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AT

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

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

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P R O C E E D I N G S

Introductory Remarks

DR. FREAS: Welcome to the second day of the ransmissible Spongiform Encephalopathies Advisory Committee Meeting. I would like to state that the conflict of nterest statement that was read into the record yesterday ertains to today's discussions as well and we ask all embers of the audience, if they come to the microphone, ne, please identify themselves and then, two, publicly tate any financial affiliations with any firms that they ay have.

Thank you.

Dr. Brown?

Topic 2

Committee Discussion (Continued)

DR. BROWN: Good morning. If we really get racking, only half the committee is here, we can probably get through several of the votes. We are, in fact, beginning today with the conclusion of yesterday's deliberations on Topic 2 which concerns tissues and cells and cell products.

We held off all of the discussion and the voting until today. I think, actually, quite seriously, we can vote on question 1 because there is no way that we can vote in any other way than yes. But, I will read the question

and you will see why; compared to the risk of transmission of variant CJD by blood transfusion, is there a significant risk of transmission of vCJD from human cells, tissues and cellular and tissue-based products that are transplanted, implanted, infused or transferred?

The answer has to be yes because the cornea is demonstrably infectious. So I suggest we vote on that and get to the important question which is what are the relative risks for different cells and tissues.

Is there discussion before we do this? Ray?

DR. ROOS: Now, this is variant CJD.

DR. BROWN: That's right; this is variant.

DR. ROOS: Do you know that the cornea--

DR. BROWN: No; we don't.

DR. ROOS: Oh.

DR. BROWN: But we know that the cornea alone, among tissues with standard CJD, has been infectious and there is no reason to suppose that, in this one tissue, variant would be less rather than more infectious than standard CJD.

DR. ROOS: I think we probably have--

DR. BROWN: Relative to blood, bear in mind, which is not--

DR. ROOS: I think we have no data, Paul, on natural variant CJD in humans as far as tissue distribution.

Maybe I am wrong.

DR. BROWN: We have PrP data.

DR. ROOS: PrP data.

DR. BROWN: In all the tissues that have been looked at, the amount of protein in variant CJD exceeds that. In fact, there is not any demonstrable in classical.

DR. ROOS: So we know minimum infectivity at the moment.

DR. BROWN: Yes.

DR. ROOS: But, clearly, we don't know the tissue distribution in its natural--you know, of human to human.

DR. BROWN: Right. And we have no information whatsoever on infectivity in blood which we have already decided posed a potential risk. That is why I say I don't think the committee can really justify any other vote but yes. But we will see.

Ray, why don't you start the voting, on this particular question; compared to the risk of transmission of variant CJD by blood transfusion, is there a significant risk of transmission of variant CJD from human cells, tissues and cellular tissue-based products that are transplanted, implanted, infused or transferred.

DR. ROOS: Yes.

DR. DETWILER: Yes.

DR. EWENSTEIN: Yes.

DR. BURKE: Yes.

DR. McCURDY: Yes.

DR. PICCARDO: Yes.

DR. GAYLOR: Yes.

DR. BOLTON: Yes.

DR. BROWN: Yes.

DR. BELAY: Yes.

DR. CLIVER: Yes.

DR. LURIE: Yes.

DR. WILLIAMS: Yes.

DR. PRUSINER: Yes.

DR. FREAS: The vote was a unanimous yes vote.

DR. BROWN: Is Dr. Nelson going to be here?

DR. FREAS: I have not been notified. I am assuming he is on his way.

DR. BROWN: The vote on that is 15 to 0, is it not?

DR. FREAS: That is correct.

DR. BROWN: Now we have a question about which we really have virtually no information whatsoever. We can discuss it a bit, if you would like, and that is what are the relative risks for different cells and tissues. Does anyone want, for the record, at least, make a comment about this?

DR. FREAS: Dr. Brown, may I just correct; the

total was 14. The vote was right. My math was wrong.

DR. BROWN: Is there anything we can say about the relative risks for different cells and tissues? I have just said that probably, based on what we know, the cornea would represent as close to a known relative risk as we have information for. Based on the distribution of infectivity in classical CJD, we can presume that the lymphatic system would be a system of tissues which would compose a comparatively higher risk than, say, muscle or bone.

But the fact is, we have no experimental data on infectivity in variant CJD. So we can't know anything; right?

DR. ROOS: I guess the other comment that is worth making is that when tissues donated for a pool, clearly there is more danger so that a blood donation that might,end up in a large pool for blood products would have more potential problems from a biohazard point of view than a donation of tissue-to-tissue to no pooling. That is true for dura mater as well as blood.

DR..BROWN: In other words, a single tissue, individual-to-individual, is a dead-end track, by and large.

DR. LURIE: Just sort of to echo, in a way, what Ray is saying, aside from cornea which is associated maybe with cases of CJD, the same is true for dura mater. In fact, obviously, there are forty or more of those. So that

would be--I think cornea and dura mater are in a separate category from everything else.

DR. BROWN: That's right. I had forgotten. Dura mater is--is that correct, FDA people--considered to be a tissue rather than--dura mater comes under the aegis of this question.

DR. SOLOMON: Currently, it is a medical device. But we are planning to make it a tissue and it does come under the discussion.

DR. ROOS: The committee has already stipulated extraordinarily stringent precautions for dura which probably would make, in practice, singling dura out irrelevant. But I agree it should be in there because it is a tissue.

DR. LURIE: I think the broad way of thinking about this, again, is balancing presumed risk against likely impact in terms of reduced supply if there were any restriction of any kind, the sort of matrix we have used for blood donations.

DR. BROWN: This is question 2, is what you are addressing now.

DR. LURIE: I think so.

DR. BROWN: Question 2 addressed the possibility of action by the FDA considering the potential impact on supply. We are not on question 2 yet. I agree, it is a

consideration, but I think we should defer discussion of it.

DR. SOLOMON: Could I ask the projectionist to put up the list of tissues that are under consideration?

DR. BROWN: That is a good idea.

[Slide.]

DR. PRUSINER: I was just going to say that what Ray said really is a double-edged sword because, in some cases, of course, where you have an aliquot of something from one individual and now it is dispersed and diluted and the titer of BSE prions is relatively low, then it goes below the biological level.

So it is not always much worse. Sometimes it is better. But I wanted to say that I just wondered if we could think about this in a slightly different way. I wondered whether, where it is practical--I am sure, in many cases, it is not practical, such as in stem cells and marrow transplants, but where tissues have a long half life and a bank, I wonder if we ought to, somewhere along the line,, be thinking that whatever tests, no matter no crude they are now, in terms of immunodiagnostics, ought to be applied to these tissues.

At least there ought to be some thought to begin to think along that line. I don't know about specific recommendations, but I just wonder if we ought to try and go in a direction where there is a little more knowledge

because, as Paul Brown said, at the moment, we really don't know anything about the tissue distribution of variant CJD.

DR. BROWN: I agree and I think we can, perhaps, get into that when, again, we talk about question 2 because one of the open-ended questions that they ask is are additional data needed, or should we gather additional data that might alter any decision we make.

So this is a list of regulated tissues and cells. My own read, just based on classical CJD and what we know about PrP distribution is really what I said before. I think, probably, eye tissues, cornea, sclera, dura mater, cornea1 lenticules, and, conceivably hematopoietic stem cells would be, from what we know, I think, in the hierarchy of probable ultimate knowledge about the risk would be probably at the top of the list and everything else underneath it.

I don't know if that would be useful to the FDA. I suppose it would be if we make certain votes subsequently. It won't be useful at all if we don't.

DR. McCURDY: You mentioned hematopoietic stem cells. Yesterday, Dr. Confer commented that at least the peripheral blood stem cells are heavily diluted by lymphocytes. We know that you can find variant prions in the tonsils and other lymphoid tissue. Has anybody looked carefully enough in peripheral blood lymphocytes from

variant cases to know?

Also, it is my recollection that one of the FDA people working on this has found PrP, at least in platelets. I don't know about abnormal.

DR. BROWN: There has been a lot of work on the normal protein in platelets which,' in humans, is loaded. But there is no necessary correspondence between the amount of normal and the amount of pathologic. That is one thing.

The second thing is, in one study recently published, the plasma- -unfortunately, it is not cellular component, but the plasma from about twenty-odd patients with CJD--or, perhaps--I'm sorry; perhaps it was platelets. Do you remember this paper? This was a paper about two or three months ago. It was a paper that was focussed--it is from Great Britain.

It was a paper that was focussed on normal protein and in platelets. They also studied about twenty-odd CJD patients--it was almost a throwaway line in the paper--none of whom had any PrP that was proteinase-resistant. So the conclusion was there was no pathologic protein, whereas there was plenty of normal protein.

The other fact is that we do know that bone marrow was positive, presumably in a single BSE cow. It is not much, but it is all we have and it would be plausible to suppose that the origin of cells, in blood, which we have

already decided pose a possible potential threat, would be present at their birth as well as their maturity.

DR. EWENSTEIN: I was just going to make the same point about the lymphoid tissue. I think, as we take a look at the list in the absence of apparently rigorous dissection of all of these tissues that have been available here so far, the only other ones that I would worry about would be some of the fluids.

I don't know, for example, in semen, whether the white cells in that fluid might not have--

DR. BROWN: These have been looked at in other forms of CJD and no infectivity has ever been documented.

DR. EWENSTEIN: In other forms, I know. But when we think about the difference between CJD and variant, I think the lymphocyte distribution is the difference that I am concentrating on here. So I just bring it up because I think the risk here is of **a** different nature as well because we are talking about elective procedures and we are talking about the possible infection of a would-be embryo.

So I think that one would have to put, I think, a question mark on that until we had some real data.

DR. BURKE: The other factor that plays in here that is a bit different than the blood is the requirement for close matching in some of these, particularly the bone marrow. As I understand it, there may be a significant

number of people that would not match if--

DR. BROWN: This is correct, Don. But I do want to stick to question 1. This is really under question 2; that is, all of the benefit aspects will be discussed after we make a vote on question 1. Question 1 really is a scientific question.

DR. BURKE: Fair enough. I will hold it.

DR. BROWN: This is not, actually, a yes/no vote. I don't think, actually, we have to vote on it because this is a kind of a discussion. So we are going to escape a vote.

DR. DETWILER: Just one other scientific thing. You said about bone marrow, but in scrapie, in sheep, on occasion, there had been evidence of infectivity also in bone marrow. I think that is maybe why the FDA had asked Dr. Priola to come and to show the differences in the diseases and that variant CJD, at least with the peripheral, may be closer to scrapie than BSE. But that is just to add that.

DR. BROWN: That is a good point. Scrapie has been one of the diseases that marrow has occasionally been positive in.

Let's go on to question 2, then. Here I think we need not be restricted just to considering the potential impact on supply, although that will be a very important

consideration. Another consideration is a kind of allied consideration of what is practical, how long can you keep a cornea, how long can you keep stem cells.

If we are talking about interviews, if we are talking about testing, the logistics play into this part of the benefit part. So I will just 'open discussion on anything that you have in mind for question 2.

Linda?

DR. DETWILER: I would want to echo Dr. Prusiner's thing about the testing. I think if you look to the animal world and say that right now, around the world, there are thousands of tests being conducted. They are being conducted in a couple of hours.

The logistics of holding carcasses and moving that can be done. So I think you hear, "Well, you know, it is going to take a while." That is being done by the thousands. So I guess I don't buy that that can't be done and the logistics can't be set up. I think if you are worried about variant CJD of two tissues possible, you have a number of methodologies, immunohistochemistry, Western blot, some other techniques.

