variant CJD was reported to be different from the classic forms whereas, in at least two of the three patients, the PrP-res was similar to that in the majority of sporadic CJD patients.

Exposure of the patients in the new-variant CJD to the BSE agent was highly plausible because of the widespread occurrence of BSE in the United Kingdom whereas exposure to chronic-wasting-disease-infected venison in our three cases was not so clear.

Finally, all the reported new-variant CJD cases had a methionine-methionine homozygosity on codon 129 whereas each of our three patients had different polymorphisms at codon 129 of the prion-protein gene, in case 1 with methionine-methionine, in case 2, valine-valine. Case 3 was methionine/valine.

[Slide.]

In addition, in collaboration with state wildlife and agriculture representatives, Dr. Linda Detwiler's group at USDA collected and tested over 1,000 hunter-harvested deer and elk brain samples from the areas where the venison consumed by the patients originated. All these deer and elk brain samples tested negative for chronic wasting disease by immunohistochemical. All the samples were obtained from the areas where these patients actually collected their venison.

[Slide.]

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[Slide.]

In conclusion, although the occurrence of three unusually young CJD patients who were reported to have regularly consumed deer and elk meat suggested a possible relationship of their illness with CWD, our follow-up investigation found no strong evidence for a causal link between CWD and CJD in the three patients.

However, our conclusions are limited to the three patients and continued surveillance remains very critical to continue to monitor the possible transmission of chronic wasting disease to humans.

Thank you.

[Applause. 1

DR. BROW-N: I have one question for you, Ermias. By analogy to the BSE situation in variant CJD, are there any characteristic or distinctive glygotyping patterns in deer or elk that might also have been seen in any of the patients glycotyped? That seems to me to be, by analogy, probably the single most important phenomenon that might totally blow away the straw man that you have constructed.

DR. BELAY: We have considered that possibility. Dr. Pierluigi Gambetti has been involved in studying the glycoform ratios of PrP obtained from chronic-wasting-disease-infected animals. I will give Dr. Gambetti a chance to comment on that.

DR. GAMBETTI: These studies are very preliminary

ut, in our hands, the protein, the scrapie prion protein rom the chronic wasting disease is what we call type 1. It s the unglycosylated isoform migrates at 21 kilodalton. he ratio of the glycoforms, as I said, we haven't examined sufficient number of cases, but, so far, it looks like it s not remarkable. It looks certainly not like one of the ew variants.

So, in terms of proteins, scrapie prion protein, he chronic wasting disease does not seem to offer very much elp in being very typical and, therefore, from this area, e cannot draw any conclusions.

DR. BELAY: Can I add some comments?

DR. BROWN: Sure.

DR. BELAY: I think what is also relevant is what Beth mentioned in terms of the strain typing that was performed by Dr. Moore. Although it was limited to just one animal, that investigation actually suggested that the PrP scrapie or PrP-res in CWD-infected animals is actually different from any other PrP-res that we are aware of.

DR. BROWN: Right; but to make sense of that, you would need--

DR. BELAY: With the limitations of the study.

DR. BROWN: That's fine, even one. But to make any interpretation of that, you would need to do one of the cases similarly. In other words, you want to see some

orrelation between the human and the elk. I gather that as not possible.

DR. BELAY: We have not done any strain typing in he patients and also in the chronic-wasting-disease-nfected animals.

DR. LURIE: I just want 'to understand how you hose these three cases. Obviously, one criteria was their ge. But were they selected because you knew ahead of time hat they had some kind of exposure to deer or elk, or did hat only turn out in the course of your questionnaire?

DR. BELAY: No. We selected these patients ecause they were reported to us specifically these are atients who have been regularly consuming venison.

DR. LURIE: The point I want to make is you have a summary slide sort of comparing the causality elements of 3SE and this. Really, two of them were vaguely positive. One was, perhaps, increasing incidence. The other was exposure to the meat in question. Really, those were the entrance criteria into the study.

DR. BELAY: We looked into CJD cases in that age group reported to CDC even in the past. The three patients stand out because of their venison consumption.

DR. BROWN: It is the age that entered them into the study.

DR. LURIE: That is not quite what he--

DR. BELAY: That's right. What Dr. Brown is saying is correct.

DR. LURIE: So it is only the age.

DR. BELAY: The age and because they also reported venison consumption, then that triggered our investigation.

DR. BROWN: Peter, this is not a systematic study.

DR. LURIE: No; I understand that.

DR. KATZ: Do you have the venison consumption data on the earlier young cases?

DR. BELAY: Almost all of them except one. That one was a patient who died in 1981 and we were not able to trace the--

DR. KATZ: And?

DR. BELAY: None of them had venison consumption.

DR. KATZ: Ever.

DR. BELAY: That's correct.

DR. BURKE: I was going to extend that question in terms of were any kind of case-control studies done. I don't have any sense of what the U.S.-based age consumption of deer and elk is across that region of the country. Do you have any data on that at all?

DR. BELAY: Can you rephrase the question again, please?

DR. BURKE: Is there some way to do a proper case-control study with whether or not ingestion of deer or elk

is a risk factor for the development of chronic wasting or new variant or whatever at this point?

DR. BROWN: Young CJD.

DR. BURKE: Young different CJD.

DR. BELAY: As you can imagine, a case-control study in this group of diseases is extremely difficult because, by the time the patients die, you would be eliciting information that took place pretty much for a lifetime period. So you would asking questions like, "Did you ever eat venison?" and that information would have to be obtained from family members.

The bottom line is case-control studies would be complicated. But I agree that case-control studies have some value at the same time. In addition to the limitation of getting the information from the family members, case-control studies are also limited by their ability to detect a low level of transmission.

In other words, if there was a low level of transmission, you may not see any difference between the cases and the controls that you would be investigating. But such a case-control study is underway in Canada that I am aware of. They have included questions like consumption of venison and we are awaiting that study to see if that would warrant a larger-scale case-control study in the United States.

DR. BROWN: Don, the short answer is no. The CDC and Dr. Belay and Dr. Gambetti really are to be congratulated because this could have been like the anecdotal stories about squirrel meat that just hang in the breeze without anybody ever really looking into it.

I give them all the credit in the world for actually driving these as far as they can. But they are still anecdotal.

DR. PICCARDO: Case no. 1, there is no immunoblood analysis. In case 2 and 3, there are immunoblood analyses. Extensive immunoblood analyses from different areas was done or from a single area?

DR. BELAY: Do you want to comment on that, Dr. Gambetti?

DR. GAMBETTI: could you say the question again?

DR. PICCARDO: On cases 2 and 3, the immunoblood was from a single area or were multiple areas analyzed by Western blot?

DR. GAMBETTI: In case 2, several areas. The diagnosis was initially established from a biopsy and, when the autopsy tissue was obtained, it was confirmed, the result was confirmed with samples from different areas. Case no. 3, I don't remember specifically whether it was several areas, but, generally, that is our rule. We perform a Western blot on multiple samples.

DR. PICCARDO: In all cases, you saw type 1, you never saw a mixture of type 1 and 2, or a weird pattern in any of the--

DR. GAMBETTI: Case 1, we did not receive frozen tissue.

DR. PICCARDO: No, no; from cases 2 and 3, all the Western blots show a type 1 PrP.

DR. GAMBETTI: Exactly. Correct.

DR. BROWN: Just in closing this presentation, the other interesting interface that one of these patients had for this group was that he was a professional blood donor and had donated multiple, multiple, multiple units of blood even into his early clinical phase.

Now, on to the next presentation, diagnostics by Dr. Kathy O'Rourke.

Diagnosis of Elk-Associated and Deer-Associated Chronic Wasting Disease

DR. O'ROURKE: Good morning. Thank you. I would like to assure you that I am not here under false presences. I am not a veterinarian nor a pathologist and there are those people representing those disciplines here, both on your committee and available for questioning that can help you.

[Slide.]

I am a research microbiologist with U.S.

Department of Agriculture with adjunct appointments at Washington State University and Colorado State University. I was asked to talk to you about the types of diagnostic techniques that are in use and that are being developed for chronic wasting disease, both in free-ranging and in captive animals.

As you will see from the title of this presentation, I consider that elk-associated chronic wasting disease and deer-associated chronic wasting disease are separate diagnostic entities. I will try to make clear during the presentation why that is so.

[Slide.]

As you will see, the number of participants is beginning to outstrip the capability of an overhead transparency. Dr. Spraker and Dr. Williams, and Dr. Jenny and Gidlewsky, represent the states of Wyoming, Colorado and the last two the federal government. These are the pathologists that bring you the work that I will be talking about today.

Dr. Balachandran does the equivalent work in Canada currently. Dr. Creekmore, who you will have an opportunity to meet later today, perhaps, and Dr. Rhyan operate the administrative aspects of the APHIS CWD Program at this present time. We are grateful to the area veterinarians in charge and the veterinary medical officers

of APHIS who have provided us samples from captive animals.

The state agriculture departments in South Dakota, Oklahoma, Colorado, Nebraska and Montana provided samples and, in particular, Dr. Sam Holland and Dr. Tom Klein have provided extensive samples as well as detailed epidemiology of a very serious outbreak of chronic wasting disease in a captive herd in South Dakota.

The North American Elk Breeders Association are represented here today and Dr. Zebarth will be talking to you. There are others, but they don't fit on the transparency and I know your time is limited.

[Slide.]

The diagnostic marker that I will be- discussing is termed PrP-scrapie by convention and by analogy to sheep scrapie. There is no implication here that it is same protein that is associated with scrapie in sheep.

The areas of interest based on our previous results and those from around the world in sheep are to focus on the brain, the tonsil and other lymphoid organs of the head as well as lymphoid tissue in the third eyelid, in particular reference to the sheep live animal test that is being investigated currently. These are the target tissues.

Extensive surveys were made in other tissues. These remain the best candidates and I will show you why that is as we proceed.

[Slide.]

The assay that I will discussing is a immunohistochemical assay. It is done on a single piece of equipment at this point, or rather a single model of equipment, in Canada at our research lab in Pullman, in Colorado State University, University of Wyoming and at NVSL. We have available to us two different monoclonal antibodies. Again, the characteristics of these antibodies are different. I will try to point out the differences as we proceed because the use of the antibodies is critical to both the sensitivity and the specificity of these assays.

Neither of these antibodies is specific for the pathologic form of the prion protein. The tissues that I will be discussing are fixed in formaldehyde and paraffin imbedded for routine histologic diagnosis.

The pretreatments that typically reduce substantial PrP cellular reactivity are primarily the formalin fixation. However, this is variable among the different species as well as between the antibodies. Formic acid is used partly to reduce the cellular reactivity and also to increase the PrP scrapie reactivity.

Proteinase K is used in some laboratories. I have to caution you, however, that the proteinase K resistance of the prion protein is a diagnostic characteristics in the fluid phase; that is, in terms of ELISA testing or Western

blotting. PK alone does not distinguish this PrP cellular from the PrP scrapie in formalin-fixed tissues in chronic wasting disease.

[Slide.]

The sample populations that were available to us were not selected ahead of time for an optimal situation. As you know, these are free-ranging animals. So we are grateful to get the samples that we get and we work on what is available to us.

We have several different types of populations beginning, originally, or course with the free-ranging clinically affected cases in which spongiform lesions were predominant. Those, of course, were the earliest cases diagnosed before the development of immunohistochemistry. Later, we were able to extend the studies to free-ranging clinically normal deer and elk.

Because of the extensive surveillance that is done in Colorado and Wyoming and because of the participation of APHIS and the state veterinarians in other areas, we are able to group tissues depending on whether they come from the endemic area or from well outside the endemic area.

Third, we have access to captive deer and research facilities and to game-raised elk. These are the study populations that were available to us.

[Slide.]

In terms of the use of the brain in diagnostic analysis, the question has already been well raised. We needed to know for sure that we were looking at the appropriate part of the brain. Dr. Williams had originally looked at many parts of the brain. Dr. Spraker extended that work by doing very detailed anatomical mapping of the prion-protein deposition in the brains of free-ranging deer and elk. Those findings will be published later this year.

