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FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE MEETING

Gaithersburg, Maryland

Wednesday Morning, June 26, 2002

BETA

COMMITTEE MEMBERS PRESENT:

DAVID C. BOLTON, Ph.D., Chair
New York State Institute for Basic Research

JOHN C. BAILAR III, M.D., Ph.D.
University of Chicago

ERMIAS D. BELAY III, M.D., Ph.D.
Centers for Disease Control and Prevention

STEPHEN J. DeARMOND, M.D., Ph.D.
University of California San Francisco

SAMUEL H. DOPPELT, M.D.
The Cambridge Hospital, Cambridge, Massachusetts

LISA A. FERGUSON, D.V.M.
United States Department of Agriculture

PIERLUIGI GAMBETTI
Case Western Reserve University

KATHARINE E. KNOWLES
Health Information Network

JEANNE V. LINDEN, M.D.
New York State Department of Health

JEFFREY J. McCULLOUGH, M.D.
University of Minnesota

STEPHEN R. PETTEWAY JR., Ph.D.
Bayer Corporation

PEDRO PICCARDO, M.D.
Indiana University

SUZETTE A. PRIOLA, Ph.D.
Rocky Mountain Laboratories

COMMITTEE MEMBERS PRESENT (CONT'D):

ELIZABETH S. WILLIAMS, D.V.M., Ph.D.
University of Wyoming

SIDNEY M. WOLFE, M.D.
Public Citizen

ALSO PRESENT:

DAVID ASHER, Ph.D.
Office of Blood Research and Review
FDA Center for Biologics Evaluation and Research

JAY S. EPSTEIN, M.D.
Office of Blood Research and Review
FDA Center for Biologics Evaluation and Research

MAHMOOD FARSHID, Ph.D.
Office of Blood Research and Review
FDA Center for Biologics Evaluation and Research

WILLIAM FREAS, Ph.D.
Committee Executive Secretary

ELLEN HECK
Eye Bank Association of America

RICHARD HURWITZ, M.D., F.A.C.S.
LifeNet

DAVID KORROCH
Lions Medical Eye Bank of Eastern Virginia

C. RANDALL MILLS, Ph.D.
Regeneration Technologies, Inc.

P.J. PARDO
Tutogen Medical, Inc

P. ROBERT RIGNEY JR., J.D.
American Association of Tissue Banks

ALSO PRESENT (CONT'D):

ROBERT ROHWER, Ph.D.
University of Maryland VA Medical Center

RICHARD RUSSO
International Osteotech, Inc.

RUTH SOLOMON, M.D.
Office of Blood Research and Review
FDA Center for Biologics Evaluation and Research

ALAN E. WILLIAMS, Ph.D.
Office of Blood Research and Review
FDA Center for Biologics Evaluation and Research

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C O N T E N T S

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P R O C E E D I N G S

(8:00 a.m.)

DR. FREAS: Mr. Chairman, members of the committee, invited guests, members of the audience, I would like to welcome you to our 12th meeting of the Transmissible Spongiform Encephalopathies Advisory Committee. Both days of this meeting will be open to the public and you are welcome to the entire meeting.

At this time I would like to go around and introduce the members at the head table and I will wait just one second until I have a chance to sit down. After I introduce the members of the head table I will be reading to you the conflict of interests statement for this meeting.

When I call out the names if you would raise your hand I would like to go around and introduce the members at this time. In the first seat at the table right in front of the podium at the end of the

table is Dr. Pierluigi Gambetti, Professor and Director, Division of Neuropathology, Case Western Reserve University.

The next committee member is Dr. Lisa Ferguson, Senior Staff Veterinarian, US Department of Agriculture.

In the empty chair we will soon have Dr. DeArmond, Professor, Department of Pathology, University of California, San Francisco.

Our next committee member present is Dr. John Bailar, Professor Emeritus, Department of Health Studies, University of Chicago.

The next committee member is Dr. Pedro Piccardo, Associate Professor, Indiana University School of Medicine.

Around the corner of the table is Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming.

Next we have a temporary voting

member from the Blood Products Advisory Committee. He is a full member of the Blood Products Advisory Committee and a temporary member here today, Dr. Samuel Doppelt, Chief, Department of Orthopedic Surgery, The Cambridge Hospital, Cambridge, Massachusetts.

Next is the Chairman of this advisory committee, Dr. David Bolton, head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is another temporary voting member and acting consumer representative for today, Katharine Knowles, Executive Director, Health Information Network, Seattle, Washington.

Going around the corner of the table is a committee member, Dr. Ermias Belay, Medical Epidemiologist, Centers for Disease Control and Prevention.

In the next chair is Dr. Suzette

Priola, Investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

Next we have Dr. Jeffrey McCullough, Professor, Department of Laboratory Medicine and Pathology, University of Minnesota.

Next I would like to welcome back a former member of this committee who is serving a split term on this committee. I would like to welcome back Dr. Sidney Wolfe, Director, Public Citizen Health Research Group, Public Citizen.

Next we have a temporary voting member, Dr. Jeanne Linden, Director, Blood and Tissue Resources, New York State Department of Health.

Next is our nonvoting industry representative, Dr. Stephen Petteway, Director of Pathogen Safety and Research, Bayer Corporation.

Two committee members could not

join us today. They are Dr. Richard Johnson and Ms. Shirley Walker.

Now I would like to read the conflict of interests statement for this meeting:

"The following announcement is made part of the public record to preclude even the appearance of a conflict of interests at this meeting.

"Pursuant to the authority granted under the committee charter, the Director, Center for Biologics, Evaluation, and Research, has appointed Dr. Sam Doppelt, Ms. Katharine Knowles, and Dr. Jeanne Linden as temporary voting members for this meeting.

"Based on the agenda it has been determined that the committee will not be providing advice on specific firms or specific products at this meeting. Topics being discussed by the committee in open session are considered general matters

issues.

"To determine if any conflicts of interest exist the agency reviewed the agenda and all relevant financial interests reported by the meeting participants. In accordance with 18 USC 208 Dr. Sam Doppelt has been granted a waiver that permits him to participate fully in the committee discussions.

"We would like to note for the record that Dr. Stephen Petteway is serving as a nonvoting industry member for this committee. He is employed by Bayer and thus has interest in his employer and other similar firms.

"With regards to the invited guests the agency has determined that the services of these guests are essential. The following reported interests are being made public to allow participants to objectively evaluate any presentations and/or comments made by the invited speakers:

"Major Ronny Alford is employed by the Armed Services Blood Program, United States Air Force.

"Dr. Larisa Cervenakova is employed by the American Red Cross.

"Dr. Aliza Eshkol is a senior scientific advisor for Serono International.

"Dr. Luisa Gregori is employed at the Medical Research Service, VA Medical Center. She is a researcher and has contracts with firms in the blood industry and firms developing TSE removal products.

"Ms. Ellen Heck is Director Transplant Services Center, University of Texas, Southwestern Medical Center, Dallas.

"Dr. Thomas Lynch is Senior Vice President for Regulatory and Quality for Clearant. He consults with companies engaged in the production of human tissues and tissue-based products.

"Dr. Robert Rohwer is principal investigator on contracts for applied

research supported by various blood companies and companies involved in the development of TSE removal products. He also consults with blood companies and companies involved in TSE removal.

"Dr. Diane Wilson is chief operating officer, Community Tissue Services, Dayton, Ohio.

"Listed on the agenda are speakers making industry presentations and speakers giving committee updates on regulated industry and outside organizations. Since these industry and update speakers have financial interests associated with their employer and other regulated firms they were not screened for these conflicts of interest.

"All other meeting participants are aware of the need to exclude themselves from discussions involving specific products or firms for which they have not been screened for conflict of interests. Their

exclusion will be noted for the public record.

"With respect to all other meeting participants we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they wish to comment upon."

So ends the reading of the Conflict of Interest statement. Dr. Bolton, I turn the microphone over to you.