We have tonsil and brain material that could be potentially--again, it is not going to eliminate everything because of the negatives, what does a negative really mean, but it sure will give you more information than you had. I

think the logistics can be done.

We heard yesterday that it is four to five days. That is definitely doable for these tests that we have now.

DR. ROOS: Just to pursue that, I guess what surprises me a bit is that there is no commercial test available, as I understand it, for humans that can be applied. I wonder whether there isn't some way to' facilitate the development and approval of such a test because I think it would be of benefit.

One other little comment, and it is something that came up, I think, in the past with respect to blood-pooled products that were found to have a donor that had Creutzfeld-Jakob, at least in the old days, and what to do with that blood pool. I wonder about a kind of a two-tier system with respect to some of these donations.

In other words, we are talking about donor deferral that might have a travel history that is unacceptable for the blood transfusion. I wonder, in the case of critical tissue donations in which, for example, the stem cells are in short supply and we may be dealing with a situation that is life-threatening whether particular tissues that are donated for transplantation that might not satisfy the rigorous criteria that we are using as far as inclusion and exclusion could be labeled as such and used with known risk.

It wasn't clear to me whether this was being done at all at present; in other words, there might not be some tissues that are labeled as biohazards potentially.

DR. McCURDY: I think we heard yesterday that the National Marrow Donor Program is doing just that for marrows and cord bloods and things that come in from U.K. and other potentially dangerous geographic areas. So it looks like it is doable and goes through the informed-consent process which ultimately goes to the practicing physician at the bedside but, nevertheless, their policy looked pretty good to me when it was put up on the board.

DR. BROWN: Steve, we will hear from you and then, Sue, would you like to chime in on this.

DR. LEITMAN: In the case of marrow and stem cells, if, at the time that an identical six out of six antigen match is identified and what is called IDM, infectious disease markers, are measured, at that point, if a marker is positive, short of HIV, if it is hepatitis C, hepatitis B, various other surrogate markers, anti-core, that information is conveyed to the transplanting physician who conveys it to their patient and it is discussed, the relative risk/benefit of using the only potential product, transplantable product, matched problem, is weighed against the risk of possible infection transmission.

So there is lots of precedence for biohazard

labeling and in-depth discussion of the transplanting physician with the patient of the risk/benefit considerations. So that could be applied here as it is already being applied in different situations.

DR. DeARMOND: Steve DeArmond, UCSF. I want to actually address a question to the committee and maybe Stan could help a lot on this because of his knowledge of it, but in assessing the risk/benefit and trying to decrease the risk, especially for things like hematopoietic stem cells where you are taking them from living patients and you are already testing them in great detail for a variety of markers, wouldn't it be possible to further test the patient for homozygosity at 129 because; first of all, all of the new variants occur right now in methionine-methionine.

We may see a methionine-valine some time in the future, but that doesn't seem to be the case. 90 percent of CJD, whether it is sporadic or acquired by infection, occurs in people who are homozygous. It seems if that piece of information were known from a donor that you would at least increase the population, or retrieve a population, that could be a donor. You would increase it by 50 percent because about 50 percent would be methionine-valine.

Does that make any sense or is that too impractical? These are processes that are also very expensive.

DR. BROWN: I think it probably makes as much sense as, say, a test for PrP.

DR. DeARMOND: We don't know sensitivity of that test yet whether you can miss PrP in a sample and it would still be effective. That still is a piece of data that is missing.

DR. BROWN: That is true enough. On the other hand--well, we can discuss that in a minute. 129 might be an interesting and possible test to do. The turnaround on that test is pretty quick, but it may not be less than a day.

DR. PRUSINER: I agree with everything that is said. A way to think about this might be, depending on how fast you need the information back, if the PrP test is positive, you don't need to do the DNA sequencing; right? The sample is out the door. It is in the trash. It is incinerated.

If it is negative, then you might want to go to DNA sequencing. This is just an issue of time. In fact, you don't even really need to do DNA sequencing. You could set up a test just to look at 129 and you could get that information very quickly.

DR. NELSON: would you test the donor or the recipient or both?

DR. PRUSINER: No, no. You want to test the donor

in this case.

DR. BOLTON: But, in fact, in the absence of any indication that there would be variant CJD in the individual donating, you could be rejecting 40 percent of the donors for no other reason than their genotype. That makes little sense to me with a disease that is extremely low prevalence.

DR. DeARMOND: But, David, I think the problem here is you are already considering rejecting all of those people from Europe to begin with. What this test would give you is 50 percent of them back with pretty good confidence that they won't have disease.

So, as an alternative to complete rejection of all of those Europeans as donors, for instance, for hematopoietic stem cells.

DR. BOLTON: For those who would be considered for deferral based on their past travel history only.

DR. DeARMOND: Or even travel history; yes.

DR. BOLTON: To me, the thing that is most important is some sort of reasonably definitive test for the presence of prions. It is either PrP or some other test. In the absence of that, I think, especially in cases where the recipient is in dire need of this material, the best thing to do, in my opinion, is to have physician discuss it with the patient and let them, together, weigh the relative risk of an unknown but probably very low risk of danger due

to transplantation infection versus the benefit of receiving the donation.

DR. DeARMOND: I could say, though, as a physician sitting across from the patient, "Here we have some stem cells for you, or marrow, and the person who is donating them who matches with you is a person from Europe who is heterozygous for prion protein. Not only do we not find any PrP in the tissue, but this person has a highly low probability of having the disease and I think the risk for you would be extremely low."

DR. BOLTON: I would agree with that except what happens when you get to the case where the only match is methionine-methionine homozygous. Then, if we make a recommendation that that be excluded, then they don't have that option-.

DR. BOLTON: That is a possibility, but this is in lieu of a blanket rejection of all stem cells from--I am offering an alterative to blanket rejection.

DR. BOLTON: To blanket rejection. Yes.

DR. PRUSINER: I think that is the point, David. It is not that we are offering a blanket yes or no here. We are offering a procedure. We are suggesting a procedure that, then, makes the patient and the physician more knowledgeable and either more or less comfortable with the decision.

DR. BROWN: It would be in the nature of an exclusion, in the language of the FDA. In other words, Let's suppose that committee says, "Uh-uh; we don't want any corneas from Great Britain for ten years." The exclusion would be if you lived in Great Britain for ten years and you were not met-met.

DR. BOLTON: I guess I would argue that I would not suggest that the exclusion be made at all but that this information be added to the knowledge base so that, as you go down this list of what is the best tissue to transplant, when you get down to that very lowest part of the list, that this is one of the factors that could be considered if no better tissue is available.

DR. BROWN: The other way to look at this entire issue of cells and tissues is to consider donations from deceased people and donations from live people. Any deceased person, in our present state of knowledge and testing, could, if the logistics were worked out, have a test on the brain for PrP. I mean, that is done deed.

If I take the eye, in the medical examiner's case, out so that it not be contaminated, I have direct access to the brain. A simple biopsy needle will give you the best material possible for a positive test and the positive test turnaround is about six hours.

So this is a doable thing. It means a tremendous

machine of logistics and it means money and it means someone is willing to do it. But it is doable on any cadaver. The situation is completely different with a live person and it is a very dramatic split.

DR. DeARMOND: I would like to make a comment on that because we run into that situation relatively frequently with coroners' offices where they are reluctant to do anything in detail. They don't want to contaminate even their offices. A lot of the outside hospitals are that way.

But when I say that you could go in and take a needle biopsy from the brain, just drill a little hole and take a piece of tissue, that, we have found, in cases, is very helpful and, again, we can get a turnaround on that in the order of hours.

DR. BROWN: That is what I am saying. You don't have to take the cranium off to get a piece of brain. You can go through the nose. You can go through the orbit. You can go through any number of places and it has been a very useful technique, for example, in these situations where pathologists flea in panic at the word "CJD."

DR. DeARMOND: Coroners, also.

DR. BROWN: Coroners, also. Morticians, also. All kinds of people. Sometimes, they are more comfortable with the idea of a small needle hole than they are with a

limited autopsy. One wouldn't do a limited autopsy, anyway.

DR. BURKE: Sue told us about the option of discussing the potential infectious disease risks. I don't know how broadly that is done for other types of tissue transplantations in the list that we have there. Is there anybody here who can tell us is that a common procedure for things other than for bone marrow? Is it, for instance, for cartilage and bone and things like that? What about all of the other tissues there? Is this also done where, say, there is a hepatitis B marker, that you can waive that if there is an acceptable--what is seen as an acceptable risk given the desperation?

DR. LEITMAN: Other than hematopoietic stem cells which are so tightly matched, there is probably not another organ, including kidney and organs that have been transplanted for a long time, where you need that kind of matching. For kidney and liver, it is AB-0 only and there may be other choices. That may be logistics, what comes up at a certain time of the day or week.

But, in terms of tissue matching, it is stem cells that that applies to. You also have the luxury, with stem cells, in the unrelated matching program, to identify a donor and then have several days to weeks to discuss that with the patient, what the other options are, what the next-best match is.

I am not sure this helps, but there is an interval for testing. You identify the best match, based on HLA and age and gender and numerous factors that Dr. Confer discussed yesterday.

Then you can go down the list of next-best matches, depending on what country they come from, what the issues are, discuss that with the patient. I will say that, in the setting of a related donor transplant, if you find a sibling that is a genotypical match, it wouldn't matter how long they had spent in any country in the world, that person is so much better in terms of potential for cure and long-term complication-free survival that it wouldn't even--the risk/benefit is so overwhelmingly in the-favor of benefit.

So that is how a transplanter would think of it probably in the unrelated setting, too.

DR. BURKE: So it might be in a separate category from many of the other types of transplantations that we are talking about.

DR. LEITMAN: I think so.

DR. BURKE: So maybe we should discuss that somewhat differently.

DR. LEITMAN: I think I might punt this to the FDA, but I think it is unacceptable to transplant tissue from a cadaver that has any positive marker as opposed to a living related stem-cell donor.

DR. BROWN: We are going the have to watch the time again so we don't get increasingly behind schedule. Quickly, Jean-Philippe?

DR. DESLYS: Very quickly, because I was out at the beginning. Two informations; first, technically, the test which is commercially available works very well on man. It has not been validated for it. For the moment, 'in Europe, it is used for cattle and it can be used for ovine. But it works very well for man.

I am not specializing the commercialization but if I well understood, as there was no market, people didn't try to develop it for man for the moment. But it works for cattle and you can have a reply within a few hours if you use it.

The only important thing is to have brain material. It doesn't work with blood, unfortunately. But it is technically possible.

DR. BROWN: I would like to summarize what I think has happened, Dr. Lurie. In principle, it seems to me that everything in the body relative to blood has to be at least theoretically considered at least as infectious as blood. I think we have to say that as a matter of theory.

It also seems to me that, in respect to tissues and cells and cell products, that the benefit side of the risk/benefit equation is so different, so variable,

depending on the tissue, the cell, the living or dead status of the patient, that I am not sure the FDA really wants to get involved in it.

It is a funny situation where we have something that, logically, speaking might well be considered to be in the same category as blood but other considerations would seem to me to mandate that it not be put in the same consideration as blood.

Dr. Lurie?

DR. LURIE: I agree with that but, in addition to that, the elements we started to talk about were the issues of alternatives, is one. And the second issue is the issue of supply. I think that cornea and dura mater really are in a different category, not only because of the living-dead distinction that I think you helpfully make but for cornea, we heard that at least for the American market there seems to be general adequate cornea for our needs.

I am a little bit worried about restricting it so that they are insufficient for export. I think that is a sort of interesting ethical question whether that should be our concern at all.