We had to answer some important questions. First of all, certainly, in advanced disease, where is the prion deposited? Secondly, in animals that don't have histologically evident lesions, is there a particular place in the brain that is always invariably involved. And, if prions are found in only one area immunohistochemically, where would that be?

The answer continues to be the dorsal motor nucleus of the vagus which, as you know, is the medulla at the level of obex. These are small paired tissues on either side of the midline. With careful trimming and embedding, our ability to visualize both of the nuclei is very powerful because the staining is almost always bilateral.

[Slide.]

The tonsil was the next best place to go because we have extensive data from sheep demonstrating that, in about 97 percent of the scrapie-infected sheep,

immunostaining in the tonsil will proceed that in the brain. We were looking for an early diagnostic test. What is the first place we can look?

So we asked the same types of questions; where is the prion found in the animals with advanced disease. Now, it gets harder after this. Where is it found in animals that don't show evidence of disease. Again, our ability to work from sample sizes in the thousands rather than the dozens and to separate those animals based on the geographic origin of the samples was crucial to our ability to work through this.

[Slide.]

kere is where things begin to differentiate. In mule deer, in the CWD-endemic area, every deer that has been reported back to us by Dr. Williams and Dr. Spraker in which staining is in the brain, there was also immunostaining in the tonsil if that tissue was available.

Some deer in the endemic area have no detectable staining in the brain but they do have detectable staining in the tonsil. PrP-scrapie is abundant when it is detected in the tonsil, particularly when compared to sheep scrapie. No deer outside the endemic area have PrP-scrapie in the tonsil.

These findings were developed over a number of years and the tests did need to have some developmental work

done on it. We initially pooled the two monoclonal antibodies. They bind different parts of the prion protein and we had only limited information about the genetic variability within the animals, and we wanted to be able to maximize our chances of finding every single animal, so we pooled the two monoclonal antibodies.

However, it became clear, over time, that, as the sensitivity of the assay was increased by certain pretreatments, particular proteinase-K pretreatment, we were beginning to see an odd sort of staining in areas outside the endemic area that did not look the same way that we saw staining from animals in the endemic area, but it couldn't be disregarded.

We found that only one of the monoclonal antibodies retains its tight specificity for PrP-scrapie in these fixed tissues. So, at this point, prion staining of the tonsil in preclinical deer is done with only one of the two monoclonal antibodies.

The take-home message here is that very large samples sizes are needed and the point about test validation is very well taken. At this point, these data are now based on a retrospective look at a hundred samples of deer with known CWD; that is, the most conservative definition which is spongiform lesions in the brain. The negative control sample is 300 samples of deer from outside the endemic area.

[Slide.]

In sharp contrast, elk have been tremendously difficult to work on. Some elk with prion staining in the brain, particularly those animals with histologic lesions and widespread immunostaining do, in fact, have prion detectable in the tonsil. However, this staining is not at all abundant and three years ago we were still feeling that we might not see prion staining in the extraneural tissue of elk.

We are able to see it. It is not abundant. The cellular form of the protein keeps its reactivity to one of the monoclonal antibodies, even after formic-acid pretreatment and even after formalin fixation; that is, the cellular prion protein is readily detectable in elk samples using antibody 89 but not antibody 99. So, again, careful choice of the primary antibody was critical here. We also need to use the most sensitive assays available to us at this point to even see something.

We only see it when we see advanced disease. So we have to caution you here that we see staining in the brain of elk when we don't see it in the tonsil, exactly the opposite of what we see with deer and opposite of what we see with the majority of sheep with scrapie.

[Slide.]

Therefore, in summary, earliest detection of CWD-

positive animals, based on the immunohistochemistry techniques available to us today and in use, in deer, the earliest site for diagnosis is the tonsil or the other lymphoid tissues of the head. In elk, the earliest diagnostic site remains the obex carefully collected and trimmed so that the dorsal motor nucleus of the vagus can be detected optimally bilaterally.

[Slide.]

These techniques are really terrific. However, they don't address the essential question; how early in disease can an animal be diagnosed. As you already know, in any infectious disease, there is a lag time between infection and the appearance of the diagnostic marker at detectable levels.

In the TSEs, this lag time can range from weeks in experimental mice to months in sheep and years, perhaps, in some of the other TSEs. In the sheep studies that we are conducting, we have a little bit of an advantage since most sheep are infected soon after birth and we are able to make some guesses based on the age of the sheep about whether it is an appropriate animal to sample or not.

However, in chronic wasting disease, this studies done by Drs. Miller and Williams suggest that the disease might be transmitted to animals outside that perinatal period. Therefore, we are not able to take an animal, look

at its age and make a guess about whether we might find detectable staining or not.

Therefore, I can tell you where the earliest place is that we can find prions. I am not able to tell you what a period of time is in which that animal cannot be diagnosed because of the limitations of our testing and because of the biology of these diseases.

[Slide. 1

The diagnostic site that certainly does not appear to be useful right now in cervids is the third eyelid. Lymphoid tissue accumulates in the third eyelid of sheep. This is the bulbar surface of the nictitating membrane in sheep. That lymphoid tissue is abundant in lambs and can be sampled in animals up until about age 4 or 5 when it is difficult to find adequate tissue.

Our studies to date on sheep have indicated that that tissue accumulates prions in roughly the same kinetics as the tonsil, although at a slightly lower rate. Estimated sensitivity of a third eyelid immunohistochemistry test using our current techniques is about 85 percent when animals over 14 months of age are tested.

The specificity of the test is greater than 98 percent. We applied this test to mule deer, first of all, and found out that the bulbar surface of the nictitating membrane of deer is highly enriched in

lymphocytes. However, these appear to be solid sheets of T-lymphocytes. They are not the secondary germinal centers which are round, discrete areas, easy to recognize microscopically.

They primarily consisted of a stroma of follicular dendritic cells in which macrophages and B-cells predominate. These are the antigen-presenting sites in the lymphoid tissue. They are abundant in sheep and they are almost nonexistent in most of the deer that we looked at. Therefore, we have stopped looking at third eyelid on deer.

[Slide.]

In contrast, in elk, these are huge animals compared to the sheep that we have looked at. They have really big eyelids. Dr. Zebarth will talk to you next as an expert in collecting these third eyelid biopsies, where we are able to sample animals exposed to chronic wasting disease on a facility in South Dakota, animals that were housed in quarantine by the Elk Research Council.

The animals were sampled over time and followed through profession to chronic wasting disease. As with the tonsil, however, even when we do see staining, it is not abundant. We did not see immunostaining in the animals until probably six weeks or so before the animals went on to die,

The animals were sampled only every four to six

months so we don't have tight time curves on this. However, right now, our working conclusion is that while PrP-scrapie could be detected in the third eyelid of elk, it would only be useful as an immediate test preslaughter and only to indicate that the prion may be distributed outside the brain. It is not the earliest diagnostic site.

We predict that there would be many animals infected with chronic wasting disease--elk, that is--with staining in the brain but not in any of the lymphoid tissue including the third eyelid.

[Slide.]

Our conclusions, therefore, based on the findings of today is that deer-associated chronic wasting disease could be detected best by analysis of the tonsil, compared with the brain for confirmation and realizing that the tonsil-positives will outweigh the brain positives.

The tonsil contains relatively large amounts of PrP-scrapie and their paired tissues. Therefore, they lend themselves well to adaption to other test methodologies; that is, one tonsil can easily be formalin-fixed as a gold standard for reference and the other tonsil could be used in other types of assays.

There is tremendous interest, of course, out there in the world to make better, faster, cheaper, more high-volume TSE surveillance testing and we are working with all

laboratories requesting assistance using large tissue banks submitted by the Colorado Division of Wildlife. So the tonsil down the road in deer lends itself to larger-scale surveillance.

[Slide.]

In elk, we don't have that advantage. Right now, the staining of the brain is critical. The safest technique is to take an entire cross-section through the medulla at the level of the obex. Therefore, we don't have a paired tissue to use for other types of test methodologies. The immunostaining, however, is very, very sensitive.

In the hands of trained pathologists, we can detect two or three infected neurons. The fact that they are usually staining bilaterally lends an extra confidence to this. So the staining here, if the samples are taken correctly, is very, very sensitive and specific. However, it is time-intensive. It takes several days for these tissues to be processed and, in terms of slaughter samples, Dr. Spraker has worked with us on animals that need to have results back again with five days. That can be met, but only with the willingness of the pathologists and their technicians to work through weekends since we have been unable, so far, to convince people to work only on Monday mornings with tissue collection.

There is no other tissue in the elk that we have

yet identified that has the diagnostic significance of the brain but I must add a caution here. We have looked, not as extensively, at tissues in the gut as we have in the tonsil. We don't yet see any evidence that we have a huge buildup for prion in the gut that would precede that in the other lymphoid tissues in elk, but those studies are ongoing right now.

[Slide.]

Work in progress, then; we are working on development of rapid diagnostic tests for deer-associated chronic wasting disease so that, optimally, someone who harvests an animal in an area that is endemic or may be on the fringes of the endemic area would be able to know within a matter of a day or two whether that was an infected animal or not.

We certainly are looking at more cost-effective Large-scale surveillance tests so that, as the United States moves towards scrapie eradication, they will be able to do very effective, large-scale ongoing surveillance for chronic wasting disease to try to bring that disease under control next.

[Slide.]

We are looking at improved methods for detection of lymphoid-associated PrP-scrapie in elk. However, we can only detect what is there. Bioassay will be needed to

decide whether our biochemical means are underestimating the true amount of infectious tissue there.

There are certainly people out there that are developing transgenic mice that have an elk or a deer gene. Our ability to do in vivo testing on animals in a timely, efficient manner will be critical to our understanding of the distribution of infectivity in these animals.

We are also looking at the relative genetic susceptibility to elk-associated chronic wasting disease. Elk, but not deer, have a reported polymorphism at codon 132 which corresponds to codon 129 in humans. There are some changes upstream that change the numbering, but this is the corresponding codon to codon 129.

In elk, the animal can have either a methionine or a leucine or both, and we are looking at genetic susceptibility. Elk with the methionine-methionine homozygous state appear to be predisposed. However, heterozygous animals have certainly been diagnosed. The prevalence of leucine-leucine homozygous animals is so low that it will take a challenged study to determine if there is any resistance there.

Thank you.

[Applause.]

DR. BROWN: Dr. O'Rourke, I had one or two questions. Did I infer correctly from your presentation

that there is, at the moment, no data on the infectivity distribution in the tissues of either elk or deer with chronic wasting disease, apart--

DR. O'ROURKE: Beth can address this.

DR. WILLIAMS: I would say that the only ones that we have true infectivity studies on would be brain, and not for the other tissues. We do have evidence of PrP deposition in other tissues, but not in terms of bioassay.

DR. BROWN: The PrP--1 was going to say, barring infectivity assays, does the PrP distribution resemble that seen in other TSEs?

DR. WILLIAMS: Scrapie would be the best analogy.

DR. O'ROURKE: In mule deer.

DR. WILLIAMS: In mule deer; that's correct. In elk it may not be quite as much involved in the lymphoid tissue.

DR. O'ROURKE: That's correct. Elk seem to be intermediate between the TSEs in which only the brain is involved versus the models like sheep in which the lymphoid tissue is heavily involved. Elk are a new diagnostic challenge because they fall in the middle there.

The difficulty with doing infectivity studies on chronic wasting disease is that there is not currently a useful mouse model. The disease doesn't go readily into the mice that are used in conventional bioassays, so we are

waiting for a transgenic mouse to be available. It is not just that it will make it faster. I will even make it feasible to do those studies.

DR. BROWN: The second question is, in those animals, the deer, in which tonsil had PrP and brain did not have PrP--in those animals, were different areas of the brain sampled? I find it very difficult to believe that there are animals with positive tonsils and negative brains.

DR. O'ROURKE: Oh, no; that is not surprising. This is what happens in sheep scrapie, for a period of time. These are hunter-harvested animals of all different ages, probably suggest that these animals were in the first year to year and a half of infection.

DR. BROWN: Okay. So these are early-incubation-period animals.

DR. O'ROURKE: I'm sorry. These are what we have presumed to be early-incubation animals, clinically normal, hunter harvested. I apologize for not making that clear. In the animals that are clinically affected or that have staining in the brain, tonsil and brain always correlate. A small percentage of sheep are brain only. Mule deer, tonsil and brain, but tonsil first.