DR. BOLTON: Thank you, Bill. We will now have an announcement by Jill Warner on behalf of Dr. Zimmerman.

MS. WARNER: Good morning. I have just a brief announcement to make on behalf of CBER. As many of you on the committee and those in attendance to day are aware, one of the most dynamic and growing areas of product development in biological products is the area of tissues, cellular and gene therapies.

In order to facilitate the

coordinated development of these products, the research, review, and policy, we are announcing the formation of a new Office of Cellular, Tissue, and Gene Therapy Products.

This new office will consolidate the staff and functions from our current Division of Cellular and Gene Therapies in the Office of Therapeutics and Research and Review currently and also the human tissue program staff from the Office of Blood Research and Review.

Our target date for the new office is October of this year and the kinds of products that will be regulated in this new office include cellular therapies, tissue-based products, tissues, also gene therapies, transplantation products, and we welcome your comments as we go forward. We look forward to working with this committee on the TSE issues that affect these and other FDA-regulated products.

If you do have comments that you

would like to submit Dr. Cheryl Lard Whitesford, who is our CBER ombudsman, would be happy to take your call or your e-mail.

Thanks.

DR. BOLTON: Thank you, Jill. This morning I would like to welcome you all, especially the new members or new returning members of the committee. We have a rather full agenda today so I won't say much.

We are going to be discussing many issues related to tissues, cellular-based and tissue-based products for trans-plantation. I think at this point we should just move right on with this.

I understand that one of our speakers, Dr. Paul Brown, may or may not be able to attend this morning. Paul was feeling a little under the weather so he is scheduled to speak at two different times, at 9:30 and somewhat later than that, 10:45. If Dr. Brown is able to make it he will

combine both of his talks in one segment and present them both at 9:30. I just want everybody to be aware of that.

At this time without further ado I will open up our first topic for discussion which is the Validation of Procedures to Prevent Contamination and Cross-Contamination with TSE Agents of Human Tissue Intended for Transplantation.

The first presentation in this is the introduction and background, which will be presented by Dr. Ruth Solomon. The title of this is Current and Proposed FDA Regulations and Guidance pertaining to TSE and Human Cells, Tissues, and Cellular and Tissue-Based Products Intended for Transplantation. Dr. Solomon.

DR. SOLOMON: Good morning. The first topic today is a discussion of the validation of procedures to prevent contamination and cross-contamination with TSE agencies of human cells and tissues

intended for cross-contamination.

These human cells and tissues would include cellular therapies, hematopoietic stem cells, reproductive cells and tissue, musculoskeletal tissue, skin, dura mater, heart valve allografts, and others.

FDA requests advice from the TSE Advisory Committee on the measures for donor screening, measures for tissue recovery and processing, and design of a clearance study appropriate to prevent contamination and cross-contamination of human cells and tissues intended for transplantation by TSE agents. The new term for these products are human cells, tissues, and cellular and tissue-based products or HCT/Ps.

There are three approaches to reduce the risk of TSE transmission by cell and tissue transplantation. The first is careful screening of the donor for TSE and risk factors of TSE and testing if and when

validated.

The second approach would be control of recovery and processing of cells and tissues to prevent contamination and cross-contamination and the third would be the use of steps during manufacturing of cells and tissues to remove or inactivate TSE agents.

The talks today will discuss each of these three approaches in more detail. We know that unlike blood transfusions given to humans there have been documented cases of iatrogenic transmission of CJD to the recipients of human cells and tissue products. Dr. Brown will discuss this further but, just briefly, there have been transmissions of CJD through human dura mater transplantation. Most of these are from dura mater from different donors that had been commingled during processing.

There have also been transmissions of CJD through corneal transplantation.

There has also been transmission through human pituitary derived growth hormone administration and this will be discussed by Dr. Eshkol.

Dr. Brown will also discuss the potential transmission of vCJD and CJD by other human cells and tissues and will give the experimental evidence in animals.

Now I would like to give you a background on FDA's regulatory approach to TSE transmission, actual and potential, by human cells and tissues. I will review the current tissue regulations, the current recommendations that are in the form of guidance to industry, and then the proposed cell and tissue regulations and the proposed recommendations and guidance.

Since FDA is in the process of finalizing the proposed regulations and issuing draft guidance we thought that this was an appropriate time to discuss TSEs and relate them to cell and tissue

transplantation.

The current tissue regulations were finalized in 1997 and they can be found in 21 CFR Part 1270. These regulations cover screening and testing of potential donors for HIV, HBV, and HCV. TSE is not included in this final rule.

There are also requirements for written procedures and record keeping. One of the requirements in the section on written procedures says that a tissue establishment is required to have validated procedures to prevent infectious disease contamination or cross-contamination during processing and this is contained in 1270.31(d). This final rule also contains information about inspection and enforcement.

Along with the final rule we issued a guidance for industry called "Screening and Testing of Donors of Human Tissue Intended for Transplantation."

This guidance document did recommend screening for CJD and recommended to defer donors with a diagnosis of CJD, a family history in a blood relative of CJD, a history of receiving dura mater transplant, a history of receiving human pituitary growth hormone.

Recently this past March we also issued another final guidance for industry called "Validation of Procedures for Processing of Human Tissues Intended for Transplantation." The purpose of this guidance was to clarify Section 1270.31 of the rule. This guidance explains that infectious disease contamination includes viral, bacterial, fungal, and TSE agents and we would expect that tissue establishments have validated methods to prevent contamination by viruses, bacteria, and fungi at this time. Dr. Farshid from FDA and several tissue processors will discuss process validation later.

We also said in this guidance that validated methods to prevent contamination by TSE agents would be expected later if and when such methods are agreed upon by scientific experts such as the members of this committee and become available.

CDRH, which currently regulates dura mater, issued a guidance document in October '99 entitled "Guidance for the Preparation of a Pre-Market Notification Application for Processed Human Dura Mater." This guidance contains all of the above donor suitability recommendations and also recommends that a potential donor of dura mater with any degenerative or demyelinating disease of the CNS or who has died in a neurologic or psychiatric hospital be excluded.

This guidance also recommends growth and histologic exam of the full brain, disinfection by a method validated to reduce CJD infectivity, and the prohibition

of batch processing.

Now for the proposed regulations and guidance. In September 1999 FDA proposed a rule entitled "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." This proposed rule would require screening of all cell and tissue donors, including a medical history interview, for risk factors and clinical evidence of HIV, HBV, HCV, human TSEs including CJD, and also there would be additional screening for particular human cells and tissues. It also would require testing of all cell and tissue donors for HIV, HBV, HCV, and syphilis and additional testing for particular human cells and tissues. We received comments on this proposed rule and we are in the process of finalizing it.

In addition we proposed a rule on January 8, 2001, entitled "Current Good Tissue Practice for Manufacturers of HCTPs

Inspection and Enforcement." This proposed rule would provide controls over facilities, personnel, equipment, environment, incoming materials, labeling, storage, process controls, process validation, record keeping, adverse reactions, and product deviation reporting and tracking and would also contain information about inspection and enforcement. We have received comments on this proposed rule and it is also being finalized.

I would like to point out that this GTP proposed rule would prohibit the pooling of cells and tissues from different donors during any part of manufacturing. By "pooling" we mean placing in physical contact or mixed in a single receptacle; however, this proposed GTP rule would also provide an exemption or alternative from any GTP requirement. A firm could submit a request for an exemption or alternative accompanied with valid data.

For instance, a request might be submitted for an exemption to the pooling prohibition. FDA would weigh the potential increased risk of contamination and cross-contamination with emerging infectious disease agents such as TSE agents against the potential benefit of improved elimination of conventional infectious disease agents such as viruses, bacteria, and fungi. Dr. Taffs will be discussing a risk assessment. There will be several talks about single donor processing versus batch processing from Dr. Lynch, Dr. Brown, Ms. Wilson, and Ms. Heck.

