about how much beef people consumed. I think that is really wrong.

DR. GAYLOR: In fact, we ought to go more than a factor of three because the impact on the military, we have heard, is more than it would be for the general public. So, if we are going to look at impact, then it would go more than a factor of three.

DR. PRUSINER: We just heard the impact is not a problem, that they can fix it up. He just told us he can take care of it. So, I just really totally disagree with everything you have said.

DR. LEITMAN: Let me just reiterate that the effect on the civilian blood supply is the same because every person in the military is there for 18 months to 3 years. So, when they come back into the civilian population we would be eliminating all Americans and their dependents who served in that period in Europe. All of them. That is still a 3 percent loss, predicted loss by the REDS data to the civilian donor supply.

DR. BROWN: Yes, that is true. When they go inactive and come back and start wanting to donate to the civilian blood supply, they are 100 percent excluded.

DR. ROOS: Just two points. First, although beef is imported into these bases, as you noted, Paul, there may be dietary specialties of U.K. and France that are important

nd not actually mirrored in these military bases that may e important to pathogenesis. So, I have a little less oncern perhaps about this U.K. beef, or it might of nterest to get more detail with respect to exactly whether t was processed or cooked, etc.

But another point, I mean the question here, if ou read it literally, is whether we suggest some other olicy and I think the answer is yes, and I don't know rhether the FDA really wants us to come up with a number at .he moment.

DR. BROWN: It just occurs to me why don't we just ay yes and punt the whole issue back to the FDA? Say yes ithout specifying what. We should probably give them a lue, however, if it is possible, as to the direction of hinking. Is our direction of thinking altering a time? That is the only direction I can think of but there may be thers.

DR. ROOS: But, you know, when we came up with the six months it did have to do with benefit-risk --

DR. BROWN: That is right.

DR. ROOS: -- and what the damage was to the blood supply.

DR. BROWN: That is right.

DR. ROOS: And, I am not sure that we know that if we now limit residence in Europe of the military to one

'ears, or a year and a half or two years, or three, and that s why I have some difficulty --

DR. BROWN: Right, and Stan is entirely correct in laying that six months was based on benefit rather than risk because we didn't know anything about risk, and we still lon't know anything about risk, but the benefit was that we eliminated close to 90 percent of person years in the U.K., on the one hand, and did not damage the blood supply more than two percent, on the other hand. So, these were really the two elements of the formula that we used for the six months and, logically speaking I suppose, again we have no more science now than we did then and, therefore, if that decision was made on that basis for the civilian community it is conceivable that consistency calls for the same basis to be used for the military. Colonel?

COL. FITZPATRICK: Let me clarify on Dr. Leitman's comment. Allan and I discussed his slide afterwards and he had age corrected and, if you recall, he had reduced the lumber by about 16 percent. When we discussed it, it was in the light of really it shouldn't be age corrected because as chose individuals age-they will become of an age to donate out they won't be able to donate because they or a family nembers was stationed in Europe during that time. So, the actual number is over 3 percent, probably about 3.3 percent.

DR. BROWN: Another thing that the committee could

dlo would be to vote yes and then, as has happened before, ask for information which a subsequent committee meeting could consider.

DR. DAVEY: That is certainly a reasonable course. Listening to the data that are somewhat sketchy and insubstantial about the impact, although there are some warning flags, and hearing about the impact on the military blood supply and the civilian blood supply, rather than give the FDA just an unspecified yes, without any guidance, I would suggest that it might be a more prudent course to give the FDA a no at this point and perhaps, if necessary, revisit this at a future meeting.

DR. BURKE: The reason that the six months was chosen is that we tried to optimize the risk-benefit ratio. In the military population, which is a closed system, if we tried to optimize it for the military it won't be six months because the number of persons who will be deferred will be much greater because everybody that we are talking about in that system will have been overseas. A much higher percentage go overseas than whatever it is -- 10 percent of donors in Chicago who'go overseas. So, we would have to re-optimize whatever that ratio is for the percentage of people who will be spending that period of time in a risk situation, or perceived risk situation. So, I disagree. It has to be recalculated and I think the military can provide

those numbers. Without those numbers in hand, I think we are just guessing about what that interval should be.

DR. BROWN: I don't think we disagree. Did I indicate that we shouldn't recalculate?

DR. BURKE: If we didn't disagree, that is great!

COL. FITZPATRICK: We are talking about a finite group and a finite period of time. We are talking about 1980-1996 at this point, with known procurement of beef from U.K. sources so that that 4.4 million number, in regard to this issue before the committee, is a static number.

DR. BROWN: Right.

COL. FITZPATRICK: No, as far as France, and Portugal and those, it is different but it is a static number at this point.

DR. BROWN: Would it be possible for Allan and somebody from the military to put together the same kind of two-parameter figure showing loss to blood supply versus potential exposure to U.K. beef, in the way that we did for the civilians, so that somebody could, if they chose to do it, make a decision using the same basis? That is what you wanted, wasn't it, Don, more or less?

DR. BURKE: I think we both wanted it.

DR. BROWN: Okay.

DR. KATZ: Do you have any estimate out of that 4.4 million who is still in the military? I would guess not

too many. This is primarily an impact on civilian centers.

COL. FITZPATRICK: That is where my 15 percent Loss comes from. There are only about 215,000 active duty members left on active duty and about 217,000 family members. So, in aggregate I have about 442,000 that I have to deal with.

DR. BROWN: So, basically we are talking'about half a million people.

DR. BOLTON: **I** would like to clarify something. My understanding is that the six-month U.K. rule already covers those in the military who served in the U.K. Is that correct? What we are talking about here really is those who were in the European Theater but were not in the U.K.

COL. FITZPATRICK: Yes, that is true.

DR. BOLTON: **So,** their diet is, at most, 25030 percent U.K. sourced meat and the rest is either U.S. beef or local economy beef. So, I think in that case that adjustment of the risk factor is warranted. You are really talking about somewhere between a three- and five-fold reduction in risk, and so you could rationalize, if there is any way to rationalize this, the 24-30-month period of time.

DR. BROWN: Yes, we can rationalize the risk ratio but what we don't know is the effect of the various time periods on the blood supply. I mean, that is what we don't know anything about.

DR. BOLTON: It is clear that an 18-month cut-off time point is going to have a major impact, but 24 months would have much less impact. So, in terms of that the risk-benefit ratio for the military themselves is much better at a 24-month or greater time period cut-off than 18 or 6 months. Is that right?

COL. FITZPATRICK: I can say that a 24-month break would have an impact on both the civilian and the military donors, probably more on civilian because that applies to, the single soldiers who are there and may no have made a career of the military and are now out. As far as Dr. Brown's first question, I know that Allan and I could get together on the demographic data as far as the effect on both donor populations and analyze that. We have the quandary on the risk factor and we would have to ask for guidance from you and Col. Severin on what ratio or factor could be used to factor in the risk based on the consumption of beef, and how we go about determining that.

DR. LEITMAN: Dr. Brown, could I make a comment? You have a natural experiment ongoing. You have zero cases out of 4.4 million at risk, in contrast to 90 cases out of 55 million at risk who resided in the U.K. So, that is less than 1/10 of the risk. There are no cases right now. It is possible that there is actually no risk because, as someone stated, the dietary habits in U.K., the cuisine in France

nay be very substantially and critically different than what into packaged beef that went to military commissaries. So, the risk may be extremely low, approaching zero. You have no data to suggest otherwise.

DR. GAYLOR: But the number of years are not the same there. You are comparing U.K. years, people who have been there 20 years, where the military may be only three or four years. So, you get another factor of five.

DR. BROWN: Maybe it takes five years of constant eating before you begin to play Russian roulette with whatever it is that you have eaten. That is true. We just don't know. We don't know, for example, if it takes six successive exposures over a period of a week or two weeks or a single exposure will do it. I mean, there is just no information. Even experimentally there is no information.

DR. MCCURDY: Looking at the issue of the blood supply, if you were to interdict all people who lived in Europe you would have a very heavy impact on one major blood center and one major metropolitan area, which may be very difficult to overcome. The military is likely to have an impact, perhaps a smaller impact but nevertheless an impact that is spread over the entire country. If the blood supply can cope with that loss, then you may have a leg up the next time you have to consider this as to whether you should move on to the rest of Europe. There may come a time -- I hope

and don't believe it is soon -- where the blood supply of the whole country may not be sufficient because of the multiple deferrals that are added. I think that is a ways away.

DR. BROWN: I propose that we vote on question (b). I think it is possible for the committee to say no, of course, and they can say yes, and they can say yes'with the proviso that they need additional data to even begin to formulate a suggestion. If you would like to vote on that, worded as such, that is to say the yes with the qualification that the committee is really unable to formulate any specifics about what that policy should be but that we do feel that something ought to be done -- yes?

DR. EWENSTEIN: Given the nature of this question being so vague, I mean, I would rather vote on a question that recommends that an impact study be done.

DR. BROWN: Okay. Shall we word it in that way, an impact study?

DR. EWENSTEIN: With the goal of trying to find an optimal period of time of exposure of military personnel for blood donation deferral.

DR. BROWN: Yes, it would be an impact study of estimated risk versus effect on blood supply. That will be the question we will vote on. Either we vote no, or yes with the recommendation that an impact study be conducted to

examine the potential risk versus the impact on blood supply.

DR. EPSTEIN: I think that the impact of a majority vote yes is that the **FDA** should go away and try to develop the issue a little better along the lines suggested, like an impact study. I think the'implication of a vote now is that it is the sense of the committee that this'risk does not rise to the level that we should be developing a policy. So, I think it is useful to have a yes or no vote before we consider whether we want any additional votes. Personally, I don't think we need an additional vote. We got the message.

DR. BROWN: Shall we go on to the next issue?

DR. EPSTEIN: I think it is important whether the sense of the committee as a whole is that we should continue to work on developing a policy or not. Because what we are really talking about in terms of looking at an impact study is how to develop a policy, and I am a little bit uncertain what the sense of the committee is.

DR. BROW-N: Fine, we will vote on the question as written and then put on a little caveat. Yes?

DR. CLIVER: One thing I wanted to interject before we actually go around is that it seems that we are saying that this decision needs to be based on something that isn't really science. We accept that. We realize that a decision has to be made and the science isn't there. My

feeling is that our charge to FDA ought to be to go ahead and look at this from an expediency standpoint, which is where the six months came from or the ten years came from, but don't necessarily come back to this committee with it. Go ahead and consider these factors and go with it.

DR. BROWN: Well, part of the caveat was not necessarily that they come back to this committee, although I have no idea what other committee it might go to. I think the FDA likes expertise brought to bear in public on their decisions, and I think they are probably right to do so. In any case, let us vote on this as written, which is do members of the committee suggest some other policy for deferral of U.S. military personnel or dependents due to exposure to U.K. beef products? Stan?

DR. ROOS: Since I was defeated for the last one, I have to vote yes this time.

DR. WILLIAMS: Yes.

DR. LURIE: Yes.

DR. CLIVER: Yes.

DR. BELAY: I can't really vote on this issue without knowing what the impact is so I abstain.

DR. BROWN: Yes.

DR. BOLTON: Yes.

DR. NELSON: Yes.

DR. GAYLOR: Yes.

DR. PICCARDO: Yes.

DR. MCCURDY: Yes.

MS. FISHER: Well, I voted yes on (a) so I am going to abstain.

DR. BURKE: No.

DR. EWENSTEIN: Yes.

DR. DETWILER: Yes.

DR. ROOS: Yes.

DR. FREAS: There were two abstentions, Ms. Fisher and Dr. Belay. There was one no vote, Dr. Burke. All the rest were yes.

DR. BROWN: Which is **13.** Is that correct?

DR. FREAS: It should be, yes. Thirteen yes, one no, two abstain.

DR. BROWN: And, I think the transcript will reflect the direction of the committee's thoughts on what kind of further information would be desirable before anybody made a specific decision.