Beth?

DR. WILLIAMS: I would say one other thing in terms of pathogenesis work that we have done. It certainly

indicates that in animals that are slaughtered post inoculation that the lymphoid tissues do become positive before the brain does, which is to be expected.

DR. BROWN: As usual; right.

DR. O'ROURKE: I'm sorry; as usual for mule deer and sheep, not as usual in elk. That is why my initial title slide urges you to consider elk-associated diagnostics different from deer-associated diagnostics because the distribution of the prion is profoundly different in extraneural tissues.

DR. BROWN: Thank you very much, Dr. O'Rourke.

The final presentation of this morning is an industry perspective presented by Dr. Zebarth of the American Elk Breeders Association.

Industry Perspective

DR. ZEBARTH: My name is Glen Zebarth. I am a practicing veterinarian, do commercial practice primarily on cervids and elk. I have been involved with a group called the Elk Research Council and we have maintained a herd of infected animals and submitted tissues to Dr. O'Rourke and Dr. Williams and Dr. Spraker.

[Slide.]

I have been asked to present the industry perspective on chronic wasting disease. The North American Elk Breeder's Association has taken an active and leading

role in developing and implementing a control program with the goal of eventual eradication of CWD in farmed elk. The program includes a certification of a herd's CWD status.

I would, at this time, go down to item no. 2, the scientific evidence that the industry is aware of would indicate a lack of evidence of transmission of CWD to humans or cattle and most of these items have been covered earlier, the species-barrier evidence from Rocky Mountain lab, the oral-transmission study that is underway by Dr. Beth Williams. There is an interim report on that on twelve cattle that were exposed orally and are presently free at three years post-exposure.

Correct me if I am wrong, Beth, somewhere.

There was a cross-species transmission study done by Dr. Gould at Colorado State University and was conducted in the geographically targeted survey area of Colorado and Wyoming. It involved twenty-two ranches where cattle were commingling with free-roaming deer in the endemic area. 262 cattle brains were followed through slaughter, collected and analyzed and were negative for the demonstration of prion.

[Slide. 1

Item d, on the next sheet, is the only data that I am aware of in regard to velvet antler and is very limited. So I would not propose to interpret that for any more other than exactly Dr. Rubenstein's comments contained here.

From South Dakota, Dr. Holland, the state veterinarian, had submitted to Dr. Rubenstein eleven antlers. Three of those were from animals that were brain-positive on slaughter. Three were unknown status and the rest were negative on brain examination. A detectable prion was not found at the log infectivity of three logs of infectivity.

In real-life experiences, as Dr. Miller reported earlier, free-ranging elk have a documentation of being in the endemic area from 1981 and in b, under there, I would say that there is a misprint and it should be, "hunters have been exposed to and consuming animals from CWD-endemic areas for at least twenty years with no apparent variant CJD occurring," apparent to us. We need to add that, please.

The take-home message that I would like to leave with the committee today is that the North American Elk Breeders Association, as an industry, has been active in trying to responsibly deal with this occurrence and has worked in developing proposed regulations, has provided financial support of ongoing scientific research, has supported the search for better diagnostic tools, has, through the Association and an organization called the Elk Products Board, developed quality processing and manufacturing standards for elk products.

When CDW was first diagnosed in a commercial

farmed operation in December of 1996 and January of 1997, in the farm facility in South Dakota, the elk breeders of South Dakota voted unanimously to support emergency legislation through the State of South Dakota that had the goal of banning the sale of products from any of those herds. Those herds were quarantined.

Subsequently, seven herds were identified in South Dakota. Six of those have been depopulated and the final herd has a few remaining animals that have been identified as genetic LLs and are scheduled to be moved to NADL at Ames, Iowa for an LL-challenge study.

[Slide.]

The North American Elk Breeder's Association, in August of 1998, convened a symposium in Kansas City at which time a model program for the control and surveillance of CWD was formulated. That problem was taken and submitted to the United States Animal Health Association in October of 1998 and was passed through the Alternative Agricultural Committee and the Wildlife Diseases Committee and was published and put out to state veterinarians, to the state agencies, as a model control program to use for a template.

As of this date, eighteen states have adopted and are in some varying stages of a control program.

[Slide.]

On the very last sheet, this is basically somewhat

.milar to what Mike had on his map. There actually are
ome more states that are included in here than I think your
map shows. These states are the primary states that have
armed animals and the estimate is that 80 percent of the
armed animals are contained in these states. As you can
ee, it is a variety of a mix of different programs.

You can go back to the first page, please.

[Slide.]

The main component of the CWD model control and
he goal for eradication program is really two factors. One
s a verified inventory. The elk industry is already one of
he most regulated farmed-animal industries in the United
tates. This means that we already have excellent inventory
ecords on herds and animals.

In most of the states where farmed elk are raised,
y law, the owner is required to have a license with the
oard of Animal Health in that state and is required to
ubmit an annual inventory. Some of those states, that
inventory is verified by a third party and some not. Anyone
who is on a CWD eradication, on this program, has to have a
third-party-verified inventory.

The second major component of the program, then,
is that the brain is examined on every animal that dies,
regardless of the cause, that is in excess of sixteen months
of age. So the two components of the program are a verified

inventory so that we can verify that we know we looked at the brain of every animal that expires, regardless of the cause, and then the diagnostic tests that we have used, examination of the brain, as a follow-up to the information Dr. O'Rourke just gave us.

This also, then, has the process of--we have in the states of North Dakota, South Dakota and Colorado, the entire states are--by law, all of the herds are mandatorily required to be in this program. Those states are going on thirty months. so we have three states with a fairly large number of herds that we have thirty months of a certified status.

In other words, the brains have been examined systematically from all of the animals that have died that were in excess of sixteen months for thirty months in those three states. We think that is a very critical fact in that we are starting to accumulate some herds that we have verified status and we can have some comfort that these are herds that not only do we say they have not had an occurrence of the disease, but we have looked and we have some proof of examination that there isn't something going on there.

At the present time, and with the state programs, it varies with different states as to whether there has been a ban of products out of those herds. We have checked, and

all of the herds that have been infected, the seventeen herds that Dr. Miller spoke about, none of those herds say that they have sold elk velvet antler into the trade since they were diagnosed.

[Slide.]

The industry supports ongoing research and a dialogue. This basically just underlines some of the facts of the research that Dr. O'Rourke is doing. As she mentioned, we did maintain a herd of fifty-two elk that were obtained from infected herds in a biosecure facility and did serial sampling. We maintained those animals for four years and subsequently they all went to slaughter.

Out of that, we also sampled, and have worked with Dr. O'Rourke, on the LL-genetic screening. We are taking some of those animals now for an LL-challenge at Ames.

One other study that is being done is on of the infected facilities has been depopulated and we are now in the process, with the South Dakota Board of Animal Industry and with the Colorado Division of Wildlife in a project and node1 study and reintroducing some animals in an environmental contamination study there.

[Slide.]

NEABA supports, requests and urgently needs indemnity. The importance of an indemnity and the importance of the industry to work with USDA APHIS

Veterinary Services is that if we can obtain indemnity, then we will obtain a lot greater compliance from the herd owners to be in the program.

If we do not have any indemnity and we are requesting people to be in the program, and they are diagnosed and we put them on a permanent quarantine, we basically, financially, have ruined them. So what'the goal is of the industry is to survey and monitor every herd in the industry and to then, as soon as a herd is identified, to depopulate that.

That is the model that has been accepted and is in place now in Canada. The benefits of indemnity would be for a fair-market value. Indemnity would increase the market value of certified products and the market value, then, would be an incentive for the breeders to comply with the program.

The value of breeding stock gives meaning to federal requirements for monitoring interstate movement and the indemnity will enable more states to implement mandatory participation and immediate depopulation of any herds.

The elk industry not only has state regulations but it has a breed registry program where the value of the animals has made it economically advantageous that these animals, basically, are all registered and have a DNA profile, or record. So these animals can be tracked. If a

positive case is--they have a unique ID and they have a DNA profile and they can be tracked back to their origin.

[Slide.]

Many states have controlled licensing and inventory programs and especially the states that have had some cases and especially the states of North Dakota, South Dakota and especially the state of Colorado.

The elk industry is basically--the estimate I have is approximately a $1 billion industry in the United States, the farmed-elk industry, with gross sales of elk farm and velvet antler estimated at $150 million. The elk industry has a track record of aggressively addressing disease issues in that the same general format that we are proposing to address CWD was used for brucellosis and tuberculosis and that a model program was formulated, adopted by some states that have gone and approached USDA APHIS Veterinary Services.

UNMRs were written. Indemnity was created. That resulted in brucellosis--there has not been a case of brucellosis in a farm cervid herd for seven years. So we can, with some confidence, say that is eradicated in the farm population. There has not been a case of tuberculosis for two years, a newly discovered case.

That was done after nine years from the initial outbreak as far as t.b. and six years after a federal

program. The CWD program, then, that we are proposing or requested in the process of working with USDA APHIS, follows these same general guidelines of a control program that would be enforced by interstate movement, would be supplemented by indemnity so the producers have an incentive to rapidly and quickly dispose of and totally depopulate any identified herd.

We see this as the best guarantee we can give the public that no products from these herds that are either from infected animals or animals that have been in contact with infected animals, would enter commerce or get into the food chain. So the goal is to look at, aggressively, and identify every herd that is positive and immediately depopulate that herd.

We are confident that, with diligence and with the assistance of USDA APHIS Veterinary Services, that that is not easy but is doable.

Thank you.

[Applause.]

DR. BROWN: Thank you very much, Dr. Zebarth. Why is Pennsylvania still asking for elk to be sent to their state?

DR. ZEBARTH: I would refer that to Dr. Miller. That is free-ranging.

DR. BROWN: I don't know. Pennsylvanians

apparently think that it was wonderful in Colonial days to have elk ranging around the state. They have initiated a program to bring elk from the west.

DR. ZEBARTH: Mike, would you care to address that? There are a number of eastern states that have been involved in reintroduction of free-ranging animals; is that correct?

DR. MILLER: Exactly. I am sure it is part of a national species expansion program that the state is involved in. You would really need to get the folks from Pennsylvania to speak specifically to why they are doing that.

DR. BROWN: Is there any awareness--I am sure there is, but let me ask a different thing. Are they aware of the potential problem in this kind of interstate commerce of elk?

DR. MILLER: Certainly. As I mentioned, we won't allow animals to be taken from places where we know chronic wasting disease occurs. I think the states right now that are receiving animals are well-aware of the problems and trying to do what they can do insure that animals don't come from populations that are likely to be infected.

The same way with the elk industry.

DR. ZEBARTH: The elk industry proposes to do that but proposes, also, to do one step further because we have

the ability to identify and control these animals, we would propose, eventually, to only move animals that would have a certified status.

DR. MILLER: There are plans, I think, underway and desire, certainly, to try to identify free-ranging populations of animals that can be., to the best of our technical ability, certified as free. Certainly, there are places in the country that they could get animals from.

DR. BROWN: Would that certification include a third-eyelid test?

DR. MILLER: It wouldn't do a whole lot of good, it doesn't sound like.

DR. WILLIAMS: It wouldn't be third eyelid. It most likely would be a brain test on harvested animals to certify the free-ranging herd as being a negative herd.

DR. O'ROURKE: I have been asked to provide third-eyelid tests on animals that are intended to be reintroduced into the Great Smokey Mountain Park. Those animals are being sourced from a place in Canada in which the animals are free-ranging but protected from ingress and egress by free-ranging animals.

I have told them that if they choose to archive those tissues, they could feel free to do so. But, because the test right now does not have very much value, I didn't want to give them a false sense that they were, in fact,

guaranteeing the CWD-free status.

The geographic source of the animals is the key issue for them.

DR. BOLTON: How are the carcasses from the depopulated herds disposed of?

DR. ZEBARTH: The carcasses, primarily, have been incinerated and then, in a biosecure, land-fill facility.

DR. BOLTON: I have another question. Do you have an idea of prevalence of CWD is within an infected herd, a farmed herd?

