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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE**

Monday, October 6, 1997

8:30 a.m.

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Versailles Ballroom I through III

MILLER REPORTING COMPANY, INC.
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8120 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Paul W. Brown, M.D., Chairperson
William Freas, Executive Secretary

MEMBERS

Linda A. Detwiler, D.V.M.
Leon Faitek
Barbara W. Harrell, M.P.A.
William D. Hueston, D.V.M., Ph.D.
Lawrence S. Lessin, M.D.
Stanley B. Prusiner, M.D.
Raymond P. Roos, M.D.
Lawrence B. Schonberger, M.D.
Edmund Tramont, M.D.
Gilbert C. White II, M.D.
Sidney M. Wolfe, M.D.

TEMPORARY VOTING MEMBERS

Richard D. Penn, M.D.
Raymond Sawaya, M.D.

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P R O C E E D I N G S

Welcome and Administrative Remarks

DR. FREAS: Mr. Chairman, members of the committee, invited guests and public participants, I would like to welcome all of you to this, our second meeting of the Transmissible Spongiform Encephalopathies Advisory Committee.

I am Bill Freas, the Executive Secretary for this committee. Should anyone in the audience need to communicate with members of the committee, please do not directly approach these members. Please see me during a break or during lunch, and I will be more than glad to relay your message to the members of the committee.

Today's presentations are all open to the public and everyone is welcome to attend the entire program today.

At this time I would like to go around the table and introduce to the members of the audience those seated at the table. Starting on the audience's righthand side of the room, the first chair is the transcriber, of course, not a member of the committee. The next chair is empty but will soon be filled by Dr. Linda Detwiler. She is senior staff veterinarian, U.S. Department of Agriculture.

Our first committee member is Dr. Raymond Roos, Chair, Department of Neurology, University of Chicago.

I would like to ask the committee members to raise their hand just so the people in the audience can see you.

Next is Dr. Gilbert White, Professor, Department of Medicine, University of North Carolina.

Next is Mrs. Barbara Harrell, our consumer representative, Director, Division of Minority Health, State of Alabama, Department of Public Health.

Next is Dr. Edmund Tramont, Professor of Medicine, Medical Biotech Center, University of Maryland.

Next is Mr. Leon Faitek, a consumer advocate on this committee from San Diego, California.

Next is Dr. Richard Penn, a temporary voting member for today's meeting. He is Professor, Department of Neurosurgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

Next is Dr. Sidney Wolfe, Director, Public Citizen Health Research Group, Washington, D.C.

Next is our chairman, Dr. Paul Brown, Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke.

Next it is my pleasure to introduce a committee member who last night it was announced that he had received the Nobel Prize in Medicine, and that is Dr. Stanley Prusiner, Professor of Neurology, University of California

School of Medicine.

[Applause.]

DR. FREAS: The next seat is Dr. Lawrence Lessin, Medical Director, Washington Cancer Institute.

The next is Dr. Lawrence Schonberger, Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, Center for Disease Control.

Next is Dr. Raymond Sawaya, Professor and Chairman, Department of Neurosurgery, University of Texas-M.D. Anderson Cancer Center.

Next is Dr. William Hueston, Associate Dean, Virginia-Maryland Regional College of Veterinary Medicine.

There will be two seats at the end of the table for FDA speakers and participants who will not be members of the committee, but may join the table for presentation, answering questions throughout the day.

There are three committee members who could not make it today. They are: Dr. David Hoel, Professor and Chairman, Department of Biometry & Epidemiology, Medical University of South Carolina; Dr. Katherine O'Rourke, Research Microbiologist, U.S. Department of Agriculture, Agricultural Research Service, Washington State University; and Dr. Karen Hsiao, Associate Professor, Department of Neurology, University of Minnesota.

I would now like to read into the public record the Conflict of Interest Statement that is required for this meeting.

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

Pursuant to the authority granted under the Committee Charter, the Commissioner of FDA has appointed Drs. Richard Penn and Raymond Sawaya as temporary voting members.

Based on the agenda made available it has been determined that the agenda addresses matters of general applicability, therefore, waivers of general applicability approved by the Agency on April 16, 1997, for all members of the TSE Advisory Committee apply for this meeting.

Further, it has been determined that all financial interests in firms regulated by the Food and Drug Administration which have been reported by the participating members, consultants, invited guests as of this date present no potential for an appearance of a conflict of interest at this meeting. The general nature of matters to be discussed by this committee will not have a unique and distinct effect on any committee members' personal or imputed financial interest.

In regards to FDA's invited consultants, guests, speakers, the Agency has determined the services of these participants are essential.

The following reported interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by consultants, guests, and speakers.

The interests are as follows:

Dr. Maura Ricketts, a guest speaker, is a principal investigator for the CJD Surveillance System in Canada.

Dr. Robert Rohwer, a guest speaker, is a principal investigator on a contract supported by the American Red Cross, and he has a contract with the Swiss Red Cross. He also consults with regulated firms.

Dr. Raymond Sawaya, a temporary voting member, acts as a medical adviser to the Transplantation Research Foundation on allograft dura mater issues. This is a voluntary function for which he receives no remuneration.

Ms. Marian Sullivan, a guest speaker, is employed by the National Blood Data Resource Center, a nonprofit organization, as the Executive Director. Four regulated firms have made contributions to her organization. In addition, three firms have representatives who serve on the

National Blood Data Resource Center's board of directors.

Dr. Robert Will, a guest speaker, is negotiating a research project on CJD with a regulated firm.

The following participants have no interests to disclose: Drs. Diringer, Penn, Soucie, Tateishi, and Steers.

In addition, the following speakers are representatives of industry and therefore they were not screened for their presentations at today's meeting. They are: Dr. Michael Fournel, Bayer Corporation; Mr. Art Heinrichs, Lifelink Tissue Bank; Dr. Theodore Malinin, University of Miami Tissue Bank; Ms. Gerry Oster, Biodynamics International; and Dr. Peter Page of the American Red Cross.

In the event that the discussions involve specific products or firms for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvements and their exclusions will be noted in the public record.

A copy of the waivers are available by written request under the Freedom of Information Act.

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 firms

whose products they may wish to comment upon.

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

DR. BROWN: Good morning. I think that it is important for not only the members of the committee, but those in the audience and the speakers, perhaps most of all, to be reminded that we are asked to give answers at the end of the day to two very specific questions, these two and only these two.

The questions are: Taking into consideration the clinical benefits of dura mater allograft and the adequacy of alternative products, for what surgical procedures is there a need for dura mater allograft?

The second question is: What measures or safeguards should be used to minimize the risk of CJD transmission associated with the surgical use of dura mater allograft?

At this time we have a few introductory comments by Linda Sherman, who is the Senior Adviser for Medical Policy to the Deputy Commissioner for Operations of the FDA.

Dr. Sherman.

Welcome and Introductory Comments

DR. SHERMAN: Thank you, Dr. Brown, for those words, and good morning. Again, my name is Linda Sherman and I am the Senior Medical Adviser for Medical Policy to

the Lead Deputy Commissioner for Dr. Michael Friedman.

I have the pleasure this morning of representing Dr. Friedman and all my colleagues at FDA in welcoming you to the second Transmissible Spongiform Encephalopathies Advisory Committee meeting.

Dr. Friedman, who was unavoidably called away for a meeting with Secretary Shalala, sincerely regrets not being able to join you for this important discussion that will take place both today and tomorrow. However, he wanted you to know how much he appreciates your willingness to be able to participate in this meeting.

As you know, the issues with TSEs are very complex. We are dealing with a set of diseases for which our scientific knowledge base is incomplete. Therefore, the Agency looks to you, the experts from academia, the community, and other parts of government to provide us with the most up to date advice, so that you can help us at FDA and other government agencies to reach the best possible decisions related to TSEs, so that we may ensure the health of the American people.

Since you last convened in April of '97, several milestones have occurred. First, on June 5th of this year, FDA published its final rule to prohibit mammalian tissue in the feed for ruminant animals. It became effective in

August of this year.

Second, on July 30, 1997, the European Commission issued a policy decision which prohibits certain tissues, the so-called specified risk materials, or SRMs, or generally neurological tissue of cattle, goats, and sheep over 12 months of age, banning them from food, pharmaceuticals, feed, and cosmetics.

This ban applies to any country regardless of its BSE status that exports products to the European Union. Effective January 1, 1998, governments will have to comply to certify that the SRMs were removed from source animals at the time of slaughter in order to export to the European Union countries.

As we speak, a FDA delegation headed by Deputy Commissioner for External Affairs, Sharon Smith Holston, is headed towards Brussels to meet with European Commission officials to discuss the potential impact of the EC's decision. The delegation will express the U.S. concern that the decision will impact on the availability of potential important medical products needed worldwide.

Third, it gives me the great pleasure to announce on the October 7th, 1997, tomorrow, the publication of a Notice of Availability in the Federal Register of FDA's guidance for industry entitled, "The Sourcing and Processing

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of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy in FDA-Regulated Products for Human Use."

Some copies should be available here either today or tomorrow, and if they are not, the document is currently already available on FDA's Home Page on the Internet.

Once you get to the Home Page page, the document, which is 15 pages long, can be downloaded from the option More Choices, and from there go to Guidance Documents.

It is particularly gratifying to make this announcement because the guidance document was developed with consideration of the advice that the Agency received from this distinguished panel of experts.

The committee reviewed data on the sourcing and processing of materials used to make gelatin, as well as data from an experimental study on the effect of gelatin processing on the infectivity of a spongiform agent.

Based on the FDA review and the many points made by the Advisory Committee members, FDA made six recommendations which I will not cover at this time. The guidance is a Level 1 guidance document consistent with Good Guidance Practices, and the Agency will be soliciting comment. However, it will implement the guidance immediately because of the public health concerns related to

the use of gelatin.

This document represents the Agency's current thinking on reducing the potential risk for transmission of BSE related to the use of gelatin and FDA regulated products for human use.

Now to return to the business at hand, this second Advisory Committee has been convened to address two additional areas of concern related to medical products and TSEs. Once again we seek your advice as we approach these delicate issues in uncharted territory.

Today, you will be asked to consider the safety and risk-benefit of processed human dura mater as an implant for surgical use with regard to the risk of Creutzfeldt-Jakob disease transmission.

Tomorrow, you will be asked to deliberate on another difficult area concerning TSE-implicated secondary products, for example, a TSE-implicated plasma derivative that was either added as an excipient or used as an agent in the manufacturing process.

I look forward to the various presentations and to hearing the committee's deliberations on these difficult issues over the next two days.

On behalf of Dr. Michael Friedman and the entire FDA, I thank you all who are gathered here today and

tomorrow for being a part of this important process.

I would like to take two seconds to congratulate Dr. Prusiner on his Nobel Prize on behalf of the FDA and Dr. Friedman.

Thank you.