Now for the proposed guidances. Two weeks ago we issued a draft guidance for industry entitled "Preventive Measures to Reduce the Possible Risk of Transmission of CJD and vCJD by human cells, tissues, and cellular and tissue-based products. This is the subject of Topic #2. Dr. Greenwald will discuss this draft guidance further but as a

background for my topic, for this topic, the draft guidance briefly would have certain recommendations for donor screening for CJD and would recommend deferral for CJD or variant CJD diagnosis, dementia, degenerative or demyelinating disease of the CNS, or other neurologic disease of unknown etiology, deferral for risk factors for CJD such as a blood relative with CJD, receipt of dura mater or human pituitary growth hormone, and it would also include risk factors deferral for variant CJD such as the cumulative time spend in the UK, Europe. It addresses military people stationed in Europe and their dependents. It also addresses blood transfusion in the UK and receipt of bovine insulin manufactured from cattle in the UK. Basically it is the same recommendation that all of you are familiar with in the blood donor guidance except there is an exception made to HLA-matched hematopoietic stem cells.

In addition to the screening measures that I just mentioned in the draft guidance that Dr. Greenwald will discuss several other screening measures have been suggested. One of them is to have an upper age limit for donors of cells and tissues. The thinking behind this is that the median age at death from CJD is 68 years or in the older population; however, in considering such a recommendation we would be concerned about the long incubation period and the probability that the donor would be infectious during some portion of the incubation period.

An upper age limit was proposed for blood donors by the blood industry but was not implemented. You should realize that proposing an upper age limit may seriously reduce tissue supply. For instance, 50 percent of US donors of ocular tissue are age 61 or older.

The tissue bank and eye bank

standards do not recommend any upper age limit. This is left to the discretion of the eye or tissue bank director to set donor age limits in the firm's SOP; however, there are age limits in industry standards for semen donors. They have to be less than 40 years old, oocyte donors less than 35 years old, donors of cardiovascular tissue less than 61 years old.

A second possible additional donor-screening measure would be to exclude donors for head trauma. The rationale here is to avoid possible CNS contamination of the cells and tissues that you retrieve. Again, head trauma is not addressed in the industry standards and we have to realize that such an exclusion may reduce the tissue supply. For instance, 13 percent of eye donors cause of death is trauma.

Then we could consider some additional donor testing measures such as a brain autopsy and that should be found

negative in order to accept the donor. Dr. Hogan is going to discuss the brain biopsy and the brain autopsy.

With the brain autopsy we should remember that there could be a delay in distributing time-sensitive human cells and tissues such as cornea. The brain biopsy if we were to use that would need to be validated to show that it is predictive of autopsy diagnosis of TSE.

So we would like the committee to evaluate the appropriateness of each of the measures and the controls that will be discussed today or others that you recommend to prevent TSE transmission to the recipients of human cells and tissues.

Again, we are dividing this into additional donor screening and testing criteria, then specified methods of recovery and processing of cells and tissues, and under that specific methods of decontamination of surgical instruments and

work surfaces and the removal and/or inactivation of TSE agents. Both of the latter topics will be discussed by Dr. Rohwer.

In addition we would like you to consider this question. Should pooling or commingling of human cells from different donors during manufacturing ever be permitted? If so what controls should FDA require in assessing whether a request for an exemption from the proposed pooling prohibition should be granted?

Finally, the questions that will be asked at the end of this topic. Question number one, which of the following measures and controls is or are appropriate to prevent TSE agent transmission to recipients of human cells and tissues? Additional donor screening and testing measures to determine donor eligibility or exclusion such as upper age limit, head trauma exclusion, negative brain biopsy, or

autopsy? Specific methods of human cell and tissue recovery and/or processing to prevent contamination and cross-contamination such as the decontamination of instruments and surfaces? We will be asking you how should this be accomplished.

The methods for removal and/or activation of TSE agents during manufacturing and single donor aseptic processing versus permit pooled processing under circumstances, which circumstances and with adequate controls, which controls? Also, if you had other appropriate measures and controls we would appreciate hearing them.

The second question will ask you to comment of the design of a satisfactory TSE agent clearing study for human cells and tissues in terms of the following criteria. What would be a suitable TSE agent strain and animal model? Can we accept measurement of abnormal forms of prion protein alone or

would we require infectivity bioassays? Can we accept substantial reduction and how much should that be or require complete elimination of detectable prion protein and/or infectivity? Should we accept a single validated method or require that more than one validated method be included in the study and any other suggestions for the design of a clearance study that you may have?

Thank you.

DR. BOLTON: Thank you, Dr. Solomon. We have a little time if there are some questions from the committee at this point for Dr. Solomon.

Seeing none, then we will move on. Our next speaker is Dr. Rolfe Taffs. He will tell us about the risk assessment models for estimating the risk of transmitting TSE by human tissue intended for transplantation. Dr. Taffs.

DR. TAFFS: Good morning. I'm

very pleased to have an opportunity today to present information on risk assessment models after the transmission of TSEs by human tissues intended for transplantation.

During my talk I ask you to keep in mind two important points. The first point is that this talk represents the views of the author and is not the official position of the Food and Drug Administration. Now, that having been said, the second point is that you will note later in the talk that many assumptions are made in risk assessments. Not all of these assumptions are established scientific fact, nor is there complete agreement on some of the numerical values used in the models that I will present but my goal this morning is to describe the development and application of probabilistic risk assessments in estimating TSE exposure risks associated with the use of human tissues.

Efforts have been made in the past

to quantitate the risk of TSEs associated with the use of pharmaceutical products. The first citation shown here is often called the German Model.

The second citation is a paper that appeared in the PhRMA Association Journal BioPharm a few years ago.

The third citation is a more recent report on harmonization of risk assessments for the scientific committees of the European Commission outlining the essential elements of quantitative risk assessment.

While no detailed guidance on risk assessment for tissues is currently available from the FDA the agency attempts to harmonize with other regulatory authorities wherever possible. The EC risk assessment publications are available on the Internet and they provide a reasonable framework for harmonizing approaches to science-based risk assessment and for

developing risk-assessment models.

The last citation is a recent risk assessment model for cornea transplantation providing one example of the various approaches that might be taken to assess TSE risks associated with the use of allograft tissues.

Risk analysis can be thought of as a comprehensive, structured approach to dealing with risk. It is comprised of risk assessment, risk management, and risk communication. This presentation focuses on risk assessment.

The elements of risk assessment include hazard identification, exposure to assessment, hazard characterization, and risk characterization. Hazard identification examines the source of a risk capable of producing an adverse effect together with a quantitative description of that adverse effect. Exposure assessment evaluates the levels and the duration of

exposure to the risk. Hazard characterization seeks to determine the dose-response relationship and the mechanisms of those critical effects. Risk characterization estimates the probability of the occurrence and the severity of the adverse effects along with attendant uncertainties.

I think it is important to consider that variability and uncertainty in the risk model should be described. Risk assessment and risk assessors need to explore the scientific basis for the risk estimation and explicitly state the assumptions made in modeling risk in order to avoid any false sense of precision. The assumptions and constraints of the model should also be described.

Now, the principles outlined in this slide are really not so foreign. All of us are risk assessors. We evaluate the risks that we encounter every day. I have

an anecdote to illustrate the components of this slide. I have a risk mitigation strategy so that I know I will arrive at meetings such as this on time so I always leave early.

I had a little problem coming to the last advisory committee meeting. It had to do with a flat tire. Now, the risk mitigation strategy that I had in place at the time was to leave early. It turned out not be quite fully effective so I performed an additional risk assessment that involved the likelihood that I would encounter a nail in the road and that I would have an opportunity to change a tire or have my tire repaired so that I would still arrive at the meeting on time.

Other factors that were incorporated in that risk assessment included the age of my tires. So I instituted a new mitigation strategy that involved buying new tires and I made this

meeting on time. That's an example.