DR. ZEBARTH: We have seen two different scenarios in the farm population, one in the index herd, the original index herd in South Dakota. Correct me, Beth and Katherine, if I am wrong on this. It was a concentrated feed-lot situation and there ended up being a high rate of incidence in a group of bulls, 125 bulls, that had a high incidence, in the neighborhood of 36 percent.

The other farm situations we have seen have generally been much, much lower incidence than that, at 1 or 2 percent. The industry is taking the position and the desirability, one case and it is out. That has been our experience.

DR. BOLTON: One final question for me, In the depopulated farms, have any of them been repopulated and, if so, how long ago has that occurred?

DR. ZEBARTH: So far, no. The owners have voluntarily or in conjunction with--most of those have set up a herd plan with the state veterinarian and there has not been any depopulation in any of those facilities. We are proposing, under environmental contamination, to repopulate with a controlled number of animals from a certified-free herd into one small area in one of those facilities.

DR. BURKE: Don, do you know what percentage of your captive animal herds in this country are operating under your aegis?

DR. ZEBARTH: Dr. Creekmore might have that. I would say 50 percent and that is an estimate. But that would be my estimate at this time. The states that I maintained are 100 percent. The two largest states for farmed elk are Colorado and Minnesota. Minnesota is a voluntary program. There are 204 herds in Minnesota. 137 of them voluntarily are in the problem.

DR. PRUSINER: Could you give me a little idea of the elk-farming industry relative to the deer-farming industry that produces venison? This is a billion dollar industry with $150 million in sales annually? How many animals does that equate to and then could you give us the same numbers for deer, or do you know them?

DR. ZEBARTH: I do not know for deer. For elk, the number is approximately 110,000 farmed-elk in North

America of which approximately half of that would be in Canada and half in the United States. Canada is 52,000 and some.

DR. PRUSINER: How many are killed each year?

DR. ZEBARTH: I do not know that. I do know that in our looking and monitoring levels, checking the normal mortality of animals sixteen months of age and over is 1 percent. The number of animals slaughtered in the United States this year, there are a couple of individuals in the audience that are in the meat industry. My estimate would be a total of 800 to 1,000 head.

DR. PRUSINER: 1 percent?

DR. ZEBARTH: No, no; two different things. 1 percent death loss in a herd, and then the animals that were taken to slaughter, healthy animals taken to slaughter-

DR. PRUSINER: 10 percent.

DR. ZEBARTH: The previous year was about 800 animals.

DR. PRUSINER: So that is 1 percent. 1,000 animals slaughtered out of a herd of 110,000 is 1 percent are slaughtered in a year.

DR. ZEBARTH: Okay. There are not very many of them slaughtered.

DR. PRUSINER: So how do you make money? How do

you make $150 million a year out of this?

DR. ZEBARTH: Sale of breeding stock.

DR. BROWN: Velvet antlers.

DR. PRUSINER: wow. What an industry.

DR. ZEBARTH: There are several components. Velvet antler is one economic proponent. There are a lot of people that own and have elk just because the regality of the animal and that is especially true of deer, but a lot people have elk just for the sake of having them and seeing them.

DR. PRUSINER: wow. Okay.

DR. BOLTON: Are game preserves included in your grouping?

DR. ZEBARTH: In the surveillance, yes. Their heads are examined in hunter operations. Yes.

DR. BELAY: How widespread is the use of antlers? It is from every dead animal? Is it 50 percent? Can you give us an estimate?

DR. ZEBARTH: Please repeat the question. I'm sorry.

DR. BELAY: How widespread is the use of antlers? Is it from every dead animal that antlers would be used?

DR. ZEBARTH: No. The velvet antler is a traditional product. It is harvested at a very specific stage of growth which is about a four- or five-day period of

time. It is harvested with an anesthesia of the antler, sawed off and immediately frozen. It is harvested above the growth line so that is an annual removable product.

DR. BROWN: Most of that is probably exported; is that true?

DR. ZEBARTH: Exported. . 70 percent of the world's supply goes to South Korea.

DR. LURIE: You said in your comments that the elk industry is one of the most regulated farm-animal industries in the country. What I mostly hear is a voluntary program to which 50 percent of elk herds do not belong, some state laws, not in every state, half of which are voluntary, and no federal requirement that should an animal come down with CWD that the entire herd be depopulated.

I don't know, but that--

DR. ZEBARTH: Those are all excellent arguments that we have proposed that we need indemnity to facilitate and then we need this to be made a program disease. The industry has requested to USDA APHIS that this would become a program disease and then the things you mentioned would Logically follow, follow in that interstate movements requirements, depopulation of infected herds and indemnity for--

DR. LURIE: But those things are not in place right now in a widespread way.

DR. DETWILER: May I comment on that? That is something, actually, the USDA has requested but they have 2,,000 herds. So you can imagine. You have to get the attention of Congress in order to do that. So that is why even recommendations from this committee carry weight in that regard.

DR. LEITMAN: I have a question for Linda. How does this compare to scrapie? In CWD, there is no evidence that the disorder has crossed species barriers into humans, from what we have heard this morning. That is true for scrapie in sheep as well. If a sheep herd, or a member of a sheep herd, has scrapie, does the herd have to be decimated?

DR. DETWILER: Have to be? No, not any longer. We have had a scrapie program from 1952 to the present. From 1952 until 1982, 1983, it was complete flock depopulation. We found that drove the disease underground, that you had one animal that might be newly introduced and all the sheep had to go.

We have actually, now, gone to a process where high-risk animals are removed. This is even changing as these new tests come on board, so high-risk animals are removed. Then the flock gets monitored after that with the certification so that you could--and, sometimes, if it is heavily infected, the flock is depopulated, but it is not mandated federally. In some states, it is. So there are

combinations now.

DR. ROOS: Isn't there some evidence of interspecies spread of scrapie, for example, TME? I don't know whether the data is that good.

DR. DETWILER: To my knowledge, there is no association with scrapie and TME. I think there has been speculation in the early literature about sheep. There has been speculation about cattle with TME. But none of those have been, to my knowledge, any conclusive evidence with TME.

Now, scrapie, with experimental transmission, yes. It has been transmitted to a number of species but not to my knowledge in any natural route.

DR. BROWN: I think, as you have probably noticed, we are not breaking. What I would like to do now is hear the open public hearing presentations and then we shall have lunch. Then we shall discuss this issue immediately after lunch.

Open Public Hearing

DR. FREAS: Following our Federal Register Announcement, I have received four requests to address the committee during the open public hearing. The first request is Mr. Dan Marsh. Is he present? The second request I have seen is from Barbara Fox from the North American Deer Farmers Association.

MS. FOX: I will pass.

DR. FREAS: The third request, Lloyd Riddle from Natraflex Brands.

MR. RIDDLE : Nobody else wanted to get between the crowd and lunch, I see. I will dispose of this quickly. Good morning and thank you for allowing me to share my comments with you. My company, Natraflex Brands, is the leading velvet-antler dietary distribution company in the United States. We estimate we have about two-third market share.

I am here to share with you, and the general public, some information regarding the safety of our product and the steps our company takes, as well as the general elk industry takes, to insure that our products continue to be safeguarded from CWD.

Let me state from the outset that Natraflex maintains documentation on the source and the chain of custody of our velvet-antler material and our records show that we have not purchased velvet antler from any ranch or any farm that has had a CWD-positive case diagnosis at the time of the purchase nor have we made a purchase from any farm or ranch that has had a subsequent CWD-positive case diagnosis.

Product safety is paramount to us at our company and the following are just some of the steps we take to

insure that our products are safe. Number one, Natraflex limits our velvet antler purchases to growers and states that are enrolled in state- or provincial-run CWD surveillance and eradication programs.

This means that those growers must submit the brains of required animals that perish or that are slaughtered to the state veterinarian for CWD testing. You can't find what you are not looking for. All of our suppliers are--in most cases, required by law--looking for CWD. In fact, our principal supplier of velvet antler is also used as the negative-index herd, if you will, for CWD live-animal testing.

This herd is subject to extensive veterinary and health review by some of the world's leading TSE scientists.

Number two, as a matter of policy, public perspective and common sense, we do not, and have not, sourced any products of any kind from any ranch that is or has ever been under CWD quarantine.

Number three, notably, and from a statistical management perspective, to date, Natraflex has sourced fresh velvet antler from only fifteen growers. As a consequence, we know exactly where our product comes from and we continually monitor these sources for quality and safety issues.

In fact, as you have heard from earlier speakers,

although CWD has been known to exist in the wild population for several decades, the elk and deer industry responded very proactively when CWD first appeared in farm stock several years ago and have worked with various state agencies to adopt state-run CWD surveillance programs. Some of these programs have been in place for as long as thirty months.

These programs are beginning to approach, or exceed, the generally accepted CWD incubation period and, as a consequence, several states are considering issuing CWD status certification similar to the accreditation you heard received for t.b. As you heard from Dr. Zebarth, there is a proposal to USDA to make this a national program. Natraflex welcomes these programs as a double check and as a validation on our own existing standards as well as providing confidence to the consuming public.

Number four, Natraflex supports USDA, American Elk Products Board, and North American Elk Breeders Association quality control and feed standards. These standards mandate, among other things, that farmed elk and deer feed not contain prohibited mammalian proteins, unlike the former European practice of feeding TSE-infected animal protein to cattle.

Natraflex also strongly supports the national model CWD eradication program developed by these same

agencies provided that the program included herd indemnity to maximize surveillance results and for basic fairness reasons.

Five, each batch of velvet antler we produce is thoroughly tested in an independently licensed laboratory not only for compositional conformity to our standards but, also, for food-borne pathogens and other contaminants such as heavy metals. When a live animal test for CWD is validated, we will require that test as well.

Six, Natraflex maintains comprehensive, chain-of-custody records that trace each bottle's lot number back to the ranches that produced that antlers. Each bottle of our product can be traced back to the farms that produced it and none of our supplying farms has ever had a CWD-positive case.

Seven, finally, all of our products are packaged at an FDA-licensed and inspected facility and are labeled in compliance with FDA regulations. CWD is rare among farmed elk and deer and complete eradication measures are advancing rapidly. Further, we have seen no scientific evidence that shows CWD can be transmitted to humans. Centuries of elk, venison and velvet antler consumption by humans would seem to bear this out.

The bottom line is that there is no evidence that velvet antler poses a public-health risk. However, and let

me be very clear on this point, Natraflex does not rely on centuries of empirical evidence or the science alone. We share the commitment of the elk and deer industry, USDA and the FDA to have safe and effective products. We will continue to take whatever steps are necessary to insure that our products are guarded against CWD.

Given the science and the information presented, and given the comprehensive array of Natraflex quality control and chain-of-custody procedures, we believe that you can be confident the our velvet-antler supplements are safe.

Thank you for the opportunity to share my comments this morning.

DR. FREAS: Thank you, Mr. Riddle.

Our next speaker is Dr. Michael McDonnell from the North American Elk, LLC.

DR. McDONNELL: Thank you. I am Dr. Michael McDonnell. I am a researcher in the beef industry but I also happen to be part owner in a slaughter facility and meat-distribution facility for elk.

In general, you have had specialists here today that describe CWD in great detail. I am going to try and give a quick overview and also a view from the meat industry. One thing, or two things, that we all agree with is we want to have a safe food supply and, really, we wish that we could control and eradicate this problem so that we

idn't have to have this type of discussion.

The first question that I look at from the meat ndustry is the question of is CWD directly transmissible to umans. I think, from what we have seen here, we have not een direct data but it may be premature to call it that it s not a risk. But it is also premature to declare it a isk. We need to work on it more. My desire would be to ry to eradicate it so that we don't have to discuss that articular part of it.

As a meat company, and there were some questions sked of other producers and I was glad to be able to come p here and make some statements. Whenever we have a highly uspect herd, or a herd that has had a positive animal in t, all the meat, all the internal organs, from that herd ill be destroyed at the direction of the state in which we re, whether it is burned, whether it goes to a landfill or hatever. We try to be as safe as we can.