We now arrive at the next major topic for the day, which charts unexplored territory in terms of similar considerations of deferral of donors of human cells, tissues and cellular and tissue-based products. We now have a number of presentations and we will see if we can get through two, three of four of them before we take a short break. The first presentation will be background on current and

proposed policies for blood, human tissue and dura mater regarding CJD and vCJD. This will be presented by Dr. Solomon who is a member of the FDA. Dr. Solomon?

Background on Current and Proposed Policies for Blood, Human Tissue and Dura Mater Regarding CJD and vCJD

DR. SOLOMON: Thank you.

[Slide]

I am going to provide some background information on the current and proposed FDA regulation on human cells and tissues. First, the current regulation. These products are diverse and the regulation has been diverse. There is a category called human tissue intended for transplantation that does not receive FDA approval. Another group, the cell and gene therapies are regulated as licensed biologic products. Still other tissues are regulated as medical devices, such as dura mater, heart valves and cornea1 lenticulas.

Historically, FDA has not regulated hematopoietic stem cells, except if they are extensively manipulated, nor has it regulated reproductive cells and tissue. FDA does not regulate organ or bone marrow transplantation. This is regulated by another federal agency, HRSA.

[Slide]

We began regulating human tissue intended for transplantation in 1993, and published a final rule in 1997

which was codified at 21 CFR 1270. Under this category would be included musculoskeletal tissue, like bone, ligaments, tendons, fascia, cartilage, ocular tissue such as corneas and sclera, and skin. These regulations focus on a determination of donor suitability through donor screening, that is, looking for risk factors and clinical evidence, and donor testing for certain specific agents -- HIV-l; HIV-2, hepatitis B and hepatitis C.

[Slide]

The donor screening process involves a donor medical history interview, which is a documented dialogue with the donor if living, or with an individual knowledgeable about the donor's medical history and relevant social behavior. It also includes physical assessment, review of medical records, any laboratory test results, coroner and autopsy reports, if available.

[Slide]

An exception to the requirement for the donor medical history interview occurs with corneas procured under legislative consent. There are three states that have laws that permit retrieval of corneas by medical examiners or coroners without the consent of the next of kin. In these cases, the physical assessment is required. All available information is reviewed, and the cornea1 tissue, when sent to the ophthalmologist, is accompanied by a statement that

it was determined suitable in the absence of the interview, and was procured under legislative consent.

[Slide]

Although the regulations I have just described do not address TSEs, a guidance document that we issued in July, 1997 states that, although not directly within the scope of 21 CFR 1270, FDA' is aware that screening for possible risks of exposure to CJD is recommended in industry standards, and these risks include known family history of CJD; receipt of human pituitary growth hormone; and receipt of dura mater transplant.

The tissues that are known to have transmitted classic CJD are dura mater and cornea. Dura mater is currently regulated as a medical device. In July, 1999 the Center for Devices issued a guidance on processed human dura after several discussions with this advisory committee. The guidance contains strict controls of the dura mater recovery and processing. For instance, a donor is disqualified if he has a diagnosis or known family history of CJD; receipt of pituitary growth hormone; receipt of dura mater; a degenerative or demyelinating disease; or other neurologic disease; or has died in a neurologic or psychiatric hospital.

[Slide]

In addition, this guidance for dura mater

recommends a gross and histologic examination of the brain, the archiving of brain and dura mater tissue, testing for prions by a validated test when available, CJD disinfection by a validated procedure, manufacturing controls such as aseptic recovery, procedures to prevent cross-contamination, for instance, no co-mingling with'tissues from several donors, and use of disposable instruments. There are also record-keeping and tissue tracking requirements.

[Slide]

Nest we will move on to the proposed FDA regulations. In February of 1997 FDA published a proposed approach to the regulation of cellular and tissue-based products. This was a unified risk-based approach in which all human cells, tissues and cellular and tissue-based products intended for transplantation would come under one umbrella. That is, all manufacturers of these cells and tissues would be required to follow the same minimum requirements.

To date, we have published three proposed rules and are working on one guidance document. In 1998, we issued a proposed rule on establishment registration. This has been finalized and is on display today and will be published tomorrow.

In 1999, we issued a proposed rule on donor suitability. We are in the process of reviewing comments to

the docket for this proposed rule.

This past January, 2001, we issued a proposed rule for current good tissue practice.

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The scope of the proposed approach would include all of the cells and tissue products that FDA currently regulates. That is, the human tissue products, the musculoskeletal tissue, ocular and skin tissue, the cell and gene therapy, medical devices, as well as two types of products that have not previously been regulated by FDA, hematopoietic stem cells from peripheral blood or umbilical cord blood and reproductive cells and tissue.

Under the proposed approach we would plan to make dura mater and heart valve allografts -- we would consider them regulating then as tissues instead of medical devices, but these same controls have been incorporated into the donor suitability and the good tissue practice proposed rules.

[Slide]

The proposed rule on donor suitability would require the screening of all donors for risk factors and clinical evidence of HIV, HBV, HCV and now we have included the TSEs. It would also require the testing of all donors except autologous donors for HIV-l, HIV-2, hepatitis B, hepatitis C and syphilis.

[Slide]

Again, the donor screening would involved the medical history interview, physical assessment and review of medical records.

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However, there would be no exception from the donor medical history interview for corneas procured under legislative consent laws. The reasoning behind this is that risk factors, signs and symptoms of TSEs would be expected to be uncovered in the donor medical history interview, but would be less likely to be found during other parts of the screening process.

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FDA specifically requested comments on this proposal and we received mixed comments -- this is on the requirement for a donor suitability interview, and 57 comments were opposed to having the interview be required; ten comments supported having the interview be required.

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I also want to point out that in the donor suitability proposed rule we would not prohibit the use of cells, tissues and tissues from an unsuitable donor, that is, a donor with a behavioral risk factor or a positive test in certain situations. In other words, there is an out-clause. If the cells and tissues were for family related

allogeneic use, reproductive tissue from a directed donor, or there is a documented urgent medical need, by which we mean no comparable cell or tissue is available and the recipient is likely to suffer serious morbidity without the product.

[Slide]

This could only occur though provided that the product was labeled biohazard and the physician was notified of the screening and testing results, authorized the use, explained the risk to the recipient or authorized representative, and agreed to obtain consent.

[Slide]

We are in the process of developing a draft guidance on donor suitability. This draft guidance will be made available for comment. It may contain specific information to assist in complying with the donor suitability rule. It may contain specific questions to ask regarding risk factors for and clinical evidence of TSE, both classic CJD and, depending upon how the committee advises us, vCJD.

[Slide]

I am skipping the next four slides in your handout to save time and now I will read the charge to the committee. FDA asks the committee to evaluate the risk of transmission of vCJD through the transplantation,

implantation, infusion or transfer of human cells, tissues and cellular and tissue-based products, and compare this risk to that of the transfusion of blood and blood products for which precautionary measures have already been adopted.

Based upon this evaluation and considering the potential effect on supply, the committee is asked to recommend whether FDA should defer donors of these'cells and tissues who have possibly been exposed to the BSE agent through residence in or travel to BSE countries.

In addition, the committee is asked to consider how information about residence or travel history can best be obtained. This is particularly relevant to the situation in which corneas are procured under legislative consent. Again, this term relates to state laws that allow the medical examiner or coroner to procure cornea1 tissue in the absence of the consent of the donor's next of kin and, hence, in the absence of a donor medical history interview with the next of kin.

[Slide]

Now I will read the questions. The first question, compared to the risk of transmission of vCJD 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? What are the relative risks for different cells

and tissues?

[Slide]

Just to remind you again of the diverse group of cells and tissues that we are talking about, there would be musculoskeletal tissues, bone, cartilage, ligament, tendon, fascia, ocular tissues, cornea, sclera and skin, cellular products such as chondrocytes, hematopoietic stem cells, pancreatic islet cells, to name a few, reproductive cells and tissues, semen, oocytes, embryos, dura mater, heart valves, cornea1 lenticulas, some combination products like skin plus a synthetic matrix. Just to remind you again that FDA does not regulate vascularized organs or hematopoietic stem cells from bone marrow if they are minimally nanipulated and a different federal agency regulates those. So those are not on the table today. Thank you.

[Applause]

DR. FREAS: Thank you, Dr. Solomon. Dr. Gibbs is scheduled for the next presentation and Dr. Asher will be giving it. Thank you.

Tissue Distribution of Infectivity in Human TSEs

DR. ASHER: I am sorry that Dr. Clarence J. Gibbs, Jr. wasn't able to be here today to present the results of studies on the distribution of infectivity in humans with spongiform encephalopathies, work that he began with Carlton Guideshek in 1963 and which continued for more than 30

years. Joe is resting at home now. He is feeling better after a couple of weeks in the hospital, but he is simply not well enough to prepare or deliver a talk. Fortunately, ır chairman had written a careful summary of the work, with several co-authors including me, in 1994 and Paul kindly provided an update of what few results have accumulated ince then. The slides, the conclusions and all of'the istakes are mine.

[Slide]

Three hundred cases of transmissible spongiform ncephalopathies, studied from 1963 to the present, ncluding 282 cases of various types of Creutzfeldt-Jakob isease and its Gerstmann-Strussler syndrome variant, not, f course, vCJD and 18 cases accrual.

[Slide]

The suspensions of tissue were prepared, noculated intracerebrally, sometimes by other routes, into variety of primates, in early years chimpanzees, later ıainly squirrel monkeys and some other New World monkeys, he animals were observed for long periods of time, sometimes for many years.

[Slide]

I won't review the criteria for positive and ıegative animals. Essentially, a positive animal was one chat had histopathological or later Western Blot evidence of

pongiform encephalopathy.

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Four neural tissues -- three tissues, one fluid, ontained detectable infectivity; 90 percent of all brains ested; 80 percent of eyes, which Nick Hogan will comment on ater in the afternoon; 4/6 spinal cords and 3/26 spinal luids.

[Slide]

Infectivity was also detected in 5 non-neural .issues, 50 percent of lungs and smaller percentages of .ymph node, kidney, liver and spleen.

[Slide]

The infected human tissue -- the human brains ısually contained at least 10,000 primate intracerebral Lethal doses per gram of tissue. Pooled data suggested about $10^{4.8}$, that is about 62,000, 63,000 monkey lethal doses per gram of human brain tissue. Infected primates contained a Little bit more, somewhere between 10^5 and 10^7 lethal doses per gram. A limited number of other human tissues were evaluated and they contained much small amounts of infectivity. All the numbers tested were very small, usually less than 1000 lethal doses per gram.

[Slide]

Other tissues from human TSEs did not transmit disease to primates, and those included 12 specimens of

blood of various kinds and 3 specimens of bone marrow and ıe other tissues listed here.

[Slide]

Aside from CSF, no human fluid secretion, xcretion transmitted disease to primates. As you see, the ımbers are also very small.

[Slide]

There are obvious limitations of negative ransmission attempts of this sort. Except for brain, only mall sample sizes were studied; small numbers of specimens; nd small volumes of tissues and fluid. There is evidence or a species barrier that would reduce the sensitivity of nfectivity assays. That is, even in monkeys we can't be :onfident that a lethal dose for a human being would be detected in a monkey because limits of detection in primates :or human infectivity, of course, are unknown. There may be ?ariation in the distribution of infectivity of humans with 'SEs during clinical illness and, of course, nothing at all ıs known about infectivity of TSEs during the asymptomatic incubation period. People during the incubation period are simply not identifiable or accessible for study.

We encourage additional studies of the distribution of infectivity in human TSEs, which should now oe possible using transgenic rodents susceptible to the human-human agents and I think a comparison of the

sensitivity of those rodents to squirrel monkeys would be useful to bridge the results to those of this series of studies.

[Slide]

So, in summary, infectivity using primate assay infectivity was consistently detected, that is, at least 50 percent of attempts in brain, eye, spinal cord and the lung of persons with TSEs. Infectivity was detected less often, greater than 10 percent but less than 50 percent of attempts positive in cerebrospinal fluid, lymph node, kidney, liver and spleen. Infectivity was not detected in a variety of other tissues, fluid secretions and excretions of persons having with TSEs, but the numbers of samples tested were very small.