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

Open Public Hearing

This, as you know, is an open public hearing and on our agenda now is opportunity time for the public to make themselves heard on this particular issue, and that will be handled by Dr. Freas.

DR. FREAS: Mr. Chairman, at this time, in response to the announcement in the Federal Register we have not received any requests from members of the public to speak at this morning's open public session.

Are there members here this morning who would like to address the committee?

[No response.]

DR. FREAS: At this time I see no hands. We will have another open committee hearing tomorrow morning at 8:55, and if anybody would like to address the committee, they are more than welcome to do so during the scheduled open public hearing tomorrow morning.

Thank you.

DR. BROWN: Thank you, Bill.

The next four presentations will occur sequentially before the morning break.

The first will concern the background against which this committee has been asked to advise the FDA, and the next three will concern themselves with the procurement, that is, the source and processing of dura mater.

The background presentation will be given now by Dr. Elizabeth Jacobson, Deputy Director for Science, Center for Devices and Radiological Health of the FDA.

Background-Overview of the Human Dura Mater

Issue and FDA Regulatory Controls for Processed

Human Dura Mater Products

DR. JACOBSON: Good morning. I would like to extend a warm welcome to our panel and our speakers today. I know some of you have come from a very long way to participate in today's meeting and we appreciate your willingness to share your experience and your expertise in the use of dura mater implants and alternatives, and a special thanks to Dr. Prusiner for showing up the morning after the Nobel was announced.

My task is to remind everyone of the background of this issue. I think it is a little like bringing coals to

Newcastle to talk about this to this group, so I am going to try to be as brief as possible, so we can get on to the presentations and the discussion, which I know everybody is waiting for.

We are here today because of recent events concerning the use of processed dura mater implants. As you know, in March, the World Health Organization recommended a ban on the use of dura mater as an implant because of reports of CJD in a number of recipients, and at the same time, Japan's Health and Welfare Ministry banned the use of dura mater in brain surgery.

Because FDA had established safeguards and guidelines in the late eighties to minimize the possibility of such infections, and because we have had no confirmed cases of CJD transmission by dura since these guidelines have been implemented, the Agency decided in March not to restrict the distribution of dura mater cleared for U.S. markets at that time, but we also decided to hold a public meeting to reevaluate the issue, and that is why we are here today.

Our safeguards and guidances are the results of our experiences in dealing with contaminated processed dura mater that was imported into the United States in 1987, our interactions with the tissue industry, and our experiences

with other processed human tissue implants.

The use of tissues as implants has been around for a long time in the United States, certainly before the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act, and this use was at that time perceived as practice of medicine and generally was not actively regulated by FDA.

Because some tissues introduce special health concerns, we began to regulate tissues on a case-by-case basis in the late eighties and early nineties. Dura mater was one of the first tissues to be regulated by FDA as a medical device.

[Slide.]

I am going to put up just kind of a very brief and abbreviated summary, and you can follow through as I talk.

In February 1987, the Center for Disease Control and Prevention reported the first of two U.S. cases of CJD in a person who had received a dura mater graft. The dura mater was a Lyodura brand sold by a German company, and although Lyodura had not been distributed in the U.S., American physician were obtaining the product from Canada through the regular mail.

The contaminated graft tissue came from dura mater tissue that had been processed by pooling the tissue from many cadaver donors rather than processing individual

donor's tissue separately.

Over the next five months, we consulted with our Neurological Devices Advisory Panel. We issued a warning to the medical community on the potential risk of transmitting CJD to surgical patients through the use of contaminated Lyodura product, and we banned the importation of Lyodura, preventing this product from entering the U.S. The ban on importing Lyodura is still in effect, and this product has never received premarket clearance for distribution in the United States.

Dura mater was discussed at two meetings of the Neurologic Devices Panel in 1989 and 1990, and at the 1990 meeting, the panel recommended placing human dura mater in Class II for neurosurgical use.

[Slide.]

After considering the panel recommendation, FDA decided to subject dura to all device requirements, which included the necessity for 510(k) submissions and Good Manufacturing Practices.

The classification of human dura mater has not been finalized, so it is still considered a preamendments Class III device.

We also issued two guidance documents to assist FDA staff and manufacturers. There was a guide for 510(k)

review of processed dura mater in 1990, which was shared with processors and providers, and there was also a compliance policy guide on general principles and controls necessary to process human dura mater for implantation in 1991. This guide was for FDA staff.

These guidance documents cover the appropriate screening of potential donors. They recommend procedures for examination and quarantine of brain tissue and histological examination of the brain of donors although we know that histologic exams of every donor is not being done, and that is one of the things we should talk about today.

The guidances warn against pooling of dura mater tissue from different donors and it provides procedures for recordkeeping and facility control.

Since this increased regulatory control has been in effect, there have been, as I said, no confirmed cases in the reports in the U.S. of CJD related to dura mater implants. So since 1990 then, tissue providers wishing to market dura mater must submit a premarket clearance application to FDA for review.

In our review and in our inspection for Good Manufacturing Practices, we look to see if donors are adequately screened to minimize risk of transmitting diseases, if dura mater is appropriately processed, and if

the appropriate records are kept and maintained.

Of course, the rest of the overhead outlines what I said earlier, the WHO recommended a ban in March, that Japan did ban in March of this year, and that we are holding this meeting today to reassess the safety.

I would also like to mention as a related matter that at FDA, we are looking at ways to provide more appropriate oversight for all processed tissues, and a new comprehensive approach for regulating cellular and tissue-based products in which the Center for Biologics Evaluation and Research would be the lead, was published in the Federal Register in February of '97.

According to this proposal, dura mater would be regulated as a tissue product under Section 361 of the Public Health Services Act, and not as a medical device. This proposed approach would include requirements for donor screening, recordkeeping, and good tissue practices, which are essentially Good Manufacturing Practices tailored to the special needs of tissues.

But the regulatory route, that is, regulation as a device or a tissue, really isn't the question. That is only the mechanics of how we get it done. What is important and why we are here today is what the scientifically-based safeguards need to be regardless of the regulatory route

that we take to institute these safeguards.

As you know, dura substitutes, such as bovine pericardium, Silastic dura substitutes, and gortex have been cleared for market in the U.S. While dura substitutes are appropriate in many surgical repair procedures, there is a real question about whether they can be used for all repairs, so the charge to the committee today then is to assess the safety of processed human dura mater as an implant for surgical use with regard to the risk of CJD transmission considering its purported clinical benefits and the adequacy of alternative products.

I would like to thank you all once again for coming and I look forward to a very interesting, informative, and productive day.

DR. BROWN: Thank you, Dr. Jacobson.

Maybe the same question has occurred to other members of the committee as has occurred to me, and you might be able to answer this.

The FDA ban on the importation of Lyodura, which was stipulated explicitly in 1990 or '91, as you showed on the slide, would that have made the mailing through U.S. mail from Canada of a Lyodura graft illegal and subject to penalty or not?

DR. JACOBSON: That is a good question. I imagine

it would. That would be interstate distribution. People can mail things through the mail. Of course, we have no control over what goes through the individual mail, we can't look at every package, but that was one of the reasons why we also did a big publicity effort at the time, making sure that people understood what the risks were and that this particular product was associated with a real hazard.

DR. BROWN: So prior to the import ban itself, it would not have been illegal to mail a Lyodura patch into this country even though Lyodura had not gone through any qualifying consideration by the FDA?

DR. JACOBSON: Well, I would say that it would be illegal, it was not an approved product for use in this country.

DR. BROWN: So if a product is --

DR. JACOBSON: I mean we would have to check with the Compliance folks. This is kind of an esoteric question.

DR. BROWN: Yes, I guess, although it is not especially esoteric from the point of view of the possibility of the manufacturer of anything which can fit into an envelope doing an end run around FDA regulations.

Thank you. Does anybody else have any questions for Dr. Jacobson? Larry.

DR. SCHONBERGER: As one who was involved in the

investigation in 1987, I certainly was not left with the impression in discussion with FDA that what had happened was illegal. I think that is too strong a word in terms of the shipping from -- it came from a Canadian firm that mailed it to the U.S., this Lyodura. It was not in my understanding illegal what they did. It was a way of around --

DR. BROWN: Would it have been illegal following the import ban in 1991?

DR. SCHONBERGER: That, I do not know.

DR. BROWN: So, before 1991, it would not have been illegal, it would not have been approved, but neither would it have been illegal. Following 1991 and the import ban that was explicit, it would have been illegal. Okay.

Stan.

DR. PRUSINER: Paul, could you give us a little more background on this? I am not aware of the details of the shipment from Canada.

DR. BROWN: Larry, would you like to -- I mean as far as I know, what had happened was that -- just why Germany or this particular firm in Germany evidently decided that it did not wish to subject itself to examination for whether or not it could be officially imported, and therefore did this end run through Canada, a Canada firm, which then mailed dura mater to any surgeon who wanted it in

this country.

DR. SCHONBERGER: Paul, in our investigation, it was certainly my impression that the company in Germany was not aware that its distributor in Canada was distributing to the United States, or at least they denied knowledge of that and specifically indicated that they asked the company to stop that practice.

DR. PRUSINER: What were the dates? When did all this start?

DR. SCHONBERGER: Well, CDC was informed of a 28-year-old pregnant woman who had CJD, which in and of itself was shocking to us. I mean we don't get that many reports.

DR. PRUSINER: I am asking the years when the dura started to be shipped from Canada into the United States.

DR. BROWN: At least through the entire 1980s.

DR. SCHONBERGER: The particular date I guess of this one was -- the product was made in 1982, but was shipped into the United States and used in this patient I think in 1985.

DR. PRUSINER: So, in other words, for a long time this firm in Canada was shipping Lyodura into the United States before any of this came to anybody's attention?

DR. BROWN: Certainly for a matter of years, yes.

DR. PRUSINER: So, in other words, if I am to understand this correctly, then, there was a continuing practice up until it became illegal with the import ban.

DR. BROWN: Yes.

DR. PRUSINER: Is this everybody's understanding?

DR. SCHONBERGER: It may have stopped after -- there was a meeting held as part of the investigation of the case in 1987, I believe it was, and the company met with FDA and with CDC and indicated that they were not any longer going to be using the product in the United States, and that they were also going to change the procedures, the methods by which they made the product beginning in May of 1987. I believe I have got the dates right.

DR. BROWN: Any further questions?

I have just been informed that Art Heinrichs from the Lifelink Tissue Bank in Tampa, Florida, one of the U.S. producers of dura, will not be present this morning.

DR. FREAS: Just to follow up on that, because Mr. Heinrichs could not be here, late Friday night he did write up his speech, and there are copies of his speech that he would have given in all the blue folders at the committee table, and there will be a limited number of copies for the members of the public if they ask at the reception table.

DR. BROWN: So, we are left with two speakers, one

of whom is from Biodynamics International, located in Florida. It is interesting. All of these firms are in Florida.