Any positive animals that come back will be estroyed. Only animals that test negative will be allowed nto the human food chain. The elk industry has done a very ood job of self-policing itself in that 80 percent of the lk herds that have had an initial positive have voluntarily epopulated their herd. By the end of this year, the emaining herds will be depopulated.

Some data that I will share with you in the herds

that we have been involved with the depopulation, if the herd was depopulated within six months of the initial positive sighting, we have had zero incidence of positive animals. If the time frame goes to one year to two years after the initial observation, we have a 7 percent infection rate in those herds.

If we go to the third year and on out, the infection rate goes up to 30 percent. Therefore, we would like to get indemnity so that we can eradicate this earlier because the quicker we break that chain, the less problems we will have in the long run.

We have had some discussion of elk being a nonamenable animal, which means it falls in a grey area and is really under FDA control because it is not under USDA. I would ask that the FDA consider putting it under their umbrella with USDA like they do FSIS and allow the APHIS program to be used in both the domestic and the wildlife, similar to what meat inspection is done by FSIS so that we could have a uniform program and could work to the eradication of this problem.

Thank you, sir.

DR. FREAS: Thank you, Dr. McDonnell. Could you stay for a question?

DR. McDONNELL: If you word it that way, yes, sir.

DR. BURKE: The question is if a herd is

depopulated and then they restart a new herd there that there is a progressive increase in the--

DR. McDONNELL: No; I'm sorry. If we have an initial animal diagnosed positive, and then we depopulate the herd within six months of finding the initial animal, we find no other positives in the herd. If we wait a year to find that, then we find 7 percent. The longer you'wait, the more it builds up and, if we can do it quickly, we can nip it in the bud and stop it.

DR. NELSON: What do you mean by "depopulate?"

DR. McDONNELL: Kill everything.

DR. NELSON: All the animals are killed?

DR. BROWN: Does that square with what we heard from Katherine and you, that is there was one 35 percent bull herd and the rest of them were flat-out said to be 1 to 2 percent. This sounds like it is a different set of data.

DR. McDONNELL: Those are the ones that I have been personally involved with. There have been three herds or four herds that I have not personally been involved with. I am just going on the data that I have been involved with.

DR. WILLIAMS: There is a situation with some of our experimental herds within the endemic research facilities where we do have cases where animals have been removed from particular paddocks and then animals from CWD-negative herds reintroduced into those facilities. Under

those circumstances, with environmental contamination and potentially fence-line contamination, we have had prevalence in those herds up to 50 or 60 percent.

DR. BROWN: So this is an extraordinarily contagious disease, relative to something like scrapie which is 1 to 2 percent, BSE which maybe' doesn't get horizontally transmitted at all. But, certainly, by comparison with scrapie, in terms of the data such as it is, this is explosive.

DR. WILLIAMS: Linda, do you want to comment on the occurrence or the prevalence of scrapie within endemic flocks?

DR. DETWILER: At least in things that are monitored--again, whenever you have controlled programs, I just have to caution you, you skew your data because if you get the first one, or what not, and the flock is depopulated, then you eliminate this finding. So scrapie is usually reported a little bit higher, Paul, 2 to '5 percent in most flocks. But you can have up to 10 to 20 percent infection.

Now, in retrospect, that is work done in the '80's prior to the genotyping. Probably now, if you went back and genotyped those, probably ones with higher prevalence, you would probably see some genetic differences in there. That is my own guesstimation.

DR. BOLTON I have a question, again, going back to the disposal of the animals, when the herd is depopulated, all of animals' carcasses are burned or incinerated or are they retested and only the positive animals are incinerated and the other animals are butchered and the meat used?

DR. McDONNELL: Using the data that we collected earlier, depending on how long we have for the infection to progress, if it is a short-term--you know, immediately or soon after we get the original where we do not anticipate any positives, those animals are held under a retaining order. Usually, the samples are sent to Terry Spraker at Colorado State. Those animals that test positive are all destroyed. Those animals that test negative would be allowed into the food chain.

DR. BROWN: One other question. In the herds of animals which you have allowed to progress over time up to several years, what happens to the placentas in these herds; that is to say, you have got a herd. You know there is an infected animal. You let the herd continue to exist.

I am looking for a method of transmission. In this kind of a herd, would the placenta be source of cross-contamination because it would be fed on by a number of animals?

DR. McDONNELL: I am going to pass on that

question because that is not my area of expertise but I will answer it in a different way. We have had it in herds that are all male and we have transmission in velveting herds where there is no placenta present.

DR. BROWN: At the same kind of rate; that is, 7 to 30 to--

DR. McDONNELL: We don't have enough of those herds to establish a real positive number there. I was throwing those numbers out with the idea of saying we need-- the earlier we get on it, the better control we have.

DR. BROWN: And, at a minimum, you have got some transmission in all-male herds.

DR. McDONNELL: Yes.

DR. BOLTON: What is the density of the animals in these meat farms? Is this like a feed-lot situation or is the more like a wild--

DR, McDONNELL: No; they would be dispersed enough that grass still grows in the pasture, if you want to say that.

DR. BOLTON: How many animals per acre, for example?

DR. McDONNELL: Five animals per acre? Four to ten? It kind of depends on what part of the country you are in, what the grass-carrying capacity is.

DR. ZEBARTH: The one herd that I spoke of that

had the high incidence was a feed-lot situation. There was no vegetation in there. We are talking about 125 animals in *a very,* very small area. That is the only herd that we know of that had the real high incidence. The other herd, of which he speaks, that was maintained for a long time was the herd that we were maintaining and hoing the serial sampling on. So that is why that herd was maintained and that is why, when that herd was killed, there was a fairly high infection rate.

DR. BOLTON: I am just asking the question in general, in the elk that are bred and kept for meat production, what would be the general density of the--

DR. ZEBARTH: It would vary according different parts of the country or vegetation, but a rule of thumb would be no denser than one animal per acre and, as a general rule, probably one animal per three acres.

DR. McDONNELL: In general, about twice the number of elk stocking rate than you would for cattle would be the normal. And that varies all over.

DR. PICCARDO: I need some clarification. Let me see if I understood correctly. If an animal is infected in a flock, then the whole flock goes through testing at the state; is that what you said?

DR. McDONNELL: If they are depopulated; yes. My company's standpoint is that we test everything that we

Laughter whether they are suspect or not as a monitoring rogram.

DR. PICCARDO: Right; but the ones that test egative, that means, by immunohistochemistry?

DR. McDONNELL: Yes.

DR. PICCARDO: Go back to the food chain?

DR. McDONNELL: They can go back.

DR. PICCARDO: They can go back? What do you mean y "they can go back?" There is no rule?

DR. McDONNELL: Some herds choose not to have them o back. There was a herd that was slaughtered two weeks go and we passed on it because I thought it would have a igher infection rate than it actually did. We passed on hat herd. So they were all destroyed even though they ested negative.

DR. PICCARDO: So there is nothing legal. It is your decision, basically? It is not like you are enforced to do one way or the other.

DR. McDONNELL: That is correct. Unfortunately, being a nonamenable animal, there are a lot of grey areas. I have had a number of requests, with both USDA and FDA, for further guidance to narrow up a lot of those loopholes. I have got to say the regulatory people look at me and say that I am a little bit odd to be asking for more restrictions but I feel it is appropriate in this area.

DR. PICCARDO: I don't follow very well the logic on this because if this is a highly infectious disease, and then the animals that tested negative are allowed, at least in this grey area, to go back to the food chain--

DR. McDONNELL: The human food chain.

DR. PICCARDO: Right; even worse.

DR. McDONNELL: But we have not seen it be infective yet into the human side.

DR. PICCARDO: No, no; I understand. But the issue of the negative is, of course, we know nothing about the preclinical stage, et cetera, et cetera. So we are in a grey area where we don't know enough. You have a positive animal. You have some negative animals. And then the decision is in a grey zone of what is going to happen with that and there is no regulation.

DR. McDONNELL: There is no regulation. Unfortunately, we have no test--if we can not find the presence of a compound, the general process is we assume it is not there. If we take a stand to remove all animals from the food chain, then we run into difficulties in the beef and the swine industry because it is a difficult question.

DR. BROWN: I think what you are getting at, the answer, it seems to me, is that there is a decent possibility, under these conditions, for animals that are undetected but infected to enter the human food chain. I

think you both agree about that,

DR. PICCARDO: You are absolutely right, Paul. But, then, I have another question maybe for Beth or Linda. For the ones that tested negative on immunohistochemistry in humans--in humans where it is supposed to be more ideal conditions, if you wait long enough, or the material is fixed long enough, sometimes you might have a negative by immunohistochemistry due to the long fixation or the not-ideal condition of the material.

How ideal is the material that you test?

DR. WILLIAMS: It is variable. But, in general, especially the plants that have been used to doing this, we get good samples from them. We get the right part. And they are typically only fixed for a short period of time because the carcasses are hanging and, obviously, they don't want to leave them hanging for very long if they are going to move on into the food chain.

So they do send us pretty good samples. I will say that we have a little bit of information in terms of experimentally infected elk looking at the time at which we can detect PrP in the brain. This would be for elk. It is a little bit different than deer, as has been mentioned. By six months, post oral inoculation, we can detect it at the obex.

In those two cases, the staining was relatively

strong suggesting that it could have been picked up even prior to six months. But, again, experimental or inoculation.

DR. BELAY: Dr. Brown, it was my understanding that there is actually a proposal to change what we are discussing in terms of whether or not a test-negative animal from an infected herd should be allowed to go into the human food chain. My understanding was there is a proposal to change that. Is that true? I am asking this question to Lynn. Dr. Creekmore?

DR. DETWILER: Isn't that what the committee is supposed to be discussing?

DR. BROWN: No; it is not. No; we have to decide whether or not residence in northern Colorado for six months is a deferral criterion.

DR. NELSON: If you are an elk.

DR. BELAY: Let me rephrase my question. We have heard about a national plan to eliminate or eradicate chronic wasting disease from farmed elk. My understanding was, as part of that national plan, any animal that tests negative, as long as that animal is coming from a CWD-infected herd, it would not be allowed to go into the human food chain regardless of whether or not the animal was positive or negative.

DR. BROWN: This is for your own curiosity; right,

rmias?

DR. BELAY: Right.

DR. BROWN: Because it has nothing to do with the ssue.

DR. BELAY: Correct.

DR. BROWN: Linda, can you answer that, or can nybody?

DR. CREEKMORE: My name is Lynn Creekmore. I am ith USDA APHIS Veterinary Services, the National Animal ealth Program staff, and I am the staff veterinarian orking on the chronic wasting disease proposed program. ight now, the proposed program isn't dealing with that ssue of whether or not test-negative animals from a ositive or exposed herd should or should not enter the food hain.

The thrust of the program, as Glen described, is o have a herd-certification-intensive surveillance program rith the primary response to a positive herd being that of lepopulation with payment of indemnity. There is another ption within our program also of a long quarantine period. he question of what can or cannot happen to the animals while they are under that quarantine period in terms of products or slaughter is something that we are looking to the food-safety and public-health agencies to give guidance on.

DR. BROWN: We are closing, now, the public hearing. There may be further discussion on various points that were raised, both by our formal presentations and the public speakers. We will now adjourn for lunch.

DR. FREAS: Was there anyone else in the audience who wanted to address the committee in this open public hearing?

DR. BRACKETT: I just wanted one clarification both from what Linda said as well as what Ermias said. It goes back, and I would like to direct the committee back, to the questions that were asked which is we are really looking at the science available to look at the questions so that we can make some decisions. So that is really what the basis is for infectivity.

DR. FREAS: If there is no one else in the audience at this time wishing to address the commission, then I guess we are going to go for lunch.

DR. BROWN: We will reassemble here at 1 o'clock. It is now 12:20.

[Whereupon, at 12:20 p.m., the proceedings were recessed to be resumed at 1:00 p.m., this same day.

AFTERNOON SESSION

[1:10 p.m.]

Topic 3

Committee Discussion

DR. BROWN: We will have committee discussion. or the members of the committee, I have an option from the DA. We do not need formally to vote on **each** of the ten uestions--actually, five questions and five subquestions--n this particular issue. But they would like a sense of hat the committee is thinking about each of these uestions. It seems to me that two or three of the uestions are extremely easy and they really didn't need to .sk our advice at all.