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It remains possible that infectivity might be present inconsistently or in small amounts in those negative tissues, fluids, secretions or excretions of persons with TSEs or incubating TSEs, however, no evidence that I am aware of, anecdotal or epidemiological, suggests actual transmission from person to person by ordinary contact with those materials. Thank you.

[Applause]

DR. BROWN: Thank you, Dave. I would point out that among the tissues that Dave was talking about that were

not demonstrated, as he said, is blood.

The next presentation will be by Sue Priola, the istribution of infectivity now in animal TSEs.

Tissue Distribution of Infectivity in Animal TSEs

DR., PRIOLA: As Dr. Brown said, I will be talking bout tissue distribution of TSE infectivity in animal iseases, and what I am going to be talking about is rimarily the work of Rick Race and Bill Hadlow. It is a eries of very extensive studies they did at the Rocky iountain laboratories in the '70's and '80's. Rick was riginally supposed to present this talk; I am just ubstituting for him today. This is really entirely his rork.

[Slide]

Just to review, we all know what the known major CSE diseases in animals are, scrapie in sheep and goats; of course, BSE; chronic wasting disease and transmissible mink encephalopathy in captive mink. What I am going to focus on today really for most of the entire talk is scrapie, natural scrapie in sheep and goats, where the infectivity is found and what that tells us about the pathogenesis of the disease, how it is maintained and passed between animals.

I will touch extremely briefly on BSE because I think everybody here is really familiar with that data, and I won't talk at all about chronic wasting disease. That is

oing to be discussed tomorrow, even though Rick is doing ome work on that.

[Slide]

So, just to remind everybody that the most ensitive way to assay tissue distribution of TSE nfectivity is, of course, the infectivity bioassay. Of the ›ioassays, the most sensitive way to do it is in the natural ıost, and this is because if you transfer infected sheep :issue into a non-infected sheep and get infectivity you ıave no species barrier and you have to deal with that ›roblem. The problem with this, of course, is that titration and even just looking for infectivity without quantitation is extremely expensive in the natural host because of the number of animals and expense involved in terms of facilities.

So, most people choose to go the mouse assay, and the caveat with this is I think we are all aware that, first of all, you need to know that you have a good, susceptible mouse strain and there are susceptible mouse strains available, of course, and it is less sensitive by about three logs than the natural host assay. The big advantage is that you can actually get quantitative data and use that, as you have seen, to sort of make estimates as to how much infectivity is present in which particular tissues.

One caveat that I want to bring up with any study

using infectivity bioassays is analyzing naturally infected animals versus experimentally infected. The results can be variable in terms of distribution of infectivity and level of infectivity, and this is likely due to either route of inoculation, the particular dose of agent and even the strain of agent. So, where possible, you want to stick to the natural situation, animals naturally infected in the environment.

Of course, the second way to look at tissue distribution of TSE infectivity is detection of abnormal prion protein which always correlates with infectivity. If you have that there, you have infectivity. It is not terribly quantitative no matter, I don't think, what technique use -- immunohistochemistry, Western Blot; ELISA is more quantitative but you really can't relate it to how much infectivity is there, and that is the problem. Sensitivity, of course, is also an issue. It is far less sensitive even than the mouse bioassay.

[Slide]

So, what Rick and Bill did for several years at Rocky Mountain labs was to take advantage of a naturally infected flock of sheep, down in Mission, Texas, that was composed of animals brought in from scrapie-infected flocks around the country. So, there was a very high incidence of scrapie in this flock of sheep. They looked at animals from

birth all the way -- you know, SO, 60 months down the line both preclinically and clinically for scrapie infectivity in over 30 tissues. They did this by end-point titration in the mouse bioassay.

So, when they looked at animals less than 10 onths old they never found, by mouse bioassays, infectivity n any tissue tested, lymphoreticular system, central ervous system -- none. So, for naturally infected animals elow 10 months there is no infectivity detectable.

When they looked in animals from 10 months of age p to 25 months of age, you can see that you start to see ow to moderate levels of infectivity in several different ymph nodes, muscle, spleen, the ilium and the proximal olon -- so parts of the intestine, and these are all issues that are either part of the lymphoreticular system r are very rich in lymphatic tissue. You can detect infectivity in scrapie-infected preclinical Suffolk sheep in hese tissues. It is not consistent. Not every animal has infectivity present in every tissue but it is very clear that that is the earliest point where you can detect it.

You don't see anything in the CNS in this study until you get up to 25 months, and there they found one animal who still was preclinical but now had infectivity in the CNS.

[Slide]

So, when they looked at clinical animals, it is the same batch of tissues but two things have changed. You see a lot more infectivity and a wider distribution, and this probably represents replication and spread of the ıfectious agent so that now from animals aged 34 months to 7 months that are now clinically'ill naturally with ɔrapie, you see high levels of infectivity throughout the ymphoreticular system -- tonsil, spleen, ilium, colon. Now ɔu can pick up even infectivity in the nasal mucosa and the drenal gland.

I just want to mention that if you look at one of he lymph nodes that is most commonly possibly by the ioassay it is the mesenteric lymph node.

[Slide]

If you look for the abnormal prion protein -- and, think this is 8 animals total, you can detect abnormal ɔrion protein in 6/8 at various levels but not in another 2 hat tested positive. So, this is what I mean about ariability and sensitivity of an assay like a Western Blot ersus a bioassay.

[S l i d e]

So, when you look at neuronal tissues of these infected animals, basically what Bill and Rick found is that in the CNS the infectivity is quite widespread throughout various portions of the brain, even in the pituitary gland

at low levels. It is in the spinal cord, sciatic nerve and the cerebral spinal fluid at very low levels.

[Slide]

This slide is just to show you that the regions of ne brain in these animals that have the highest level of nfectivity in the natural situation is around the brain tern.

[Slide]

So, what this tells you about natural sheep TSE nfection is that because they first picked up infectivity n tissues such as the retropharyngeal lymph nodes and ortions of the gut, transmission is probably by oral or ontact transmission. I will show you that it is likely that he placenta is a very likely tissue through which this ould happen. It occurs soon after birth. Following that arly exposure you get first replication of the agent in the Lymphoreticular system, then in the CNS and then, of course, it eventually replicates in high enough levels to kill the animal. Infectivity is detectable preclinically only in the Lymphoreticular system in general, and the titer over time increases and the distribution becomes broader.

Now, one of the things that is a concern in situations like this is maintenance of the infectivity within an infected flock and how that occurs. There were studies done by Ian Patterson, 30, 40 years ago, that

suggested fetal membrane tissues and placental tissues of naturally infected sheep could, in fact; transmit -- or, ıfected sheep could, in fact, transmit infectivity.

[Slide]

Rick revisited this question in the last few ears, and what he found -- all you have to look at on this lide is the black bars -- if he took placental tissue from 0 scrapie-positive pregnant ewes and tested it for nfectivity by mouse bioassay, 8 of those 10 were positive, of them rather low but 6 of them actually quite high.

[Slide]

When he looked for abnormal prion protein, he ound a perfect match. He gets 8 of 10 positive with, again, arying levels of the prion protein but it is all there in he placenta, suggesting that in the natural situation one ray in which these infections can be maintained is through ral or contact transmission with placental tissues that ıave been voided by the ewe.

[Slide]

So, in summary, the distribution of infectivity in uffolk sheep naturally infected with scrapie is restricted o the lymphoreticular system but it can be all over the lace -- nasal mucosa, parts of the intestine, the placenta and the CNS. The negative tissues, all other tissues they tested, including blood, salivary gland, heart, lung,

kidney, skeletal muscle were negative.

In conjunction with this study, the herd down in Mission, Texas also contained goats, and it has long been known that transfer of infection of scrapie from sheep to goats can occur in flocks and goats are very susceptible to scrapie.

[Slide]

So, they also took a look at clinically ill goats from the same flock and found almost an identical distribution of infectivity in both the non-neural tissues, so again, all the lymph nodes were positive -- these were just 3 goats from 38 to 49 months of age. Again, the proximal colon, the ilium is positive, the adrenal gland and the nasal mucosa.

[Slide]

If you look at the neural tissue, it is again the same as in the sheep. You see rather low levels in the spinal cord but relatively high levels, quite high levels in some parts of the CNS.

Now, one point I want to bring out is the difference between bioassays in the natural animal versus bioassays using a mouse, as I mentioned earlier. Again, Ian Patterson did a study where he experimentally infected goats intracerebrally and then did a bioassay back into goats. So, what he did was take tissues from those infected animals,

injected goats IC and looked for infectivity.

[Slide]

He found basically what Rick and Bill had found, with a couple of exceptions. He found that salivary gland and in one instance skeletal muscle was positive for infectivity in tissue from goats which had been experimentally infected with goat scrapie. So, this difference where he picks up infectivity in salivary gland and muscle could be due to the goat bioassay. So, going from goats back into goats, or could be a difference between experimental infections.

When Rick and Bill had done experimental infections of goats, they also picked up the salivary gland and that was by a mouse bioassay but not muscle. So, there are these differences that you have to keep in mind when you assay these tissues, and the system you are using to assay them.

[Slide]

So the summary for goats is about the **same** as for sheep, except that in experimental goat infections you can pick up some infectivity in the liver, muscle and salivary gland. You can also get it in placenta so the transmission may be similar to what it is in sheep. Again, blood was always negative, serum, bone marrow, milk -- all of these tissues were always negative. So, that is the same as in

heep.

When you compare this to BSE -- now, there has nly been, of course, the most thorough study that has been one, and I think it is almost concluded, which is the study y Dr. Gerald Wells, in England.

[Slide]

This is the one I think we are all pretty much familiar with, where he took cattle orally infected with BSE and assays by mouse bioassay for the presence of nfectivity, starting at 2 months post-challenge up to 40 days post-challenge. What he finds in this experimental node1 using the mouse bioassay, as you have heard, is that there is infectivity preclinically in the distal ilium first and it is at very low levels. When he passes this into mice only a few of the mice get sick. So, probably there are low Levels. The same is true for the dorsal route ganglia. Of course, later in disease all of these tissues come up positive. There was the one instance where he had one sample come up positive from the bone marrow clinically, and there is some question as to whether, as always in TSE diseases, when you see just one example of something if it is real or contamination.

[Slide]

So, in summary, overall conclusions from natural TSE infections in ruminants -- the earliest detectable

nfectivity is always in lymphoreticular organs or other rgans rich in lymph tissues. Obviously, as I think we all now, scrapie in sheep and goats differs from BSE in cattle oth in terms of distribution of infectivity -- it is much roader in sheep and goats, and in terms of horizontal ransmission. So, while there is evidence for horizontal ransmission of scrapie in sheep, there is really no onvincing evidence, at least that I am aware of yet, of orizontal transmission of BSE in cattle. So, sheep scrapie s really not a valid model for BSE pathogenesis.

The implications of the negative tissues, as Dr. sher just said for the human point of view, is that you can lever really say that they are truly negative or just that infectivity is so low that it is below the level of sensitivity of the bioassay you are using. But, in any case, Low titers would always make it difficult to transmit efficiently, particularly across any sort of species barrier. I will stop there.

[Applause]

DR. BROWN: Thank you, Sue. Our next presentation focuses down on cornea, and will be presented by Dr. Nick Hogan, University of Texas Southwestern Medical Center, who spent some years at the NIH working, actually, on infectivity with respect to the eye in an experimental model, and he will probably tell us a bit about that. Nick?

CJD Transmission by Cornea1 Transplantation

DR. HOGAN: I would like to thank the committee for inviting me here. What I would like to do today is tell you a little bit about the natural history of cornea1 cansplantation in humans, and also discuss some of the ssues regarding the biology of these agents in the animals.

[Slide]

Why should we be concerned? Well, the literature as three cases that are present that we need to deal with. here has been one definite case that was reported in 1974 n the United States; one probable case, reported in 1997, rom Germany; and one possible case from Japan, in 1994.

[Slide]

In addition, there are now three patients that are t risk because of an accident in the United Kingdom. There as a donor that came down with sporadic CJD, and before her Liagnosis could be established both of her corneas and part of her sclera were transplanted into three other ndividuals. I will go into that in some detail in **a** moment.