Following that, there will be a presentation by Theodore Malinin from the University of Miami Tissue Bank in Miami.

Now we shall hear from Gerry Ann Oster.

Procurement and Processing of Human Dura Mater

Gerry Ann Oster

MS. OSTER: Good morning. I am Gerry Oster, the Director of Operations for Biodynamics, as well as the Director of the tissue bank for Biodynamics.

Later on, for questions, I have in attendance with me our legal counsel, Mr. Jonathan Kahn, who will assist in answering any questions.

[Slide.]

My thanks to the TSE Advisory Committee for inviting Biodynamics International to this most important meeting. My presentation has been prepared to inform about Tutoplast dura mater - the product description and use, the safety of Tutoplast processed tissue, and medical need.

[Slide.]

Tutoplast dura mater is a solvent dehydrated resorbable anatomic human tissue graft. The collagenous

connective tissue with dimensionally intertwined fibers retains the multidirectional and mechanical strength of native dura mater, while providing the basic formative structure to support replacement by new endogenous tissue.

Our product has been cleared by the FDA and is in compliance with its 510(k), Quality Standards, AATB Standards, the State of Florida, with our own specifications and with our Quality Program. We have been licensed in the State of Florida since 1995 and we most recently were inspected for renewal and had no observations.

The raw material is recovered in the United States and Europe following strict adherence to the Interim Rule, which will be Final in January of '98. Biodynamics does not perform the harvest of dura mater per se, but contracts with several recovery programs to carry out the tissue procurement. These tissues are processed at our facility in Florida, and we are awaiting the status of our AATB accreditation inspection.

Upon receipt of the tissue, a strict quality control regimen of recordkeeping begins, from quarantine tissue log-in documentation to computer data entry. Tissue from donors will be processed predicated on acceptable serological results for HIV-1 and 2, hepatitis B surface antigen, HCB antibody, HTLV-1 and syphilis tests.

The processing core is a Class 10,000 Controlled Environment Processing Lab and final handling of tissue prior to packaging and sterilization is conducted under Class 100 conditions.

Process personnel must perform their duties by adhering to rigid universal precautions. Each tissue is individually handled and maintained in an intimate labeled container. All steps in the proprietary Tutoplast process are documented in great detail by trained personnel.

[Slide.]

Tutoplast dura mater is indicated for use in neurosurgical applications. We are aware that physicians may elect to use our product for orbitoplasty in the area of facial surgery and in the realm of pediatric surgery involving large gastric repair or tracheal stenosis, and other procedures as well.

Labeling, inclusive of Directions for Use, specify neurosurgical use and incorporate current regulations for labeling to include Contraindications, Precautions, Utilization, Warning, Adverse Effects - including reporting instructions, Sterilization, Storage, and a statement of serological testing for infectious diseases.

The benefits of Tutoplast dura mater offer greater confidence for the clinician and the patient. The

bioimplant is resorbable - examinations reveal that the collagenous tissue is ultimately surrounded by well-vascularized, cell-rich unspecified granulation tissue composed of macrophages and fibroblasts.

Our product has a greater tensile strength, no vascular gaps such as seen in freeze-dried dura, and has no evidence of enzymes or antigenicity. There have been no reports of sensitization with subsequent rejection following a transplant with Tutoplast dura.

The greatest benefit of Tutoplast dura is safety. History of this product, as well as the elements of donor screening and testing and a unique validated process which handles individual tissues have resulted in no threat for infectious viral disease or CJD transmission. Tutoplast dura mater provides quality of life - the best principles of health span versus life span.

Substitutes for damaged or removed tissue have existed for more than 100 years. Experiments began with rubber, gold foil and other materials which resulted in severe tissue reactions.

Some satisfactory outcome occurred early on in animal experiments with synthetics, such as cellophane, polyvinyl alcohol, Orlon and others. There is little doubt that these trials led to the current use of modern synthetic

materials.

Serious complications have been reported in patients with dural grafts from dura mater substitutes - hemorrhage, infection, re-exposure of the brain when reopening a craniotomy site, formation of thick connective tissue capsules or hematoma, and possible neurological deficit. Xenotransplantable tissues are available today, but complaints of infection and reaction to the membranes have been reported.

The first reported autograft occurred in 1893. Autografts continue to be used extensively by surgeons around the world because they are assumed readily available. The risks to the patient are evident from documentation of additional surgery for tissue removal.

These risks include difficulty harvesting an adequate amount of tissue for the application, potential infection at this harvest site, prolonged anesthesia time, and extended recovery time. The burden to the patient as a consumer is cost.

[Slide.]

Safety of tissue transplant is foremost on the minds of everyone in attendance. Biodynamics has placed emphasis on the safety of Tutoplast processed tissue for more than 20 years. Our program includes comprehensive

donor screening and testing, the inactivation and sterilization steps completed in the Tutoplast process, tissue tracking from recovery to end user, and, of course, our track record speaks for itself.

[Slide.]

Donor screening is a critical element of donor selection and approval. The potential donor is rigorously screened and tested through scientific means to identify the possible presence of risk of infectious diseases which may cause the tissue to be unsuitable for transplant.

Biodynamics adheres to current FDA and state regulations and AATB Standards in the donor screening process. Specific questions are presented to the interviewee to determine high risk behavior and medical history.

Serological testing is performed on blood samples which have been determined not to be plasma diluted. All tests are performed in CLIA laboratories which utilize FDA approved kits and reagents. Procurement must take place within 24 hours of death and there must be records of refrigeration of the body.

A detailed report of the physical exam must accompany the donor chart to Biodynamics. We have specified that recovery in Europe must include not only all of the

aforementioned information, but also a translated autopsy of the donor.

All of the above information, as well as available hospital and EMT records, police reports, and any pertinent information must be assembled and reviewed within the master donor chart.

Biodynamics employs a full-time medical director who in conjunction with QA, reviews every donor chart for the presence of required, acceptable documents and information. The medical director's review includes a determination of a histologic exam of the brain if indicated by the donor's medical history or other factors in the donor chart review. If this information is not included in an autopsy, he will classify the donor as unsuitable for processing and the tissue will be rejected. It is his responsibility to approve only those donors who meet the criteria set forth by FDA, AATB, and Biodynamics.

[Slide.]

What is the Tutoplast process? It is a patented process. It is in compliance with its 510(k). It is a process which meets strict quality control and manufacturing requirements for safe bioimplant processing.

The Tutoplast process is a science and technology-based method for virally and immunologically

inactivating and sterilizing tissue, rendering it contamination free, and preserving it for surgical transplant.

Beyond screening and inspection of the source material, the actual Tutoplast processing of the tissue eliminates or neutralizes bacterial and conventional viruses which are of the greatest concern today, including HIV and hepatitis, and unconventional viruses or prions such as CJD, while maintaining the biomechanical properties of the healthy tissue. The Tutoplast process leaves no deleterious residue and minimizes antigenic potential.

Bacteria which may be present when the tissue is recovered are completely destroyed and removed during the process. Each tissue undergoes microbiological analysis prior to and following sterilization with no detectable evidence of contamination.

Inactivation of conventional viruses is accomplished as demonstrated in validation studies. To prove that even high numbers of viruses can be inactivated, dura mater was incubated for four weeks in a virus culture. During this time, the viruses propagated exponentially.

Each individual processing stage was then tested with this high concentration. Every single stage alone was capable of inactivating these high virus concentrations.

Since all Tutoplast donors are tested before the grafts are preserved, such high pathogen concentrations can reasonably be ruled out. Therefore, the Tutoplast process closes the diagnostic window.

Unconventional viruses or prions, whose nature is still not fully understood, cause spongiform encephalopathies in animals and CJD in man. They are resistant to common disinfection and sterilization methods. The pathogen concentration increases continually in the infected host until death.

The brain contains by far the largest concentration of all tissues. The only demonstrably effective method for heat-sensitive and chemical-sensitive tissue is inactivation by sodium hydroxide, as documented by Dr. Paul Brown and other researchers. It has also been documented that various organic solvents are effective in treatment against these pathogens.

The efficacy of such treatments in the Tutoplast process has been tested and found to be effective. Studies have been conducted worldwide in light of the serious consequences of CJD transmission. Using scrapie models, esteemed researchers such as Dr. Carlo Masullo of the Institute of Neurology in Rome have analyzed the levels of peak concentrations versus the reducing capability of the

Tutoplast process.

The results of his study clearly demonstrated that treatments with sodium hydroxide, hydrogen peroxide and organic solvents are capable of reducing the level of infectivity to the point that the odds of contracting CJD are 1 in 3.5 million, which is lower than the overall risk of the general population to naturally or iatrogenically acquire the disease.

Similar studies and analyses have been conducted on individual and combined elements of the Tutoplast process, with similar outcomes, that Tutoplast processed tissue represents the highest possible degree of safety at present.

Most interesting, a recent study conducted by Dr. Eisenmenger at the University of Munich has shown that Tutoplast processed dura undergoing DNA trace analysis resulted in no amplification or less than 10 picograms of DNA per 1 gram of dura mater. Based on the sensitivity of these tests, there was no identifiable human DNA.

Since there are no specific tests for these prion organisms, our exclusion criteria are especially strict. The relatively low pathogen concentration at this point is inactivated in just the same way as in the peak concentration tests. Therefore, there is no risk of

transmitting TSE disease with Tutoplast in light of the present state of knowledge.

[Slide.]

Quality control of the Tutoplast process is the foundation of our Quality Program. As previously mentioned, donor screening and serological testing for infectious disease is the initial step required to begin the processing of tissue.

Tissue is placed in prepared containers with storage medium under controlled conditions until beginning preservation and sterilization processes. All tissues are unambiguously labeled and must pass standards for size, structure, cleanliness and quality before being released for processing. No donor pooling is allowed.

Tissues are cleaned with saline solution of various concentrations, resulting in the osmotic destruction of cells so that the source tissue is reduced to its fiber and mineral components.

Inorganic agents, such as hydrogen peroxide and sodium hydroxide, are used in specific concentrations and for specific time periods shown to inactivate HIV and the agents responsible for CJD.

The denaturization of soluble proteins is achieved without significant alterations in the collagenous structure

of the tissue. The tissue is then preserved by the extraction of water using organic solvents. Through a gentle method of preservation, the dense collagenous fiber structure is retained.

The organic solvents used are completely removed, without residue, at the end of this process. The organic solvents used for this part of the process have the benefit of disinfectant properties also capable of inactivating HIV as well as being effective on the CJD pathogen.

Following preservation steps, the tissue is cut into standard sizes and packaged in transparent pouches for inspection. Each tissue is microbiologically analyzed before and after gamma irradiation sterilization and dura is tested for mechanical strength performance.

A Finished Goods package of tissue is composed of tissue sealed in a double-peel pouch system. Each outer pouch is properly labeled with the contents, size, expiration date, reorder number, a bar code, and company information.