Probabilistic risk assessment provides a means to obtain specific objectives. Risk modeling lets us quantitate the relative contributions of the parameters in the risk model, identify critical elements for further research, and ultimately to obtain accurate information to aid in making regulatory decisions. In the case of TSE risks associated with the use of human tissues this third objective has not yet been completed although certainty considerable progress has been made.

Sensitivity analysis, also known as importance analysis, lets us examine the relative contributions of different parameters in the risk model. By "parameters" I mean all of the elements that can be incorporated in the model and could affect the outcome of the risk assessment calculations.

The objectives of sensitivity

analysis are to evaluate the effects of changes in the model parameters and identify those parameters that have the greatest impact on the magnitude of risk. Sensitivity analysis lets us examine the assumptions, the variability, and the uncertainty in the model and quantify the impact of each of the parameters on the outcome of the risk assessment.

I must point out that to my knowledge this important feature of risk assessment has not been addressed in previously published models of the risk of TSE in the use of human tissues or pharmaceutical products.

Efforts are ongoing in the Center for Biologics, Evaluation, and Research to develop quantitative science-based risk assessment models, including a generalized model for tissues that could be applied in specific circumstances as adequate data become available. Tissue risk assessment

models for CJD have several components. Some of these are listed here: Disease prevalence, donor availability and utilization, sources of uncertainty, and the potential impact of infection within the donor pool are incorporated in the model. The model includes diagnosed cases of CJD, undiagnosed symptomatic cases, and asymptomatic cases during the incubation period of the disease.

Data inputs for the model include a population age distribution, age-specific all-cause deaths, age-specific rates of CJD deaths, and age-specific donor utilization for a given tissue. The model also incorporates parameters for donor screening, processing, and possibilities for cross-contamination. The results I will present shortly were obtained from this generalized model and it is important to note that different tissues vary with regard to their procurement, tissue processing, and

implantation procedures. These unique features need to be taken into account in a risk assessment for any given tissue.

Some sources of information are readily available to develop risk assessments for CJD in tissues. Four sources that I have used for modeling are shown here, including published estimates of CJD incidents, age-specific mortality, population estimates from the US Bureau of the Census and, as an example of data available for a specific tissue, information on cornea donations available from the Eye Bank Association of America.

At the same time I should note that for many tissues comprehensive and accurate information on donor utilization and tissue processing are not readily available and such information would be needed to provide reliable estimates of the risk. Efforts to compile such information for different tissues should be encouraged

and acknowledged.

As one simple example of the information available for CJD-risk models this figure shows the age distributions for CJD incidents in the United States and the United Kingdom adjusted for the nearly five-fold difference in population between the two nations. The distributions are remarkably similar as has been noted in a number of publications.

As an example of the information available for tissue utilization this slide compares the age distribution for cornea donors and for all caused deaths in the US. All caused deaths are shown in hundreds adjusting the scale and the figure so that the difference between the two distributions is readily apparent. Note the observed reduction in cornea use from potential donors over the age of 70 attributable to cornea procurement and implantation practices at different locations within the

United States.

The point is that the age distribution for the utilization of a specific tissue may not correspond with the potential donor pool reflected in age-specific all-cause death rates so reliable information is needed for specific tissues if we desire to model CJD risk accurately.

For the generalized risk model the variables listed here were identified as important parameters. These include the number of symptomatic cases that are undiagnosed or not detected by current screening methods, the number of asymptomatic cases, and CJD prevalence. Additional screening procedures or donor exclusion criteria can also be incorporated in the model.

Other important variables include decontamination, that is, reduction in infectivity that may result from processing steps, the effect of cross-contamination or

commingling, batch size, and the numbers of donors, recipients, and graft materials that may be used in a given transplant procedure. These topics will also be discussed in detail by other speakers later today.

To illustrate how these parameters fit in the overall strategy for risk assessment this diagram places the CJD risk model in a framework consistent with the risk assessment elements shown in an earlier slide. The underlying distribution for donors, disease, and population are considered as a part of the exposure assessment.

Recovery, processing, and transplant procedures are also captured under exposure assessment. The risk characterization includes several parameters shown on the next slide. Risk characterization includes the proportion of missed cases, incubation period, symptomatic period prior to diagnosis, and actual

disease prevalence. The parameters captured under exposure assessment are also listed here.

Two important points must be made. The first is that except for the number of donors in the model these parameters are not regarded as single-point estimates in this model. Instead the calculation of the risk depends on the underlying distribution of each parameter. This is probabilistic risk assessment. Each input distribution reflects the variability and uncertainty for the individual parameter. For example, the estimate of the proportion of missed cases is modeled as a range of values from .5 to 10 percent using a triangular distribution whose most probable value in the model is 1 percent.

The asymptomatic period is modeled on a range of values from 5 to 40 years with a median of 10 years. Other components include prevalence, number of donors in a

batch, number of transplant items per donor and recipient, medical history review, cross-contamination, and reduction in infectivity by tissue processing, and these are all components of the probabilistic risk model.

In calculating the risk the distributions for each of these parameters are repetitively sampled at random using the median as the most probable value for the distribution. Each iteration computes the number of exposures that would occur and following 10,000 iterations an output distribution can then be calculated showing the mean number of exposures and its variability given input distributions. This method is often referred to as Monte Carlo analysis. The number of donors used in this illustration was fixed at 25,000 per year. These distributions are easily adjusted in the model to coincide with the values to be expected for a given tissue procurement

process and transplant procedure.

The next step was to quantitate the number of exposures to CJD-infected tissue that might occur in one year under different model assumptions. The two parameters that were varied in the comparisons that I am about to show were medical history review and commingling of tissues during processing. The 75-percent value indicated here for medical history review actually is modeled by a distribution of 60 to 85 percent expressing the variability or uncertainty in a proportion of cases where we assume that the medical history is complete, accurate, available for review, and used without error to detect infected donors. The 100 percent value assumes that the review is effective in every case. The distribution for commingling assumes that commingling occurs in half of the process tissues and results in cross-contamination if infected material

is present.

The likelihood of the presence of infectious material was based on the other parameters in the model and those parameters were not varied for these comparisons. Results are shown in the next four slides expressed as means and probability distributions for the number of exposures per year based on an input of 25,000 donors.

These comparisons are meant as examples of the application of the model and are not intended to represent a given tissue or process. This output distribution shows the mean number of exposures per year and its probability distribution when medical history review is effective in approximately 75 percent of the cases and where commingling may occur in half of the processed tissues.

Under the assumptions of this model the estimate of the number of exposures is 8.4 per year for 25,000 donors.

The fifth and the 95 percentiles are indicated below the histogram.

When the same model is run in the absence of any commingling the mean number of exposures per year per 25,000 donors declines from 8.4 to 1.7. As shown here, assuming 100 percent medical history review, the model estimates that the number of exposures would be 5.5 per year when commingling occurs. The same model estimates that 1.4 exposures would occur in the absence of any commingling.

The results of these four models are summarized in this table. The variability of the means is expressed as a 5 to 95 percent confidence interval for the mean number of exposures per year. One advantage of this modeling approach is that it allows other parameters to be evaluated such as additional donor exclusion criteria, age, for example. Under this set of model assumptions, using 8.4 as the baseline

number of annual exposures, exclusion of donors over age 60 or 65 would be expected to reduce annual exposures to 1.1 or 2.6 respectively. At the same time a large proportion of otherwise suitable donors would be excluded by these criteria as shown in this table.

A most useful outcome of the model is the ability to compare the model parameters to determine which of them have the greatest importance. Sensitivity analysis was conducted to see which parameters are driving the risk in the model. The two examples I will show are for the models incorporating 100 percent medical history review in the presence or absence of commingling.

This figure is called a tornado diagram. The length of the horizontal bars indicates the relative impact of the parameters on the estimated risk. In the presence of commingling and batch size are

the greatest contributors to the risk. The other parameters in the model are shown in order of magnitude of their impact on exposure risk. Note that the number of transplanted tissues is a significant contributor to the risk model but it is less important than commingling and batch size under the assumptions in this model.