[Slide]

I am going to talk about the details of these cases because it is very pertinent to what we **are** discussing today about the risk of cornea1 transplantation. In the United States case, in 1974, the recipient of the cornea1 transplant was a 55-year old white female with Fuch's

dystrophy, a problem with the cornea, who **18** months after ransplant came down with progressive myoclonus, lethargy and ataxia. She died 26 months after the transplant and the utopsy showed spongiform neuropathology and, in fact, her rain was transmitted to chimpanzees.

[Slide]

The donor for that case was a 55-year old male who ad died after a two-month history of ataxia, myoclonus, and progressive dementia and his neuropathology, which was erformed some weeks after the corneas had been ransplanted, showed typical spongiform neuropathology.

Now, because of the coincidence in time, that is, pproximately **18** months between the time of the ransplantation and the time that the recipient came down ith disease, it was presumed that this was a direct ransmission human to human. That is given the rarity of the lisease and the time of incubation, which is approximately hat in chimpanzees after intracranial inoculations. There as been no absolute proof that this was a human to human ransmission, however, it is reasonable to assume that it as. That is why it is being called definite.

[Slide]

In case 2, the case from Germany, the recipient as a 45-year old white female with keratoconus who had a penetrating keratoplasty or cornea1 transplantation twice,

once in 1965 and once in 1982. She died after an 8-month history of ataxia, myoclonus and progressive dementia with flexion rigidity.

[Slide]

There was extensive study on her pre-death. She had no prion mutations noted. She did have homozygosity at codon 129 met/met. She had slowing of her EEG with biphasic discharges, and her CSF showed neuron specific enolase in a very high amount. Because of this, she was felt to be clinically CJD. However, the family did not consent to an autopsy so there is no pathologic proof.

[Slide]

The donor for this person was a 63-year old white female who died after a three-month history of incoordination, myoclonus, memory loss, and the neuropath report had shown spongiform change in these areas of the brain. The original slides were not available. Let me remind you that this is 30 years after the transplantation that this patient came down with the disease. The original slides were not available for review. All that was available was the report.

[Slide]

The donor in 1982 for that patient -- there are no records.

[Slide]

Case 3 is the case from Japan, and this was a 63-ear old Japanese female who died 3 years after the onset of dysarthric, dysmetria, dysdiadochokinesia, myoclonus, aranoid hallucinations, and her autopsy showed typical CJD n the brain. She had had a cornea1 transplant 15 months arlier.

[Slide]

In this report there was absolutely no information iven about the cornea1 donor. We have no idea whether this erson had signs, symptoms or pathology consistent with reutzfeldt. So, it is listed in the literature as a ossible case but I think there is a lot to be asked about his question. The only thing we know is that she had **CJD** nd she had a cornea1 transplant. There are other such cases hat are certainly around, and Dr. Gambetti knows of one hat we are currently investigating in Ohio. The question is whether or not this is real.

[Slide]

What about the at-risk cases that are currently in he United Kingdom? The donor for these cases was a 53-year old Scottish female who died of lung cancer in February of '97. Now, in the weeks prior to her death her family described her as falling over, staggering gait, acting like a senile old lady, and it was presumed that this was CNS metastasis of her lung disease. At autopsy, her death was

ecause of her lung disease and her brain was taken. owever , there was no review of that immediately. The brain as kept for the visiting neuropathologist, who came nfrequently to this hospital, to look at when he got there.

[Slide]

In the meantime, both of her corneas and part of ıer sclera were transplanted. One, in March of 1997, to a 9-year old man. In the same month, a cornea to an 85-year old woman and in the next month, in April of '97, sclera was transplanted to a 34-year old man.

[Slide]

It wasn't until November of '97 that the ıeuropathology confirmed Creutzfeldt-Jakob, and this was not ıew variant; this was sporadic Creutzfeldt-Jakob disease. The recipients were notified of the risk that they had in December of '97, and in January of '98 two of those three patients elected to have the tissues in question removed. The third did not. There are no clinical signs, however, in any of these recipients to date, and I have information from Bob Will as of about a month ago.

[Slide]

In summary, the literature shows one definite case of transplantation, the U.S. case, the only case in the United States; one probable transmission in Germany; and one possible, I would say questionable case in Japan. But there

are 45,000 cornea1 transplantations done in this country every year. So, in the last 20 years over a million. Why, in the United States, have there not been more cases given even the rare incidence of Creutzfeldt-Jakob disease sporadically? I think there are biological factors operating as well as epidemiological factors, and I am going to go into those briefly.

[Slide]

Well, first of all, where, in the eye, do these prions reside? In 1986, while I was in Stan Prusiner's lab we did some work on titering these agents in different portions of the eye, and it is clear that the brain harbors the highest amount of infectivity and it goes down from there to cornea.

[Slide]

Graphically, and with the numbers shown here in terms of titers in 50 log units, brain has about roughly 9 log units of infectivity. It goes down from there to cornea at the lowest at roughly about **5.** These two bars indicate 7 seeks in which these hamsters with scrapie were preclinical. They did not have disease yet clinically, and then after they developed the symptomatic disease.

So, the amount of agent in the cornea is roughly an order of magnitude lower than it is in the brain, 10^5 versus 10^9.

[Slide]

The only other study that I am aware of that has looked at this regional characterization was done by Marsh and Hanson, way back in '74, where cornea1 epithelium was scraped off and looked at for transmissibility and, again, they support my data, that is, there are about 5 log units as opposed to brain. The data that Dr. Asher talked about with Creutzfeldt-Jakob disease transmission in primates is the only study that has been looked at with Creutzfeldt-Jakob disease in ocular tissues, but I have to stress that those were whole eyes. It included retina and portions of optic nerve so it was not just cornea.

[Slide]

What about the experimental cases? This has been atttempted to be replicated experimentally. The most positive case was done by Manuelidis in 1977 where CJD-infected cornea was minced up and then placed in the anterior chamber of guinea pigs. Four of those six animals developed what was called clinical disease. Two of six were asymptomatic up to 600 days. The animals would be expected to come down with disease at about 277 days. All six, however, had spongiform encephalopathy according to their data.

[Slide]

In contradistinction, Teishi tried this in CJD-infected mouse where he emulsified mouse infected CJD

cornea, injected it in the brains of six mice. All mice were clinically free of disease way out in the incubation period, way beyond the time they should have come down, 2.8 years later, and only one of those mice had spongiform neuropathology.

[Slide]

Herzberg, in 1979 has tried the only real transplantation experiment where he transplanted CJD-infected corneas from Capuchin monkeys into two recipients, and all of these animals remained free of disease up to 55 months later, again, way out beyond where you would expect disease to come down. The grafts were clear and they looked very good, and there was no spongiform neuropathology in either of these clinically free animals.

[Slide]

I think there are other factors at work as well, and genetic sequestration may be playing a part in this as well in terms of transmissibility in the cornea. Brown, in 1994, looked at 56 cases of iatrogenic CJD, 92 percent of which had allelic homozygosity at codon 129, out of only about 50 percent in the normal population.

[Slide]

So the question becomes does the homozygosity at codon 129 accelerate pathogenesis in iatrogenic disease, and does the heterozygosity have any role to play in eventual

clinical disease after transplantation?

[Slide]

Then there is a series of cases that have never been transmissible, human CJD cases which have never been able to be transmitted. Traub, in 1977, found about 14 percent of cases that he could not transmit at all. With Brown, in his examination in 1994, it was about 9 percent.

Now, as you heard this morning, Dr. Brown refers to this not as that you can't transmit CJD; it is just that it was a failure of transplantation. That is, if you had been able to go out long enough perhaps these animals would have come down with disease from these patients. So, there is a question here.

[Slide]

Interestingly, these non-transmissible cases tend to be younger, that is, 53 years of age. They had a longer duration of illness, out to 28 months. But the reasons for this, as I mentioned, are a little unclear.

[Slide]

I think by far the one reason that there are not more cases of Creutzfeldt-Jakob after cornea1 transplantation is because of the institution of screening methods that were instituted in the early '80's. I am not going to go through these because Dr. Glasser is going to talk about this extensively and in the interest of time I

will skip over this slide and the next. But, the donors are specifically asked questions about Creutzfeldt-Jakob disease and death due to unknown neurologic disease.

[Slide]

I might stress that the cases in Britain at the time that this happened, in 1997, there really was no uniform eye banking system in place. Since that time there has been a lot more organization. Again, this is the same donor questionnaire.

[Slide]

So, to date, all we have is one definite CJD transmission in the last 25 years, and this case occurred before the institution of donor screening questions that are currently in place. Thus, I think the risk under the current regulations, not talking about what has been proposed here but the current regulations -- the risk of transmission of Clreutzfeldt-Jakob disease by transplantation is extremely small.

[Slide]

Dr. Kennedy is going to discuss this in somewhat more detail in the next talk. Thus, I think the risk of transmission of CJD by cornea1 transplant is extremely small because there are low titers of agent in the cornea, and experimental transmission studies support that. There is the apparent genetic transmission restriction requiring -- maybe

not but at least suggesting homozygosity at codon 129 as being important. There is a low numerical risk of transmission in that the incubation period may be extremely long, and again, there is low risk of transmission because of reasons of donor screening that is already in place. As I said, Dr. Kennedy will discuss that. Thank you very much.

[Applause]

DR. BROWN: Thank you, Nick. The companion presentation, if I may say so, will be presented by Dr. Kennedy. The title is CJD risk among cornea1 donors. Probably what we really mean is CJD risk among cornea1 recipients. Is that so?

DR. KENNEDY: That is so.

CJD Risk Among Cornea Donors

DR. KENNEDY: Thank you, Paul, and I would like to thank the committee for inviting me to make this presentation.

[Slide]

About one year ago the Eye Bank Association of America contacted me and asked if I would assist in drawing together a committee to review these issues concerning Creutzfeldt-Jakob disease as it relates to cornea transplantation. I am, however, not a member of the Eye Bank Association of America and I am not representing them here today. Our committee was independent.

The members of our committee included two neurologists, Dr. Brown and Dr. Johnson, as well as members with expertise in cornea transplantation, eye banking and epidemiology.

[Slide]

Our objectives were to review the reported information on the occurrence and transmissibility of Creutzfeldt-Jakob disease; quantify the risk of CJD among cornea donors; and then, from there evaluate the possible screening strategies to determine whether there would be reasonable ways of reducing the potential risk.

[Slide]

We used four sources of information to base our calculations or as the basis for them. First were the death rates of Creutzfeldt-Jakob disease in the United States as reported by Holeman and others from the Centers for Disease Control. The pool of death rates from all causes represents potential donors. U.S. population instruments, and then data on the numbers of cornea donors and the age distribution of cornea donors was given to us by the Eye Bank Association of America.

[Slide]

There are three sources of risk of Creutzfeldt-Jakob disease among donors that we dealt with, and this is how we divided up our calculations. First, there is the risk

from preclinical or asymptomatic Creutzfeldt-Jakob disease. That is, during that period where the disease is incubating but symptoms have not yet occurred. The second period is from the beginning of symptoms up to the point of diagnosis. So, during that time, a relatively short period where the symptoms are manifest but they either aren't prominent enough yet or the physicians have not yet established a diagnosis. Then, finally the category where the diagnosis of Creutzfeldt-Jakob disease has been established, and also included in this category would be those persons who died of Creutzfeldt-Jakob disease but who never had the diagnosis established.

[Slide]

I will spend a little bit of time on this slide because I think it is important that you understand what assumptions went into our calculations because the calculations are certainly only as good as our assumptions were.

To begin with the category of diagnosed cases, those patients included in this were those patients who died of Creutzfeldt-Jakob disease without having a diagnosis. The committee discussed this and the estimates were that 99 percent of such cases would be eliminated by current screening criteria, as outlined by Dr. Hogan in the previous talk.