But I think that cornea is something for which there is not an alternative but for which there seems to be adequate supply. Dura mater, on the other hand, there seems to be both inadequate alternative and inadequate supply. So

I think that those two certainly are in a different category from everything else where the supply in one equation is very different.

DR. BROWN: The question we are asking is focused on donor deferral. If there is no more discussion, we will take a vote on it. The question is, the committee has previously assessed the risk of transmission of variant CJD by blood and has made recommendations accordingly. Based upon the committee's assessment of the risk of transmission of variant CJD by human cells and tissue and considering the potential impact on supply, should the FDA recommend donor deferral criteria for possible exposure to the BSE agent?

Stan, you are first.

DR. PRUSINER: I say yes.

DR. WILLIAMS: Yes.

DR. LURIE: Yes.

DR. CLIVER: Yes.

DR. BELAY: No.

DR. BROWN: No.

DR. BOLTON: No.

DR. NELSON: No.

DR. GAYLOR: Yes.

DR. PICCARDO: Yes.

DR. McCURDY: No.

DR. BURKE: No.

DR. EWENSTEIN: Yes.

DR. DETWILER: Yes.

DR. ROOS: Yes.

DR. FREAS: To verify the no votes, the no votes were Drs. Burke, McCurdy, Nelson, Bolton, Brown and Belay. That is six no votes, nine yes votes, no abstentions.

DR. BROWN: What deferral criteria should the FDA recommend; exclusion only for certain types of cells and tissues? Let's tackle that one first, those who have voted for some form of deferral. Linda?

DR. DETWILER: Paul, as I understood it, or this is another question here, there is this other possibility of testing, like on the cadavers, or is that--

DR. BROWN: That is not, I think, a part of any yes vote; that is, there are no qualifiers attached to that. You can add, or we can add, that as a deferral criterion.

DR. DETWILER: That is where I would like to go in that realm of adding that as a deferral criterion.

DR. BROWN: Let's add, as small Roman numeral v. here-:

DR. PRUSINER: Big Roman numeral V.

DR. BROWN: Big or little, how do you want to word it, as a recommendation for PrP testing, a recommendation for PrP codon 129 testing?

DR. DETWILER: I will leave that to the human but

definitely PrP in tissue.

DR. BROWN: So as a criterion, we will say, PrP detection test.

DR. LEITMAN: Is this recommendation for all cadavers from which tissue is to be harvested? Any tissue?

DR. DETWILER: That could be discussed. I definitely think for, like, cornea and the dura mater, these very high-risk situations.

DR. LEITMAN: For brain tissue that makes sense.

DR. DETWILER: Or eye tissue.

DR. LEITMAN: That's brain.

DR. BROWN: I think it would have to be brain tissue. I think you might get some false security if you got a negative on any other tissue that we know about. So it would be PrP detection test on brain tissue.

DR. LEITMAN: So my question, if you are harvesting and it is not a recent death and it is not part of the brain, if it is recent death and you are harvesting kidneys or--

DR. BROWN: My understanding is that then you would get a brain biopsy before you administer the kidney. Is that right? Do we all understand that?

DR. DETWILER: Correct.

DR. CLIVER: Would this apply only to people who would be deferred under the criteria we have established for

blood, though? We are not going to say universal brain testing for every donor, say, in the United States.

DR. BROWN: I think the exclusions are totally up for grabs. They are not dependent on what has been already recommended for blood.

DR. CLIVER: But, once again, people who have never set foot outside the United States would not come under this at all, I should hope.

DR. BROWN: That is the way I read it. We are talking about deferral.

DR. CLIVER: Okay; that is what I wanted to verify.

DR. PICCARDO: Paul, regarding PrP testing, Linda mentioned two things, which is immunohistochemistry and Western blot. My question to the FDA people is if the Western blot has been approved as a diagnostic test. I think it has not.

DR. BROWN: I think the answer is no on both counts. There is no validated test for PrP in this country.

DR. PICCARDO: Anyhow, I agree with what has been said. I think it is a valid way to go.

DR. BROWN: Since we are talking cadavers, could we also add that it should be a Western blot rather than--or should it be an either/or? I think most people consider the Western blot, a quick tissue extraction and Western blot to

be the most sensitive detection of PrP.

I would think, since we have got a dead body, that we ought to get the optimal test.

DR. DeARMOND: I don't think you know that. We don't know whether if a two-site immunoreactive--we are not sure that a two-site IRMA or some other type of biochemical test isn't more sensitive and is as specific. That hasn't been determined. So I would leave it open that PrP testing by Western or any other technique that will specifically identify it. I don't think you want to box yourself into Western.

DR. BROWN: That is probably a good idea. I don't see, at the moment, any way that you can persuade a critic that any immunohistochemical test is not picking up normal PrP. I don't buy into that but a lot of people do.

DR. DeARMOND: I don't either because I do the immunohistochemical and we can see the smallest amount in one brain region. But, in the practicality, you can't do that for a rapid test because that requires serially sectioning the brain.

DR. McCURDY: You might get around it by just recommending a validated test and let FDA decide how it should be validated.

DR. BROWN: That is a good idea. Let's word it, "a validated PrP detection test on brain tissue."

DR. LEITMAN: This is still very fuzzy. The commerce, the commercial traffic, in organs from cadavers from overseas must be infinitesimally small unless I am missing something. Most of the deaths from which organs are obtained in the U.S. are traffic accidents or murders or homicides or I am not sure what in which case most of the time, you can't get a travel history.

So I don't know what this is going to be applied to. For someone who dies who was a former immigrant from England, but that is going to be a very rare case--so what are we asking that this be applied to?

DR. BROWN: Cadavers that have lived more than six months in Great Britain.

Jay, did you want to say something before Dave? I didn't recognize you. I'm sorry.

DR. EPSTEIN: I think the committee has gotten around to recognize that FDA cannot recommend an unapproved test. So we hear the comment that when tests become available, we should make use of them. I think that is self evident. I think the point Susan is making is in what setting is it applied?

Is it applied to all donations? Is it applied only when there is a positive travel history, a residency history, or is it applied only when you have both a travel history and a high-risk tissue or is it applied always to a

high-risk tissue regardless of the travel history?

I think that is the useful thing to be advised on now. To tell us to recommend a test when there is no test is sort of moot although I appreciate the importance of raising our awareness that that is where we want to go.

DR. BROWN: I think the 'FDA should take under advisement the committee's enthusiasm for testing and, perhaps, initiate or invite candidates to validate.

DR. BURKE: Let me point out there is not a consensus on the enthusiasm for this. We have not established that point.

DR. BROWN: Okay.

DR. EPSTEIN: You see, the thing is that right now we don't have a test and right now we could ask for history, So we want to be advised on whether we should be doing that as an interim measure or a permanent measure, whether or not tests come down the road.

I think the comments, obviously, are helpful about testing although whether to do it and when to do it is, I think, the tricky part.

DR. BROWN: It is true, and I am somewhat to blame for confusing the issue because I was thinking about testing globally, not just in terms of residence histories but one of your criteria for regulation or guidance in terms of safety of tissues and cells irrespective of deferrals and

travel history, just as a good idea to include in the mix of things that you consider for safe administration of tissues and cells.

DR. PRUSINER: I think you are absolutely right. That is, I think, the sensible approach that you come to as you go through this discussion.

DR. BROWN: Don, you were not enthusiastic. Tell us about that.

DR. BURKE: In principle, I am enthusiastic about using tests where they are available, but the implementation of a test before it is ready can lead to huge problems. I lived through the development of the AIDS diagnostics and the criteria for interpretation of Western blot and what you tell people who you have false-positives with.

So there are a huge number of potential problems that come out of employing a diagnostic before it is ready. That is my reason for conservatism here.

DR. BROWN: We did include the word "validated" in this criterion.

DR. BURKE: That's fine. And, as was pointed out, when it is validated, then it may be time to talk about it.

DR. BROWN: Well, you can talk about it any time. We are not recommending a test be done before it is validated. We are not recommending implementations. We are simply saying that this would be an excellent criterion if

such a test is validated.

DR. BURKE: And I will be very supportive at that time.

DR. BROWN: Then I can reinsert the word "enthusiastic?"

DR. BURKE: You can use enthusiasm for a validated test; yes.

DR. CONFER: Dennis Confer from National Marrow Donor Program. I would like to give the committee a little information that might help you put risk in perspective. Regarding hematopoietic stem-cell transplant recipients, particularly the unrelated donor type that we are really concerned with, the vast majority of these patients have a life expectancy without transplant that is on the order of one to two years.

75 percent of the people we transplant have cancer. Those are almost all leukemias in various forms or lymphomas. The remaining 25 percent either have acquired bone-marrow failure, aplastic anemia, or they are children with various inborn errors of metabolism like the Hurler's syndrome and the like who have a life expectancy of a few years untransplanted or they are children with immune deficiencies who have a life expectancy of several months, untransplanted.

Patients who undergo hematopoietic stem-cell

transplant from an unrelated donor have a 40 percent mortality in the first three months. So these patients, when they have decided to go to transplant, have already accepted huge risks, have terrible underlying diseases.

I think that discussing with these patients the risk of TSE in that setting is a minor risk to those patients. I don't think that testing should be done on the unrelated donors, on their stem-cell products. I don't think that these donors should be deferred when they are the best donor for the patient who is trying to survive what is otherwise a fatal disease.

DR. BROWN: Of course, that could apply also to dura mater which is used very often on patients with diseases just as serious as those you have mentioned, but we still do it.

DR. McCURDY: Thinking it over, it seems to me that, to address Jay's question, where you should use it now might--now being when it is validated for this purpose--would be when you are transplanting neural tissue, corneas, dura, and that sort of thing, that when you get a test that is validated for use on blood, then it might be reasonable, or will be reasonable, I think, to apply it to other tissues most of which are perfused with blood.

But recommending application of a test to other than neural tissue at the present time is quite a ways in

the future, I think.

DR. BROWN: We have already decided that we are not going to do that. In fact, the question is worded, "If yes, what deferral criteria should FDA recommend?" It would be reasonable to answer that, "validated positive PrP-detection test in brain." That would be a recommended deferral criterion.

What about deferral criteria otherwise listed in terms of different cells and tissues, countries of visitation and time of exposure? Do we need to consider each one of these in turn?

DR. BOLTON: I would like to say that, except for dura mater and cornea, I would prefer that no deferrals--of course, I voted no to the first part, but if we are going to suggest deferral criteria, I think, for those two tissues, it makes sense. For the other ones, I would still prefer to see that decision left up to the transplanting physician and the recipient.

DR. EWENSTEIN: I think we are trying to grapple with an almost bewildering number of different tissues for which we have not had the same sort of formal presentations and analyses that we were able to have for blood. But I think that what we are trying to leave the FDA with is a sense that there are high-risk tissues that I think we agree on, that there are probably very low-risk tissues.

I think that the high-risk tissues should be considered at least with the same criteria that we have considered blood which is probably a low-risk tissue, except that we do a lot of it.

I just reiterate my own personal concern about the semen donations not in the personal-donor-directed use but especially in the anonymous banks because I think there is a different level of responsibility with that kind of tissue. I would just leave that one in an unknown category until we have some additional data on that.

DR. BROWN: So we have exclusion only for certain types of cells and tissues. Question; which ones? We will vote on this but, in terms of phrasing the question, should I put down, for which ones, cornea, dura. Is there any sentiment for listing others other than I think you want embryos and semen? That is a difficult thing to vote on because some people, for example, might not agree with semen and embryos but they would want cornea and dura.

It is possible that we should not vote on this at all and just discuss it and give the FDA a sense of what tissues. On the other hand, you guys have already said you want a deferral. You have got to have it concrete.