Such as the first question; are there scientific lata or other scientific evidence for transmission of TSE irom an infected elk or deer to uninfected deer or elk. It .s an interesting transposition, actually, isn't it; elk to leer, deer to deer--okay; elk or deer to uninfected elk or leer and, if so, how strong are these data?

DR. BOLTON: Strong enough to have an epidemic?

DR. BROWN: Strong enough to have an epidemic; exactly. So I don't think we really need to spend much time on that. Of all the things we heard this morning, that is probably the most secure.

DR. BOLTON: Could they give us more questions

like that?

DR. BROWN: Yes; I was going to say, we would love to have more questions on which we had some scientific observations on which to base our responses. The second one is not bad either; are there scientific data or other evidence for transmission of a TSE to people consuming or using products made from deer or elk with chronic wasting disease.

Remember to keep your focus on the things that FDA has some control over; namely, foods and cosmetics. We are not talking, for example, about an elk rancher who might, through contact, develop the disease. We are really talking about products. So the question, again, is are there scientific data that consuming or using products made from deer or elk with CWD are transmissible to humans.

Anyone who might have a comment on that?

DR. BURKE: Before we left the first one, I wanted to be sure that I understood. It appears, for chronic wasting disease, there is more evidence for horizontal transfer than there is in BSE. In BSE, there is relatively little evidence for sustained--

DR. BROWN: That is absolutely correct.

DR. BURKE: Just to make sure. So that the reason for the question here is largely to differentiate between the epidemiologies of these two types of diseases.

DR. BROWN: That is a good point. I guess so. That is very acute. I couldn't see the reason for the question, but I think you have hit on it.

DR. BURKE: I will try to interpret the next one, t00.

DR. BRACKETT: Actually,' the reason we wanted to know that is if you have an exposed or an unexposed group of animals and they were moved in with exposed, are they, now, at risk, horizontal transmission.

DR. BROWN: And the answer, based on what we heard today, is certainly yes. Is there any disagreement on that? What about people? I would have said no, not on the basis of the data we have now. But I wouldn't cross off the possibility; right?

DR. PICCARDO: Right; so there should be further investigation. There should be a clause there.

DR. ROOS: I don't think we have any data to support transmission of CWD to humans. The issue, really, is how good is the surveillance system and what are we really looking for and, if it is a very atypical presentation and case, as it might be, would we miss it altogether. So I think it is open-ended.

DR. BROWN: I think that is a good point that I was going to make, also, Beth. I should know this because our laboratory conceivably has done it, but I am not aware

of it or I can't remember. Has CWD been put into any primate?

DR. WILLIAMS: It has been put into squirrel monkeys and it was positive in one case.

DR. BROWN: out of--

DR. WILLIAMS: I don't even know how many--Dick Marsh did the work and I don't know how many squirrel monkeys he inoculated.

DR. BROWN: It was intracerebral inoculation?

DR. WILLIAMS: Intracerebral inoculation; yes.

DR. BROWN: It looked rather like TSE?

DR. WILLIAMS: Yes; it was a spongiform encephalopathy.

DR. BROW-N: Because there is no reason--in spite of what you heard this morning, or you might have taken away from this morning, a priori, there is no reason to equate a syndrome due to CWD in a primate with the syndrome of variant CJD. It might look like blue-bottle fever. We have no idea. But it is not likely and, from what you say, it is very unlikely that it would turn up as a very unusual unrecognizable syndrome in humans.

so if it looks like a TSE--and I won't go through the rest of it.

DR. ROOS: I wanted to note that the pathology is very different. I wondered whether there was data about the

subhuman primate transmission and its pathology.

DR. BROWN: That is a good point, also, about the primate neuropathology.

DR. WILLIAMS: Unfortunately, that was not well examined and the slides are gone. I have not been able to retrieve those slides. I, personally, haven't looked at them so I can't comment on how the spongiform encephalopathy in that squirrel monkey might compare with other intracerebral inoculations of other TSEs. I can't comment on that. I know it was a spongiform encephalopathy but that is not based on my personal examination and the slides appear, and the blocks appear, to be gone.

DR. BROWN: It is particularly interesting because mule deer have the nicest daisy plaques of any species outside humans.

DR. WILLIAMS: Actually, white tails have it even better. But that is right.

DR. ASHER: The neuropathology of TSEs experimentally transmitted have frequently not closely resembled those from the original host. That is true of kuru and it is even true of new-variant CJD and BSE.

DR. BROWN: It may be a question of degree. Let's just take kuru. The plaques don't transmit but the spongiform change certainly does.

DR. ASHER: Right, but the pathology is very

strikingly cerebellar in humans--

DR. BROWN: Yes; the topography is different but no neuropathologist would miss the diagnosis on that account.

DR. ASHER: But one distribution was not predictive--

DR. BROWN: Yes; you can't predict an identical neuropathology. But it is recognizable.

DR. PICCARDO: As long as it is with spongiform changes because when you move into plaques, then you have a big problem.

DR. BROWN: Yes; unless they are immunopositive.

DR. PICCARDO: Yes, of course. But what I am saying is that the experience in the transmission experiences show that the spongiform changes, although the topography might be different, are easy to transmit but the plaques are very hard to transmit.

DR. BROWN: Or they don't. They are simply not a part of the species reaction. Look at BSE in cattle. They don't have daisy plaques.

DR. PICCARDO: Right.

DR. BROWN: Not a plaque in a cow. But it is the pathogenic marker of the neuropathology in humans. so you can't predict.

DR. PICCARDO: I guess my point has to be

broadened not only to the neuropathology but also to the neurologists. There are prominent neurologists here. In order to look for these weird cases, other neurologies, the Academy of Neurology, or whatever, doing an active surveillance, looking for unusual cases of CJD, et cetera.

DR. BROWN: I think Pierluigi probably, and maybe other people--yes; you are certainly accumulating, increasing numbers of cases of CJD both typical and atypical such that there is an increasingly good chance that these atypical cases will be brought to your attention. I mean, you are actively searching them out and you are becoming known as the place to which such brains would be sent, not the only place, necessarily, but a major place.

So I think, Beth, it would be a very useful thing now to initiate an experiment of CWD in primates fed to squirrel monkeys and really look that in not necessarily a big, systematic way, but if you had three or four squirrel monkeys infected with a strain from, for example, an elk and three or four with a strain from a deer, you could sample. You could even take a brain biopsy. You could do all kinds of things now instead of ten years ago when there was much less interest.

DR. WILLIAMS: There are lots of projects to do. Funding, and all these kinds of things, obviously, come into play but I agree. It would be very interesting.

DR. ROOS I don't think that the CJD surveillance program is well advertised in the general neurology community. Maybe I am mistaken about that, but in journals and at meetings, at least up until this point. Ermias, maybe you have some idea about how many cases do you think you are missing in your registry?. What percent of general neurologists know about your registry?

DR. BELAY: Which registry are you talking about? We have several mechanisms for CJD surveillance. The one you are referring to is probably the national center that Dr. Gambetti is the head of. Dr. Gambetti will probably speak for himself that just recently have gave a talk in the American Association of Neurology.

I will let Dr. Gambetti speak for that. He went to a major neurology association meeting trying to advertise the system and encourage them to utilize this national center for diagnostic and surveillance purposes.

Dr. Gambetti?

DR. GAMBETTI: I agree 100 percent with the statement that our national surveillance center, that the National Prion Pathology Surveillance Center, is not really seeing a representative number of cases. So I agree with the statement that it is not really fulfilling his job. Why we are not seeing in a year a sufficient number of cases.

I give you some numbers. In the Year 2000, we

nave examined or received already examined--for example, from Dr. Prusiner and DRM Laboratories, a total of 109 cases. Now, these represent the prevalence of CDJ in the United States as the same as in Western Europe, just 35 to 40 percent of the cases suspected.

Those cases are very thoroughly examined. However, as I said, they represent only 35 to 40 percent of the cases. We try very hard to increase this number. It looks like there are at least three problems and all, of course, are related to the fact that our resources are, at the time, limited.

One of the problems is exactly as Dr. Roos indicated. We have been unable, and maybe Dr. Belay can explain better--

DR. BROWN: I think we don't need or want a long explanation. It is a little off focus.

DR. GAMBETTI: But that was the question.

DR. BROWN: No, no; the question was would--I don't mean to be rude, Pierluigi, but we are off the focus. The question was is there an adequate surveillance, a systematic adequate surveillance. The answer is no.

DR. GAMBETTI: The answer is no.

DR. BROWN: It is not your fault.

DR. GAMBETTI: But you have to give me a chance to explain why. Yes; you have, because otherwise we are left

with the idea that the surveillance is doing nothing and it is not true.

The reason why we cannot see many more cases is one, we have been unable, for a question of regulation, to contact the neurologists at the national level. We have been able to contact several times neuropathologists and pathologists. I am planning to present, to give a presentation, at the American Academy of Neurology, the plenary session. So we try to inform all the neurologists.

Second, and perhaps the major reason, autopsies. The autopsy rate in the United States is about 20 to 30 percent, no exception for CJD. So autopsies are not performed. If we had more resources, we would reimburse the institution for performing autopsies. I am sure that the autopsy rate will go up.

Third, we have to have a system like the European surveillance center in which the family of the patient and the caring physicians are contacted when the patient is alive and right away a rapport, a relationship is established, and the patient is followed and, if he expires, an autopsy is performed regularly.

So these are the thing I am trying very hard to pursue. Unfortunately, so far, the resources have not been sufficient to do all this.

DR. BROWN: Thank you.

Is there more discussion on this question?

DR. NELSON: The other issue is do we know the extent of exposure of the human population.

DR. BROWN: To TSE?

DR. NELSON: To potentially infected animals, either, because we have heard that animals from a herd that may have a case are tested and enter the food chain. There may be other exposures.

DR. BROWN: Is the distribution of products, let's say meat, from elk and deer widely distributed throughout the country or does it stay more or less closer to home in the regions where the farms are located? I am sure somebody from the industry who is here can answer that question.

DR. ZEBARTH: The meat primarily would be consumed in the local area. It is more of a cottage industry so it would be consumed in the local area. The greatest exposure would be free-ranging animals. As far as the farmed industry, they would be primarily locals.

DR. BROWN: Would you refresh my mind and, perhaps, that of the committee on what products are in commerce from deer and elk other than meat and velvet antlers?

DR. ZEBARTH: Those would be the products.

DR. BROWN: Those two.

DR. ZEBARTH: The meat and the velvet antler.

DR. BROWN: The meat primarily as--

DR. ZEBARTH: Primarily as steaks to local areas and upper-scale restaurants. It is not really a ground meat industry such as in bison.

DR. BOLTON: Just to add to that, the restaurant--and excellent restaurant, I must admit--that we ate at last night, venison was on the menu as was calf brains.'

DR. ZEBARTH: The venison you ate almost certainly was New Zealand red deer, Cervina. There is a lot of elk, venison, consumed in restaurants in the United States. 99 percent of that is New Zealand red deer, Cervina. The domestic elk industry has very, very low, almost virtually no penetration into that market.

DR. NELSON: What about deer? The white-tail deer are all over the United States but is it just the localized, Western deer only?

DR. ZEBARTH: I would let some of the wildlife people speak to that. Primarily, white-tail venison consumption is hunter consumption. I don't think there is a large commercial white tail venison market. I am not the one to speak to that.

DR. NELSON: But it is throughout the United States, pretty much.

DR. WILLIAMS: White tails are found throughout the United States, but the disease is located just in the

corners that you saw.

DR. BROWN: What we are hearing is that most venison consumed in this country doesn't come from this country.

DR. BELAY: Dr. Brown, I think the question is not this exposure to venison but exposure to potentially chronic-wasting-disease-infected venison. I think 'what we can say is if we compare this situation with what happened in the United Kingdom, for example, where hundreds of thousands of infected, BSE-infected, cattle may have actually been consumed by the population in the U.K., the possibility that a huge chunk of the population in the United States would be exposed to chronic-wasting-disease-infected elk would be very, very minimal, particularly just because it is limited, geographically limited, to a specific area.