Now, if you divide that into two groups, the group of potential donors who have had the diagnosis of CJD established, we are not aware that there has ever been a case where someone who had the diagnosis established before death ended up having a cornea taken and being transplanted. So, we think that risk is very low. The category of persons who have died of Creutzfeldt-Jakob disease but have never had a diagnosis established, that is a little more slippery as to how many such patients might actually exist. But the committee's feeling was that given the current screening criteria and given the high level of detection of patients who have the diagnosis, only about one percent of such subjects per year would get through the current screening process and end up in the pool of potential donors.

Now, for the second category of risk that we dealt with, that is, those persons who were symptomatic with Creutzfeldt-Jakob disease but the diagnosis has not yet been established, we made the assumption that none of those potential donors would currently be eliminated. So we are kind of loading the question in favor of doings screening by that assumption. For this calculation we assumed that the duration of the symptomatic period, that is, from the time when symptoms first develop to when the diagnosis is established, would average six months.

In the third category of risk, the group with

preclinical or asymptomatic disease that would still be incubating but symptoms would not yet have developed, we made the assumption that the incubation period would be ten years. So, those are the assumptions on which our calculations that I will show you are based.

[Slide]

From those assumptions and the data sources that I mentioned earlier, we calculated the numbers of donors that we might expect to have Creutzfeldt-Jakob disease in the annual pool of about 45,000 cornea donors, and it works out to about 1.3 cases among this annual total of about 45,000. Given that we assumed an incubation period of 10 years, most of the risk according to this calculation is in this category of preclinical disease.

[Slide]

From that, several sort of screening considerations should be discussed. First, screening for symptoms of Creutzfeldt-Jakob disease is not going to detect or eliminate any of the potential donors who might be in this preclinical category because, by definition, those subjects do not have any symptoms to detect by screening. That was approximately 90 percent of the total risk.

These two categories were lumped together, those who had symptoms without a diagnosis, those with diagnosed Creutzfeldt-Jakob disease and potential donors who had died

of Creutzfeldt-Jakob disease without having the diagnosis. There would be a total of about one such case -- adding all of these together -- about one such case every eight years, or about one case per 368,000 donors.

Another factor that came through in the calculations is that the risk of Creutzfeldt-Jakob disease among donors is much, much less among younger donors. In fact, it is about 40 times lower among donors less than 40 years old than among older donors. That is an important consideration with screening.

[Slide]

The importance of it comes through in the question that was posed to the committee about legislative consent donors. It works out that the legislative consent donors are much younger. The age distribution is much younger than it is for other donors, and for that reason the total risk of Creutzfeldt-Jakob disease among legislative consent donors is approximately 40 percent less than just the preclinical or asymptomatic risk alone among all other donors.

So, it is a huge safety factor, the age distribution, and the importance of this is that estimates have been made that if it is necessary to go to family members to do a donor medical history interview, that because of the difficulty of locating the family members and conducting the interviews in the short time that is

available after the sudden, usually traumatic deaths that make up this legislative consent category, it is estimated that the range of up to 90 percent of these donors may be eliminated for that reason because of not being able to conduct the interview, not because of the risk. So, this could potentially lead to a paradoxical result. That is, we strive to make the donor pool more safe so we are going to ask more questions, but the fact of asking the questions causes the group that is perhaps the safest group, because of the young age distribution, to be eliminated, thereby making the overall donor pool at somewhat greater risk.

[Slide]

Other calculations that we did were to take that one case of symptomatic or diagnosed Creutzfeldt-Jakob disease that might occur in the donor pool once every eight years or so, or once out of every 368,000 donors, and if we did ask questions about symptoms and we screened on that, how many otherwise suitable donors would we lose for each one of those with CJD eliminated from the donor pool? That depends on the specificity of screening. It also depends on the sensitivity. And, for this analysis we made the generous assumption that all of those symptomatic patients would be identified by the screening. So, again, it loaded it in favor of screening. You can see that the number of otherwise suitable donors excluded would range in the thousands even

if only the highest risk age group were screened in that manner.

[Slide]

Finally, I wanted to just show a cornea that is scarred so you would have an idea of how the donor corneas are used. This scarring limits vision of this patient.

[Slide]

This is the same patient after having a cornea transplant, and you can see how the clear window has been restored in order to bring this patient's vision back. There are two points that I want to make with this. One is that the worldwide demand for corneas far exceeds the supply and will continue to for the foreseeable future. So, anything that is done to needlessly limit supply will have an impact on the number of people who can have their vision restored through cornea transplantation. Even in the U.S., as Dr. Hogan mentioned, there is concern about the donor supply, and the National Eye Institute has funded a study actually to try and increase the number of older donors, but which actually goes right into the highest risk age group for Jreutzfeldt-Jakob disease.

[Slide]

In conclusion, currently the risk of CJD transmission following cornea transplantation is remarkably low. As Dr. Hogan mentioned, in the United States there has

been one case reported in the past 26 years and from 1974 there have been more than 600,000 cornea transplants in this country. The estimated risk of Creutzfeldt-Jakob disease is lower, approximately 40 percent lower among legislative consent donors and it is simply a function of the younger age of those donors.

Finally, the screening for symptoms of Creutzfeldt-Jakob disease will likely not be an effective practice because of the relatively large number of cornea donors that would likely be lost from this process and because the demand for donors currently exceeds the supply. Thank you.

[Applause]

DR. BROWN: Thank you very much, Dr. Kennedy. There will be two very brief comments about Dr. Kennedy's presentation by Dr. Taffs first, and Dr. Belay second. Dr. Taffs?

Comments

DR. TAFFS: Good afternoon. Thank you very much for the opportunity to comment on the preceding risk assessment.

[Slide]

In seeking advice from scientific committees on matters of public health, regulatory control authorities often consider results of risk estimates.

[Slide]

Recently a report was published on harmonization of risk assessments for the scientific committees of the European Commission Health and Consumer Protection Directorate-General. The report outlined the essential elements of quantitative risk assessment, and indicated that variability and uncertainty in the risk model should be described in order to provide useful information for further decision-making.

Risk assessors should investigate the scientific basis for the estimation and explicitly state the assumptions made in modeling risk to avoid any false sense of precision. The risk assessment should be fully documented, indicating all the assumptions and constraints to ensure that the process is transparent. The report should be publicly available to give stakeholders and opportunity to comment and to subject the report to peer review. Sensitivity analysis should be included to evaluate the effect of changes in the model and the result of the risk estimation.

[Slide]

The objectives of sensitivity analysis are to identify the elements of the risk model that have the greatest impact on the magnitude of risk, and determine the extent to which assumptions, variability and uncertainty in

the model can affect the results of the risk assessment.

[Slide]

The sources of statistical information used in this analysis are shown here. Published information on age-specific incidence of CJD, mortality, population, and cornea donation in the U.S. were used to evaluate the sensitivity of the risk model of CJD infection in the cornea donor pool.

[Slide]

The calculations of age-specific rates of CJD infection within the donor pool were performed to examine the impact of the sources of uncertainty in the risk model. The effect of differences in assumed rates of CJD incidence, diagnosis, and asymptomatic cases were evaluated. The ability of additional screening criteria to detect symptomatic CJD was assumed to be 100 percent and was held constant throughout the analysis.

It should be kept in mind that the results of this analysis are intended to explore the sensitivity of the risk model and not to determine a best estimate of actual CJD risk in the donor pool.

[Slide]

Parameters that were varied in the sensitivity analysis included the percent specificity of additional donor screening, the rate of cases that for any reason are not excluded by current screening, symptomatic cases that

are not yet diagnosed, asymptomatic cases of CJD and CJD prevalence in the U.S.

[Slide]

The model was used to calculate the time in years until additional screening would detect one true case of CJD in the donor pool, the number of donors incorrectly excluded, the number of donors and CJD-infected donors in the donor pool over the same time interval, and the percentage of infected donors that would be detected.

[Slide]

The effect of varying the assumed percentage of missed symptomatic cases of CJD is shown in this slide. This refers to CJD cases that for any reason should be but are not excluded by current screening criteria. On average, a six-month incubation period of symptomatic CJD prior to diagnosis and a ten-year asymptomatic incubation period was assumed, similar to Dr. Kennedy's model. Later tables in the analysis use a similar format so I will explain this table in a little detail.

Specificity indicates the percent specificity of additional donor screening, and is shown in the first column. The numbers of erroneously excluded donors that would result are shown in the following columns. The four rows beneath the table show, first, the time interval in years until the detection of an additional case of CJD

within the donor pool. 'Please note that the calculated 8.3 years is very similar to the result that we saw in the previous presentation. Next, the number of cornea1 donors and CJD-infected donors in the pool during the same time interval. Finally, the percentage of infected donors hypothetically detected by the additional screening.

In the table, as the percent specificity'of the screening increases, there is a decrease in the number of donors erroneously excluded. As the assumed percentage of cases missed by current screening increases, there is a decrease in the time until additional screening detects a true case of CJD in the donor pool. Although the number of donors erroneously excluded at a given specificity decreases across the table, the percentage relative to the total number of donors in the donor pool during that same time interval remains the same. What changes is the percentage of CIJD-infected donors **that are detected by additional** screening, increasing from 0.8 percent to 4.8 percent across the range of missed cases indicated at the top of the table.

This approach is useful to contrast the results of risk assessments under different sets of assumptions. At 80 percent specificity and 1 percent missed cases the proportion of the donor pool erroneously excluded is 20 percent, while the proportion of CJD-infected donors detected by additional screening is less than 2 percent.

In contrast, at 95 percent specificity and 20 percent missed cases the proportion of the donor pool erroneously excluded is 5 percent, while the proportion of CJD-infected donors detected by the additional screening approaches 5 percent.

[Slide]

The effect of varying the assumed incubation period is shown in this slide.

[Slide]

The assumed symptomatic period is varied in this slide.

[Slide]

And, the assumed prevalence of CJD in the U.S. population was varied in this slide, and the details of the information are available for the committee's consideration but in the interest of time I would like to go on to the next slide.

[Slide]

This sensitivity analysis indicates that the estimates of the number of cornea donors with CJD and the number of donors that may be erroneously excluded by additional screening can vary substantially depending on identified model assumptions. Uncertainty in the assumed number of cases missed by current screening, and the specificity of any additional screening could have a

substantial impact on the result and application of the risk assessment.

I conclude this commentary by saying that these elements of the model merit some further attention in considering cornea1 CJD risk estimates, and I thank you for your attention.

[Applause]

DR. BROWN: Thank you very much. Dr. Belay?

DR. BELAY: These are not my comments. Dr. Schonberger was asked to review and comment on Dr. Kennedy's analysis. After he prepared his comments, at the last minute he was unable to attend because of an illness. He was hospitalized. So, he gave me his comments and I have to admit that I didn't get a chance to review the analysis. I did not have a copy of the report. So, these are purely Dr. Schonberger's comments.

The results of Dr. Robert Kennedy's analysis should be interpreted with the understanding that they are very much dependent upon underlying assumptions that are not based on solid evidence and, thus, they may or may not be valid.

I would like to underscore three such important assumptions. First, the underlying assumption in the analysis about when human corneas become infectious. Although this is unknown, the analysis assumed that corneas

are infectious during the preclinical stage of CJD and that the number potential infectious preclinical CJD cornea donors in the United States is appropriately estimated by assuming a ten-year period of infectivity for the corneas before onset of the donor's disease.

However, it is reasonably possible that corneas do not become infectious until after the onset of CJD; or perhaps only for a relatively short period before that time. If, in fact, corneas do not become infectious until the onset of CJD, this situation would mean that 100 percent of whatever small risk of CJD transmission by corneas exists might potentially be preventable through screening procedures. The analysis in press, however, indicated that only 9 percent of the risk of CJD transmission by corneas would be potentially preventable by screening procedures. This latter, largely assumption based conclusion about the small proportion of risk preventable through screening could negatively influence people's perception about the importance and usefulness of screening.

A second important assumption that influences the quantification of the-risk of CJD among cornea donors, and potentially our understanding of the utility of screening them for signs and symptoms of CJD relates to the likely number of persons with CJD without ever having been diagnosed correctly and, therefore, who are not excluded by

current screening criteria. No one knows the actual number of these misdiagnosed CJD cases. The assumption in the analysis in press, however, is that this number would be no greater than 1 percent of the total number of reported cases, or 2.6 cases per year nationally. The actual number of misdiagnosed cases that could be missed by current screening could be on the order of magnitude greater than that used in the analysis.