DR. DETWILER: Just semen, again, in the animal species with TSEs, both in sheep and in cattle, in sheep even with wide peripheral-tissue distribution of

nfectivity, the work done with semen--again, the animal umbers were limited--but when you took semen and inoculate ight into mice, they were unable to cause disease and then, ollected from infected rams, watched the progeny and there as no evidence of transmission.

The same thing with BSE 'with even more work done ith BSE.

DR. BROWN: Those of you who voted yes, you better ome up with something.

DR. **EWENSTEIN:** There was a slide, and **I** don't emember exactly how it was phrased, but there were certain exclusions that the FDA had placed. I think some of our concerns were already recognized on that slide. Could we Look at that again because I think it covered--I think it Left the appropriate doors. It had to do with medical emergencies. It had to do with some other very particular circumstances where **I** think we would all agree that the benefit outweighed the risk.

DR. BROWN: The other way that I could handle this would be to ask those people who did vote yes individually to stipulate which tissues they want to be the subject of deferral.

DR. EWENSTEIN: If we could just look at the slide. I think this was well thought out and I think it covered a lot of the issues that we would be most concerned

with. I think that we have already discussed this in a couple of different possible settings but I think if you think about it, it eliminates most of the risk to the benefit, if you will, of some of these procedures.

So what we are really left with are either the more anonymous donations or the donations where there is-- well, by this exclusion, there is not an urgent medical need that will be unmet.

DR. BROWN: It is not prohibited if there is documented urgent medical need. A neurosurgeon might say there is an urgent medical need. I am in the middle of an operation. I better use a dura. Urgent medical need is a loose phrase and subject to a great deal of interpretation.

DR. EWENSTEIN: Even for the use of unapproved drugs where we don't even have the time, necessarily, to get the proper human subjects' consent and the like, we are always allowed, as physicians, that last escape clause. I think that is appropriate. You do have to justify it afterwards.

DR. BROWN: You had brief comment?

DR. DuBORD: Yes. Paul DuBord. I am speaking as a transplant surgeon and not as a representative of any organization. I heard the description of CJD being very high risk. I think it is important to recognize that you have the stability of CJD elsewhere in the world except for

variant CJD of 1 to 1.2 in a million.

To describe that as high risk, I think we have to be careful of how we look at that.

DR. BROWN: We are talking exclusively about variant.

DR. DuBORD: We are talking exclusive variant CJD.

DR. BROWN: And we don't know what the risk of variant is.

DR. DuBORD: And we don't know a whole lot about this particular disease process.

DR. BROWN: It seems to me what you are saying about classical CJD is irrelevant to the discussion.

DR. DuBORD: Okay. We will discard that. But the classic CJD is pretty stable. Variant CJD, there are so many unknowns about that. It has never been transmitted, that we know of.

DR. BROWN: It has only been around a little while.

DR. DuBORD: That's correct and we have long incubation periods.

DR. BROWN: I will let you continue; go ahead.

DR. DuBORD: Thank you. But I think we have to look at the risk-management issues here and look at the risk/benefit ratio we have for the donors. Some of the things that you are talking about or throwing around this

morning have enormous negative impact, from the administrative point of view, from the technical point of view, from the financial point of view, and, basically, may have no real benefit to the patients.

That is the bottom line is what benefit are we going to give these patients. Are we kidding ourselves here when we don't know a lot about this particular issue. I think we really have to look at the risk-management issues and the benefits of the decision that you are making.

Thank you.

DR. BOLTON: I would like to make a comment on that as well, that in the case--we are going back and comparing this with the risk of blood contamination in the blood supply. I think that there are different epidemiological considerations in that.

The blood supply, if it were contaminated, especially in pooled blood or there were systematic problems that were resulting in many units being contaminated, that could result in an amplification and a much more serious epidemic whereas most of these issues are one recipient at a time and it is much less of a concern.

So I think that it makes more sense to allow the recipient and the physician to consider these on an individual basis rather than trying to legislate things or make exclusions from a much broader population.

DR. BELAY: I agree with what David said. The .ngle overriding decision-making process, in my mind, should be whether or not we are hurting any patients, whether or not we are decreasing the supply or the vailability of any tissues or products for the patients.

That is one of the reasons I voted no for this .estion.

DR. BROWN: I think we can vote on A. We have ust been relieved of the responsibility of having to vote n B. The committee always wants additional data so why on't we vote on A. and send a signal to the FDA that we eed more data, if they haven't already got it.

DR. BOLTON: A. only comes into play if we voted o. Since we voted yes--I mean, the yes carried. I didn't ote yes.

DR. BROWN: I can't have it both ways.

DR. BOLTON: That's right.

DR. BROWN: I had hoped no one would notice that.

DR. BOLTON: I should have been quiet.

DR. ROOS: David's point is that these issues should be discussed between the physician and the recipient, out, in order for that discussion to be held, you need data. So I think travel history and the issues with respect to blood provide some useful data. This doesn't mean that the donor is deferred and won't be used. It just means that

these donors and the donations are in a different category and labeled as such, and there is information available that might be of value.

In other words, it could be that if you are the recipient, you would prefer to get an American cornea than a U.K. or maybe even skin from an American rather than a U.K. So I think this is valuable information, especially because we really don't know the tissue distribution.

I am not saying that we would discard the tissue but just label it and get the information that is important.

DR. BOLTON: Ray, I would agree with you but my understanding is that if the FDA were to adopt a deferral policy, that, essentially, those tissues would not be used, and those donors would not be--

DR. ROOS: Yes; my definition of deferral here was different from yours. In other words, I think they are identified and described and I think of things, perhaps, in two tiers and designated as such rather than rejected.

DR. EWENSTEIN: But I think you have to think about what we are saying here. A man shows up and says, "I have been in the U.K. for a year during the high-risk period and I would like to give some blood today. I would also like to sign a card that, if I get into an auto accident on my way home, you can have my cornea."

And we say, "No; you can't give the blood but we

are not going to worry about it when it comes to the cornea." Yet, we have never transmitted a TSE to a human through blood but we at least have one documented case--obviously, the denominators are going to be very small because the natural incidence of CJD is so small.

We already have at least one documented case, maybe a couple of other cases, plus some experimental data that it may be possible. So it seems to me, administrative concerns aside, that it makes no sense to have that same person deferred from blood and not from cornea.

There may be circumstances where we just don't know. I am not sure that the risk is great enough that, in the absence of a medical history or travel history, we are going to defer the unknown patients. Maybe that is an unreasonable position. But if we know, and we have already deferred him from blood, I can't see taking the cornea.

DR. BOLTON: But I specifically said dura mater and corneas. I don't have an objection to that deferral. But if you are looking at a bone-marrow transplant and your perfect match has been in the U.K. for seven months, that seems to me an insignificant risk considering everything else that is going on.

I would rather have the physician and the recipient be able to make that decision rather than the FDA to say, "I'm sorry; that donor is deferred. You can't have

that bone marrow."

DR. EWENSTEIN: Yes. I think in donor-directed cases, and you can define it in a couple of ways based on tissue matching or for reproductive reasons based on family circumstances, then you can do this as a one-on-one discussion. Where it is going into an anonymous pool, I am saying it makes no sense to put the cornea into an'anonymous pool if you have decided you can't put the blood into that anonymous pool.

DR. BROWN: Nick, quickly, and then we are going to finish.

DR. HOGAN: I want to make a couple of quick recommendations here from my perspective. First of all, if you are talking about exclusionary criteria with history, you are talking about all of the medical-examiner cases probably not being able to get histories, so we are excluding all of those that we talked about yesterday.

So you are not going to be able to get a travel history from those. That is fine as long as you are aware of that.

DR. BROWN: We are not on this question, yet, Nick. That is the next question.

DR. HOGAN: Secondly, there are no corneas imported from Europe. Thirdly, if you implement a test, we are talking about 45,000 cases for a very small risk, huge

administrative problems. I know you have already addressed that but it is important to consider when you talk about an unvalidated test.

DR. LEITMAN: Could I say one thing?

DR. BROWN: Yes; go ahead.

DR. LEITMAN: In this slide and the one preceding it--no; not this one, the ones that Bruce asked for that were put up, FDA already has policies in place for donor-directed tissues, if you will. I propose that those are adequate from the discussion that I have just listened to now from the data that was presented and that we don't recommend that FDA make any changes right now in-those.

There is already a requirement for biohazard labeling, for the physician being notified of results, for getting informed consent. So that seems to be adequate right now, given the uniqueness of those tissues.

And then I want to comment on Bruce's comment. Blood is available in greater--slightly, hopefully, greater supply than the need. But we have heard today and yesterday that organs are not. That is the big difference. I have no problem telling a donor that they are excluded from donation because of a one-year sabbatical in London, which we do all the time.

I have a problem telling them to take their organ-donor card out of their wallet. I think it is a different

level of urgency, of need, of tissues that can be obtained and impact on patients.

DR. BROWN: I'm sorry, committee. We are moving on. What we are leaving the FDA with is what they are--

DR. SOLOMON: I just wanted, for the record, to say we are not considering organs in this discussion.

DR. BROWN: That's right. Organs are not covered. It is clear, the one thing from this discussion that is clear is that there is a great variety of approaches to this issue as discussed by this committee, that there is no consensus by the committee on the exact stipulations of donor-deferral criteria. That message has come across very clear.

A close vote on whether or not the FDA should get involved in donor deferral at all and no possibility of arriving at a consensus as to what kind of criteria should be used. So the FDA is satisfied with our discussion, our marginal but definite decision, that the FDA should consider deferral criteria and an inability to have a consensus about exactly what those criteria should be.

We are moving on to the next question which is the final question on this topic before we move to chronic wasting disease and that is, if a deferral policy were to be put in place, could information about the donor's risk factors for CJD and variant CJD be obtained; i.e., is a

donor medical history interview required.

If there is no discussion, we will vote on that question. The question is, is a donor medical-history interview a requirement for--actually, that is not how the question reads. I mean, I read the question, but if a deferral policy is put in place, should a donor medical-history interview be required.

DR. BOLTON: Since we can't settle 2B about a deferral policy, I think it seems pointless to argue and discuss much about 3.

DR. BROWN: I am happy with that.

DR. CLIVER: One small afterthought, though. I think we could recommend that, at such time as a validated PrP test for human brain tissue is available that, in these instances--not across the board for cornea donations, whatever, but in these instances, that we recommend that that be applied as a criterion lacking a donor medical-history interview.

DR. LURIE: I think, Paul, the other question here is a legal one that I certainly can't answer which is these, in effect, are state laws, unless I am incorrect about that. There is a question of whether or not the FDA has any authority to, in effect, overrule the state law for this limited group of people.

MS. WARNER: If I can clarify that last point

about the state laws. We do have authority to overrule or preempt those state laws if it were appropriate, in the interest of public health. So what we are asking is whether it would be appropriate to preempt those laws to the extent that it would be necessary to obtain a donor medical history.

DR. BROWN: Stan?

DR. PRUSINER: I was just going to say that I think, stepping back from this for a moment and trying to look ahead, there will be validated tests. They will come along and, at that point, then whoever is on this committee will sit down, reconsider all this and, from that landscape, you will come away with, I think, some much more clear recommendations.

We are having a very fuzzy time because we are trying to put several hypothetical issues on the table, things that are going to happen in the future. So I think that to try to come to conclusions now is extremely difficult because we don't have these kinds of things in place.

DR. ROOS: We, of course, actually made recommendations with respect to dura mater both local as well as international sources in which we recommended a validated test. I think that that is reasonable, perhaps, to extend to corneas when that test is, in fact, available.

I think, with respect to the travel history, if one cannot obtain a history, from my perspective, the cornea still could be used for transplantation. But, again, perhaps some description of this cornea in the absence of a travel history should be linked to that particular tissue.