This pouch system is placed in a carton along with the package insert and a Tissue Utilization Record. Labeling complies with current FDA regulations, AATB standards, and the Tutoplast 510(k). As you can see, each step is documented by trained personnel and retained in a

Lot History File.

All procedures are maintained in a Device Master Record, appropriately updated and controlled by both Quality Assurance and Operations. Rejected tissue is documented and destroyed as medical waste in compliance with the laws of Florida and AATB standards. No issue is released to Finished Goods until all records have been reviewed and approved by QA and Operations.

[Slide.]

Tracking donor tissue from point of recovery to the end user is accomplished by Biodynamics through strict recordkeeping and documentation of tissue shipment. Each product for transplant is maintained in a database for the purpose of moving the item in and out of Finished Goods inventory.

Each package contains a Tissue Utilization Record, which allows the end user to record location, patient, and procedure information on the preprinted, postage-paid addressed card. Upon receipt of the Tissue Utilization Record, Biodynamics maintains a filing system by donor recovery site and donor identification. We also maintain tissue reference samples representing every unit available for transplant.

[Slide.]

Biodynamics International has a track record which presents a very positive image of the Tutoplast process, and more importantly testifies to the well being of the transplant recipients and the judgment of their surgeons in choosing Tutoplast tissue. In more than 500,000 applications in approximately 25 years of transplant history, there have been no reported cases of viral disease or CJD transmission.

[Slide.]

The annual volume of Tutoplast dura is in excess of 1,000 units. Typically, one dura mater will yield five units ranging in sizes from 4.5 square centimeters to 55 square centimeters. The demand far outweighs the supply as indicated in our current backorder of hundreds of units.

Biodynamics believes that this vote of confidence by United States surgeons, as well as our dedication to providing the safest bioimplant, allows Tutoplast processed dura mater to remain the tissue of choice.

We have provided detailed information to the World Health Organization in support of our Tutoplast processed dura mater. It is clear from their most recent publication that they acknowledge that in some cases there may not be any good alternatives to human derived dura mater for duraplasty.

The World Health Organization clearly recommends that dura transplants be allowed where no reasonable alternative is available for a specific patient. The World Health Organization report also acknowledges that all dura mater products are not equally safe. Indeed, the cases which the report mentions did not involve Tutoplast dura.

The World Health Organization report establishes the following three criteria for selecting the type of dura mater to be used for transplant:

1. The dura mater must be from a single donor and not pooled from different donors.

2. Potential dura mater donors must be carefully screened for neurological disorders including CJD.

3. The dura mater must be subjected to validated viral inactivation procedures that have presumably been approved by a recognized national health authority.

Clearly, Biodynamics Tutoplast dura satisfies all three of these criteria.

We agree with the recommendation that the practice of medicine and patient need govern the transplant of dura mater. Tutoplast dura mater should be used only when in the judgment of the individual patient's physician, its transplant is the safest and most effective treatment for the patient. The availability of Tutoplast dura mater

therefore allows physicians to decide the best alternative for patients based on medical needs.

DR. BROWN: Thank you very much. You might want to stay there because I have at least a dozen questions and perhaps members of the committee have the same or different dozens.

I am going to ask committee members if they have any questions before I raise those that occurred to me.

Yes, Leon Faitek.

MR. FAITEK: In one of your slides, it shows that you require autopsy reports from Europe. Is there a similar requirement for tissue acquired in the U.S.?

MS. OSTER: The current standards require that if an autopsy was performed, we must have a report of that here in the United States on U.S.-recovered tissue. If there was no autopsy, we are dependent on our medical director to review all of the comprehensive records and make a final decision on that particular donor. Donors can be recovered without autopsy in the United States.

MR. FAITEK: But it is required in Europe, but not in the States?

MS. OSTER: We require it, Biodynamics requires an autopsy on every donor from Europe.

MR. FAITEK: But not in the States?

MS. OSTER: No, it is not a requirement. If it is performed, we must have a copy of that for review.

DR. BROWN: Other questions from the committee?
Stan.

DR. PRUSINER: Could you go back -- I didn't understand the math in the last two overheads. There was one where you had 500,000 units, and then you have 1,000 units? I was confused.

MS. OSTER: No. In 25 years there have been at least 500,000 applications of the Tutoplast dura in surgery. We are supplying approximately 1,000 units annually out of our facility in Florida. The 500,000 refers to what have previously been distributed by our counterpart in Europe. Biodynamics also exists in Germany. We have a plant in Germany.

DR. PRUSINER: So the 1,000 units is for the United States, the 500,000 is for Biodynamics worldwide over 25 years.

MS. OSTER: That is correct.

DR. BROWN: And there was a greater than 1,000. Is that much greater?

MS. OSTER: Not much greater. I just rounded off my numbers. So it is 1,000 and change.

DR. BROWN: So it is approximately 1,000.

MS. OSTER: Right.

DR. BROWN: Ray, you had your hand up.

DR. ROOS: I have a couple of questions. First, remind us all what dura mater is. You mentioned there was a small amount of DNA there. I mean how much cellular component is there? You mentioned that there is no rejections, so presumably there isn't a lot of histocompatibility antigen expression in this material?

MS. OSTER: That is correct. After our process, there is no antigenicity which would cause a reaction. The process itself does a thorough protein breakdown. We have done not only studies in labs, but also there have been histomorphological examinations of the tissue to look for other factors that could cause problems of rejection, and we do not detect it.

DR. ROOS: I guess the other part that I was especially interested really had to do with the interview process and the collection itself. Maybe you could just go over that. For example, what are your exclusion criteria for the donors of this tissue, and is there any standard way of collecting the material itself?

MS. OSTER: To answer your first question, there are requirements that we must abide by. They have been published in the Interim Rule as far as donor screening.

The AATB also has very specific questions that have been reviewed by FDA and were just recently published in the AATB Information Alert, and Biodynamics goes beyond that and institutes even more rigid questions.

Typically, you are looking for high risk behavior to rule out individuals who may participate in lifestyles that would not be desirable, and indicate a tendency toward acquiring diseases, such as HIV.

DR. BROWN: Ms. Oster, we are talking today specifically about Creutzfeldt-Jakob disease.

MS. OSTER: Yes.

DR. BROWN: So, what are you specific exclusion criteria for this disease?

MS. OSTER: In the interview questions that are put to the interviewees, they would like information as far as any indications of dementia, other symptoms typically displayed by people that may have CJD. We have added those questions, I believe it was about two years ago. AATB has also incorporated those in their recommended lists of questions. So the interviewees are asked very specific questions alluding to any type of symptoms that CJD might display.

Also, the interview, we have a dura transplant, is there a history of CJD in the family, and so on, and so

forth, incorporating that entire area.

And your second question I forgot.

DR. ROOS: The second question had to do with removal of the dura mater and whether there was any protocol that was advised and followed uniformly by your tissue collection program.

MS. OSTER: Yes, we have specific procedures for recovery that we put out in our recovery manual. Typically, dura mater is recovered during autopsy by medical examiners although people are trained, recovery people are also trained to do it, and they must follow our prescribed, as well as AATB, standard procedures for recovering that dura.

It can be done in an OR setting, in a morgue. Again, we specify that an aseptic procedure be used and that they follow all appropriate universal precautions in doing these recoveries.

DR. BROWN: Gil, you had a question.

DR. WHITE: Just a couple of clarifications. What percent of your donors are above the age of 50, what percent have autopsies, and what percent have brain histology as part of those autopsies? Can you give us those numbers?

MS. OSTER: To answer the third one, it is a very small percentage. That is not a procedure that is routinely done. It may be done during part of autopsy and therefore

it will be in the report, and our medical director will review that information.

The number of donors over 50 years of age right now is probably in excess of 50 -- it is higher than that -- it is probably about 70 percent. We receive a lot of tissue in the State of Florida, and as you know, there is a higher population of older individuals there.

But also from around the United States, we have a large donor population, and I would say it's about 70 percent.

DR. WHITE: And autopsies?

MS. OSTER: Autopsies are performed on about 80 to 85 percent of our donors.

DR. BROWN: But you said without neurohistologic exam of the brain?

MS. OSTER: There may not have been one performed, and it is our medical director's responsibility to review those autopsy records, as well as the interview process.

DR. BROWN: Of course, autopsies to us don't matter a bit as long as neurohistologic exam is not done, autopsy is irrelevant.

DR. WOLFE: You said there was a small -- what is the small percentage that you estimate have neurohistological brains, 5 percent?

MS. OSTER: On the autopsies that come in?

DR. WOLFE: Of those that are autopsied.

MS. OSTER: Less than 25 percent.

DR. WHITE: That wasn't quite my question though.

The question was what percent of your units have had brain histology?

DR. WOLFE: Well, she said 85 percent don't have any autopsy at all, so it's --

DR. WHITE: So, it's 25 percent or 20 percent?

DR. BROWN: Is it fair to say that overall probably 5 percent or less of your donors have not had histologic exams of the brain?

MS. OSTER: Less than 5 percent?

DR. BROWN: Total.

MS. OSTER: That is probably fair, yes.

DR. BROWN: Yes, a question over here.

DR. LESSIN: From a single harvested dura specimen -- and I presume and perhaps you can enlighten us on whether the entire dura is harvested from a single cadaver -- but from a single specimen, how many applications on the average are derived?

MS. OSTER: The dura mater that we process is just the area contained within the immediate cranium. We do not do anything that proceeds down into the lower cerebellum or

into the spinal cord. We are looking for that skull cap dura mater.

On average, we yield approximately five units from dura. They can range anywhere from 4 1/2 square centimeters, very small pieces, to the largest size we provide right now which is 5 by 11 centimeters. We rarely provide a half or a whole dura.

DR. LESSIN: So the maximum number of individuals who might have received a graft from a given donor would be?

MS. OSTER: Approximately five.

DR. LESSIN: Five.

MS. OSTER: It could be more, it could be less.

DR. TRAMONT: I am interested in your followup or your so-called Phase IV studies. Do you keep a database of every person who has received your product?

MS. OSTER: No, we don't have a database of everyone who has received our tissue. We track where the tissue goes, where it has been distributed to, and we receive information back once the product has been used from that end user, and that is what we maintain as a file.

DR. TRAMONT: Who is the end user?

MS. OSTER: The surgeon.

DR. TRAMONT: So you don't know individuals who have received this.

MS. OSTER: Oh, yes, we do. The surgeon provides that document back to us, and on that document is patient and procedure information.

DR. TRAMONT: Good. Now, is there any active tracking of those patients over their lifetime?

MS. OSTER: By Biodynamics?

DR. TRAMONT: Yes.

MS. OSTER: No, sir.

DR. TRAMONT: Do you know if anyone is tracking that?

MS. OSTER: No, sir.