Complicating estimates of this number are both the likelihood that misdiagnosis of CJD are much higher than 1 percent, but also the probability that current screening procedures by many tissue banks are more comprehensive and tighter than is implied in the analysis. Some tissue banks currently screen not only for diagnosed CJD cases but for cases diagnosed with other neurologic indices including, for example, unexplained neurologic disease or progressive encephalopathy -- illnesses that, if excluded, would potentially also exclude some of the misdiagnosed CJD cases.

As I mentioned to Dr. Kennedy a couple of weeks ago, it could be useful to recalculate the risk of CJD among cornea donors assuming a 10 percent, rather than 1 percent, relevant rate of misdiagnosed cases of CJD. This changed assumption for the analysis would also affect the predictive ratios for incorrectly excluded donors for various additional screening methods. Clearly, the higher the

assumed number of misdiagnosed CJD cases that could potentially be excluded by screening methods, the more important such screening becomes.

The third important assumption relates to the interpretation of the results of the analysis. The existence of only one reported CJD transmission by cornea to date in the United States was assumed to reflect less the problem of under-identification and under-reporting of such transmissions and more on biologic or other factors that prevent their occurrence.

Although this assumption may be valid, the following observations suggest caution about discounting or underestimating the possibility of the under-reporting of cornea1 graft transmission of CJD in this country. Between 1975 and 1999, given the hundreds of thousands of U.S. recipients of cornea grafts, one could reasonably expect that half a dozen or more would have developed sporadic CJD by chance alone. During this 25-year period, however, none of these coincidentally associated U.S. cases in cornea1 graft recipients were reported in the literature. Given that there exists no diagnostic test to distinguish between causal or coincidental occurrences of CJD in cornea1 transplant recipients, the absence of reported coincidental associations between 1975 and 1999 suggest caution in interpreting **a** similar absence of reported causally

associated cases during this same period.

I would like to acknowledge the overall high quality of the analysis conducted by Dr. Kennedy and colleagues, and the importance of their having very carefully identified and evaluated key factors influencing the impact of increased screening on donor supply and the risk of cornea1 transmissions of CJD.

Their analyses alert us to the important potential for unintended consequences to the safety and supply of corneas should additional screening procedures be implemented. Even tough new screening procedures that happen to disproportionately reduce the number of younger donors of cornea transplants, for example, could lead to the unintended consequence of reducing prion disease safety of corneas because of the much lower frequency in this country of CJD infectivity in young persons. Thank you for your attention.

[Applause]

DR. NELSON: I have one question. Maybe you can answer for Larry, I don't know. But there are 45,000 cornea recipients per year and you are talking about no diagnosed cases in about a 20-year period. With **a** rate of 1 per million you would expect only one, isn't that correct? So the fact that one might have been missed -- I mean, I am not sure how many we would have expected, or did I miss

something?

DR. BELAY: I think he was talking about the entire 16-year period.

DR. NELSON: Sixteen times 45 is roughly a million, and if it is one per million per year, would you expect only one case?

DR. BELAY: No, one per million per year'would translate into about one per 10,000 for a lifetime.

DR. NELSON: So there are multiple years.

DR. BELAY: That is correct.

DR. NELSON: The years are additive.

DR. BELAY: One per million would be just for one year. For the 26-year period --

DR. NELSON: Right.

DR. PRUSINER: As another quick point, it is one in 10,000 people who die who have CJD. It is one per million of the whole life population.

DR. BELAY: That is correct.

DR. BROWN: One other point, I personally don't think either cornea1 transplants or neurosurgery, which is another surprising absentee from cases of iatrogenic CJD, are due to non-recognition or under-reporting. And, I can tell you that the European CJD surveillance system which has identified some thousand-odd cases in CJD now in the past two years with extensive histories of medical and surgical

procedures, they haven't come up with a case of cornea1 transmission or neurosurgical transplantation either. In other words, over several years, in an area of the world where this kind of thing is being covered like a blanket, they still don't get any cases due to cornea1 transplants or neurosurgery. So, I don't buy into the notion that these figures are due to under-recognition. I think the other two points may be valid but not that one. Laura?

DR. MANUELIDIS: There are a couple of things you should know. First of all, just to clarify an issue, Nick refers to CJD as Tateishi and what we use in one sentence. In fact, what we use, we use sporadic CJD which is very different than what he is referring to in Tateishi's lab and strains can be quite different in what they do. In fact, actually what we use can prevent Tateishi strain from replicating in the brain.

Second of all, many people who get cornea1 transplants get them late and the dose is extremely low. I know from having done those experiments that we used the trochar and we put in little pieces and there **was** no other route in. And, the optic nerve and other kind of studies have been positive. There is no reason to think the cornea doesn't have some infectivity. The lack of risk, I think, comes from the fact that there are relatively few people who get sporadic CJD so, therefore, that is one of the things.

The second fact is that people may die of other causes and never be diagnosed with CJD, or never develop symptomatic CJD who are much older in the population -- not that the cornea itself doesn't have some inherent infectivity, at least in sporadic CJD.

DR. BROWN: We will go on to the next presentation.

DR. BELAY: May I comment, Dr. Brown, about under-reporting?

DR. BROWN: Yes.

DR. BELAY: If you look at the incidence of CJD -- I am talking about sporadic CJD, for example, in the United Kingdom it has been increasing through the 1980's and also 1990's. They also recognize that this increasing incidence is primarily attributed to detection of more cases of CJD as the years went by. So, not only is there the possibility that corneas might be missed, in fact, there is a good possibility that even sporadic CJD patients may have been missed, especially in the 1980's.

DR. BROWN: Yes, but we are talking about the 1990's, and 1980's is before the period that I am referring to. That is, I am referring to the last decade when active surveillance of CJD was occurring not only in the U.K. but all over Europe. Sure, before active surveillance you could miss cases but that doesn't explain what has happened in the

Last decade.

The next presentation will be from Dr. David Glasser, who is going to talk about the legislative consent; safety and supply of cornea1 transplants. Dr. Glasser?

Legislative Consent: Safety and Supply of Cornea1 Transplants

DR. GLASSER: Thank you. I would like to thank he committee for the opportunity to address them.

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I would like to first begin by discussing the EBAA's medical standards.

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The medical standards are developed by the EBAA medical advisory board, or MAB. This has consisted of experienced cornea1 surgeons, eye bankers and academicians. The medical standards are reviewed and accepted by the American Academy of Ophthalmology on a semi-annual basis, and they represent the standards which all accredited eye banks must adhere to. The standards are scientifically based and their goals are to ensure the safety of eye bank personnel and the safety and efficacy of eye tissue for human transplantation.

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The medical standards require donor screening to construct an adequate donor profile. This donor profile then

is used to determine the suitability of tissue for human transplantation. All donors must be screened, including tissue obtained via legislative consent.

[Slide]

Donor screening must include identification of the donor, serologic testing, physical assessment of the donor, tissue evaluation, donor history evaluation and medical director oversight. I think we are spending most of our time today talking about donor history evaluation.

[Slide]

All available records must be reviewed by qualified personnel, to include information from at least one of the following, according to the EBAA standards: Pathologist's or medical examiner's physical assessment or death report; medical examiner's investigative report; medical record or hospital chart; treating physician interview or family interview. Of course, according to 21 CFR 1270, all cases need a donor medical history interview with the exception of those obtained via legislative consent.

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In the EBAA's medical standards there are specific and somewhat less specific exclusions aimed at reducing the risk of TSE -- Creutzfeldt-Jakob disease, family history of blood relative with CJD, recipients of human-derived

pituitary human growth hormone, and recipients of non-synthetic dura mater grafts are the most specific exclusionary criteria. Less specific criteria include donors who have a diagnosis of progressive encephalopathy; active viral encephalitis or encephalitis of unknown origin.

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Death of unknown cause; neurologic disease of nestablished diagnosis and non-prion diseases, PML, SSP, eyes syndrome and rabies.

[Slide]

Well, how effective is this screening program? In he U.S.A. the one case that we have heard about that was reported in 1975 was the first case of presumed or probably transmission from a donor to a recipient of CJD. That case led to the establishment of the screening criteria which I have just described. Since that time over 600,000 cornea1 xansplants have been performed in the United States with no additional reported cases. I would comment that this number is closer probably to 600,000 than to one million because we haven't been transplanting 45,000 corneas a year for the last 25 years. That time has increased gradually over the years.

In addition, there have been two international reports, which you have heard about already, one in Germany and one in Japan, of presumed transmission, and the one

donor in the U.K. who died with neurologic symptoms initially attributed to metastatic brain disease who was later discovered to have CJD. The three recipients who received ocular tissues from this donor remain disease-free now at more like four years after the transplant.

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This is the issue that has us all wondering, can TSE screening be improved? What about brain biopsy? Well, if brain biopsy were required, time limitations for the use of the cornea1 tissue would probably eliminate most or all of the viable cornea1 tissue.

What about donor history screening for specific symptoms? This has been raised in the literature by Dr. Hogan who you have heard from, and has been discussed by the medical advisory board, which charged Dr. Kennedy and his group with addressing it. Obviously, screening for specific symptoms cannot detect asymptomatic cases and, as we have heard, even with a very conservative estimate of 100 percent sensitivity and 90 percent specificity and assuming a 1 percent non-diagnosis rate, over 36,000 donors would be incorrectly excluded for each donor correctly excluded. That 1 percent number was arrived at, obviously without any specific knowledge but our best estimate from the neurologists on the panel. Even if that were 5 times higher, we would still have over 10,000 donors excluded for every

correctly excluded donor.

Finally, what about requiring a donor medical history in legislative consent cases? The EBAA also asked Kennedy's group to address this issue.

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According to their report, which has been accepted by the MAB, as you have heard Dr. Kennedy say, tissue procured via legislative consent comes from a younger donor population. These younger donors are less likely to harbor TSE, and the risk of preclinical, symptomatic and diagnosed CJD combined among donors obtained via legislative consent is still 40 percent less than the risk of preclinical disease alone among all other donors.

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The advisory board felt, based on this report, that there is currently no scientific basis for concluding that a donor medical history interview would reduce the risk of TSE in donors whose ocular tissues are procured via legislative consent.

[Slide]

But what would happen to the supply of corneal tissue if a donor medical history were required in all legislative consent cases in order to try to determine if a donor had spent a significant amount of time in the U.K. or other areas where BSE was prevalent? According to the banks

that use this tissue, they estimate that their availability of legislative consent tissue would be reduced by about 90 percent if a donor medical history interview was required, and I think you heard Dr. Kennedy describe the reason why -- the time required to obtain that information versus the time that the tissue remains viable.

But how bit a problem is this? Only about 5-10 percent of donors of transplantable corneas are obtained through legislative consent in the U.S. So, this amounts to probably 2,000 or 3,000 transplanted corneas per year. That is a relatively small number but there are major local variations in the percent of transplantable corneas obtained via legislative consent.

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In Puerto Rico, Boston, Miami and San Antonio the majority of transplantable corneas are obtained via Legislative consent. In Houston and Baltimore it is about half. In Seabrook, Maryland the number is much smaller but it is enough to make the difference between scheduled surgery and having waiting lists. These are fairly soft number estimates from the banks that use this tissue.

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So, requiring a medical history interview for tissue obtained via legislative consent would create local shortages of cornea1 tissue in several major metropolitan

areas. Local shortages are not easily remedied by importation of tissue from other U.S. banks or by substituting tissue that is currently exported. Tissue that is currently exported is often very difficult to **place** in the U.S., often because of time limitations or **age** considerations of the donor and this is something that is going to be addressed via further education and investigation regarding the viability of these corneas. EBAA members also do not import foreign tissue.