In other words, I think it would be a mistake to restrict the supply of corneas because of somebody'in an accident and this inability to obtain a history in time. On the other hand, I think it might be a good description of the sample, itself, and information that could be shared with the recipient.

DR. BROWN: Laura?

DR. MANUELIDIS: I still have a little bit more concern about bone marrow than the rest of the committee even more so than blood because remember that these cells can live for a long time in the recipient. So it is not like something that is thrown out. I think that is the problem with tissue and cells is that they can harbor something in a small amount and come out much later simply because you don't get rid of them.

I think that is one of the problems with something which is acellular, for example, like dura mater which can just harbor some stuff and nonspecifically stick to infectivity. I think that you really have to think about that when you talk about tissues.

So I think that is something that you should not exclude, necessarily.

DR. DAVEY: Paul, I think, also, and maybe the FDA can help me there-- 1 think the FDA, on occasion, has allowed, in their information sticker, if you will, on a biological product, some kind of information stating that, "This product has certain inherent risks such as," ‘whatever. Maybe there could be just a blanket labeling of these products saying there is a small, but undefined, risk for certain diseases such as new variant CJD. That might cover it.

DR. BROWN: A question, I guess, is whether or not the FDA really wants to get involved in anything on so little scientific evidence. It may be a very prudent thing not to be ultraconservative for the next six to twelve months and wait until we have a little data on the distribution of infectivity in variant CJD before they promulgate recommendations.

Clearly, the committee is at a loss simply because we don't know. It has been my experience as the chairman that when these discussions become progressively diffuse, it is a good signal that we are arguing from no facts. Therefore, ı think that is the end of this discussion.

You can say what you would like.

DR. KENNEDY: Dr. Brown, what I was wanting to

mention is just a point from yesterday that the donors obtained through legislative consent are much younger than the other donors and so our calculations of risk that were presented yesterday was that the risk among those donors is approximately 40 percent less already than it is among other donors.

If you lose those donors by requiring a medical-history interview, you may actually end up leaving the average level of risk in remaining donors greater than what it is now.

DR. BROWN: Right. I think we appreciated that from your talk, Dr. Kennedy.

We are going to move now on to Topic 3 which is a discussion of issues related to chronic wasting disease and its potential for human exposure.

Topic 3

Discussion of issues related to deer and elk infected with or exposed to chronic wasting disease in the U.S. and potential for human exposure to various animal TSE agents should be considered by the FDA in determining suitability of blood donors

DR. BROWN: For this topic, we have a series of five speakers, the first of whom will talk about regulatory issues. That is Dr. Brackett from the FDA.

FDA/CFSAN Regulatory Issues

DR. BRACKETT: Thank you, Dr. Brown.

[Slide.]

My name is Bob Brackett and I am a senior microbiologist and also serve as the lead for TSE issues in FDA's Center for Food Safety and Applied Nutrition, or CFSAN. CFSAN is responsible for regulating cosmetics, dietary supplements and most food products other than most meats and poultries. These last two products are regulated by the United States Department of Agriculture.

This morning, we are going to be discussing issue 3 which is chronic wasting disease, which is a TSE of elk and deer primarily in the western states. But, before we actually hear some of the more detailed discussions by the following speakers on this issues, I wanted to provide you with a brief background of why FDA and CFSAN, in particular, is concerned about chronic wasting disease and how this issue came to be a subject for discussion at this meeting.

Although I may touch upon some of the points that will later be discussed by the speakers following me, I will leave the details up to them. My goal this morning, really, is to put the subject into perspective.

The first point I would like to address is the question why is FDA even involved in chronic wasting disease issues. After all, I mentioned only a moment ago that it

was UDSA who was responsible for regulating meats, and this is true.

[Slide.]

USDA's Food Safety and Inspection Service has regulatory authority over most meats. However, the meat products for which they have authority are very specific and are listed under the Federal Meat Inspection Act. These animals include cattle, sheep, swine, goats, horses, mules and reindeer.

[Slide.]

All other meat products, particular game meats such as elk and deer that are traded in interstate commerce fall under the regulatory authority of FDA.

[Slide:]

The legal framework under which FDA regulates deer and elk is the same as with all other foods that it regulates; namely, the Federal Food, Drug and Cosmetic Act and the Public Health Service Act. Although deer and elk are not major food products in terms of production volume, FDA is, nevertheless, committed to assuring the safety of these products as well as the other products it regulates.

I would like to also point out that animals that are harvested by hunters for their own use are not regulated by FDA and this is under the purview of the states.

[Slide.]

The primary reason why FDA has focused on chronic wasting disease at this time is really an indirect result of the growth of the elk and deer industry in the recent years. The breeding and raising of captive elk and deer is a small but growing industry primarily in the West and in the Midwest although it does occur in other states as well.

These animals are raised for a number of'different reasons including hunting stock, breeding stock for other ranches, antler velvet or sometimes referred to as velvet antlers and, of course, meat.

[Slide.]

As you will probably hear from the speakers that will follow, chronic wasting disease was first identified in captive deer herd about thirty years ago. Since that time, the disease has also been identified in wild dear and elk in Colorado and Wyoming and, just recently, in Nebraska as well as in captive herds in about five US states and at least one province in Canada.

Chronic wasting disease has been primarily treated as an animal disease and has been addressed by state authorities, primarily state veterinarians. At present, each state decides how best to handle cases of chronic wasting disease. The actions could vary from something like destroying an entire herd in which chronic wasting disease was confirmed to simply quarantining suspect animals.

Most importantly, from FDA's food safety perspective, however, is what happens to the products of these animals.

[Slide.]

The possibility that deer and elk infected with a TSE could be used for human food or cosmetic products put this issue squarely into the responsibility of FDA. It is, in fact, this possibility that has prompted FDA to take a closer look at this issue from the food-safety perspective. A more difficult related question concerns that of deer and elk that have been exposed to infected animals; that is, do exposed animals, but not necessarily clinically or pathologically positive, represent a risk for spreading a TSE to humans.

[Slide.]

Although no human illnesses have yet been traced to chronic wasting disease, at least one report, which was provided in the committee's packet, has been used as evidence to suggest that the question as to whether chronic wasting disease could be transmitted to humans is still valid.

We are aware that there is research going on in this area that could support or refute this notion and we would hope that the committee members who are closer to the research would be able to provide us with some insight.

So, in closing, FDA questions whether or not either deer or elk actually infected with chronic wasting disease or those animals exposed to chronic wasting disease could transmit a TSE to humans. FDA will weigh the evidence used to answer these questions in formulating policy and deciding on actions in dealing with products of infected or exposed animals.

With that, I will quickly read through the questions.

[Slide. 1

Question 1; are there scientific data or other scientific evidence for transmission of a TSE from an infected elk or deer to an uninfected elk or deer and, if so, how strong are these data or evidence.

[Slide.]

Are there scientific data or other scientific evidence for transmission of a TSE to people consuming or using products from deer and elk with chronic wasting disease. If so, how strong are these data or evidence?

[Slide. 1

Question 3, are there scientific data or other scientific evidence for a transmission of a TSE to people consuming or using products made from deer or elk exposed to chronic wasting disease. If so, how strong are these data or evidence?

Then, a subpart of question 3, is the potential, if any, for transmission to humans different depending on the types of exposure; for example, the offspring of chronic wasting disease-infected elk or deer, a pen mate of those deer, animals that are in close proximity but not necessarily in the same pen as the infected deer, animals exposed to equipment used in the transportation or' slaughtering of these animals, or animals on the same ranch with no direct contact with the infected deer.

[Slide.]

Question 4, are there scientific data or other scientific information assessing the potential or actual infectivity of different tissues or other animal parts from chronic wasting disease-infected deer or elk. An example of these parts might include bone meat versus meat on the bone, neurological tissues, velvet antler, organs or glands, or byproducts of slaughtering such as gelatin.

[Slide.]

Question 5, if there is a potential for transmission of TSE from infected or exposed animals or animal parts to humans, what is the likelihood of transmission.

Again, here is a subpart, is the potential, if any, for transmission to humans different depending on the route of administration to the tissue; for example, oral,

transdermal, inhalation or injection or other.

With that, we will go on with the speakers.

[Applause.]

DR. BROWN: Thank you, Dr. Brackett. A very clear charge. I think, for a change, we will be able to make some recommendations based on science for topic 3.

We are going to have a discussion of background information on chronic wasting disease presented by Dr. Miller from the Colorado Division of Wildlife.

Background on **Chronic Wasting Disease**

DR. MILLER: Good morning.

[Slide. 1

I have been asked to provide the committee with some background information on chronic wasting disease of deer and elk as a foundation for the rest of today's discussions. I am sure that all of you, as members of this advisory committee, are at least somewhat familiar with this disease so much of this is probably going to be review for you.

In the next twenty minutes or so, I plan to briefly review some of the key features of chronic wasting disease, its history, our approaches to understanding its distribution and occurrence and what we currently know about its status in both free-ranging and farm cervids.

The information I am going to provide is a

synthesis of data, much of it previously published--it has been generated by a number of very talented scientists who have been collectively and collaboratively working on chronic wasting disease for over two decades.

In particular, please recognize the contributions of Drs. Beth Williams, Terry Spraker, Katherine O'Rourke, Tom Thorne and Stuart Young who have all made substantial contributions to our collective understanding of chronic wasting disease in deer and elk.

[Slide.]

Chronic wasting disease, or CWD, as most folks prefer to refer to it, is a naturally occurring transmissible spongiform encephalopathy affecting native North American cervids. It is believed to be caused by one or more unique strains of infectious self-replicating prion protein.

The strain of prion that causes CWD is demonstrably different from the strain that causes BSE and also appears different from at least U.K. scrapie strains. The true origin of CWD remains unknown despite what you may read on the web or in the newspaper. Whether it began in scrapie or as a sporadic disease of deer or elk is, and probably always will be, a mystery.

The known natural host range for CWD is limited to three cervid species from two genera; mule deer and white-

tail deer from the genus Odocoileus and elk from the genus Cervus. All three species show comparable susceptibility to CWD but there do appear to be some species or genus-specific differences that may influence tissue distribution and transmission.

The hallmark clinical signs of chronic wasting disease are emaciation and abnormal behavior. In practice, subtle changes in behavior attentiveness and locomotion can be detected in most infected animals some months prior to the development of end-state clinical disease. Intercurrent infections, particularly aspiration pneumonia and trauma, can confound both clinical and post-mortem diagnoses and, consequently, as with the other animal TSEs, laboratory diagnosis is necessary to confirm infections.

Important epidemiological features of CWD include a prolonged incubation period that averages somewhere in the range of twenty to thirty months with natural infections. Susceptibility to infection appears to be relatively uniform among species, between sexes and across age classes. There is evidence for genetic influence on susceptibility in elk but not deer.

CWD appears to be maintained naturally in both captive and free-ranging cervid populations in the absence of exposure to contaminated feeds or other likely outside sources of infection. Direct or indirect animal-to-animal

transmission, not necessarily along maternal lines, drives epidemic dynamics. In addition, contaminated environments is likely play a role in epidemic dynamics and the recurrence of disease in some situations.

[Slide.]

Chronic wasting disease is not a new prion disease. The clinical syndrome of chronic wasting was first recognized in captive mule deer in Colorado in the late 1960s but actually tying the first recognition of a disease like this to its first occurrence seems like a substantial leap of faith.