DR. TRAMONT: So there could be events that are occurring that are lost, we don't know, that may be attributed to this product?

MS. OSTER: That is always a possibility. We rely on them reporting adverse reactions or contacting us in the event that we would have to do an MDR, and that has not occurred to date.

DR. PENN: On this same issue, what percentage of neurosurgeons return reports to you?

MS. OSTER: Zero.

DR. PENN: Hospitals?

MS. OSTER: Oh, return the reports?

DR. PENN: Yes.

MS. OSTER: I apologize.

DR. PENN: That may be close to the fact, too.

MS. OSTER: We receive about a 50 percent return on those cards that we send out with the tissue. It is not an easy task to enforce the return of those when they use the product. If I may explain, for years a postcard system was used, and therefore information about a patient would appear on a postcard, and there were concerns of confidentiality on that.

We now provide a document that is folded, so it is containerized information, and we are seeing more returns now since we have changed the system. It has been about a year and a half, two years now. We can't enforce them returning that. There is no requirement for them to return that information to us.

DR. BROWN: Ray.

DR. ROOS: Just going again over the issue of the interview itself. Who actually conducts that? In other words, you mentioned that you would reject someone that had a family history, and is that one relative or two relatives, and are there actual questions that are distributed to the person who conducts that interview, is there a standard interviewee, and what kind of documentation is there of the interview itself and what the answers are to those

questions?

MS. OSTER: There is a recommended interview process that AATB has published, and we are attempting to enforce that particular format with all of our recovery programs. There are very specific questions to the interviewees regarding the issues that I addressed earlier.

The interviewees may be next of kin, may be a physician, may be a partner or significant other that the interviewer feels is qualified to address the specific questions.

The interviewer is typically what is known in the tissue bank industry as a coordinator. This person may be a trained nurse, they may be a member of an organ procurement organization. The process may start with organ recovery followed by tissue harvesting.

So there are highly qualified individuals who are trained to deal with the family members who typically is a spouse, a sister, a brother, a child, to deal not only with the medical and high risk behavior issues, but to deal with it compassionately.

DR. ROOS: And is there written documentation specifically about --

MS. OSTER: Absolutely.

DR. ROOS: -- no family history of

Creutzfeldt-Jakob disease?

MS. OSTER: Yes. Every question is answered with a documented answer. It is signed. If it is a telephonic interview, then that is also documented and recorded.

DR. BROWN: I think the committee would like to have a copy of that interview format. I am certain that the FDA would like it, perhaps they already have it, for our own consideration.

The other thing, of course, we all know it is difficult to absolutely 100 percent exclude a disease X on the basis of interviews. I assume most -- well, I have a lot of questions -- but you said you are attempting to enforce this interview format. How does one go about that?

I mean we know, for example, in some countries that there have been exclusions of pituitary glands taken from patients with dementia. We also know that the pituitary glands from patients, not only with dementia, but with CJD, have been taken and put in a pot that was later processed for growth hormone.

So, how does one go about enforcing this kind of selection?

MS. OSTER: In the case of European recoveries, we are working very closely with our technical director at Biodynamics in Europe, as well as the medical examiners at

the pathological institutes that we are using.

They must go through the same process that we go through here in the United States. Is there 100 percent confidence? We are as confident with this program as we are with the program here we have in the United States, and we are working very closely right now with the FDA to take this step by step to assure that compliance is met as much as we can assure it to happen.

DR. BROWN: Ray.

DR. ROOS: How many actual sites do you have in which you are collecting this tissue in countries in Europe? Just to give us some idea.

MS. OSTER: In Europe, there are three countries. In the United States we have approximately --

DR. BROWN: What are those countries?

MS. OSTER: I am sorry?

DR. BROWN: What are those countries?

MS. OSTER: The Czech Republic, Hungary, and the Ukraine.

DR. ROOS: And how many institutions in those countries?

MS. OSTER: One each.

DR. ROOS: Just one hospital.

MS. OSTER: That is correct.

DR. ROOS: Why those particular countries?

MS. OSTER: Our technical director at the time felt that he had the ability to go in and speak with them and work with them to assure compliance with our specific issues here. We are driving the program from this side.

As a matter of fact, I have been over there once to work with these documents, and our QA manager will be leaving next week to go to each of these individual recovery sites. This is a program that we are holding hands with and babysitting very, very carefully.

DR. ROOS: Do you pay the donors?

MS. OSTER: No, sir.

DR. BROWN: What proportion of your donors, what proportion of duras, shall we say, of the total proportion of duras that you process have their origin in foreign countries, these three in a given year?

MS. OSTER: Right now it is about 1 percent. We have just started the program. So we have received tissue from -- dura from these countries. It is not processed, it is in quarantine until we complete our document review with our local FDA compliance officer.

DR. BROWN: So presently, virtually 100 percent of your duras have a U.S. origin, but unless we throw a monkey wrench at you, you anticipate an increasing proportion of

duras from abroad?

MS. OSTER: Yes, that is correct.

DR. BROWN: Stan.

DR. PRUSINER: Could we go back to the various studies that you have carried out? You gave a number that the odds of contracting CJD from a dura implant were 1 in 3 1/2 million. This was after a series of inactivation studies with sodium hydroxide, peroxide, and organic solvents.

Maybe following up on Paul Brown's request, I don't know, you will have to tell me, Paul, or Dr. Freas, can we request from you the details of this inactivation process and the details of this study that generate this number?

DR. BROWN: This is certainly one of the crucial questions that was on my block. Without infringement upon your patent, this committee has to know the precise conditions of the inactivations that were carried out specifically with a view towards CJD. Organic solvents I am thinking of, and sodium hydroxide.

We need to know times, we need to know concentrations, and short of that, the committee is not in a position to be able to judge the validity of what you say.

DR. FREAS: Dr. Brown, if I could interrupt. Of

course, we are in open session today. I could call for a closed session to get this material. As you know, during the open session, the sponsor could not present trade secret or proprietary information.

DR. BROWN: It was just pointed out to me that -- is the process patented?

MS. OSTER: Yes, it is.

DR. BROWN: So the details would be presumably in the patent application or approval?

MS. OSTER: Yes.

DR. BROWN: Is this a bad thing for you to tell us about sodium hydroxide at the moment, or is that --

MS. OSTER: I can tell you about sodium hydroxide.

[Laughter.]

MR. KAHN: My name is Jonathan Kahn. I am counsel to Biodynamics. As a matter of fact, all this information is in the 510(k). The Food and Drug Administration reviewed the viral inactivation process as part of the 510(k) review, and the company would be happy to provide to the committee information with respect to the studies that were done after the submission of the 510(k), that also document the validity of the inactivation process as it applies to CJD.

What we would like to do, if the committee approves, is to provide that information, at least some

further information on the viral inactivation process as confidential information.

FDA already has it, but the committee does not, and we can provide -- it is quite a number of volumes of information at FDA -- and we can provide summaries or parts of it to you as you wish.

DR. BROWN: Well, the committee is a bit handcuffed at the moment in order to judge this. I appreciate the offer to make this available short of which we have no basis on which to make any judgment at all, and as Stan said, and as I reiterate, I haven't seen any published data on this at all. I am unaware of very much published data on inactivation of dura, and I must say I am a little surprised, if it worked, that it wasn't published.

MR. KAHN: Well, surprisingly, part of it relates to your process that you have discussed, Dr. Brown, and in fact we would be happy to give you that information. It is mostly from foreign studies. I am not sure they have been published yet. Some of it may be unpublished data.

We would happy to provide that to you, but in fact the viral inactivation process itself has been something that we have discussed with FDA for years and years. As a matter of fact, the entire 510(k) review was prompted by the Lyodura Safety Alerts back in the mid-1980s, and I can tell

you that the Food and Drug Administration scientific reviewers reviewed the inactivation process in great detail as part of the 510(k) review, as well as reviewing all of the donor screening records and the other safety precautions put in place, and I think it is -- one of the other factors that is important is that over 25 years and hundreds of thousands of transplants, there has not been one indication of a viral transmission from this process. So I think that should give you some comfort, and I think that if there was any kind of CJD transmission, it wouldn't have been something the doctor or the family would have kept quiet. We would have heard about it. And that has been the experience over the years in the U.S.

DR. BROWN: Well, I think that is a wonderful track record. On the other hand, I am not absolutely persuaded that a case that occurred 15, 20, or 25 years after the fact would have been revealed.

In short, is there a good reason why the committee, for example, does not have details on the inactivation procedures as we did during the previous meeting with gelatin? I mean this should be part of the presentation. I mean there is nothing confidential that I know of about an inactivation procedure that is well known to everybody, which is sodium hydroxide, for example. Why

ajh

don't we have that?

DR. CIARKOWSKI: I am Art Ciarkowski with the Center for Devices.

We have some of the information in the 510(k) applications. We thought that by inviting the manufacturers here to discuss their process, the 510(k) applications are disclosable. So the information there is available. So we felt that when the manufacturers are asked about this process, they would be able to discuss that during the open session.

DR. BROWN: Shall we do that?

MR. KAHN: Well, some aspects are confidential trade secret information, and Gerry knows better than I as to how much of that is confidential.

DR. CIARKOWSKI: Well, you say, if the information is in the 510(k), then, that information is disclosable.

MR. KAHN: Not necessarily, Art. Parts of the 510(k) are marked trade secret and confidential. Under FDA regulations, those parts remain confidential until the FDA makes a decision or the company makes a decision as to the disclosability of it, and that has not been done with respect to this 510(k).

But I don't think there is anything secret here, we are not trying to hide anything.

DR. BROWN: Well, then, let's have it.

MR. KAHN: Pardon me?

DR. BROWN: Let's have it then.

MR. KAHN: I am just trying to figure out what parts of this are confidential.

DR. BROWN: You just said nothing --

MR. KAHN: I don't know. I am just a dumb lawyer. I would allow Gerry to figure that out.

DR. BROWN: Let's redefine things a little bit. We want any information. We want all information from any study in which a procedure has been directed towards the elimination of CJD infectivity.

Now, that can be done I assume -- you will have to give me some advice on this -- either in a sheet that we have as a committee or in public.

MR. KAHN: Dr. Brown, we specifically sent a letter to you which describes the process -- you have it in great detail on your desk somewhere -- as part of the letter we sent to Japan, and we sent you a copy of that. So it is somewhere on your desk.

DR. BROWN: Me personally?

MR. KAHN: You personally.

DR. BROWN: I never got it.

MR. KAHN: Well, we also called you several times

to discuss it with you, but we never got a call back.

DR. BROWN: That is understandable in my present position.

MR. KAHN: The key to it is, I think, is that we are more than happy to share it with you. We know you are an expert in the area. We would like you to have it. We would like you to evaluate it. There is a tyranny of time here. I don't think we can do it within the next 10 minutes, but I absolutely can guarantee you that we would like the committee to have that information. We would like to, you know, sing it to the winds, because we think it is what distinguishes us from everybody else in the world including Braun's Lyodura product which has led to a lot of the problems including the Japanese ban.