In the absence of commingling, the same model estimates that the number of transplanted tissues is the largest risk driver, having moved up from 4th place in the previous diagram. As the input parameters are modified, for example, by imposing additional screening or mitigation procedures, the magnitude and order of the risk drivers can change.

Sensitivity analysis allows us to identify significant parameters in the risk model and consider risk mitigation strategies or focus on the parameters where better scientific parameters where better

scientific information is most needed.

Several parameters in the models I've described are limited by lack of good information. These so-called data gaps are areas in which better information would improve the accuracy of the risk model. More data are needed on the amount of CJD agent that is present in or could contaminate tissue during procurement from a CJD-infected donor, the progression of CJD and the infectivity of different tissues during the course of the disease, the extent of reduction of CJD agent that might occur during processing of tissues from a CJD-infected donor, the donor utilization and allograft implantation practices for specific tissues, and the extent of cross-contamination by instruments or equipment that might occur during processing.

In conclusion I hope I have shown in these examples that probabilistic risk assessment allows detailed evaluation of

exposure under differing model assumptions. It should be recognized that different tissues and processing methods have unique models and should be assessed separately.

The modeling indicates that commingling is potentially a major driver of risk. Other parameters such as the number of transplanted tissues are also significant drivers. Finally, additional data are needed to provide accurate estimates of exposure of allograft recipients to TSE-infected tissues.

I must thank my CBER collaborators in this work for their priceless expertise and enduring support, Dr. David Asher in the Office of Blood Research and Review and Dr. Steven Anderson in the Office of Biostatistics and Epidemiology. As a final comment, other presenters at this meeting will discuss important topics highly relevant to these risk assessment models, including possibilities for additional

testing, the impact of batch processing, cross-contamination, disinfection, and clearance.

I anticipate that the models I have discussed this morning will be further developed as an outcome of those presentations. I also hope that we might consider the information shared today in the context of developing quantitative risk assessments that improve our ability to make good decisions regarding the safe use of human tissues.

Thank you.

DR. BOLTON: Thank you, Dr. Taff. Are there questions from the committee?

Yes, John.

DR. BAILAR: You start your risk assessment model with what's becoming a standard four-step kind of thing, hazard identification and so forth. That model was originally elaborated for carcinogens and I'm not sure that it really applies in full

force here.

You've shown that it can be useful but as you went on you slid off into a multiplicative model and I wonder if the analysis might be simplified and the need for data clarified if you just began with a straight-through multiplicative model. Here is the probability the potential donor is infected, here's the probability that if it is infected the screening measures will remove that donor from the pool, here's the probability that the infection will survive the processing, and so forth. If you take it step by step like that I think the whole thing might become a good bit more clear. I'm not sure the bottom line would change, but I think also the data needs would stand out in starker contrast.

DR. TAFFS: I agree. The efforts of the committee that met to harmonize risk assessments in the European Commission efforts attempted to identify the elements

of risk assessment that are in common between all of the different applications of risk assessment and identify those elements that were unique and they attempted to construct a framework that might be useful for risk assessors to evaluate a particular problem and develop a model.

Now, in fact the risk assessment computations are conducted in exactly the process that you indicate; that is, all of the parameters are incorporated into a single model and evaluated sequentially in order to come up with the probabilistic computations that I showed today. So in practice the actually computations and evaluation of risk proceed in the fashion that you describe.

The point to having such a framework in place that uses the four components of risk assessment is to be sure that someone developing a model for the first time thinks about all of the different

components that are necessary in order to be certain that all the parameters are in place when the calculations are conducted.

DR. BOLTON: Dr. McCullough?

DR. McCULLOUGH: My question has to do with the medical history review. I'm sorry if I missed this explanation but you use the term "medical history reviewed." Does this mean the history was obtained but was not medically reviewed or that there were parts of the history that were not known or not obtained? Can you elaborate on what you mean by that?

DR. TAFFS: Yes, in the model we allow for several possibilities. One is that the review is unavailable. Another is that the review is not used, for example, in the cases of legislative consent. Another is that the medical history is incomplete or inaccurate, and another is the possibility that the medical review leads to some error. So those are captured under the distribution

60 percent to 85 percent that was used in this generalized model.

DR. BOLTON: I have a question. Have you taken the parameters, say, that may be available from dura mater transplants and tried to plug that into the model to see what results you get since we have known transmissions with a certain period of time that you might be able to evaluate the usefulness of the model? Have you done that?

DR. TAFFS: I think that is a very interesting prospect. In any case a risk assessment model should be verified against available data when the date become available and are sufficient in order to provide a good evaluation of the model. In that regard I think it might be possible at some point in the near future to examine the reliability of the model as applied to specific tissues, for example, cornea transplants.

At the same time I think we all have to recognize that a great deal of information is yet needed in order to generate a model that's capable of producing accurate estimates. Even so, the utility of the model in identifying the parameters that are the greatest drivers of risk makes it a very useful tool in assessing risk drivers and coming to some conclusions about good strategies for reducing or eliminating risk.

DR. BOLTON: I would agree. In my opinion one of the best uses of these models is to identify the gaps in the information that are most critical because when you begin to plug in the parameters and see how the model behaves sometimes those areas will stand out very clearly.

This committee and the FDA obviously are very concerned about those caps in knowledge that lead us either to be unable to make decisions or to be unable to make rational scientifically-based

decisions.

DR. TAFFS: I agree completely.

DR. BOLTON: Are there other questions? Dr. Bailar?

MR. BAILAR: One other comment on a minor note, the probability bounds that you show are based solely on what a statistician calls sampling error. They do not reflect bias in the data. They do not reflect problems in the model. The real bounds of uncertainty could be wider, maybe a great deal wider. You might want to comment on that on further analysis.

DR. TAFFS: I think as the model develops we will be able to represent the distributions for the individual parameters much more accurately. That depends on the availability of solid scientific information.

As just one example, a mitigation strategy such as decontamination during processing, to the extent that that

decontamination is validated then the distribution for the impact of this decontamination on the outcome risk assessment becomes much more precise and its impact on the total risk is quantifiable.

Until that information becomes available we are in a position of having to assign distributions for the individual parameters that reflect current understanding but are not necessarily based on established scientific fact.

DR. BOLTON: Further questions or comment?

Thank you, Dr. Taff.

Our next speaker is Dr. Nick Hogan, who will be presenting additional testing measures, the potential value of post-mortem transorbital frontal lobe needle biopsy. Nick.

DR. HOGAN: Good morning. Well, I'm glad to hear that batch and commingling are a big problem because there is no batch

or commingling for corneal donors.

I was asked today to come and talk with you about possible alternatives should testing for CJD be required. We have come up with some interesting issues that we need to discuss.

This really stems from the meeting in January of 2001 of this committee where after the voting it was commented on that there would be a recommendation that when a test for TSE-associated prion protein is validated such a test should be applied to tissue donors. It comes from the charge statement today, of course, which this committee might also consider that an autopsy or failing that a brain biopsy validated to show that it is predictive of an autopsy diagnosis of TSE be performed on some or all cadaveric donors.

Well, any of these that applied, be they autopsy or brain biopsy, you have to know that there are greater than 45,000

corneal donors per year and based on the way this is done for corneal donors there is first a medical history exclusion and then the corneas are obtained. This would have to be applied to all 45,000 corneal donors regardless of the fact that subsequent testing for, say, hepatitis or for viability of endothelial cells might exclude that tissue.

This just shows a corneal transplant, essentially functionally blind and then after the transplant. Now, if an autopsy is required what impact would this have on the system? Well, the current autopsy rate in the United States is somewhere between 10 to 13 percent. That translates in major centers to between four and ten per week.