Based on what we know about its distribution and occurrence, it is quite plausible that CWD actually arose in captive and/or free-ranging cervids forty or more years ago. In 1977, Dr. Williams and Young recognized CWD as a TSE and, within a few years of finally having a clear-cut diagnostic criterion, chronic wasting disease was first detected in free-ranging elk and deer in Northeastern Colorado and Southeastern Wyoming.

However, there almost certainly were cases prior to these first cases being detected in the early '80's. Similarly, the first diagnosis of CWD in a farmed elk was made in Saskatchewan in 1996. In retrospect, this most assuredly was not the first case to occur in the elk industry in either Canada or the U.S. So, although there

may be some value in recognizing these milestones in the history of chronic wasting disease, it is important not to interpret these as absolute time lines for the emergence of this disease.

[Slide.]

Before proceeding into what we know about the status of CWD in both free-ranging and farm cervids, I want to provide a bit of context on how we have come to know what we know. To truly appreciate how much we know about chronic wasting disease, it is important to compare approaches for detecting CWD with traditional approaches for detecting TSEs in other animal species.

Dr. O'Rourke is going to be talking about diagnostics in much greater detail so all I am going to offer for now is kind of a conceptual overview. For both scrapie and BSE, there has tended to be a focus on clinical cases as a means of detecting new infections. This is clearly an effective approach, particularly when such diseases are reportable, but there are biases and limitations inherent in this strategy.

These surveillance programs are often conducted in an atmosphere of adversity where there may be substantial economic penalties for owners of infected animals or herds. The end result of all this is a strong tendency for underreporting of these diseases and, consequently, for

underestimating their severity.

[Slide.]

I hope all of you realize that animals showing end-stage clinical disease represent just the tip of the iceberg with respect to the overall infection rate in a population of interest. Those of us working with CWD also recognized this some time ago and have modified our surveillance programs accordingly.

[Slide.]

Initially, we used histopathology, brain-stem samples, as an adjunct to surveilling populations for wasting disease and actually gained a much better appreciation of the size and shape of that iceberg.

[Slide.]

Beginning in 1996, we adopted immunohistochemistry of brain stem as our screening tool and, again, improved our appreciation of the iceberg's depth and magnitude.

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Since last year, thanks largely to the efforts of Drs. O'Rourke and Spraker, we have been able to use IHC of tonsillar tissues to gain an almost, but probably not entirely complete, picture of the CWD iceberg.

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We know even these IHC-based estimates of wasting disease prevalence are a little low, but, in fact, they are

much closer to truth than data that may be generated by other means.

[Slide.]

Based on pathogenesis data from both experimental and natural CWD infections in mule deer and assuming at 24-month disease course, tonsillar IHC probably fails to detect infections only in the first couple of months after infection and is increasingly reliable as the disease progresses. The appearance of IHC staining in brain stem and subsequently the appearance of spongiform encephalopathy and clinical signs can also be used to stage disease and to confirm infections at the population level.

Elk are somewhat more problematic, as Dr. O'Rourke is undoubtedly going to describe later. Overall, however, the approaches currently used to detect wasting disease do offer a much higher probability of detecting cases than reliance on clinical disease alone.

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Another important point is that the surveillance systems for chronic wasting disease in free-ranging wildlife evolved in the absence of regulatory or economic pressure. To date, the motivations for reliably estimating the distribution and prevalence of chronic wasting disease in native wildlife populations have been two-fold.

One is scientific curiosity. The second is an

accompanying sense of responsibility for both acquiring and conveying to the public accurate information about this disease and its occurrence in public resources.

Similarly, the farmed-elk industry recognized early on the value of detecting chronic wasting disease in their herds as a basis for effective disease management. In this environment, three somewhat distinct approaches to surveillance have evolved and are currently in use in varying combinations.

Appreciation of the details of these applications is important, I think, in understanding the data on CWD status.

[Slide.]

The foregoing caveats not withstanding, surveillance for clinical suspects remains an effective tool for detecting new foci of wasting disease infection in both captive and free-ranging settings. Under these systems, clinical suspects are samples whenever they are available, Histopath of brain stem is usually sufficient to make a diagnosis that I see as a welcome adjunct. Data are clearly biased, though, and consequently of little use in estimating prevalence.

This approach is actually very similar to traditional scrapie surveillance in the U.S.

[Slide.]

In some captive settings, wasting disease surveillance is extending, though, and has been applied to all natural mortalities and, in some cases, to all mortalities regardless of proximate cause. Several states and the Canadian government have adopted this approach in rules that regulate their elk industries.

Mortality-based surveillance is also an effective tool for detecting new foci of infection and has resulted in the disclosure of several infected elk farms over the last three years. Here, again, histopath of brain stem is usually sufficient but IHC is also a useful tool.

Inherent biases in these data limit their uses in, again, estimating prevalence. This approach is considerably more aggressive than traditional scrapie surveillance in the U.S. and has facilitated CWD detection in the elk industry.

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Finally, those of us investigating wasting disease in free-ranging populations over the last decade have developed efficient techniques for conducting geographically targeted random sampling of harvested deer and elk to estimate prevalence and monitor trends. In these surveys, sections of obex and, more recently, tonsillar collected and examined via immunohistochemical. Infections can be staged further by histopath.

Data from these samples represent relatively

nbiased point estimates of CWD prevalence. Unfortunately, omparable slaughter-survey data for scrapie and BSE have ot been reported formally confounding comparisons of pidemic severity between wasting disease and, for example, crapie in the U.S.

This lack of comparable data has perhaps fostered ome of the popular misconceptions of about chronic wasting isease.

[Slide.]

Using various combinations of these three urveillance approaches, we have developed a good basic nderstanding of CWD status in North America. At present, here do appear to be two distinct epidemics occurring in North American cervid populations. One epidemic focuses free-ranging cervids in southeastern Wyoming, northeastern Colorado and extreme southwestern Nebraska.

The other epidemic is occurring in a relatively small number of farms or elk herds scattered across the U.S. and Canada. Although a common source for both epidemics has been speculated and would certainly be the most parsimonious way to explain the origins of wasting disease, no common thread actually linking all of these events has been demonstrated to date.

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Alternatively, not knowing how or when chronic

wasting disease originated in the first place, it is conceivable that whatever event gave rise to wasting disease once could have occurred again in farmed elk and that the two epidemics are, in fact, not directly related.

Regardless of whether or not they have a common route, these epidemics, as well as we understand them today, appear to be essentially unrelated epidemiologically and are probably best considered independently.

[Slide.]

What I first want to do is give a quick overview of the highlights of the wasting-disease epidemic in free-ranging deer and elk. Chronic wasting disease has been recognized in free-ranging deer and elk since the early 1980s. This epidemic is likely related in some way to the cases originally reported in captive research animals, but which came first is truly a chicken or egg question that we are probably never going to answer.

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Initially, clinical cases were recognized in both free-ranging deer and elk in northeastern Colorado and southeastern Wyoming. Surveillance for clinical suspects has been ongoing in both states since the first cases were detected. Harvest-based surveys were conducted intermittently beginning in 1983 and annually in some areas beginning as early as 1990.

Since 1996, we have been using IHC to enhance detection of infected animals. In all, about 7,000 deer and elk harvested in northeastern Colorado and southeastern Wyoming have been sampled. Ongoing random surveys have revealed a single endemic focus of chronic wasting disease that primarily involves mule deer but also includes white-tail deer and elk where they occur in that area.

That is the area in orange in the slide here. We are going to zoom into that, now.

[Slide. 1

As described in our publication from last year, we know from these survey data that chronic wasting disease is endemic across about 40,000 square kilometers of contiguous mixed native habitats that spans portions of northeastern Colorado and southeastern Wyoming. New data from Nebraska Game Fish and Parks Department and USDA Vet Services extends this area just slightly into the extreme southwestern corner of Nebraska.

They recently reported a case just right there. It is about as close to Colorado and Wyoming as you can and still stay in Nebraska, but it does extend that into Nebraska.

The most intensively infected area that is shown here in these darker red shades extends from the Laramie Mountains south into the northern front range of Colorado.

In this area, average wasting disease prevalence exceeds 10 percent in sampled mule deer.

This high-prevalence ridge is surrounded by areas of successfully lower prevalence, as you see with the lighter orange areas going to yellow. On the fringes of the endemic area, prevalence is actually 1 percent or less in deer. Elk reside in the western half of this area'where the mountains start, right along here, and, throughout the area where they occur, prevalence is 1 percent or less in that species.

Where white-tail deer ranges overlap with mule deer, wasting disease prevalence is similar in both species. The spatial pattern of relative prevalence of this disease strongly suggests that what we are seeing is actually an epidemic occurring in slow motion extending geographically through natural animal movements.

Our computer models suggest that chronic wasting disease has likely been present in some of these more heavily infected areas for thirty-five years or more.

[Slide.]

The good news is that, at present, chronic wasting disease in free-ranging deer and elk appears to be confined to this single endemic focus, right here. Surveys have been conducted over the last four years in other parts of Colorado and Wyoming as well as in portions of a number of

nearby and distant states and provinces by responsible wildlife management and animal-health agencies.

These are the states and provinces that are shown in green on the slide. None of the areas surveyed, the shown-in-green surveyed areas, have shown any hint that other foci of chronic wasting disease presently exists in free-ranging cervids. In all, over 7500 deer and elk from these areas have tested negative through the 1999 sampling season and about another 5200 samples are in the process of being examined.

At the very least, I think these data clearly demonstrate the chronic wasting disease is not uniformly prevalent across all of our native cervid populations in the U.S. and Canada.

[Slide.]

So, to summarize kind of the highlights of wasting disease in free-ranging cervids, it does appear to occur as a single epidemic focus in the wild to primarily involve mule deer, that it has been ongoing for several decades and to show some evidence of slow natural spread.

[Slide.]

I want to briefly comment on approaches for managing chronic wasting disease in free-ranging cervids. I know there is going to be a lot more discussion later about the elk industry and what it is doing, but we are not, as

wildlife managers, entirely clear on how to best manage this problem.

Despite that, a number of actions are ongoing. First and foremost, public information and education regarding this problem has been ongoing since the mid-1990s, well before April of 1996. Since CWD was first recognized as something more than just a handful of interesting diagnostic cases, our strong desire has always been to insure that the public is aware of this problem, where it is and is not, and what is being done.

Those who suggest anything to the contrary are simply wrong. Our surveillance and research has been important in improving our understanding of the magnitude of this program. Until very recently, there have been no large infusions of funding to study chronic wasting disease and much of the work has actually been supported by state wildlife management agencies, intramural university funds, and in-kind contributions made by the very fine folks who are collaborating in this work.

Despite the lack of funding or broad interest until fairly recently; I hope that you can all appreciate the contributions to understanding that all these things have brought.

One of the tools for managing wasting disease has been, and continues to be, selective culling of clinical

suspects throughout the endemic area. It has been ongoing for some time, but we have intensified our efforts over the last ten years.

We also have a self-imposed moratorium on translocating free-ranging deer and elk from populations where wasting disease is endemic as well as from populations adjacent to those endemic areas. Finally, we continue to control chronic wasting disease-infected populations through annual harvest to either maintain or reduce population size. We believe allowing these herds to expand unchecked is likely to exacerbate both the severity and spread of this problem.

[Slide.]

Turning now to the disease as we understand it in farmed elk; as is the case with chronic wasting disease in free-ranging cervids, chronic wasting disease in farmed elk has likely been present for quite some time. The first report of the farmed elk with chronic wasting disease came from Saskatchewan in 1996. It was a routine submission of an animal with a chronic pneumonia that was refractory to treatment.

Nearly two years later, a similar case was submitted from a South Dakota elk farm. Subsequently, epidemiological investigations as well as submissions made voluntarily or in compliance with mandatory surveillance

rules have led to disclosure of infections in eighteen game farms in five western states and one Canadian province. There **are** a few others that remain under investigation.