So our view is we would like you to have it, we will provide it to you. I am not sure we can do it within the next 10, 15 minutes.

DR. BROWN: How about the next two hours?

MR. KAHN: I am not sure. Gerry, how much --

DR. BROWN: We need it before the end of the day if we are going to come to any decision whatsoever, and I am frankly more than surprised, I am shocked that this wasn't part of this presentation.

MR. KAHN: Well, you know, Dr. Brown, there is

details of scientific information. We are given 10 minutes, and it is very difficult I think within 10 minutes to describe the entire inactivation process. We had quite an amount of information --

DR. BROWN: If we could have avoided all this discussion, you would have had an extra 10 minutes altogether anyway.

MR. KAHN: Well, it is very difficult to prophesy exactly what the concerns of the committee are going to be before they --

DR. BROWN: Well, let's not belabor the point. Is it possible for this committee, one way or another, before the day it out and before we have to judge the applicability or the advisability of using this, to have all relevant information both from you and from Dr. Malinin made available. If you guys are doing tests that inactivate CJD, we need to know about them.

MR. KAHN: Well, it is in the 510(k), as I stated, so FDA does know about it, and, Gerry, if you could, could you describe it generically right now for the committee without revealing anything confidential, do you think?

MS. OSTER: Yes.

MR. KAHN: Why don't we give it a shot, and then if you need something further, we will try to accommodate

you. This is a key issue. We are very sensitive to the fact you want to know about it, and we would like to get you everything we can.

DR. BROWN: Okay. Just a second. Yes.

DR. SCHONBERGER: I just wonder if you could clarify when this process for this product began, that is, the use of sodium hydroxide. Is this something that is relatively new or has this been used in that 20, 25 year history?

MR. KAHN: This is the Tutoplast process. It has been part of the process for time immemorial since the Tutoplast process was started.

MS. OSTER: Since the beginning.

DR. BROWN: When was that, the beginning?

MR. KAHN: Twenty-five years ago?

MS. OSTER: I think it was 1972 or '73, I don't know the specific year. Early seventies.

MR. KAHN: Gerry, do you want to take a shot at the process?

DR. PRUSINER: I would like to ask that we not have a generic review of this process. I think without the details, the precise concentrations, and without the bioassay data that was alleged to determine this number, that I don't want to hear this. I don't want to spend my

time. I would like to specific numbers. That is my request to the chairman.

DR. BROWN: I agree. I don't think that you orally can provide us with log loss, for example, for a given concentration. I think you would have had to bring a slide. Barring a slide, I think you are going to have to make out a table or in some way get to us absolute experimental details as though they were published.

MR. KAHN: Well, having in my 25-year career sat through dozens of FDA committee meetings, I think no matter how brilliant, with Nobel laureates on the panel, I think it is going to be very difficult for you to evaluate this on the fly today. We can provide you with the data --

DR. BROWN: Trust us.

MR. KAHN: Okay. We will try to get you as much as we can, Dr. Brown, but I am not sure it is going to work, but we will give you as much information as we can. I will call the company, and we will get you as much information as we can.

DR. BROWN: Good. Are there other questions? Yes, two from my right side.

DR. SAWAYA: I just want you to clarify one thing. You had mentioned about the freeze-dried process that the patches become avascular. Did I hear you correctly?

MS. OSTER: Just a moment, please.

DR. SAWAYA: I realize it is not a process that you use in your company, but I want to make sure that I heard correctly.

MS. OSTER: I believe that the microscopic exam of the freeze-dried tissue has displayed the presence of vacuoles.

DR. SAWAYA: Vacuoles?

MS. OSTER: Yes. Hold on. I did not commit all of this to memory.

DR. PENN: Maybe we could have the next speaker address that, because they use a freeze-dried process.

MS. OSTER: I do have an answer. I indicated that there were no vascular gaps, such as found in freeze-dried tissue, and this was based on documents I read about the freeze-drying process of dura mater.

DR. SAWAYA: I agree the next speaker can address this, but I wanted to know if there was a specific reference that you had on that, that's all.

DR. BROWN: Will.

DR. HUESTON: In the situation that you have a patient where the questionnaire history or the clinical signs of the patients, the presentation of the patient prior to death, or the autopsy suggests neurologic involvement, in

those cases there is histopathologic examination of the brain. Am I just reciting this correctly?

MS. OSTER: In the interview process, if there is an indication of anything that you mentioned, that donor will not be recovered for Biodynamics. It will be ruled out at that point in time.

DR. HUESTON: In which cases then is there actually histological examination of the brain? So you are saying if there is any history of dementia in the individual or if there is --

MS. OSTER: Evidence in the autopsy.

DR. HUESTON: -- evidence in the autopsy, they aren't considered at all.

MS. OSTER: Now, we may have the tissue prior to that autopsy report being made available to us. It's a timing issue. As soon as we see that autopsy, that donor, that tissue will be rejected. It will not go through the process.

DR. BROWN: When you say "when you see the autopsy," what short of microscopic examination in the autopsy would cause you to reject it?

MS. OSTER: That is not what I meant. The autopsy report itself may come in two to three weeks following the receipt of the donor's tissue. When we review the autopsy

report, if there is evidence of histological examination that would reveal the symptoms of CJD as far as spongiform evidence, that tissue at that point will be rejected.

DR. BROWN: Right, and that constitutes less than 5 percent of all donated tissue, correct?

MS. OSTER: Approximately, yes.

DR. HUESTON: I am still confused. Which case is that? If there is histology, brain histology, which presumably was done as a result of there being some concern about brain lesions --

MS. OSTER: Possibly.

DR. HUESTON: And if there is no evidence then of histologic change in the brain, do you continue to use those tissues?

MS. OSTER: Yes.

DR. HUESTON: And histology then is the only screening test that you are examining, if brain histopath is done, gross histology is the only test that you are currently using as a screening test on that select group of patients?

MS. OSTER: Yes. Our medical director will include that information in his review.

DR. BROWN: If there are generic type questions that would also apply to the next speaker, we might go on

the next speaker. Go ahead. Barbara, did you have a question?

MS. HARRELL: My question is about the consent, whether or not you know about the consent procedure. The question is, is the consent of the family informed or implied consent?

MS. OSTER: In the United States, it is informed consent.

MS. HARRELL: I would like to know the percent of your donors come from public versus private hospitals.

MS. OSTER: I don't have that information, I am sorry. I can get the information. I won't have it today.

DR. BROWN: Gil.

DR. WHITE: Just two short questions. One, I would like a little more detail. You say it is a non-pooled product. Has it always been a non-pooled product, and when you say "non-pooled," do you mean that duras are never mixed at any point during the process?

MS. OSTER: That is absolutely correct. To the best of my knowledge, even when they began the process in Germany, each tissue was handled individually. Absolutely, in this country, each tissue is handled and containerized individually. There is no pooling.

DR. WHITE: Even during sodium hydroxide

treatment, and so on?

MS. OSTER: Even during any step, never.

DR. WHITE: And the second question that relates to the previous question regarding changes that might make you reject a tissue, has a dura ever been rejected by the company for CJD?

MS. OSTER: Not to the best of my knowledge. We will reject as we are into the process with the dura, if an autopsy report comes back, usually, it's because there is evidence of cancer or pneumonia, or something like that, restrictions that are outside the normal parameters that we would use. To the best of my knowledge, we have not seen CJD.

DR. BROWN: Well, thank you very much again, Ms. Oster.

Dr. Malinin is our next presenter from the University of Miami Tissue Bank in Miami, Florida.

Theodore I. Malinin, M.D.

[Slides.]

DR. MALININ: I have provided the committee with a description of our experience with dura mater and also with the criteria for rejection of donors. I will therefore try to briefly summarize the process and point out some of the unique features of dura mater from which allografts are

prepared.

[Slides.]

Dura mater is a unique anatomical structure as we all realize.

[Slides.]

It is a vascular structure. On the left side of the screen is a surface photograph of the vascular matter and the histological section of the same is shown on the left side of the screen, which shows that we are dealing with two types of laminar structures.

[Slides.]

Dura is in fact a cellular structure. To appreciate this, we have to make horizontal sections through the same, and it contains some elastic fibers. On the left side is the stain preparation of the dura mater.

[Slides.]

It is primarily a collagenous tissue. It is vascularized and there is a definitive and symmetrical distribution in the collagen fibers throughout both hemispheres of the dura.

[Slides.]

This symmetry pattern has been described and is shown in the plotted chart from the scattered lights on the left side and the entire dura mater with its vasculature is

shown on the screen closer to me.

[Slides.]

The process that we use in preparing dura mater allografts is essentially the same. It was described over 20 years ago, in 1976. The dura mater is sterilized with ethylene oxide, and not exposed to any other chemical agents during the processing and treatment.

Following the freeze drying and washing, ethylene oxide sterilization is performed. It then becomes an acellular structure which retains its original configuration, intercellular composition primarily collagen, and it is rendered nonantigenic, which has been shown by us in rodent experiments, but not obviously in human experiments.

[Slides.]

This is the appearance of dura mater following freeze drying. The left side is a surface photograph. Again, there is a pattern of distribution of doubly refractive collagen, which is unaltered by the process.

[Slides.]

This is a cross-section of the dura, on the left side stained with Masson stain, and on the right side of the screen again showing two patterns of collagen distribution on the cerebral and the cranial surfaces of the structure.

[Slides.]

These are higher magnifications showing again sections from freeze-dried dura. On the left side, the symmetrical pattern of distribution of doubly refractive collagen is shown, again the outer layer with a different orientation compared to the inner layer is shown on the left side of the screen, and the vascular channels are in fact preserved by this process.

[Slides.]

If we look at the recipients, and take 100 random recipients, the age distribution of the recipients is given in the chart on the left, and we can see that it varies greatly, but for some reason females predominate in the middle age groups, so the recipients of these dura mater allografts may be children, and they will retain the graft probably for the duration of their life.

On the left side of the screen is a histological section taken from a dura graft in the right portion, where you can see the junction in the center, and this particular material is healing well to the recipient's dura mater, and it is eventually being replaced by the fibroblasts and collagen from the host itself.

[Slides.]

The allografts are prepared from selected donors.

They are divided into sections in several sizes. As I mentioned, again they are sterilized with ethylene oxide, freeze dried, but they must be reconstituted prior to implantation, and other than exposure to ethylene oxide, in our experience, we have not treated dura mater grafts with any other chemicals, as I have mentioned.

[Slides.]

The selection of donors of dura mater is rigorous. On the left side of the screen, during 1996, we had a potential of over 2,000 donors. Out of these, we have selected 534 donors from which the dura mater was excised. During the process of further evaluation, 175 of these were discarded, so we are winding with a little bit more than between 10 and 20 percent of duras prepared from the donor pool which is originally available.