Now, the corneal donor procurement in major centers is about the same, eight to ten per week, so if autopsies were required on these this would double the number of

autopsies per week that would be required. So there are essentially 45,000 additional autopsies per year or 124 per day nationwide. Obviously this is going to require additional staff in terms of taking care of and interpreting the autopsy.

Additionally, the cost of an autopsy ranges between $1,500 and $3,000. The cost of a brain-limited autopsy, I found a bargain, $750 to $2,000, and who is going to pay for this? Under current Medicare rules Medicare will not pay for autopsies and most insurance companies have gone along with that. So the cost for an additional autopsy would likely be translated to the family's responsibility.

The biggest issue about autopsy is the biological time constraint. For a cornea there is a limit of four to eight days after death in which the tissue is viable for transplant. Most centers use four. The reason for that is that the

cornea endothelium, which is at the base of the cornea, which is at the base of the cornea -- this is the surface; this is the anterior chamber side -- is responsible for keeping the cornea detergessed.

If water gets in the cornea it becomes cloudy and it will fail as a graft. This is a non-replacing tissue. It does not mitose. It starts dying immediately after death and by the end of four days roughly 50 percent of the tissue can be gone. So this is the reason why time is such a big issue here.

Now, the standard time for a full autopsy based on the College of American Anatomic Pathologists is six weeks. That's a full autopsy. It's unclear in the way the FDA charge statement reads whether they mean that it is going to be just a neuro-pathologic exam. I must assume that that is what they mean. But even if just the brain were to be opened the logistical issues

would still be in place, that is, a standard neuropathologic examination with fixing of the tissue, evaluation of the slides for status spongiosis, is on the order of somewhere, quickly, two weeks to three weeks, as Dr. Gambetti and DeArmond and others know, and this is clearly beyond the viability time.

Now, what if the brain were to be opened but just a portion of the brain to be taken, a brain biopsy with the cranium open? Well, of course, doing any frozen section analysis should be able to be done within that four-day time period, actually within 24 hours. That is about what we need in order to get a usable cornea to the recipient.

Obviously in the other diagnostic tests, Western Blot, et cetera, that might be validated by this committee they could also be done in that time period. But have we looked at other tissues as well? I would

be interested in knowing what the committee thinks about the urine and CSF testing that is also being utilized and looked at.

But even with these, again, you have to think about the biological time constraints. So after the meeting in January a year ago we were talking about these issues and what would happen if exactly this question came up and we struck the idea that perhaps since the eye is going to be removed from these cadavers anyway what about going into the brain through a transorbital approach? Is that feasible?

The problem is this is not currently a neurosurgical site that is used. There are obviously issues. If the eye is in place in a living patient it's difficult to get past the eye to the orbital roof and into the brain. There's limited flexibility and limited space.

There's only one technique that uses a transorbital craniotomy approach.

That has recently been put forward by Shanno at the University of Pennsylvania to get at skull-based tumors but even that utilizes removal of a bone flap on the frontal bone.

So we are really treading on virgin territory here and we need to totally evaluate whether trans-orbital approach would be feasible and if testing could be validated. So we need to look at whether the biopsy site is adequate, if tissue could be procured, what diagnostic tests would be used with that material, what kind of analysis would be required, what personnel and financial issues might be involved with that. I will discuss some of the issues.

Now, obviously once the eye is out the orbit is left and everything is still there, including the orbital fat, extraocular muscles, vessels, and nerves. And This is what a post-enucleation eye looks like. The eye has been removed but the conjunctiva is still present, the

fornices, the base of the conjunctiva, is present. This is the stump of the optic nerve. And the big problem, all the orbital fat and extraocular muscles are still present. You have to get through that to get to the orbital roof but if you can do that, the orbital roof is an excellent candidate because it is the second thinnest bone in the orbit, the first being the medial.

The orbital apex, which would get you to the temporal lobe, is a little bit thicker, as is shown in this slide. Here is the orbital apex at the back of the eye, here is the orbit, is thick. If you went through this you could get to the temporal lobe but going through the orbital roof, which should be approachable once the eye is gone, could get you to the frontal lobe.

As shown here in this coronal section, going up in through the orbital roof to the frontal lobe gets you to the

frontal cortex. A little bit further laterally you can get more cortex and less white matter but the further you get laterally the thicker the bone becomes.

The frontal cortex obviously is a good site for looking for agent. As has been proved in many animal models, most brain biopsies that are done *in vivo* are done from frontal lobe and, as Paul Brown has shown, looking at infectious agents in the frontal cortex versus other regions in a scale of 1 to 4, 4 being the most frontal lobe, is a relatively good site for looking for agent, representative, at least.

So how can we get to the brain? Well, you have to reflect the superior orbital tissue. You can do that with cutting and a periosteal elevator that would expose the orbital roof. Then using a chisel and a rongeur, as seen in this CT 3-D reconstruction, you could break through the orbital roof and expose the under side of

the brain. The dura could then be excised and the brain accessed.

Then the question is how do you get the tissue out? You still have a relatively tight window. We have been looking at some issues of using a trocar. This is an old test type that has a sleeve on it like a cork borer, if you would, going up through this hole and getting a core sample of brain. A needle is too small. Large-bore needles are too small to utilize for most testing, I think, or even some of these thoracic trocars which have disposable sleeves you can use to remove brain.

An issue for any family is can you if you do this reconstruct the site and the answer is yes, you just replace the orbital tissue with a placode and cotton, you put a cornea sterile shell over the top which has little hooks on it, pull the eyelid down, and, as is shown, this is pre-enucleation on the same patient and post-enucleation.

There should not be an issue regarding that.

Well, the tissue pull-out and the condition of it go hand in hand with whatever validated tests you might use; that is, if you want to use morphological analysis obviously you can't pull out brain soup or you won't be able to analyze for the protein.

Biochemical assays on the other hand don't have to be quite so intact. The volume also is an issue and perhaps a smaller biopsy might be usable. But the issue here really is the test and whatever test you use validation is going to be the key.

Then the question is does it need to be 100-percent sensitive and specific? Well, we've addressed this before and I would have to say yes, it has to be rapid and it has to be within 24 hours, 36 at the outside. It has to be reproducible and not only in the lab but also in the procurement

situation. The techs have to take from the same place, be able to get it to the labs in the same condition from case to case. There are numerous guidelines available for that.

Now, for the case of corneas there are 45,000 tests so even if you had a 95-percent sensitivity specificity you are introducing a huge number of false positives and negatives. For 98 percent it's still 900 so it really must be very close to 100-percent specific and sensitive.

As everyone knows, sensitivity declines, false negatives increase, and the risk of missing a case as specificity declines, the false positive increases, and you risk of throwing away good tissue.

Then the question is would this test adequately diagnose pre-clinical disease? We have already excluded a good majority of risk by the medical history, so could this pick up disease which is not prevalent by clinical examination or is this

just an indication for sub-testing, you only test those that don't have adequate history, of some other decision?

Once you have the tissue how do you test it? Do you test it at every eye bank or is there a regional center that you send it to to be analyzed? Obviously a regional center is going to have greater viability between tests but it is going to take some time to get the sample to them, which will again decrease your window.

There is going to be a lot more need for personnel both in terms of the procurement and the testing. You have to train them to do the tests and handle the results, administrative requirements in terms of oversight, reading, reporting, archiving, and this all comes down to the bottom line of cost. Cost will be for the instruments, if they are not disposable how you maintain them, the technician time for the procurements, sample transporting, cost

of testing, assay costs, tech costs, and, of course, the administrative costs that I just discussed with you.

Really, that is a big issue because if these costs are too huge these are going to be passed on. They presumably would be assumed by an eye bank, would be passed on to the consumer in terms of a more expensive cornea, and unless Medicare reimbursement were to go up coincidentally this could really exclude a lot of eligible recipients from having this procedure.