To date, all the cases in privately owned cervids have occurred in elk. The apparently intensity of infections in herds studied to date has varied widely and probably reflects influences of husbandry as well as the duration of infected in particular herds.

There are epidemiological connections documented through animal movements among some but not all of the infected herds. You can see some of those lines here shown on the slide. Although there is geographic overlap between the location of one infected Colorado farm and the endemic focus in free-ranging deer, epidemiological investigations really don't support free-ranging deer as the most likely source of infection in this particular case.

[Slide.]

The elk industry, in conjunction with responsible animal-health agencies, has been quite aggressive in dealing with chronic wasting disease. You will hear more about this from Drs. Zebarth and Creekmore later today, but I want to highlight a few important points here.

of the infected elk farms identified to date, only three remain under some form of quarantine and negotiated-disease management. The remaining herds, all of these in

black--I switched from red in the last slide to black here--have been depopulated or are in the process of being depopulated.

In the absence of a national chronic wasting disease-program for captive elk in the U.S., many herds were depopulated voluntarily or with the help of industry funding. At the urging of industry, Canada adopted a national CWD program last year and its implementation is under way.

Here in the U.S., several states, shown in purple, have developed regulations and programs for wasting disease that are in various stages of, actually, development or implementation. Plans for a national program are well under way.

[Slide.]

So, to summarize the disease in farmed elk, epidemiological investigations indicate that wasting disease has been in captive-elk industry for at least eleven years and probably much longer. Epidemics in captive elk herds are apparently self-sustaining, as they are in free-ranging animals and confinement may actually provide conditions allowing high incidence to develop in chronically infected herds similar to what has been described for scrapie.

There is a much wider and less predictable geographic distribution of chronic wasting disease in farmed

elk. This pattern has been shaped by extensive market-related animal movements in an industry that has expanded rapidly over the last decade.

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So, although chronic wasting disease is of understandable concern to a variety of interests, there is a considerable amount of information available to help us assess the risk and guide policy decisions. In the U.S., chronic wasting disease is probably best viewed as two separate epidemics, one involving free-ranging cervids and the other involving captive elk.

Neither of these epidemics are particularly new. Both epidemics are relatively well described, particularly in comparison to scrapie in the U.S. CWD is naturally maintained in both free-ranging and captive cervid populations and thus management will be challenging in both settings.

In the short term, CWD in captive elk is much more likely to be manageable than CWD in free-ranging cervids. I have no doubt, however, that new knowledge on chronic wasting disease and other TSEs will factor into future plans for further understanding and managing of both problems.

Thank you.

[Applause.]

DR. BROWN: Thank you very much, Dr. Miller, for a

very clear presentation. I have one question. I had thought, or my recollection was, that the first intimation about chronic wasting disease came in what were called semi-captive deer. We always used to talk about deer that were free-ranging and then came in and were fed and so forth.

DR. MILLER: That is correct. That is why the chicken-and-egg issue with respect to where this started. The animals that were used in those research facilities where chronic wasting disease was originally seen and described, many of those came from the wild. So it really is not known whether an animal brought the disease in with it, and certainly, in a captive confinement setting, it is going to take off. We have seen that in any number of cases, both in the industry and in our research facilities, or whether it started in one of the facilities and, somehow, spilled back out into the wild. We just really don't know and aren't going to anytime soon.

DR. BOLTON: I have a question. Could you tell me what percentage of the captive elk herds are actually infected?

DR. MILLER: Dr. Zebarth or Dr. Creekmore--it would be low, but, as a percentage--how many elk herds are there in the U.S., Glen? Do you have an idea?

DR. ZEBARTH: 2,000.

DR. MILLER: 2,000. So, right now, what, three

out of 2,000 are known to be infected. It is pretty small.

DR. LURIE: If I understood correctly, there was a slide there that showed what the particular states had done with regard to management, particularly of the elk program with the states that had taken action in purple. Two questions; one, what is that action, typically, and, secondly, I noticed that there was hole in the middle of the purple which looked to me like Wyoming.

DR. BROWN: It was.

DR. LURIE: Can you speak to that, please?

DR. MILLER: I can speak to Wyoming. I think Dr. Zebarth actually has a much more complete discussion of what is being done in the industry and so I am going to defer to him on that. With respect to Wyoming, there is only one captive elk herd in Wyoming. Game farming, otherwise, is not allowed in the State of Wyoming and, consequently, they really haven't had to do anything regulationwise.

I am not sure. Beth, maybe you know what they are doing with that one farm.

DR. WILLIAMS: They have talked to the managers of that farm. They are under the oversight of the Wyoming Game and Fish Department, but there is no formal program in place.

DR. BURKE: Are there any other foci anywhere in the world of similar chronic wasting disease among elk, deer

or related species?

DR. MILLER: Not that I am aware of and certainly not that have been reported.

DR. BURKE: Is there any reasonable surveillance or any efforts to identify that anywhere else in the world?

DR. MILLER: I know that the folks in New Zealand have done considerable surveillance in their red-deer industry. As far as other free-ranging populations, I am truly not sure.

DR. DETWILER: 1 can address that just a 1ittle bit. I think that is a valid assessment, that there really has not been much surveillance done. New Zealand is doing captive. I know Argentina is doing some captive but, to my knowledge, none in the free-ranging and very, very limited even in the captive.

DR. ROOS: How many animals are infected or diseased or die from the disease per year and has that been stable over the last five to ten?

DR. MILLER: In the wild, it is extremely difficult to gauge how many animals are dying out there. These are free-ranging animals that live in sparsely populated or unpopulated areas with respect to human presence. It is kind of like a tree falling in the forest when no one is around in terms of knowing whether or not they truly die.

What I can tell you is that the number of clinical submissions that we get from the public has increased in the last few years but so has our publicity campaign for getting folks to help us report this. Prevalence, which is probably a better gauge of what is going on in the populations, has remained stable over the last four or five years that we have good data for documenting that.

My gut feeling is that it is probably increasing slightly in some of these areas but it is not an explosive kind of an epidemic. Like I say, it is on a fairly protracted time scale.

DR. BROWN: Why is prevalence more easy to document? Your figure of 10 percent, was that free-ranging?

DR. MILLER: That is free-ranging prevalence based on random sampling of populations in conjunction with harvest. That is just in that one fairly narrow strip through there. The problem is getting a handle on clinical cases in the wild is almost impossible. We know what we get, but there are so many reporting biases and so many other problems inherent in those kinds of data that tracking them is--

DR. BROWN: So your prevalence figures are you go out and capture free-ranging animals?

DR. MILLER: No.

DR. BROWN: What?

DR. MILLER: We are sampling animals in conjunction with harvest. So it is a essentially **a** slaughter survey is what it is.

DR. **CLIVER:** This seems to be one of the few TSEs where there is some potential for antemortem sampling if the tonsil collection could be done in that way. Is there any thought being given to darting some of these animals and letting them loose after you have taken the samples?

DR. MILLER: We have actually been doing a little of that this last winter, or this current winter. It is easier said than done. It would be an interesting exercise but, in terms of applying that on large-scale depopulations, we are talking about, literally, 40,000 square kilometers or more of native habitat, tens of thousands of deer and thousands of elk in that area. The logistics of it would not be particularly pleasant to think about.

DR. DeARMOND: A question from Dr. Priola's presentation. Could lateral spread, in this disorder, by through the placenta and what is their behavior in dealing with placenta? A second one is, are the farm-raised animals exposed to meat-bonemeal products?

DR. MILLER: With respect to the first question regarding transmission, certainly it is conceivable that placental tissue would be involved. The cervids are very different in terms of the way they behave. They tend to go,

particularly in the wild, and fawn or calve in a very isolated setting. They almost immediately consume the placenta and as much of the fetal fluids and other things as they can because of the predator-avoidance strategy.

So, in terms of the agent being particularly effectively spread that way, probably not. It certainly could contribute, but there are other things that are contributing to its spread.

DR. DeARMOND: So only the mother eats that or do other deer come in and help?

DR. MILLER: Typically, when they are fawning of calving in natural settings, they are by themselves so they are the only one around. We have tried to collect placental tissue in our captive-deer herd, our research herd. You have to be sitting right there when it hits the ground or it is gone. They don't share.

Again, there are millennia of evolutionary pressure for them to do that because that is how they avoid having the little ones eaten.

DR. DeARMOND: And then, for artificial feed--

DR. MILLER:. As far as the artificial feed, Glen could probably address that. It is banned. Certainly, in practice, in our research facility, we have had chronic wasting disease for decades and we don't use, and to my knowledge never have used, meat and bonemeal. Certainly, in

ıe free-ranging animals, meat and bonemeal is not being
sed and certainly does not seem to part of what is
erpetuating the problem.

DR. BROWN: Actually, the more interesting
uestion is the converse; do they ever wind up as meat and
onemeal?

DR. PRUSINER: This number of 10 percent'
revalence in this slaughter sample, where is this
ublished? In all of the materials we have, I can't find
t. I ask people this and when I quote this figure,
veryone is absolutely astounded. I would like to see the
ublished data.

DR. MILLER: I will hand you a reprint when we get
lone.

DR. PRUSINER: Okay.

DR. MILLER: It is in the journal Wildlife
)iseases, October of this last year.

DR. PRUSINER: Great. Thank you.

DR. DAVEY: Dr. Miller, could you just enlighten
ıs a little bit in terms of venison and gelatin, what other
)roducts, byproducts, meat products, from these animals get
into the human food chain?

DR. MILLER: Again, I am thinking Glen is probably
going to hit on some of this stuff later on. With respect
to the free-ranging animals we harvested, virtually none.

hose were essentially animals that are taken in to private ossession and processed for meat, muscle tissue.

As far as rendering and things, I would think--the ndustry is so small right now, and there are so few animals hat go to slaughter, it is mostly custom slaughter, is it ot--Glen, very little, if any, of that, would be going into endered product or into those other products.

DR. DeARMOND: What happens to road kill, when a leer is run down in the road?

DR. MILLER: It depends on where it gets hit. In ome places, the coyotes and the magpies and the other cavengers clean it up. In other places, it is allowed for eople to pick those road kills up as long as they get the roper permits.

DR. MILLER: In California, I think you have to report it and I think they take it and they grind it up and nake it into feed for other animals; is that not right?

DR. MILLER: We don't do that; no.

DR. MANUELIDIS: You mentioned something very interesting. You said that this was not like scrapie in Europe. Maybe you could sort of expand and update us a Little bit on what the sort of experimental models of this are currently going on and if it is related, you think, to scrapie in the United States that began not to be under surveillance?

DR. BROWN: Dr. Miller, any questions that you get which you know are going to be covered subsequently by other people, you can defer.

DR. MILLER: I am not sure on that one. Dr. Bruce and her colleagues over in Edinburgh have actually put wasting disease into their mouse pathogenesis profile. I don't believe those data have been published yet. .

DR. WILLIAMS: Only mentioned in Dr. Bruce's Nature article in 1997. So it was a mention, not really a documentation of that transmission.

DR. MILLER: In terms of other studies, Linda, did she have a comment about--in terms of looking at the relationships between wasting disease and scrapie, there is obviously a lot of fertile ground there. I think the folks at Ames, at ARS, have done some work putting scrapie into elk. There are other cross-species transmission studies underway. But scrapie into deer; I don't know whether anybody has started that one yet.

DR. DETWILER: That has been talked about but I don't know. There are a lot of things that are ongoing. Since you referred to me, I just want to go back and, lest we go down the path of the sampling of live animals through tonsil, I will just really reiterate what Mike said. You heard the human community saying about doing the testing on cadavers, that that is logistically a nightmare.