[Slides.]

Now, what are the reasons for rejection? Inadequate serum samples, incomplete identification, that is, possibility of mix-up in numbers, poor physical quality, excessive postmortem interval, which is investigated retrospectively, autopsy findings. If we have gross autopsy findings relating to the brain, of course, the dura would not be collected from this individual at all, so these are related to microscopic findings.

In retrospect, historical findings and serological findings, if we look at the serology, the most donors which have been rejected are because of presence of antibody to hepatitis C virus. We have only three that we have picked up for HIV, and this is contrasted to the population, which usually carries in the neighborhood of 3 percent of HIV positivity, and it illustrates the point that historical information is very reliable and accurate in eliminating HIV carriers, but it is totally unreliable in eliminating carriers with hepatitis.

[Slides.]

The dura mater is being processed individually. It is divided into various sizes.

[Slides.]

It is then sterilized in ethylene oxide and placed in liquid nitrogen for storage prior to freeze drying. The freeze-drying apparatus is shown on the left side, and on the right side of the screen is a view of dura mater allografts which have been packaged under vacuum in glass containers.

[Slides.]

These can be maintained for up to five years. The vacuum is dasted [ph] before release, and the blue coloration, which is obtained in the presence of vacuum from

a spark test, is likewise demonstrated on the left side.

[Slides.]

If we look at the dura matters and see how many of those are prepared, we can look at the data obtained in 1988 and '89. Again, we had some 600 donors at the time and from 600 and so, we have prepared 1,100 grafts, so in our hands, on the average, we usually prepare 2 grafts from each donor, frequently single graft if large dura is required, and I don't think under any circumstances we would have more than 4 smaller grafts from the same.

[Slides.]

As I mentioned, we do sterilize dura mater with the ethylene oxide using a 12-hour cycle for sterilization.

[Slides.]

The dura mater is permeable to the gas. On the left side is an indicator showing that it has been converted with the dura mater used as a patch in the pouch, and control is found on the left side.

[Slides.]

A number of studies performed by Viomed have indicated that ethylene oxide sterilization does inactivate a number of the viruses, and that these have been tested on the dry surface as shown on the left side.

We have not subjected a scrapies virus to this

test, but have picked up as many resistant viruses as we possibly could.

[Slides.]

If the viruses are absorbed on demineralized human bone powder, again, inactivation with the same regimen is obtained and it is in cancellous and corticocancellous bone blocks.

[Slides.]

This is very much the same kind of a response that is obtained with treatment with sodium hydroxide and hydrogen peroxide, as well as with 2 1/2 megarads of radiation.

The entire process of dura mater preparation is maintained in device master record. We can trace each individual donor. An autopsy is performed universally on all of the donors. The only exception to histological brain examination is in the younger donors which are dead of trauma, and a pathologist at times may not choose to subject these brains to microscopic examination, and limit the examination to gross examination.

However, starting this year we will require that all of the brains are to be examined.

[Slides.]

We have a built-in internal control as far as

following the patient is concerned. Between 1979 and '89, we had 900 recipients of dura allografts in our own institution. This is divided between all services. Approximately, I would say 80 to 85 percent of these were on the neurological surgery service.

Since that time, an additional 800 patients have been added to the series, and 186 of those were patients who had spinal operations versus the intracranial operations.

So this provides the summary of the use of the dura mater in our hands. An inevitable question will be asked is how can we follow these patients for the periods of 20 and 30 years or so, and we cannot unless these patients return to our institution.

In the period since the University of Miami Tissue Bank was preparing dura mater allografts, which goes back a number of years, we have distributed over 30,000 of these grafts, and we have to date had no reported instance of transmission of Creutzfeldt-Jakob disease with these grafts.

Now, what else needs to be done to safeguard the recipients I think is a question we would like to ask this particular committee.

I think if the committee feels strongly that an exposure to sodium hydroxide is a desirable safety precaution in treatment of dura mater allografts, we can

certainly do so, although there are undesirable biomechanical side effects. I think these could be avoided by adjusting the concentration and by subjecting the grafts to further extensive washing procedures.

The same is true for the exposure to hydrochloride solutions, and we would be looking forward to the committee's recommendations in this regard.

In summary, we have had no problems with disease transmissions of these particular allografts. These have been prepared in response to the requests for our Neurological Surgery Department, and the Neurological Surgery Department Chairman, Dr. Green, does inform me that they would prefer to continue having availability of these grafts for their patients.

Thank you.

DR. BROWN: Thank you, Dr. Malinin.

Dr. Malinin, I had a question, and it is possible that neither you nor the Biodynamics representative would be the appropriate person to answer it, but she put on a slide in which she showed or listed adverse neurosurgical consequences when some sort of substitute for a dura was used. What was missing, of course, was a comparable listing of adverse neurosurgical consequences when dura grafts are used, and I would hope that with the neurosurgeons present,

we would get a more balanced account.

I am sure that it is just that a bad thing doesn't happen just after a substitute is used, but a certain number of bad things happen after duras are used, and I would like to see some sort of comparable information about adverse consequences for one or another of the kinds of substitutes, as well as the dura.

Is it fair to say that that will kind of come about when we have the use of the dura mater products in surgical procedures, will there also be some information about the use of non-dura mater, so that we can get some feel for just how, shall we say, desirable from the neurosurgical point of view a dura is under some circumstances?

DR. MALININ: I don't have firsthand information on dura mater used in neurological surgery. Dr. Penn and Dr. Sawaya can address and answer that particular question. Our response in preparing dura mater allograft has been specifically to the requests from our neurological surgeons for these grafts.

I am not aware of major instances of complications, that is, infections, difficulty with wound healing, cerebrospinal fluid leakage, and the like, and I repeatedly ask these questions of our own staff.

We do have a universal response for our recordkeeping in each patient which receives an allograft is duly recorded and is placed in our files. My personal experience with dura mater grafts is outside of neurological service, neurological surgery, and I didn't think it is applicable to this committee.

DR. BROWN: I just raised the question so I wouldn't forget myself, but I think that is an appropriate question or issue to be considered by each of our neurosurgical consultants and committee members, namely, Drs. Penn, Sawaya, and Steers, so why don't we just back off that and remind ourselves that it would be interesting to learn.

Ray.

DR. ROOS: I had a question as to where you get your dura maters, what institutions they come from, and also the interview process, who are the interviewers, what kind of template written questionnaire, and lastly, what procedures are used in actual to take out the dura mater itself?

DR. MALININ: Our dura mater is obtained from donors within three counties: Dade County, Broward County, Palm Beach County, and the majority of these come from Dade County. We use two sets of information-gathering material,

that is, before the individual becomes a donor and before the dura mater is released, which allows us a number of weeks to obtain additional information.

The form is a standard one, and the question is asked have there been any neurological diseases in the family or with the donor, also, the medical records are reviewed, but the amount of historical information generally that you can obtain with accuracy from the survivors, in our experience, has not been very reliable, and this is borne out by the studies which we have done both with hepatitis C and hepatitis B. Neither family members nor probably the deceased themselves frequently are aware of having a problem.

So, although social and medical history is helpful and obviously if we would have a history of senile dementia or of an individual being confined in a hospital for whatever neurological reasons, such patient is going to be excluded from the donor pool.

But I think at this stage, the selection of these donors is done with a multiplicity of sources of information, not the least of which is being examination of the brain at postmortem, and we insist that all of our donors have such an examination.

DR. BROWN: Larry.

DR. SCHONBERGER: Could you give us the total number again of in the past 30 years of how many dura you have put into recipients?

DR. MALININ: In our own institution. In our own institution, we have put pretty close to probably now about 1,800 duras or so.

DR. SCHONBERGER: And all together?

DR. MALININ: All together, between 30- and 40,000.

DR. SCHONBERGER: I think it is appropriate to tell people about the case that we are investigating now of CJD. Did you want to comment on that or do you want me to talk about that? We are currently working with their tissue bank on a case of CJD that received such a product.

DR. MALININ: I can give you what information I have on that particular individual, unless you would like to do it, and I will be glad to fill in the gaps or voids if there are any.

DR. SCHONBERGER: I think since we are discussing this, it may be worth at least bringing to the attention of the committee that there is a case under investigation. It actually was a case that appeared in the newspaper that was followed up by us with the University of Miami School of Medicine Tissue Bank.

It is the first non-Lyodura dura mater associated CJD case reported in the United States, and I use "associated" deliberately because it may be a coincidental association and it may not in fact be related to the dura, but nevertheless, I think it is worth bringing it to people's attention.

The patient, as I understand it, was a 72-year-old man who had a nine-week classical CJD illness with onset a couple of years ago, May 1995, and this was about 4 1/2 years his onset after he had an operation in Florida for the removal of a brain meningioma.

At that operation, a dura mater graft obtained from the University of Miami Tissue Bank was used, and that was November 1990.

The patient had a rapidly progressive dementia, a typical EEG plus myoclonus, speech abnormalities, aphagia, mild tremor, and visual problems. The neurologist described the illness as a textbook case of CJD, but no autopsy or biopsy was performed.

The patient's mother and the patient's aunt, the mother's sister, both died at 89 years of age or older, and had Alzheimer's disease as their diagnosis.

The investigation that we are in the process now of the source of the dura revealed that it came from a

34-year-old male firefighter who died in a car accident, and had been without any known neurologic disease. As Dr. Malinin had described, this patient's brain, because of the age, was looked at grossly, but was not put under pathologic study. There was no abnormality grossly to the 34-year-old patient's brain.

In addition to the one dural graft, the donor's cornea were also donated to two women who died about one year and just over two years after receipt of these cornea, and our investigation indicates with the help of the Miami Tissue Bank that there was no neurologic illness responsible for the death of these two recipients of the cornea.

We have also had an investigation of the hospital where the operation was performed on a dural graft recipient and thus far we have recovered no indication of a nosocomial transmission for this particular patient.

We are trying to arrange for the meningioma that was removed from the patient in 1990 to be looked at for prion. That is the only tissue that we have would be relevant.

Obviously, if the patient's surrounding tissue to the meningioma show evidence of prions, it would indicate that the dura had nothing to do with this patient's illness, but that the patient was incubating already at the time of

that operation in 1990.

Our conclusion at this point is that the history is compatible with either coincidental sporadic CJD disease in a dura mater graft recipient or possibly dura mater related disease.

I would say the ages to the case, 72, and of the donor, 34, make the coincidental association and this number that you just gave me, about 30,000 recipients, at least makes a coincidental association possible, but I think the committee should know that at least this case exists.

DR. MALININ: To add some additional information to the case, when the recipient, the gentleman with meningioma presented himself, his initial presentation sign, as I understand this, was mental confusion.