But the bottom line is can this approach to be used? Yes, the tissue procedure can be performed. We have done it in two cases. Tissue can be procured in various conditions and the testing probably can be performed in a timely manner for use in accessing should that be required. However, the costs will be high, as I have discussed, and validation will remain a problem. What test are we going to use and

can it be validated under field conditions, that is, from the time the tissue is obtained in the field?

None of this says anything about what effect on donor availability might be. If you introduce this sort of requirement families are very concerned about the appearance of the body and the additional time that this might take is certainly unclear.

We are trying to get together a reasonable questionnaire that we can provide as an analysis of this to ask family members after we have gotten through it all would you have donated this if an autopsy were required. We have to be careful because obviously you don't want to say, "Well, thanks for the corneas. That's going to cost you $1500. Would you still do it?" So I think it is reasonable to ask those questions.

But still the major barrier to

corneal transmission remains the historical exclusion. These criteria are continually updated. They were recently updated to exclude dementia of any sort, including Alzheimer's Disease except that clearly caused by train tumor, head trauma, or stroke, and there has not been a single case of corneal transmission in this country since institution of the medical exclusionary criteria. The 1974 case, the only positive case in the world, occurred before these exclusionary criteria were implemented.

So I would ask you that while determining what additional safeguards might be put in place to protect the population from CJD, a rare disease, we must remain vigilant in our pursuit against the devastating blindness caused by corneal disease which affects thousands of people in this country.

Thank you. Any questions?

DR. BOLTON: Thank you, Dr. Hogan. Questions from the committee?

DR. DeARMOND: Well, Nick, so why should we do it if the historical approach has been 100 percent safe so far?

DR. HOGAN: Well, and that's the issue. Obviously there is a risk of something getting through. That happened in the United Kingdom. It may have happened elsewhere. So with that risk of getting through, do you test? Do you test all patients? That's the question.

We are talking essentially here about availability. If you are going to reduce the age of donors 61 and over that gets rid of 50 percent of corneal donors, head trauma another 13. You're at 63 percent. Then the issue has been brought up on some of the papers that were discussed here by Dr. Solomon if variant CJD were to come to this country and we had to exclude donors that were younger than 50 because

they would be at the greatest risk we don't have any corneas left. So the issue here would be testing, to be sure, but I ask that same question myself.

DR. DeARMOND: Another question: As you know, the great majority of pathologists won't do an autopsy on a CJD patient.

DR. HOGAN: Nor will surgeons do brain biopsies.

DR. DeARMOND: No. We have been lucky that they will do it but they are very reluctant because for every one of those they have to close the operating suite for many hours with multiple personnel to decontaminate it so they don't like doing that.

But this is also risky. It's actually much more complicated, actually, than removing the brain at first sight. It may be ultimately very simple but cracking the skull and pulling out the brain is

actually a very simple procedure.

Here you have to rongeur your way up and then put a trocar up inside, the CSF is going to pour out, so the general pathologists who are doing these 45,000 corneal extracts are going to panic. Is there a simpler way or how do you deal with this contamination and the complexity of the procedure or is it too complex? Maybe that's the question.

DR. HOGAN: Well, I think either procedure is complex in terms of the containment issues but, again, the risk of those 45,000 having CJD is very low. You still have to assume that they all do. But we are working on some way to devise perhaps a trocar that could go through the orbital roof and get this biopsy in one fell swoop. It certainly would have CSF licked but your issues are well taken. We still have CSF and there will still be containment problems.

DR. BOLTON: John?

DR. BAILAR: What's the imbalance between supply and demand? How many more corneas per year do we need?

DR. HOGAN: Well, I have a slide on that. I didn't bring it. In the United States we are pretty much close to what we need. There still are people who have to wait three or four weeks to get a cornea. But eventually the majority, I would say, 90 percent of patients in this country, are able to get a cornea within a short time frame.

That's why corneas in this country are transported, are shipped, worldwide. So we do supply some corneas to other parts of the world. Some of our other speakers might be able to address that issue also.

DR. BOLTON: Please use the microphone and introduce yourself.

MS. HECK: Ellen Heck for EBAA and UT Southwestern Eye Bank. Your question

about the brain biopsies is of particular concern to me because Nick in his examples said the technician could do this. I think your risk of contamination from a technician is much greater than your risk of contamination with a pathologist and although Dr. Hogan, who works in Dallas where I work, is used to a metroplex where pathologists and neuro-pathologists are readily available I caution you to remember that at least 30 percent if not greater of the corneal procurements occur in rural areas where you will not have the access to the technology and the control of contamination that you have in a large university setting.

I think if you start trying to say that you are going to train eye bank technicians to do interorbital biopsies that our contamination concern is maybe greater than our risk concern in the cases that they might open up in a hospital room because not

all corneal procurements are done in an operating room. Many of them are done in a patient's room or in some other site which would be difficult to control.

DR. BOLTON: Pedro?

DR. PICCARDO: You are aiming to have 100 percent certainty. I mean, if I understand correctly you want 100 percent certainty?

DR. HOGAN: Of course.

DR. PICCARDO: Well, with this technique, which to me looks a little bit cumbersome, I mean, with the kind of work you put into getting a little piece of brain from a patient like this you could cut the whole brain out. I think if you cut the whole brain out you have a better chance of going to whatever you want and analyzing whatever you want because a good amount of tissue well taken, relatively well preserved, you can freeze, you can fix, you can do a number of things. With these

technicians I don't think you can.

The other thing is this is sometimes patchy so something negative here will not say anything about the rest of the brain. I think if you create a sense of security when in reality I don't think you have it.

DR. HOGAN: I agree. The issue here, the reason why it was brought up at all, was the issue of containment and we have already discussed that.

DR. DeARMOND: Well, Nick, I do think the idea is very good and validating it is going to be hard because you have to do the procedure and then do the autopsy and test. The problem is we usually get people at the end stage of the disease. We never get a person who is unsuspected of CJD. At least I've never seen on show up yet but maybe I missed it. Maybe I'm just not good enough to see it.

DR. HOGAN: I doubt that.

DR. DeARMOND: So at end stage disease we've even had some problems with the cortical biopsy two to three months before the patient died being negative and then when we do the autopsy it is clearly positive. So validation of the technique, I think, is going to be tough for those unsuspected cases of CJD but the idea, I think, is still a valid one and certainly could add some degree of confidence about the cornea. Maybe a different approach or some other mechanism because of this fear of pathologists.

And it really irritates me that they have this fear. It's unethical, it's immoral. The other physicians take care of the patient, the family lives with the patient, and the lousy pathologist won't even go in and do his job. I've even told them they should get out of this business and get into the restaurant business or something that's safer.

But accepting that they are chicken we have to come up with some simple method that would be easy, maybe a way of going laterally, a burr hole that would be very simple with a needle biopsy or a fairly large needle biopsy might be another way where they will feel a little more comfortable about what they are doing and they can see what they are doing.

I'd like to talk to you more about how we could think through such a thing because I think it's an interesting approach and it could give some more security about other transplants as well as corneal.

DR. HOGAN: Yes, and that is certainly a key here. The problem, I think, as you said, is personnel and time. So whether you go through the orbit or through the brain I think that is irrelevant. It's how you validate it in terms of what tests you are going to do, is it going to be worthwhile to do 45,000 tests to detect one

case, and is it worth the cost?

DR. BOLTON: From a naïve biochemist's point of view let me ask our neuropathologists their opinion. What about looking at the optic nerve since it is right there and we are looking for infectivity in the cornea, which is downstream from that? Is that feasible? If there was a test that could detect very small amounts of abnormal PRP what is your opinion?

DR. GAMBETTI: I have never tested the optic nerve so I have no idea how rich the optic nerve is.

DR. HOGAN: I have some slides with data on that if you would put up the last two.

DR. GAMBETTI: The retina would be eventually probably a much better area to test than the optic nerve.

DR. BOLTON: Would that simplify the procedure and would it do so if it does without compromising the reliability of the

result?

DR. GAMBETTI: Yes, to the retina would simplify the procedure. I don't know the reliability of the retina vis-a-vis the cerebral cortex.