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So, the medical advisory board's conclusions were that requiring a donor medical history interview in legislative consent cases would eliminate most donors obtained via that route; create local shortages of cornea1 tissue; eliminate scheduled surgery in other areas; increase the number of patients waiting for corneas; and possibly increase the risk of TSE due to an increase in the overall age of the donor pool, which might counterbalance and even overweigh the potential decrease in risk one would have by screening for travel to areas where BSE is prevalent.

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In addition, screening donors for specific symptoms would markedly reduce the cornea1 supply without increasing the safety of the donor pool. Requiring a donor brain biopsy would eliminate most or all corneas suitable

for transplantation. Finally, if there really is a need to improve TSE screening, what we really need are some new tests. Thank you.

[Applause]

DR. BROWN: Thank you, Dr. Glasser. I think we will push along and, with that in mind, either one of the other two presentations of the afternoon are invited to present, either Dr. Confer or Dr. Dubord. Excuse me, there is a question.

DR. DESLYS: Just a small comment on the previous presentation. All this description was done because there was no test available to confirm the possibility or not of Creutzfeldt-Jakob disease. That was true when you were doing classical immunohistochemistry. Now with the tests which are used in Europe for BSE, you need not to block slaughterhouses to give the results during the night. So, if you want, you can use exactly the same method and you will have no more problem.

DR. BROWN: Okay, that is a point that can be discussed at some length. Now we can go on. Dr. Confer?

The Risk of nvCJD in Recipients of Hematopoietic Stem Cell Transplants and the Impact of Deferring Donors from the U.K.

DR. CONFER: Thank you very much. I am pleased to be able to address the committee on a different subject than what we have been talking about. I am going to talk about

the risk of new vCJD in recipients of hematopoietic cell transplants and the impact of deferring donors from the United Kingdom. I am the chief medical office of the National Marrow Donor Program. We are a non-profit company in Minneapolis, Minnesota.

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As has already been indicated, there are really three useful sources of hematopoietic cells for transplant. The first of these is bone marrow, and it is the oldest source that has been used for many, many years. It is collected from the pelvis of the donor, usually under general anesthesia. A newer source are peripheral blood stem cells. They go by several other names, frequently abbreviated PBSC. Really what these represent is bone marrow that has been mobilized from the bone space into the blood srtream where it can be collected by apheresis. This mobilization can be done by administering hematopoietic growth factors to the donor over a series of a few days. The newest stem cell source is umbilical cord blood, umbilical and placental cord blood which is drained from the placenta after the baby is delivered and the cord is clamped. There is typically anywhere from a cup to half a cup of cord blood remaining in the placenta and the umbilical cord.

As Dr. Solomon indicated, peripheral blood stem cells and umbilical cord are under the purview of the FDA.

Bone marrow is under the purview of the Health Resources and Services Administration. But, practically speaking, any standards that we set for donors of peripheral blood stem cells will also apply to donors of bone marrow because these are basically the same people who are donating bone marrow in one setting or potentially donating peripheral blood stem cells in another. So, it is not ethically practical to have different standards for the same type of donor, depending on what type of product they are donating.

I don't know a lot about the risk of transmitting new vCJD with any of these stem cell sources. However, if new vCJD can be transmitted with lymphocytes, I do know that all of these have large numbers of lymphocytes in them. When you do the transplants, the administered total cell doses are between 10^8 and 10^{10} cells into the recipient, and it is the lowest with umbilical cord blood; it is the highest with peripheral blood stem cells. It is also true that the peripheral blood stem cells have the highest content of lymphocytes. The majority of these cells in the peripheral blood stem cell setting are, in fact, mature lymphocytes.

[Slide]

One of the critical things about hematopoietic cell transplantation is that HLA matching is required for all hematopoietic cell transplants, and this is totally different than blood matching. The HLA genes are clustered

on the short arm of chromosome number 6. There is a group called the class I genes that are single gene products and these consist of HLA-A and HLA-B, and the gene in between those two is called HLA-C. Then there is HLA-A class II which are multi-gene products, consisting of HLA-DR, DQ and DP. Each of these genes is highly'polymorphic, meaning that there are many known alleles at each of the different gene sites, both within the class II region and the class 1 region. In fact, by simple mathematics, if you calculate the total number of potential HLA types, it exceeds the world population.

What happens, however, is that these genes are in linkage disequilibrium, probably due to long history of evolution and infectious challenges, so that some HLA types are very common and others are very rare. When we are doing a hematopoietic cell transplant we look primarily at HLA-A, HLA-B and HLA-DRB1, one of these gene products in the DR region. So, there are really six genes that we are looking at because you get one of these chromosomes from the mother and one from the father.

Within a family the chance that two siblings will match, will have the same HLA type is 25 percent because this comes as a haplotype in the newborn. So, it is 25 percent and, therefore, given the size of U.S. families, if one child is sick the chance that that child will have a

matching is sibling is somewhere around 25-30 percent. So, 25-30 percent of people have a matched sibling donor. This means that for the other 70-75 percent of people their only option really is to look for an unrelated donor who, by virtue of chance, is an HLA match.

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As it turns out, there are a large number of people, now more than seven million people worldwide, who have volunteered and registered as bone marrow and stem cell donors. These are distributed among about 48 different registries around the world. It is important to note that among these seven million, only a little over half are actually completely HLA-A, B and DR typed. The rest have only been typed for HLA-A and B, and that is largely for historical and cost reasons. So, as a practical matter, only about half of these people are really readily available to serve as bone marrow or stem cell donors.

The newer stem cell product, the cord blood, is present in much smaller numbers. There are about 55,000 cord blood units. These are distributed to around 21 cord blood banks around the world. In the cord blood setting, virtually all the units are HLA-A, B and DR typed, and so readily available for transplant.

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The National Marrow Donor Program operates the

world's largest registry of unrelated stem cell donors. We started in 1987. This slide shows the growth of our registry since 1987 through September of 2000 from 8000 donors to now more than 4 million total registered donors. It is also important to point out here that our file is only about 57 percent A, B or DR typed, and that is indicated by this green line. So, they amount to about 2.4 million donors who are fully typed. The remaining donors are typed, again, only for HLA-A and B.

These donors, the fully typed donors, as it turns out, provide more than 95 percent of the stem cells transplanted through our program. The other thing I would point out about our program is that one of the reasons it has grown to the largest in the world, so much so, is because of long-standing federal support. Currently, that support comes from the Health Resources and Services Administration and also from the Office of Naval Research.

The final thing on this slide shows the growth of our cord blood registry, which is modest by comparison, with about 8000 cord blood units listed in 7 different banks that are members of our network.

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This shows what impact HLA has because even with the 2.4 million fully typed donors, this slide shows the likelihood of finding matching donors for 56,600 patients

who have searched our registry in the past. What we did, we took all these previous searches and we reran them last summer, in July of 2000, against the current registry, applying our current matching criteria. So, we wanted to see how efficient our registry had become. So, I have grouped the searches according to the number of HLA-A, B and DR matches.

And, what you can see is that, indeed, with a big registry there are more than 50 percent of these searches, more than probably about 30,000, that, indeed, identified 6 or more A, B, DR matches. So these are good search results. Some of these search results, in fact, will identify hundreds and hundreds of potential matched donors for recipients with very common HLA types. However, even with 2.4 million donors, 17 percent of the searches have no matches on them. An additional 10 percent of the searches have only one match. So, when you add these two together over a quarter of these 56,000 searches either had no donors in the file or only a single donor in the file. It is this finding that causes the transplant programs to look outside the United States and look at the other registries, particularly registries in Europe.

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Even when there are multiple donors available, transplant centers also consider additional factors in

selecting donors. So, there are other things that, if you have the luxury, you would look at as a transplant physician. These include donor age. Our data show that younger donors produce better outcomes in recipients than older donors. The reasons for that are complex. Donor size, where if you have a large recipient you don't want to pick a very small donor to try to provide stem cells for that recipient. Donor sex, there is a feeling that female donors -- bone marrow and peripheral blood stem cells are more likely to cause complications in recipients than male donors, and there are data to support that in terms of the frequency of graft versus host disease.

People are increasingly looking at donor race or ethnicity in order to try to make sure, if there are minor antigens that are of importance that may be ethnically clustered, that you are matching on those. In addition, people will look at the donor cytomegalovirus serology because if the recipient is cytomegalovirus negative you would like to have a donor who also has never been exposed to this, and there are other factors that people also look at.

[Slide]

This now shows over three years, 1988, 1989 and the year 2000, the number of hematopoietic stem cells that we received, that the National Bone Marrow Donor Program

received from unrelated donors in Europe. So these were coming from Europe into the United States for U.S. patients. What this slide shows is the United Kingdom, France, Germany and then all the other European nations clustered together.

You can see that we have been receiving about 35 marrows and stem cells -- the vast majority of these are marrows -- from the United Kingdom each year in this three-year period. France is much smaller, 10 to 7 bone marrows and stem cells in each of the years. The country that provides the most hematopoietic stem cells to the U.S. is Germany, and you can see that we are obtaining anywhere from 95 up to almost 130 stem cell products from Germany in each of these three years. Then, the other European nations provide a lot of stem cells that come into the United States, aggregated together.

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As it turns out, you might say, well, why do these vary so much? These numbers really are very close to the size of the registries. So, this is the size of the unrelated donor registries in the United Kingdom where they have 400,000 total donors registered. France has a much smaller registry, with a little under 100,000 total donors. Germany has very large registries, comprising more than 1.4 million unrelated donors. Then, the other European registries provide these other donors.

I think this illustrates the effect of HLA also because it says that the transplant centers go to where they can find the donor and the size of the registry is a major indicator of where they are going to be able to find missing HLA types.

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This slide just takes us back to that previous slide where we are looking at these numbers that I have gone over.

[Slide]

So, this leads us into this slide which how expresses all of those as a percentage of all the transplants done by our program in 1998, in 1999 and in 2000. What you can see is that these imported cell stem products comprised 16 percent of the transplants from '98' 15 percent of the transplants from '99; 11 percent of the transplants from the year 2000; anywhere from about 170 to 230 transplants in those years. I actually have no explanation for why the numbers dropped off in the year 2000. I can virtually assure you it is not because of concern about new variant Creutzfeldt-Jakob disease, but I don't have a good explanation for why the dependency on Eoreign grafts seemed to drop in the year 2000. It may go up in 2001.

[Slide]

What would be the impact of deferral upon U.S. patients based on the data I have shown you? I think that deferral of European hematopoietic stem cell donors would likely prevent some patients from proceeding to transplant. Those patients who have only one or two donors might lose their donor if, in fact, that donor were deferred because of nvCJD risk. Other patients who are currently being transplanted might still proceed to transplant, but they might proceed to transplant with second choice donors, that is, donors who were a size mismatch; donors who were older and maybe less desirable. So that might increase the risk of the transplant.

But overall the numbers of patients affected clearly depends on the extent of the deferral. If the deferral is restricted to the U.K. we are talking about 35-40 patients per year. If the deferral is extended throughout all of Europe, then you are talking about several hundred patients a year who could be affected.

[Slide]

What we believe and what we are currently doing is trying to weigh risk versus benefit. We asked all donors about six months cumulative residence in the United Kingdom. We asked donors whether they had received insulin that may have been prepared from bovine sources in the United Kingdom. If they answer yes to that, then we consider those

donors to be unsuitable. The process we follow is almost identical to that that was outlined in the FDA determining donor suitability document that you heard about earlier. That process indicates that unsuitable donors may still be used if, one, there is an urgent medical need and there almost always is in the case of these marrow and stem cell transplants; two, a biohazard label is affixed; and, three, there is documentation that the transplant physician was notified of the abnormality; the physician agreed to accept the product in spite of the abnormality; the physician has also agreed to counsel the patient or the patient's representative about the abnormality and the potential impact on the outcome of the transplant; and then, finally, the physician has agreed to obtain the consent of the patient or the patient's representative.

[Slide]

This is the final slide, In summary, it is important to note that these hematopoietic stem cell donors, unlike many other tissue donors and recipients, are matched with the recipients primarily by virtue of HLA type. Many potential recipients have few donors from which to choose. Those were the data I showed you. Elimination of some or all European donors from consideration would have a negative impact on U.S. patients, and we believe and suggest that the patient and the physician -- the patient who is going to

eceive the transplant and the physician who is going to are for that patient may be best positioned to balance the isk of this stem cell product versus its potential benefit. hank you very much.

