINER: How are you?

DR. RACE: Good. How are you doing?

DR. PRUSINER: Fine. Just a comment and then maybe you would respond to it. It seems to me that you really can't do much in the way of quantitative estimates of infectivity from sheep into mice when the highest the brain samples only begin to bring the mice down at 500 days of age because then after that there's really not a lot of time to do an endpoint titration, do all of the serial dilutions before the mice really begin to die off for other reasons.

DR. RACE: Yes, that's true. I mean, if you have the really most concentrated samples, you're still dealing with a long incubation period. So it is difficult to make those valuations.

Yes, as far as quantitative differences, it's pretty subjective. I mean, I think we all know that.

CHAIRMAN BROWN: There are no more questions, Dr. Race. Did you have other aspects of the topic that you wanted to transmit?

DR. RACE: Only if there is some other

information that you think I could be of any help.

CHAIRMAN BROWN: Evidently the Committee is satisfied, and we thank you very much. It's nice to hear your voice again.

DR. RACE: Okay. Thank you.

CHAIRMAN BROWN: Bye-bye.

DR. RACE: Bye.

CHAIRMAN BROWN: I think we'll now, since we had an abbreviated break earlier, we'll take a five-minute leg stretcher, and so in about just five minutes we'll start again.

(Whereupon, the foregoing matter went off the record at 10:45 a.m. and went back on the record at 10:52 a.m.)

CHAIRMAN BROWN: We will dismiss a question period. I think we've had opportunity to ask questions of virtually everybody, and we will proceed with -- oh, I'm sorry. Dr. Sutton is not here?

DR. FREAS: She just got here.

CHAIRMAN BROWN: Okay. We will now have three successive presentations focused on this country, and the first will be from Dr. Diane Sutton in the USDA. The second will be in my draft and unidentified FDA speaker, and that turns out to be our old friend, Dr. Honstead, and the third will be from

Lisa Ferguson.

The first presentation is entitled "Potential for Human and Animal Exposures to Animal TSE Agents in the USA." Dr. Sutton.

DR. SUTTON: My intent is to explain the past history of scrapie in the U.S., what steps have been taken from a regulatory point of view to control it, where we're at now with the program, and what's currently going on with the certification program.

It's not going to cooperate. Maybe it's on the remote here.

I just want to acknowledge that the epidemiological information came from Dr. Nora Wineland out at the Centers for Epidemiology and Animal Health.

As you're all aware, we've been knowing about scrapie for over 300 years, and it originally occurred from Europe to Canada to the U.S. with the first case being reported in 1947.

The United States Department of Agriculture initiated an eradication program in 1952, at which time a state of emergency was declared. A total flock depopulation with indemnity was the manner of control.

In 1957, source flocks -- these are the

flocks from which scrapie infected sheep were born -- were also included in the program, and animals that traced out of exposed flocks were also slaughtered.

Oops. Went the wrong way. This is my first time using this. So I'm having an entertaining time.

In 1965, the option for bloodline slaughter was introduced along with a two-year quarantine for non-bloodline animals. The theory at the time being was that it might be a genetic disease, and the majority of animals that were found to be positive were the offspring of previously infected animals.

In 1975, that option was eliminated as science became better known that it was an infectious, widely transmitted disease.

In 1978, the indemnity was increased in hopes that this would facilitate the program and also a surveillance requirement was added.

In 1983, bloodline option was once again reinstated at the request of the sheep industry.

In 1952 everyone came to the realization that the eradication program as it had existed since 1952 just wasn't getting the job done, and negotiated rulemaking process was started between the sheep

industry, renderers, USDA, state animal health officials, and other interested parties.

And what came out of that was the voluntary scrapie flock certification program, which I'll describe in detail in a few minutes.

The one thing to remember is at the time that the voluntary program came into effect, that didn't make the regulatory control program go away. We still have an active program. There are interstate restrictions on the movement of sheep that are infected with scrapie or that come from scrapie infected or scrapie source flocks, source flocks being defined as any flock from which two scrapie infected animals were born under the age of 54 months.

The other thing to be aware of is that we are currently revising the rules that apply to scrapie to make a more stringent and powerful control program. The proposed rule is currently undergoing the clearance process.

For those of you who are not inside government, that means I can't discuss the details of what's in there.

Currently, in order to get off the federal infected or source flock list, the flock has to undergo what's called a herd plan or flock plan, and

this basically requires the removal of high risk animals, cleaning and disinfection, being on surveillance program in most cases, and identifying all animals in the flock.

Since the beginning of scrapie in the U.S., we've had 943 infected flocks identified, 1,503 confirmed scrapie cases, and of course, these are only the reported cases that were confirmed at NVSL. We've had seven cases in goats. Of the cases in goats, many of them trace back to exposure to sheep, and the remainder could not be determined whether any exposure to sheep had occurred.

In the U.S., the average age of an infected animal at death is 47 months, the majority of the animals, of course, female due to the high number of female animals in any flock. Male animals typically die at a slightly younger age, 42.9 months; females at a little higher age, 47.8 months.

We have not been able to detect any seasonality with the disease. The disease is distributed throughout the U.S., and a wide range of breeds are affected, including all of these listed: Suffolk, Hampshire, Cheviot, Southdown, Shropshire, Rambouillet, North County Cheviot, Dorset, Finnsheep, Corriedale, Merion, Montadale, Columbia, Cotswold,

Border Leicester, and Textel. So there are very few breeds that have not been affected.

The vast majority have occurred in the Suffolk breed and the black faced breeds, but as you can see, the white faced breeds are well represented.

In a NAHMS study survey conducted in 1996, this was an owner questionnaire and involved voluntary reporting. Owners reported anywhere from a 0.3 percent of infected flocks up to 2.6 percent. When this was averaged out over the whole United States, it came out to 1.2 percent.

Basically the people were asked: have you seen a case of scrapie in your flock in the last five years?

These are the scrapie confirmed cases for fiscal year '98. We had 63. These are the cases to date, for fiscal year '99. As you can see, we're having comparable numbers this year as last.

These are our scrapie source flocks. We currently have six. These are the scrapie infected flocks. These are the flocks that have not completed a flock plan in order to get off of the infected list. We currently have 65. As you can see, they're well distributed.

There are a number of strategies that can