DR. BOLTON: Pedro, you are shaking your head no?

DR. HOGAN: Could we put on the last couple of slides? Go ahead. If you would allow me.

DR. BOLTON: Yes, do you have data on this?

DR. HOGAN: Yes. As you know, when I was back with Stan we did some regional data on looking at the titer of the agent in the scrapie model inoculated. The amount of agent in the retina is about that of brain. In cornea is five logs less than in brain and that's in the IC route.

The optic nerve is a little bit somewhere in between. There is a paper out from Collins' group using the ELC Western

Blot technique that looked at regional titers in eyes of variant CJD and sporadic CJD patients and compared to the amount of agent in the brain that present invariant CJD optic nerve is 25 percent, that in brain. That present invariant CJD retina is 2.5 percent, that in brain, and there is none detectible, that is, less than .00025 percent, that in brain, none detectible in sporadic CJD optic nerve or retina.

Now, we know it's there. We have done work on the animal models and we know that the PRP res is present in retina and there is a retinal destruction that comes from it. But we are working. Actually, I have a small grant to see if whether we can get the agent titered in the retina in human cases. Cases are tough to come by, as Dr. Belay knows.

DR. BOLTON: Pedro and then Suzette.

DR. PICCARDO: I'm going to repeat

something I said already. Let's start all over again. In multiple cases a patient that comes with a diagnosis of CJD the pathology is fairly clear. A neuro-pathology of the brain is fairly clear to make a diagnosis; however, we will come to cases, and I have experience in that, in which it becomes difficult.

Sometimes there is the association between the pattern of immuno-stoichiometry and PRP risk. In some cases I saw a significant amount of immunopositivity on the brain; however, on the contralateral side which we have frozen in some areas we couldn't see any PRP risk by Western Blotting, vice versa, all the permutations that you want, et cetera.

Once again in most of the cases it is clear; however, in some of the cases it is not clear even having the whole brain in your hand. So what I am afraid of is that with this system the aim is to have 100

percent certainty and it will create an appearance of something that is very well controlled when I'm not sure it will be very well controlled.

The other issue is coming to what Steve DeArmond mentioned. I think that the neuropathologists and the pathologists in general should be trained to do the autopsy and to go through the procedures. Provided you use common sense it is not dangerous. I don't see why not. Money is an issue but here we are dealing with a disease that has no cure and is fatal so I don't see any other way around it.

DR. BOLTON: Sue.

DR. PRIOLA: You stole my question earlier but I have one more. You said there were no cases of corneal transmission after 1974 when you instituted this patient background. How many corneal transplants have been done since 1974?

DR. HOGAN: In the last ten years

there have been 250,000. The data has not been collected prior to that.

DR. PRIOLA: So given that the risk of sporadic CJD is one per one to two million people would you expect to even pick one up?

DR. HOGAN: Well, that's a big question. That is a whole talk in itself. There are issues beyond the issue of prevalence in the population, especially since these are all dead. It is probably more like one in 100,000 because they are all dead people, not living people. The one per million is for living people.

There are some biological issues about the cornea, anyway. What is the titer of the agent in the cornea? Extremely low, maybe undetectable. How long does it have to be in someone in order to produce the disease? If it does produce the disease how long is the incubation period? Could it extend beyond a patient's lifetime? Most of

the corneal donations that are done are in older patients so it may not be detectible.

DR. PRIOLA: Yes, my point is that the fact that you don't have any cases since 1974 may not be due to --

DR. HOGAN: Somebody didn't report them.

DR. PRIOLA: Right, yes.

DR. BOLTON: Pierluigi?

DR. GAMBETTI: Going back in time to have a general view of the problem, I think there are several difficulties that are not very different from those the surveillance centers are dealing with. And one is that, as I think Steve DeArmond already underlined, it is really very difficult to get any procedure done on any case that is even vaguely suspected of having CJD or just to rule out CJD, just the fact that the result worked.

So one way to get around that but again will increase the costs is to have

identified centers that will perform that procedure for a reimbursement. So that means transporting. I don't know what percentage of cases which will be started that will be tested that will be tested in a major center and which will be those that are tested in rural areas where it will be very difficult to get. I don't know what is this percent. But one has to keep in mind that eventually one has to designate certain centers for the procedure to be performed.

Second, having said that, once the donor already is in that center then we also examine. University Hospital at Case Western Reserve University has examined because they were again reluctant to remove the brain. They have examined these possibilities, the burr hole, the biopsy, transorbital biopsy, and so on and at the end they came to the conclusion that removal of the brain was the most practical thing to do because you had then much more tissue to

examine and the time involved was actually less. Maybe the risk of contamination might have been a little bit more but I think you are in a relatively large center and they have the septic room, a special room, so that does not play a role.

Now, concerning the fact that how many you may miss, in our case, as Steve DeArmond way saying, we see generally cases at the end of the disease. What happens if you look at early cases? Presymptomatic was mentioned.

In our experience with brain biopsy, again, a population in which the disease may be there, is likely to be there, but at a very early stage we miss about 20 percent of the cases just on the fact that the tissue is very small rather than being representative of the whole brain like we do in autopsy because we take it from different areas.

So there is the possibility of

missing cases, especially if one uses, for example, immuno-staining. So certainly one should use Western Blot or other diagnostic tests rather than histology but by limiting yourself to small areas there is the possibility of the order of 10 to 20 percent missing, really, the case.

So major centers probably should be involved if one wants to do it and then this implies increasing costs. And once that you are in a major center it looks like probably the most practical thing to remove the brain.

DR. BOLTON: Nick, if you have your slide?

DR. HOGAN: I apologize. This was actually not supposed to be in there. This was supposed to be put on at the end. I wasn't finished with this slide. Go back two.

This is the data we had from hamster study. We looked at hamsters both

presymptomatically at seven weeks after IC inoculation and ten weeks after inoculation. These are the titers in ID50 units per gram, in cornea about five logs less than that in brain, optic nerve pretty close to brain, retina even closer. Again, that's IC inoculation.

This is what came from Wadsworth Collins' group where in sporadic CJD there was nothing detected based on this ELC Western Blot analysis. In variant CJD 2.5 percent in retina. This is compared to brain. That means if brain is 100 percent then in retina it's 2.5 and optic nerve 25. So that is the data that you were looking for.

DR. BOLTON: Thank you. I think we will move on now. I see Dr. Brown in the back of the room there. Paul, I'm sorry we kept you. I hope you are feeling a little better.

Our next speaker will be Dr. Paul

Brown. Everybody on this committee is very familiar with Dr. Brown. He is former chairman of this committee. He will be telling us two things. As I said before, we are going to combine his talks into one session. The first will be "Experience with Human Dura Mater Allograft and Pituitary-Derived Hormones: Lessons for Other Human Tissues," and we will take whatever questions the committee has for Dr. Brown.

Then we will move into his second talk, which will be "Potential for Cross-Contamination of Bone and Soft Tissue with Higher-Risk Tissues During Recovery." As soon as Dr. Brown is mic'd we will give him the floor.

Paul.

DR. BROWN: Good morning. Can you hear me all right? Well, I stand before you as testimony of the fact that high-dose steroids don't do much for dermatitis but they certainly are mood brighteners.

This will be very short in part because there is not a whole lot of data bearing on the issue that you have been asked to address and, second, because if there were it probably wouldn't help you too much. But let's reverse the order in which you thought you were going to hear these things because it's a more logical approach to give you what we have in terms of tissue infectivity and then to tell you what we have in terms of the consequences of that, which would be the tally of the iatrogenic 0transmission of cases of CJD.

So in the first slide if we could focus that, please, and lower the lights, this is the slide that I usually show for popular consumption. It's colorful and it gives the principal message which is that in human beings affected with Creutzfeldt-Jakob disease infectivity is indeed widespread in the body and not just limited to tissues of the central nervous system.