DR. BROWN: Probably more importantly, it is limited by the people who eat venison which is not the majority of the population.

DR. BELAY: If we look at Allan Williams' data from yesterday, the donor survey, the blood donor survey, he indicated to us that 62 percent of the donors actually reported venison consumption. So it is not uncommon.

DR. BROWN: That seems high. I stand corrected if that is true. Two-thirds of the American public eat

venison?

DR. BOLTON: They have at some point.

DR. NELSON: Ever.

DR. BROWN: Oh; ever. Okay.

DR. BELAY: Now, venison consumption obtained from the wild was about 40 percent from Allan Williams' data.

DR. BROWN: What proportion of the population hunts?

DR. BELAY: Again, from Allan Williams' data, it was a little over 13 percent.

DR. WILLIAMS: I might add, that data matches reasonably well with the information from game and fish agencies at around 10, 15 percent depending on the area.

DR. BELAY: Right. In fact, we used Allan Williams' data to our three patients, unusually young CJD patients, to see if the occurrence of the three unusually young CJD patients could have actually happened by chance alone, given the 40 percent or so exposure of the population to venison potentially coming from the wild.

Our statistical analysis showed that the occurrence of three cases could actually occur by chance alone, given that level of exposure in the population.

DR. BROWN: Right; so we are already working on question 3; are the scientific data or other evidence for transmission of the TSE to people consuming or using

products made from deer or elk exposed to chronic wasting disease, or at least we are leading in this direction.

I don't think we have any information on that at all.

DR. BOLTON: I think, as with question 2, there is no evidence for transmission but that does not mean that transmission could not occur.

DR. BROWN: Right. There are several subquestions here, the potential for transmission to humans depending on the kinds of exposure. These are hopeless questions even to address. The offspring of CWD-infected deer? I mean, we haven't heard a shred of evidence all day long bearing on that question. We weren't given anything to consider and I don't think we can consider a response.

DR. CLIVER: It has got to be moot.

DR. BROWN: Similarly, pen mates of--I will read these subset questions. If anybody on the committee thinks they have any basis to answer any of them, please speak up. Pen mate of CWD-exposed deer or elk, animals in close proximity but not in the same pen with CWD-infected deer or elk, animals exposed to equipment used in transportation of slaughtering of CWD-infected deer or elk, elk and animals on the same ranch but with no direct contact with infected deer or elk. That is the set of questions.

DR. BOLTON: I would propose that they are all the

same and that they are all unknown.

DR. BROWN: Any disagreement with that?

DR. KATZ: I have no vote so what I say can be taken any way you want.

DR. BROWN: Very, very seriously.

DR. KATZ: But I think the answer to 3, are there scientific data, the answer is no. Before we get onto a slippery slope about unknown and absence of proof and all that--I mean, I think that the answer to question 3 is no and should be recorded as such. There are no data, recognizing it doesn't mean there never will be data.

DR. BROWN: That's right. The question is worded in such a way so that no is the only possible answer.

Question 4, are there scientific data assessing the potential or actual infectivity of different tissues or other animal parts from CWD-infected deer or elk. I was looking ahead when I was asking about peripheral tissue infectivity of our speakers and, as you heard, there is none apart from the tonsil and third eyelid and brain. So, if there is no disagreement with that, we can dispense with that question, too.

DR. WILLIAMS: I would just say that there is some evidence from PrP examinations using immunohistochemistry for some of the nerves and for islet cells in the pancreas and for lymphoid tissues.

DR. BROWN: Right. It seems to me that what you said was that the PrP distribution was sort of intermediate between the very restricted distribution that has been seen in cattle and the much more widespread distribution that has been seen in scrapie, and CJD, too, for that matter.

DR. WILLIAMS: I would j'ust say that a number of these other tissues really haven't been examined adequately.

DR. BROWN: Right. But there is probable cause to suppose that the distribution will not be markedly different from scrapie on the one hand and BSE on the other. It is somewhere in between. So there will be peripheral tissue infectivity here and there.

DR. BOLTON: Again, the way this question is worded, the answer has to be yes. Scientific data or other scientific information assessing the potential or actual infectivity. So PrP distribution clearly indicates that there are some differences.

DR. BURKE: Here we take the term infectivity to mean detectable by any diagnostic technique.

DR. BROWN: PrP being a surrogate marker and plausible. It doesn't distinguish.

DR. BURKE: But it doesn't say human infectivity and it doesn't say infectivity for other animals. It says infectivity.

DR. BROWN: The operative word was spotted by

Dave, "potential." It probably is. I am sure there is.

DR. BURKE: We might answer this question if it said infectivity for other animals or infectivity for humans.

DR. BOLTON: If there is infectivity for other animals, then there is at least potential infectivity for humans since we don't know what the cross-species transmission efficiency is from elk or mule deer into humans. So the word "potential" there, I think, is the catchall.

DR. BROWN: I think the FDA simply wanted us to record the fact that there is likely to be infectivity in various organs, tissues and cells of disease-affected elk and deer. We have no basis, really, to predict how that distribution is going to shake out, but it wouldn't be shocking if spleens and a heart and sinus and maybe something else in a bioassay that was sensitive turned out to have infectivity. It would be very surprising if they didn't.

So the potential is there. That is about all we can say.

DR. NELSON: It seems like, from what we were told today, that the highest human tissue exposure may be to velvet antlers. However, we were told that they were not coming from infected animals but whether or not, in other

producers, or- -they could be.

DR. BROWN: And it is all going to South Korea anyway; right?

DR. NELSON: I can assure you it is in Thailand as well.

DR. BROWN: In any experiment that was undertaken, pathogenetically, that would certainly be a major tissue to assay.

DR. WILLIAMS: Those tissues are banked right now from several different pathogenesis studies and awaiting work, when and if.

DR. BROWN: Any other discussion on this aspect?

Question 5 was, if there is a potential for transmission of a TSE from infected or exposed animals or animal parts to human, what is the likelihood of transmission. If there is no objection, we will go on to topic 4.

DR. DETWILER: Should we vote on no. 2?

DR. BROWN: Would you like to? We can vote on anything that you--if the committee would like to register votes on any of those questions it is perfectly okay.

DR. DETWILER: I think the vote would go on record; right? I think that is important for the industry, for the FDA. I don't know how the FDA feels. I shouldn't speak for them.

'DR. BROWN: Why don't we very quickly, then, again, for the record, vote on 1, 2 and 3. We can run through these very quickly. 1 was the transmission animal to animal, elk to elk, deer to deer. Can I have just a show of hands? The hands are up for yes.

[Show of hands.]

DR. FREAS: Thirteen hands are raised.

DR. BROWN: Anybody on the committee believe that there is no scientific data to support transmission of CWD from animal to animal.

[One hand raised.]

DR. BROWN: One negative.

The second question, are there scientific data or other scientific evidence for transmission of a TSE to people consuming or using products made from deer or elk with chronic wasting disease. Show of hands on this one as well? The hands, again, will be for yes, there is such evidence.

[Show of hands.]

DR. BROWN: Since there are none, we will just make it concrete, a show of hands for no.

[No response.]

DR. FREAS: Fourteen no votes.

DR. BROWN: 3 just extends that. Do you want to vote on 3? Do you think 3 is important, Linda? We have no

idea about exposed to.

DR. DETWILER: I throw that back to FDA.

DR. BROWN: In this case, instead of saying consuming or using products, we are saying consuming and using products made from deer or elk exposed to, not even necessarily infected, just exposed to the disease. Show of hands for yes, there is such scientific evidence. .

[No response.]

DR. BROWN: Show of hands for no, there does not exist such scientific evidence.

[Show of hands. 1

DR. FREAS: Fourteen.

DR. BROWN: I guess we can continue on. Why not? This is a piece of cake.

DR. PRUSINER: Wait a minute, Paul. I have a question. Will you explain to us the difference between scientific data and other scientific evidence?

DR. BROWN: Well, in some cases, it is other scientific information.

DR. BOLTON: That's right. That is in 4.

DR. BROWN: That is in 4. No; I can't--

DR. BRACKETT: Data should be numerical.

DR. NELSON: We are talking about geologic or astronomical data, I guess.

DR. BROWN: Yes ; that is not bad. Data requires a

number; right?

DR. CLIVER: A parameter; yes.

DR. BRACKETT: We were interested in any kind of scientific inference, even, that would say, one way or the other. For instance, this happened in BSE. What is the likelihood it might happen in chronic wasting disease. It doesn't have to be, necessarily, although we are interested mostly in, measurable data.

DR. CLIVER: All he is saying is the question wasn't redundant. We answered both aspects of it, I think.

DR. ROOS: So 3a, Paul, is the potential.

DR. BROWN: It is potential depending on types of exposure for which we have no information at all. If so, how strong are these data or evidence? We have no data or evidence.

DR. BOLTON: The question asks is the potential different depending on the type of exposure. We don't know anything about any of the exposures. I don't know how you would tell whether they were different.

DR. BROWN: Question 4, scientific data or other scientific information assessing the potential or actual infectivity of different tissues and other animal parts from CWD-infected deer or elk.

DR. McCURDY: Are we talking about infectivity globally or are we talking about infectivity for the same

species or other species or what are we talking about?

DR. BROWN: I think my reading of that would be simply the demonstration of infectivity in any species. I think what they are trying to get at is not whether or not something is infective for monkeys but not mice or for elk but not cows. I think any infectivity measurement, any detectable infectivity by any method implies there is infectivity. It doesn't constrain us to talk about species barrier or anything else.

What we have heard about infectivity essentially is zero outside the brain. There are no infectivity measurements, as I understand what you said, outside the central nervous system in this disease in any species under any circumstances.

DR. WILLIAMS: If you are just talking about infectivity, actual transmission, that is correct.

DR. BROWN: Just infectivity; yes. On the other hand, there is this wonderful word "potential," or "actual" infectivity. I think probably Dave is right, the use of that word "potential" is probably meant to grab at PrP which would be a reasonable correlate.

Under those circumstances, we have heard this is certainly lots of PrP depending on the species and circumstances in the third eyelid and tonsil of infected animals. So there is definitely evidence of potential

nfectivity apart from the central nervous system but no vidence of real infectivity apart from the central nervous ystem. Curious phrase.

So I read question 4 as being a yes answer under hose circumstances. But the committee should now vote on hat, or we have decided we will. So, on this one, why on't we just go around because it is conceivable that there ay be differences of opinion on that. Ray?

DR. ROOS: Yes.

DR. DETWILER: Yes.

DR. BURKE: I vote yes and would like to emphasize hat my concern that, since velvet antlers is so widely used y so many people, that would be one that should have pecial attention paid to it.

DR. McCURDY: Yes.

DR. PICCARDO: Yes.

DR. GAYLOR: Abstain.

DR. NELSON: Yes.

DR. BOLTON: Yes.

DR. BROWN: Yes.

DR. BELAY: Yes.

DR. CLIVER: Yes.

DR. LURIE: Yes.

DR. WILLIAMS: Yes.

DR. PRUSINER: Yes.

DR. FREAS: One person abstained. Thirteen people voted yes with one abstention.

DR. BROWN: Does the committee agree that, on question 5, we can simply say absolutely no data on which to base an opinion?

DR. LURIE: Can I just make one very brief comment which is the fact that committee voted unanimously no to both 2 and 3 should not be taken, I don't think, as a message that there is inherently no need for government action in this area.

DR. BROWN: I agree. The way the question is worded, a light reader might say, "Ah; no problem." And they may be right, there is no problem but we haven't proved there isn't.

DR. LURIE: Right. There is still place for action.

DR. DAVEY: Paul, do you think before we move off this topic, would the committee like to consider something about indemnification? Is that our role? It might have an implication, as we have heard, both on reporting, which is certainly--there is a negative incentive to report. And also, on the more uniform depopulation of infected herds. So indemnification might be something we might want to make a comment about.

DR. BROWN: I think it is important that you made

the comment, but I don't think, for the purposes for this committee that it needs more discussion than that. The point was made in a presentation. You have made it. I agree, personally. Dr. Clive has another comment.

DR. CLIVER: I was just going to say we are advisory to FDA. If indemnity happens, it is going to be an APHIS function, I think. APHIS didn't ask.