[Applause]

DR. BROWN: It is interesting that even at the evel of stem cells females cause more complications than ales.

[Laughter]

That is just a wake up call. I will tell you what ve are going to do. For those of you who have hung around for a vote, we are not going to vote today. In view of the hour, and it is already 5:15, what I plan to do is to power right on through the two final scheduled presentations and any public statements that wish to be made, and then we are going to close up the tent. Tomorrow morning we will begin with discussion and votes. I think tomorrow will be a substantially less overcharged day than today, and I see absolutely no point in requiring the committee to try and discuss in a lively, intelligent and alert way what I think is a very important issue for the FDA. So, with that in mind, we call now on Dr. Dubord who is going to tell us a little bit about tissue and organ standards process in Canada.

Tissue and Organ Standards Process in Canada

DR. DUBORD: Greetings and salutations. What I would like us to do now -- we have been discussing a lot about BSE and general TSEs and vCJD, and what I would like to do is step back a little bit and share some ideas with you about the whole area of organ and tissue transplant regulation, and then I will bring us back to how this particular program, in fact, dealt with vCJD.

I recognize too that there are some differences in how the regulation is instituted here, in America, versus in Canada. In Canada all organ and tissue transplantation comes under Health Canada, under one agency, versus here, in America I understand that tissues and blood are going to be managed under the FDA and organs are managed by the HRSA and the DHHS.

Let's go through this program, what we have in Canada. Recognizing too that there is a vast variation in safety practices that have existed in Canada and, to some extent, here in American in regards to organ and tissue transplantation; recognizing that there is no agreement at this present time, let's say, across North American in different centers and what they do with organ transplantation. One community might be doing something because it works for us and another community may be doing something totally different because it works for them. Some donors are being excluded because of some preconception of

the medical director and in another community they are being accepted. So, there is no agreed upon standard, and the program I am going to describe to you, as far as I am aware, is unique in the world.

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Basically, we work through the different type of risk management strategies that we can look at. First of all, there is the free market that you are all very familiar with. Then you get on to education and information programs, and the higher up on the track you are, the more passive you are, the more laissez-faire you are. But when you start getting down further at the bottom end of the regulation, this is where our responsibility to the public is paramount, where in fact we have to guarantee that the product that we supply to our patients is as safe as possible.

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With the standards-based approach which we have adopted, and many of you are familiar with this is that standards is a published document, and you had a brief review of one of the EBAA just earlier, which contains the requirements and procedures for a specific activity or product and this has to be reviewed on a regular basis. What we perceive is that a standard will have the force of law if incorporated in regulation. So, what the regulator does is, in fact, give the standard the force of law, stating you

much comply with the standard.

More than one third of Canadian standards are referenced in legislation. This happens with all sorts of other standards, for example, electricity, virtually anything we build our homes with, and a lot of things in health care.

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The other issue about the standard-based approach is that it need not be written in regulatory language and, frankly, in most cases it is fairly easy to understand. It is very good at addressing emerging technologies and it is very quick to update these documents because you have panels, very similar to what you see here, made up of healthcare professionals, experts, calling in experts to discuss these issues and try and make the best decision depending on the current state of understand at that point.

We work primarily on the consensus principle. In the whole five years of the development of this program not once have we had a vote. It is by consensus. This also improves the prospects of compliance across the board and we get a buy-in, and the regulator sits at the table with us when we are making these decisions. It can be applied in multiple risk management systems, which I am not going to get into a discussion of but it is very critical.

What else do medical standards do? Well, basically

they facilitate uniform evaluation, standardized data collection and quality assurance, outcome analysis and accountability. This outcome analysis is critical, and I think that some transplant organizations, organ and tissues, nationally are much, much better at this data collection than others. For some it is compulsive. They have it virtually on every recipient. In other organizations it is very haphazard, where there is virtually no documentation. So, we are trying to, in fact, raise the level, so to speak, so we know what is happening to our patients when, in fact, they get a transplant.

Another thing that is very important with the medical standards issue is the whole issue of accreditation, which can be very comprehensive in how it is applied and the overall idea is to increase the quality of tissue and organs that are supplied to a recipient. It can be very much an educational process for those individuals participating in it, for example, any eye banking or organ transplant organization, versus inspection which is necessary in some situations, which is mainly looking in most cases at safety and good manufacturing practices. What we have done, working together with the regulator, is the regulator maintains control of this thing and regulators are very concerned about losing control. They have to have control and that is important. So, it enables the regulator to better utilize

the resources.

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What is the Canadian general standard? Well, the Canadian general standard applies to everything that is transplanted except for blood. It makes it clear and simple. We have all organs, tissues, stem 'cells, reproductive cells, ocular tissues and xenotransplantation under one document. You will say, well, how have we done this? Well, basically the general standard covers all those issues that are common to every form of organ and tissue transplantation. It covers the donor qualifications. It covers what has to be recorded. It records the histories, physicals, most of which would be accepted as regular donor screening. It also has outcomes that have to be measured in each group. Adverse reactions are defined for each group and must be reported. It also neans that there is a single authority that looks at this and, in fact, documents it.

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Of all the slides I am going to show you this is :he most important one of all, the Canadian general standard. You have this general standard that has the rules :hat apply to all. Then, under that we have what we call the subsets. There is the solid organs, tissues, stem cells, reproductive tissues, ocular tissues and then cenotransplantation. In this general standard here, this

grouping is made up of regulators, experts. We have public advocates that are members of the committee who, in fact, are recipients of transplantation who participate introduction he decision-making processes here.

The critical thing here to make all these groups work together is that each and every one of these groups has an equal seat at the table. Because I am a heart transplant surgeon doesn't mean I am any better than the guy who does skin. No single transplant is more important than any other transplant. They are our equal at the table, and the person who needs that transplant, the patient, that transplant that they need is the most important one. Because of having them all have an equal seat at the table and no one is more important, it makes for a much easier decision-making process and it has made this process work.

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It was first formulated back in about 1995 at a national conference, consensus conference, and in 1996 an expert working group was formulated. This consisted of specialists in each area that are recognized by national organizations; healthcare professionals involved introduction he area of organ and tissue transplantation; public advocates; regulators and we have an ethicist that sits on our board. It also leads to a balanced communication between all the groups, and we also are all indemnified. We

currently are covered by a one billion dollar indemnification, which in Canada are significant dollars. Down here I am not sure that counts for very much. It also encourages very active compliance and it is very balanced in the way it communicates.

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The future directions that we are going with this plan is that the standards now are at the Canadian Standard Association. Why did we do this? Well, we had a format that we kind of followed, a basic skeleton. But now we have given it to an organization and all their job, like an executive secretary, is to, in fact, write the standards. So, they are in a common language across the board and you can cross reference. For example, if stem cells become aware of an issue you can immediately refer all the way across the board to any other subset standard and the general standard to see where it is going to impact. It can work both ways, up and down.

So, it makes reviewing and updating the standard subsets and the Canadian general standard comprehensive and very, very quick to respond to any perceived needs. We are also having further consultation with the provinces and the stakeholders because in health care in Canada the provinces have to have a buy-in. In fact, surprisingly, we have unanimous buy-in by the provinces with this program. We also

are going through another public consultation process with healthcare professionals, i.e., all the programs are going to have another look at the Canadian general standard plus all the subsets that they want to look at and have the freedom to comment on. They will be put on the web introduction the next few months and, frankly, anyone here is going to be welcome to comment on these to see if we can make them better than what they are.

We are going to have an adverse reporting system and eventually a national adverse reporting system for all organs and tissues, and we are going to be trying to get a much more comprehensive transplant data collection. So we can pick up, for example, those cases of CJD. Also, it will make regulation writing easier but we are not sure exactly how that is going to work right now. I am not a regulation expert.

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So, how did this apply? How did we do with vCJD as we were presented with this case in the fall of 1998? Well, basically the Canadian blood system had said we are going to defer all donors who spent more than six months in the U.K., and we were asked to address this issue and how it would apply to all organ and tissue transplantation.

First of all, we reviewed all the data and the rationale that CBS had used in making their decision. We

also gathered what was considered the best science at that time, and we formulated an expert working group. The Bureau of Biologics played a role. External experts, public advocates were there; subset experts, all were present; prion experts and the FDA had a corresponding member on the committee. We discussed the science. We discussed the risk factors, the public aspects of both safety, perception and confidence in the system and using the precautionary principle, i.e. that the CBS had used in deferral and the fact that CBS could, in fact, augment their supply by approaching more donors, the reality was that we couldn't do that in the transplant arena.

The reality too was that CJD had been transmitted -- not variant by CJD had been transmitted both in dura and cornea1 transplantation, but our primary concern was vCJD. So, there was a potential risk of transmission and we had restricted access to our donor pool. The recipients of all transplantation have a real immediate need for that in a vast majority of cases, and the other thing that I have already mentioned is that we couldn't augment our donor pool as could the blood system.

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So, what did we do? The conclusion was that there was a risk. There was no question about that, but the risk was low. And, again we made a choice using the precautionary

principle but at the same time we decided that no deferral was necessary for organ or tissue transplantation donation. We then went on to stress and expand that and how important the medical-social interview was in this area, not only in the area of CJD and prions but looking for other infectious disease in an area where people travel as much -- for example, malaria, hepatitis and that sort of thing;

We formulated another subcommittee that formulated questions looking at CJD and vCJD specifically. We have a questionnaire now that is going to be uniform across the nation -- a medical social-interview for everything, not just for CJD. The subsets all have to comply with the basic one, but if they want to make it a little tighter and ask a few more questions, they are allowed to do that. Currently we are dealing with the issue of Alzheimer's which we are also deferring and CJD.

The upcoming issue that we are trying to deal with is record storage because, as we know, CJD has an incubation period of up to decades and currently we are only required to store records, in some areas, for seven to ten years and we are probably going to have to expand that to probably 25, 30 or more years and decide what has to be stored.

Those are the sorts of issues we are dealing with today. So, that is basically what we are dealing with in the Canadian model and the regulation and how we use it in

reviewing and looking at vCJD. Thank you.

[Applause]

DR. BROWN: Thank you very much, Dr. Dubord. Will you and others who have made presentations today be present tomorrow, Dr. Dubord?

DR. DUBORD: Yes, I will.

DR. BROWN: And other people who have presented today will be here tomorrow because I am sure the committee will want to refer to you at certain times tomorrow in their discussion. The final scheduled presentation today is being given by Robert Rigney and it is about questionnaire rates of donor deferral.

Donor History Questionnaire/Rates of Donor Deferral

DR. RIGNEY: Good evening. My name is Bob Rigney. I am the last minute fill-in for Dr. Kasprisin who, unfortunately, couldn't be with us today. I am the chief executive officer of the American Association of Tissue Banks. For those of you who are not familiar with AATB, we are a non-profit scientific organization, here in the Washington area. Our mission is to provided quality and safety in transplantation and provide tissue in quantities sufficient to meet national needs. We were founded in the mid-1970's. We published our first set of standards for tissue banks in 1984, and we just released our ninth edition of those standards last week. My purpose here today is to

review for you the AATB standards for donor screening and our history questionnaire.

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In making the donor suitability determination, AATB standards require that cells or tissues shall not be released for transplant without final review of donor suitability by the tissue bank medical director. The donor history shall include, but is not limited to the following: The acceptability of the consent; the medical/sexual/social history questionnaire; the physical assessment; results of Laboratory testing, serologies and cultures; pertinent information from the medical records including pathology and Laboratory reports; autopsy reports, if any; and other information including any information required by federal, state or local laws.

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With specific reference to disease screening, our standards require that the medical director or licensed physician designee shall not release allogeneic cells and/or tissue for transplantation from donors who exhibit any of the following findings, specifically risk factors for viral or prion-associated disease transmission as specified in Appendix II of our standards. That appendix lists the criteria preventing viral or prion-associated disease transmission through transplantation of human tissue.