To us, that is not a logistical nightmare. However, catching and using general anesthesia, because taking a tonsil--they don't lay down and say, "ahh," just at your command.

DR. PRUSINER: They don't stand up and **say** "ahh."

DR. DETWILER: Right; they don't stand up. We have done it in sheep, tried to do it in sheep, and they are captive. We have them in flocks and it is very difficult. Dr. O'Rourke is developing for the third-eyelid biopsy. That is much more logistically feasible--but even in sheep, where you have them in confinement, unless under general anesthesia.

DR. GAMBETTI: Dr. Miller, if I understand correctly, the assessment is made by immunostaining of the obex and/or the tonsils. If we had to use, really, that approach to human prion disease, we would miss some of the cases simply because there are varieties, there is change and diversity in the distribution of the PrP-sc. That may occur also in chronic wasting disease.

So I understand that it may be more taxing on the resources, but I would recommend that other parts of the brain be tested as well because, as I said, the distribution, not necessarily, is the same in all the animals.

DR. WILLIAMS I would just like to say that we

have looked at quite a number of deer and elk including mule deer and white-tail deer, looked at the whole brains and find that the disease is very stereotyped in the lesion distribution of spongiform encephalopathy, in particular, and also in terms of the PrP deposition.

The dorsal motor nucleus of the vagus is, in all cases, where the first deposition occurs and it is very stereotyped, although I completely agree that you can't assume that every single case is going to be exactly the same. So we do look at whole-brains, and not just the obex, on many of them.

DR. BROWN: It is rather more like BSE in scrapie in the sense that it tends to be distributed in the midbrain.

Don, and then we are going to go on to the next speaker.

DR. BURKE: I didn't understand the answer to the question about whether or not these had been examined by the mouse pathogenesis biotype. They have or have not and, if they have, what do the results show?

DR. WILLIAMS: One mule-deer brain has been examined through the mouse-strain typing system and the results from Dr. Bruce's work and Dr. Frazier's work was that the CWD is not like BSE. It is not like CJD or variant CJD. It is not like any of the strains of scrapie that they

have worked with. So it is basically unusual.

DR. BURKE: But it fits in the general profile of--scrapie is all over the place and so it doesn't mean, just because it is not the same, it couldn't be the same.

DR. WILLIAMS: Exactly.

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

The next presentation is by Dr. Ermias Belay from the CDC. He will be presenting information on the epidemiologic investigations of a group of young cases of Creutzfeld-Jakob disease who have a history of exposure to venison.

Epidemiological Investigations of Young CJD Cases Exposed to Venison

DR. BELAY: This one is my presentation so you can ask me questions.

[Slide. 1

I will summarize the findings of our investigation of unusually young CJD patients who were reported to have consumed deer and elk meat.

[Slide.]

The occurrence of CJD in two deer hunters and a third patient who consumed venison created a concern about possible transmission of CWD to humans. The occurrence of these cases created a concern primarily because of the unusually young age of the patients.

The occurrence of CJD in patients or person thirty years of age and under is extremely rare in the United States. The majority of the cases in this age group have been associated with either receipt of human growth hormone or dura mater grafts.

[Slide.]

This slide shows CJD cases thirty years of age and under reported to CDC during 1979 through 2000. Cases that have been associated with human growth hormone, in red or purple, and dura mater grafts are shown here. The three cases that reported consumption of venison are shown here. These other cases are sporadic CJD cases. As you can see, the occurrence of sporadic CJD, in this young age group, is extremely rare in the United States.

[Slide.]

The concern about possible transmission of CWD to humans was also raised because of the endemic occurrence of chronic wasting disease is deer and elk in the United States, as we heard from Dr. Miller today and the potential of these TSE agents, as evidenced by the new-variant CJD outbreak in the United Kingdom.

But, fortunately, as Dr. Miller told us today, the endemic occurrence of chronic wasting disease is limited to localized areas in the states.

[Slide.]

This map shows the distribution of the three cases in relation to CWD endemic areas. The cases occurred in Florida, Utah and Oklahoma.

[Slide.]

Our investigation involved reviewing the clinical records and conducting pathologic studies of all the three cases. The pathologic specimens were evaluated by Dr. Gambetti, Dr. Pierluigi Gambetti, and colleagues at the National Prion Disease Pathology Surveillance Center in Cleveland, Ohio. So all of the data that I will be presenting relating to the pathologic specimens was performed by this center, the national center.

[Slide.]

In addition, we interviewed close family members of the patients to determine receipt of human growth hormone, or human tissue grafts, in the presence of any neurosurgical procedures. We obtained dietary habits and travel history and determined their hunting practices. We specifically looked for evidence of possible exposure to venison obtained from the known CWD endemic areas.

[Slide.]

Finally, we compared the key evidence that supported a causal link between BSE and new-variant CJD in the United Kingdom to that of CWD and CJD in the three patients in the United States. This key evidence that we

used in our comparison included an increasing incidence of the disease among young cases, which was true in the United Kingdom in the new-variant CJD, recognizable exposure of the patients to the infective agent--

[Slide.]

The presence or absence of a unique characteristic pathology, and a phenotypical homogeneity among the patients and different immunoblood characteristics of the protease-resistant prion protein and a uniformity in the codon 129 of the prion-protein gene in the patients; so we used all these parameters to compare the possible lines of evidence that were generated in the United Kingdom for the new-variant CJD to that of chronic wasting disease and CJD in these patients.

[Slide.]

Case 1 was a twenty-eight-year-old woman who presented in early 1997 with the characteristic CJD signs and symptoms. The EEG was reported as abnormal. It was not classic for CJD.

[Slide.]

This patient died four months after illness onset and analysis of the prion-protein gene indicated a methionine-methionine homozygosity at codon 129 and the absence of genetic mutations.

[Slide.]

The immunohistochemical analysis showed a punctate or synaptic pattern of immunostaining with no plaques. The immunoblood analysis was not performed in this patient because of lack of frozen brain tissues.

[Slide.]

This patient was reported to have consumed deer meat during her childhood when the patient was one to six years of age. The deer that this patient consumed were mainly harvested by the patient's father in the State of Maine. In addition, this patient was reported to have consumed elk meat provided to the family as a gift during two occasions when the patient was about six years of age.

Although the exact origin of the elk consumed by this patient could not be determined, the family member indicated that the elk meat may have been obtained from Wyoming. There was no history of consumption of organ meat either from deer or elk.

[Slide.]

The second patient was a twenty-nine-year-old patient who presented with dementia beginning in May, 1998. This patient also had other neurologic signs that are compatible with CJD.

DR. PRUSINER: Was this a man or a woman?

DR. BELAY: This was a man.

[Slide.]

His initial two EEGs were reported to be normal and the CSF 14.3.3 test was negative. The evaluation of a brain biopsy specimen confirmed the CJD diagnosis.

[Slide.]

Analysis of the prion-protein gene showed valine-valine homozygosity and absence of genetic mutations.

[Slide.]

The immunohistochemical analysis showed a punctate immunostaining with no plaques. The immunoblood analysis of protease-resistant prion protein showed the type 1 pattern with a molecular mass of about 21 kiloDalton. This patient was recorded to have hunted deer almost every year since 1985 in many non-CWD-endemic areas, mainly in Utah.

[Slide.]

In addition, the patient's family reported that the patient had eaten elk meat which the patient, himself, harvested in 1995 from a non-CWD-endemic area of Wyoming which is very close to the border of Utah. The patient was reported to have regularly consumed the liver from deer and elk but not the brain or any other organ meat.

[Slide.]

The third patient was a twenty-seven-year-old man who presented with memory loss in December, 1998, This patient also developed other neurologic signs compatible with CJD.

[Slide.]

The EEG was reported as abnormal but non-diagnostic for CJD. The CSF 14.3.3 test was positive. The evaluation of his brain biopsy confirmed the CJD diagnosis in this patient. No autopsy was performed on this case.

[Slide.]

Analysis of the prion-protein gene showed a methionine/valine heterozygosity and the absence of genetic mutations. The immunoblood analysis of PrP-res showed the same type 1 pattern with a molecular mass of 21 kilodalton.

[Slide.]

This patient hunted exclusively--he hunted deer almost every year and exclusively hunted in two areas close to his hometown. He was born and grew up in that area and specifically hunted in two geographically limited areas close to his hometown.

There is no history of consumption of deer or elk meat obtained from the known endemic states in this patient. However, the plant that the patient took his deer carcasses for custom processing has also been processing about twenty elk from Colorado every year. So he used to take his deer carcasses for custom processing to a specific plant and that plant regularly processed about twenty elk every year obtained from Colorado.

However, the origin within Colorado of this elk

could not be determined. As I say, there was no consumption of deer or elk meat obtained from the known endemic areas directly by the patient.

[Slide.]

In summary, all three cases had confirmed CJD with no iatrogenic exposure or genetic mutations and none of the patients had a history of travel outside of the United States or a clinical pathologic profile consistent with the new-variant CJD. All three cases were reported to have regularly consumed deer or elk meat but none were reported to have consumed deer obtained from the known endemic areas.

[Slide.]

In addition, none of the patients reported consumption of brain or spinal cord either from deer or elk. There is some possibility that cases 1 and 2 may have eaten elk meat obtained from Wyoming. However, there are some uncertainties regarding their exposure to elk. In case 1, for example, the Wyoming origin of the elk was not absolutely certain. The patient's family indicated that they were not sure about the exact origin of the elk that they received as a gift from their family friend.

[Slide.]

In case 2, the Wyoming elk was harvested by the patient, himself, outside of the known endemic areas in 1995 which is about three years before the onset of CJD in the

patient. In case 3, as I said, there was no consumption of deer or elk meat obtained from the known endemic areas. The contamination of his deer meat by elk meat obtained from Colorado at the processing plant was possible. But it remains uncertain whether or not the elk processed in the same plant were actually infected 'with CWD or originated from the known endemic counties from Colorado.

[Slide. 1

No unique pathology or clinical pathologic homogeneity was detected among the three cases. Based on a classification scheme developed by Parchi and colleagues, case 2 was classified as a VV1 variant and, in case 3, as an MM1/MV1 variant. The MM1/MV1 variant is the most common variant described by Parchi and colleagues and represented about 70 percent of sporadic CJD patients.

The immunoblot characteristics of case **1** were unknown, but the clinical pathologic profile suggested the MM1/MV1 variant which, as I said, the most common variant seen in about 70 percent of sporadic CJD patients.

[Slide.]

The VV1 variant, to which case 2 was classified, was described by Parchi and colleagues to constitute an estimated **10** percent of sporadic CJD patients.

[Slide. 1

Because of the similarity, the clinical pathologic

similarity, of cases classified in the VV1 variant with that of case 2, we determined the hunting practices and venison-consumption histories of other members of the VV1 variant.

In none of the other four cases classified in this variant where hunters in at least two of the four cases were reported not to have consumed deer or elk meat indicating that this clinical pathologic picture could actually occur in the absence of venison consumption.

[Slide. 1

This table shows the comparison of the key evidence that supported a causal link between BSE and new-variant CJD to that of a possible link between CWD and CJD in the unusually young patients. In the new-variant CJD, there was a definite increase in the incidence of the disease among young cases which was not the case in the United States. We only had three patients during 1997 through 2000.

A unique characteristic pathology was described in the new-variant CJD where the pathology in the three patients was not different from that normally seen in other sporadic CJD patients. Clearly, there was a clinical pathologic homogeneity among the new new-variant CJD patients which was not the case among the three cases, among the three patients in the United States.

The protease-resistant prion protein in the new-