DR. KATZ: Having sat on these committees before, I, personally, would advise the FDA to communicate that sentiment to other parts of the regulatory bureaucracy.

DR. LURIE: It certainly isn't mine. I can't really see, firstly, where it is our business. But, if it is, getting into the job of indemnifying a company that is making a product with no provable scientific use for export to people in South Korea, I can't see where it is at all our business to recommend any kind of indemnification for a company like that.

DR. DETWILER: There has been precedence out of this committee on recommendations out of the FDA that was recommended a couple of years ago for APHIS, for USDA to expand the ban to Europe. That carried a lot of weight for us. So it is appropriate, at least the comments here, to take back to USDA or FDA to convey to us. It does carry some weight.

DR. ROOS: I guess the real message is our concern

about selling some of the herd on the open market despite an infection that might have occurred. The best way to handle that situation, I think, has to be considered. Indemnification might be one, but there may be other solutions to this. At least, I think the answers to the questions here raise concern about the present situation.

DR. BROWN: I would finish the issue by repeating that, in my view, the most vulnerable point of all is the escape of an infected carcass into a rendering plant. That depends not just on a regulation but on--not a regulation but on good care in insuring that that kind of thing doesn't happen. Of course, that won't ever be a 100 percent restriction. It could happen.

With the elimination of the disease, one wouldn't have to worry about it. But, as we have heard, to eliminate the disease in wildlife is virtually--it is almost unthinkable in terms of its difficulty. It could probably be eliminated, as you say, Beth, in captive animals. That would be a goal worth pursuing, but I think the danger, the prime danger, of CWD is in a cross-contamination species-jumping leap to an animal species, a livestock species, rather than a human species.

That has nothing to do with the FDA, but it is just a personal comment.

DR. BURKE: Not addressing the mechanism for doing

that, but the difference between this and the scrapie is this is a new disease. It is relatively low prevalence. It is relatively well-confined and I am persuaded by the argument that you can make a good case for trying hard to eradicate it from captive populations now in the United States to try to avoid that kind of catastrophic incident in the future.

It wouldn't address the wild herds but at least it would address one major potential threat. I think that makes sense to me. That needs to be carefully thought about and I am persuaded that that is a reasonable strategy. I am not sure it is the right one, but it is a reasonable strategy.

DR. BROWN: All one would need to get a lot of money, more money than you ever imagined possible, would be to mix up the diagnosis on two brains and report out an elk in place of a cow and find daisy plaques in a cow in Montana, say That would be very bad news.

DR. BELAY: I agree that this situation is different from the scrapie situation. It goes back to what Peter said earlier and that is that government, actually, is required in this area. One of the government actions, potentially, would be a surveillance for chronic wasting disease and the elimination program that we heard about.

Effective surveillance, I believe, would require

some form of indemnity because, other than that, there would not be any incentive for the farmed-elk owners to report chronic wasting disease if the government is going to jump and just depopulate the whole herd without indemnity.

DR. BROWN: So we have got two or three people thinking that, in the total picture, indemnity is going to be a serious consideration of the goal is to eliminate risk, potential risk, to any other species.

We will now move on to issue 4, the final issue of this meeting. This is concern a discussion as to whether a history of possible exposure to various animal TSE agents---unspecified, various; it is a mixed bag--whether they should be considered by the FDA in determining the suitability of blood donors.

The first presentation will be from Dr. David Asher from CBER in the FDA.

Discussion as to whether a history of possible exposure to various animal TSE agents should be considered by the FDA in determining suitability of blood donors

Introduction, Charge and Questions

DR. ASHER: Thanks, Paul. I can't resist putting in my own two cents on the last issue. Actually, the scenario that the chairman outlined is a concern of the FDA which has responsibility for the regulation of animal feeds. There is a feed ban that prohibits the feeding of most

ruminant proteins to other ruminants.

[Slide. 1

We are going to address now the suitability of blood, plasma and tissue donors exposed to various TSE agents of animals. The accidental infection of blood, plasma and tissue donors with animal TSE agents would be of special concern because, theoretically, at least, such infections might, then, be passed to recipients with greater efficiency than the initial infection due to loss of the species barrier, in jargon, a dead-end host would become an amplifying host.

In 1996, new-variant CJD was first described in the medical literature and was clearly linked to exposure to the BSE agent. That link increased the concern of regulators about the possibility that the BSE agent might accidentally make its way into products containing or made with ruminant components.

Our concern regarding BSE and vaccines were discussed by a joint meeting of this committee and the vaccine and related biological products committee in July of last year and the theoretical risks associated with blood products and tissues were discussed yesterday and earlier today. Other products will be considered briefly this afternoon.

The BSE/variant-CJD connection also increased our

concern about human exposures to other animal TSE agents that will be considered in this session. Three animal TSE agents have been recognized in the USA; chronic wasting disease, which has just been discussed and will be considered again, briefly, in a short time; transmissible mink encephalopathy, which has not been seen in this country since 1985. Opportunities for human exposure to mink tissues appear to be limited and I won't mention mink encephalopathy any further; and, finally, scrapie of sheep and goats.

[Slide. 1

Implications of the scrapie agent for biologics and devices were considered nineteen months ago when the committee reviewed safe sourcing of materials derived from sheep and goats for the manufacture of FDA-regulated injectable and implantable products.

Human exposures to scrapie of sheep and goats historically have not been of concern. There is a long and uneventful history of human exposures extending to infected animals and their products extending back for probably more than two-hundred years. There is no convincing anecdotal or epidemiological evidence of any transmission to humans.

CJD prevalences are similar in countries with scrapie and those without scrapie and attempts to transmit scrapie experimentally to chimpanzees have failed.

[Slide.]

However, even for scrapie of sheep and goats, there were some uncertainties. Multiple strains of scrapie agent have different biological properties and there is at least a suspicion that the BSE agent may have originated as a strain of scrapie agent. Attempts to transmit scrapie to chimpanzees were very limited and scrapie was transmitted to several species of monkeys so that there cannot be an absolute species barrier between scrapie of sheep and primates.

The committee advised the FDA to continue to avoid using sheep and goats with scrapie as sources of material to manufacturer FDA-regulated injectable and implantable products. However, no concern was expressed about human exposures to scrapie agent in food. We have had a long experience with that.

[Slide.]

The FDA has received inquiries expressing some concerns about the potential transmissibility to humans of various TSEs of animals. You have heard typical discussions during the previous hour. Except for new-variant CJD, of course, no human TSE has been attributed to infection with an animal TSE agent and BSE agent, the presumable cause of new-variant CJD, has never been found in U.S. cattle.

[Slide.]

As part of its commitment to insure the safest possible supply of blood, blood components, plasma derivatives and tissue products, the FDA now asks this committee to consider whether exposure to any of the TSE agents known to infect animals in the USA or to the BSE agent if accidentally introduced into the USA in an imported product might pose sufficient risk as to compromise the suitability of blood, plasma or tissue donors.

[Slide.]

The following sources of potential exposure to animal TSE agents within the USA will be discussed. First, products derived from sheep and goats, with goats from BSE countries including imported sheep and their progeny with an undifferentiated TSE--that is, the so-called Vermont sheep which will be described by Linda Detwiler.

Products derived from deer and elk with chronic wasting disease will be further discussed by Lynn Creekmore who has already had brief comments. And, finally, Robert Moore of our Center for Food Safety and Applied Nutrition will summarize ruminant-derived materials as components in dietary supplements.

Let me now read the charge and then the questions.

[Slide.]

Please consider whether the agent of any animal TSE that occurs in the USA is likely to infect humans

exposed to animals or to their products and whether the probability that blood, plasma or tissue donors have been infected is sufficient to warrant recommending their deferral.

Please consider whether the BSE agent is likely to be accidentally imported into the USA in products or components of products and whether, without evidence that such importation has actually occurred, exposure of donors to any products poses sufficient risk to warrant recommending deferral.

[Slide.]

Should the FDA be sufficiently concerned about the suitability of any blood, plasma or tissue donors potentially exposed to TSE agents of animals, both agents known to infect animals in the USA and agents that might be accidentally imported to consider recommending deferral. If so, which animal TSE agents present in the USA or accidentally imported, what types of product and what intensity of exposure should be of concern?

Thank you.

[Applause.]

DR. BROWN: Thank you, Dave.

The first presentation, then, will be from Linda Detwiler from the USDA and she will tell us about the flap in Vermont.

Undifferentiated TSE in Flocks of **Sheet** in Vermont

DR. DETWILER: That is probably an understatement.

[Slide.]

I just wanted to at least give a slight overview of BSE in sheep just to bring everybody--I have just three slides here to bring everyone up--I think we have talked enough about scrapie, not only today but in the past, on the committee that people understand at least what is known about scrapie pathogenesis because, in this case, in these sheep in Vermont, the disease actually could be scrapie or BSE.

Just quickly, BSE in sheep, Foster, et al., 1993 and 1996, put BSE orally into sheep. They had this negative and positive line sheep. They are just genetics. The negative line are sheep that they normally don't see the natural scrapie in. The positive line are genetically the type of sheep that they normally do see natural scrapie in.

In the negative line of six animals inoculated with half a gram of brain tissue, one did--one came down with clinical disease and then, in Bruce's strain typing, it was identified to be the same strain as BSE. So BSE-in and BSE-out identified.

In the positive line, there were five animals total. Two came down with clinical disease. However, when strain typed, they came down with a more atypical, or

something that did not look like BSE in the strain typing or ther known strains of scrapie. So they called it atypical n the research paper.

[Slide.]

So far, research of BSE in sheep, distribution of nfectivity, brain, spinal cord and spleen, and that is ctual infectivity by mouse inoculation. In the intestine, ost likely the Peyer's patches associated with the ntestine, it is PrP-res or the abnormal form of the prion rotein.

Yesterday, we heard of the one report of the blood ransfusion, 400 mls from a sheep that was fed BSE in the ncubation stage and a transfusion to another sheep that developed disease. This is ongoing research so there will be new information. So that is BSE in sheep.

Right now, it looks like it will be very similar to scrapie in sheep versus BSE in cattle, in oral sxperiment.

[Slide.]

So where is Europe on the situation with sheep. This is all experimental data. The European Union, in 1998, issued an opinion paper which stated that it was highly likely that there was exposure of their sheep and goat populations to feed contaminated with BSE. So meat and bone meal with BSE agent.

However, in the diseases, clinically, histologically, the tests for PrP to date, and they are working on some new tests, that they don't differentiate between the two diseases, scrapie and BSE. Most differentiate scrapie from the mouse bioassay system, and that can take up to two to three years. That is Bruce's system.

So, right now, what they are having to do is take what they are reported as natural cases of scrapie that might be high risk or suspect for potential for BSE, put those in the mouse bioassay systems and wait this long time to determine what disease it is.

So far, there have been no natural cases of BSE in sheep detected to date. However, the numbers assessed are small, less than 100, that have been completed. But, in regards to their public-health protection in the European Union, they have specified risk material, so the high-risk tissues from sheep and goat tissues of animals going to slaughter waiting for other data to come out.

[Slide.]

Where are we in this whole situation? 1947 was our first case of scrapie. In 1952, we put a control program in place. We then closed the door pretty much, the imports of sheep and goats, other than from a few countries; Australia, New Zealand, that are considered free of scrapie,

and then Canada with a similar program.

We didn't want to introduce any new strains of scrapie into the United States. However, the sheep industry, goat industry, asked us for new genetics and if there was a way to bring those in under a monitoring to introduce some new genetics into the country.

So, in April of 1996, the regulations were changed to allow sheep and goats to come in and be monitored under the Scrapie Certification Program for five years. Under this provision, these two shipments were imported. Originally, we thought they were from Belgium and we later found out they were actually from Belgium and The Netherlands.

They were imported in both August and November in two different groups. There were 65 head, total. The distribution was 52 went to one of the Vermont farms. Eleven went to the other Vermont farm. And then two rams went to a New York farm.

[Slide. 1

They have been monitored since entry. That was part of the requirement to come in. They have been under actual quarantine since October of '98. That was right after the opinion paper came out to give the legality or basis for an actual full quarantine.

They were allowed to sell, from premise, progeny.