The donor's brain weighed 1,600 grams and it appeared entirely normal. We had a chance to interview donor's mother, and she gave extremely detailed history of the causes of death of his grandparents and her parents and the siblings, and there has been no history of neurological disease in that family including both maternal and paternal grandparents.

DR. SCHONBERGER: Thank you.

DR. BROWN: I think, to recapitulate that case, a patient died with clear-cut CJD five years following an

operation in which a dural graft was used. It is equally -- well, it is likely I think that the answer as to the origin of the CJD in that patient will never be conclusively proved unless, as Larry says, the meningioma from the recipient can be shown already to have had the abnormal protein present.

So, it is one of those archival anecdotal cases and actually is just one more wonderful example of what a very useful procedure in this field, microscopic examination of donor brain tissue is, because if we had had that, we wouldn't be asking the question today.

Now we have a break and we will be back at 10:45 for a presentation by the neurosurgeons.

[Recess.]

DR. BROWN: The remainder of the morning is going to be divided between a set of speakers who are intimately acquainted with neurosurgery and are themselves neurosurgeons, which will give us I think on the committee a very good overall picture of the use of dura mater, on the one hand, and substitutes for dura mater, on the other, what the pros and cons are for each.

That set of three speakers will be followed by a second set of three speakers who are a mixed group, one, Dr. Will, who will describe epidemiology, and then two speakers, Dr. Diringer and Dr. Tateishi, who will describe

experimental work on dura mater.

We begin now with the first of three speakers addressing the neurosurgical procedures themselves and the pros and cons of using processed human dura mater.

The first of the three speakers is Richard Penn from the Rush-Presbyterian-St. Luke's Medical Center in Chicago, Illinois.

Dr. Penn.

**Use of Processed Human Dura Mater Products
in Surgical Procedures**

Richard D. Penn, M.D.

DR. PENN: Thank you. It is a privilege to talk to this distinguished group.

As a neurosurgeon, you will see why we have a certain amount of embarrassment through this part of the program because we cannot provide you with the types of information we would like to. That is, you are not going to see prospective randomized studies, much less prospective studies, and you are going to hear about our opinions as opposed to proven scientific ways of justifying the surgical procedures that we use.

I come to this committee having had some experience with the FDA, being on their advisory committees

and as a transplant neurosurgeon, I have in fact done some even porcine fetal transplants, and I must say from a personal standpoint I am very concerned about CJD because a neurologist at our institution, and a good friend, an epileptologist, just died of that disease this year. So everyone is concerned with the possibility of passing the disease.

I was to give the introduction for our group of neurosurgical reports to you, and what I would like to do first is go over very briefly with you the types of operations and the procedures that we use dura mater in, why we find it is important in neurosurgery and why we do need a substitute, and then I will go through a number of aspects of the questions that I was asked to address by the committee chairman.

If I could have my first slide, I have just taken an atlas and we will see more graphic pictures.

[Slide.]

I have here a picture of one of the standard atlases. This just shows the situation in which we are likely to need a graft across an area of dura that is disrupted. Here is a tumor that is growing into the dura mater. It is a meningioma, and that is a very common tumor to do so. It is involving some of the sagittal sinus and

some area dura mater here that will be not be as important.

[Slide.]

We can see the surgery now, taking out the tumor.

[Slide.]

Here is the base of the tumor and you see the large amount of dura mater that has been removed, the sinus being over here, and this is over to the other side.

[Slide.]

Then, there has to be a patching of this area, so that the brain will not be exposed, and so CSF will not leak.

[Slide.]

Another use for dura mater in patients would be a CSF leak. It can be traumatic in origin or come in an idiopathic fashion. Usually, they are at the base of the skull, and it requires an operation --

[Slide.]

-- that exposed where the leak is at the base of the skull.

[Slide.]

This slide shows the replacement of material in filling that, which usually turns out not to be totally water-tight, and here is an area where the dura has been ripped.

[Slide.]

This shows a dural graft being put into place.

So it is operations like this that we are talking about. Some may be in the posterior fossa, some are done in infants with meningomyeloceles, and many are done for trauma, and certainly for tumor surgery, and we will see other examples from my neurosurgical colleagues.

[Slide.]

So the major reasons why we need coverage of the brain are the following. First of all, we want to protect from infections and prevent CSF leakage. Having an extra barrier of tissue will confine the infections hopefully to an epidural space if they occur. Preventing CSF leakage is extremely important to us because we know that any CSF leak that continues over a long period of time is very likely to lead to meningitis.

There is also the important point of not having the cortex adhere to the cranium, and there is the possibility, at least in some animal studies, showing that if you do get such adhesions, you have a much higher incidence of seizures.

[Slide.]

The material we would like to be able to use obviously is the patient's own material if it is available and conveniently sized, so that we can fill the place that

the dura has been removed from, and fascia lata has been traditionally used.

It requires a separate operation obviously in the leg area, requires extra draping, and some thought ahead that you are going to need it as a graft material.

Temporalis fascia can be used and pericranium. Of course, pericranium would be an ideal material to use, but it is not available particularly in the elderly patients that have meningiomas for use because it is not in as good shape basically and can't be used as a graft. It has deteriorated over time.

[Slide.]

So there have been a number of things that we want in an ideal tissue replacement and that are partly provided by the human autografts, but we would want for anything that would replace it. First of all, it has to be strong, it has to have a flexibility that is similar to the normal dura, and that means it can take sutures, so that we can make water-tight closures with it.

One of the features we would like to have is that it would be gradually absorbed with time and that the regular tissue of the patient would infiltrate the dura and replace, and of course it has to be immunologically acceptable. I have mentioned the sutures. It is important

that fluid not leak through it. And of course we want no transmission of disease, and we want it easily stored, available, and very cheap. So those are the things we would like to have.

[Slide.]

I put down here the number of transplants, just give you a very order of magnitude impression of how much dura has been used as a replacement, that is, a transplanted material.

We have a number of figures. For example, from 1987 to 1994, approximately 400,000 Lyodural grafts were used worldwide. In the past 30 years, in one article there was an estimation of several million allografts, but one of the panel members thought that estimate is certainly high by a factor of maybe 32 to 100 times when they questioned a number of providers of dura.

[Slide.]

I have looked at it in a slightly different way. Texas Distribution Center gave me the following figures, that they distribute about 2,500 grafts per year, and the Tutoplast we have just heard are about 1,000 grafts per year.

Interestingly, the competition to these groups, which we will talk more about it, Bovine Pericardium, there

were approximately 20,000 grafts at 400 centers over the last three years, and they have been selling, they say about 7,000 units per year. So Bovine Pericardium is used by far more in the United States than are human cadaver dura grafts of various varieties.

If we estimate that maybe about 10,000 grafts then are used per year in the United States -- that is what the neurosurgical demand might be in the country -- and we about 80,000 neurosurgical cases per year, you see that the number of grafts is really very small compared to the number of cases, so that maybe 1 in 100 cases will require or at least the neurosurgeon will feel needs a dural graft.

[Slide.]

There have been all sorts of substitutes tried for the last hundred years, and this out-of-focus, and now in-focus slide will show you the many resourceful things that neurosurgeons have put in the brain to try to solve these problems.

Obviously, silver, gold, and platinum are not the gold standards that they should be. They all cause problems as do all the other substitutes that I have mentioned here, particularly the silicon has been well studied, and there is a very large fibrous reaction that occurs to it, and it can be associated with hemorrhages.

[Slide.]

So all these materials have failed. Some of them have been much too rigid, some have been poorly incorporated into the host. There have been fibrotic reactions with these. There have been low resistance to infections in some of them, and excessive foreign body reactivity, and then hemorrhage has been a major problem, as I mentioned, with some of the artificial substitutes.

[Slide.]

The allograft material we have covered and we will discuss in much greater detail about how that is taken.

[Slide.]

I want to mention what are the other substitutes that are being used. Now, bovine pericardium is one that is being very actively promoted, and as you can see, is the substitute that most neurosurgeons are choosing within the United States right now. It is prepared by glutaraldehyde tanning and ethanol treatment. Then you have to wash it and it is stored in a bacteriostatic solution and has to go through some processing before it is used.

Those are the tissue bank rules, but I must point out that the experience with this is very limited. There is only one published article that I have, that involves 35 patients, and that is an embarrassment that this has not

been tested in humans over a longer period of time and that we don't have more information on it.

It seems to have a number of physical characteristics that make it quite acceptable for us, but none of the questions about whether it will transmit prion diseases have been fully answered, and of course there is the worry that it will be a problem in the future.

[Slide.]

This shows a number of synthetic grafts. Obviously, that would be the answer to at least the introduction of slow viruses into patients to have something that is entirely manufactured, and a number of these are listed here. Synthetic bioabsorbable polymer sheets are going to be discussed by our neurosurgeon from Edinburgh, or synthetic cellulose has been used. Bicol is a sponge material that has been used in a number of countries, and then bilayered human collagen prepared in various ways, and then a number of other materials.

I would like to end with another slide that talks about AlloDerm --

[Slide.]

-- which is a freeze-dried acellular human dermis. Now, I should mention that this company is actively promoting the use of AlloDerm for human use, but that we have had no

published articles on it for dural replacement, but that is fair game still for these companies to provide it because it is a tissue and the neurosurgeon has a right to use it even though there has been no human experience prior to their promoting it for this particular use, nor does it have to go through some of the rigid qualifications of the materials of human transplanted dura that we have been talking about.

That is the last slide.

Now I would like to mention where I think that things stand. It is very clear to me that neurosurgeons would rather not use any material other than easily provided to them by Mother Nature, that is, the patient's own material for dural grafts.

Over 100 years, neurosurgeons have wanted to have replacement materials and have worked on them, that all the synthetics so far have failed and we do not have any large studies to show that the materials that are available now, even Gortex, are suitable for long-term human use.

On the other hand, we are stuck with patients who have large dural openings. We have the general impression, never proven scientifically, that closing the dura is helpful to patients. We have never done any controlled studies where we don't close some patients and do close others to give us guidance.

But it has been a principle of neurosurgery, just like asepsis has been, that it is better to not have a CSF leak and that is a logical thing for us.

So we are left in the situation where we cannot provide you with a type of data we would like to have. On the other hand, we are very concerned with the risks as a group of neurosurgeons and we would like to have your help in trying to minimize those risks, but still have a suitable material that we can use.

Thank you.

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

I have a question and perhaps other people do. I may have missed beat, but I was trying to figure out approximately -- and it is an approximation -- how many dural grafts are used in a year in this country. Did I come away with a figure of about 10,000?

DR. PENN: I would go by that figure with one log missing. I mean it is possible that it could be 5,000, but it could be as many as 20 or more. I doubt that 100,000 dural grafts are being done with these materials.

Now, there are other dural -- we are always using the normal fascia lata for some --

DR. BROWN: No, I am talking specifically about dura mater grafts. And that bovine pericardial grafts,

there are about 7,000 a year?

DR. PENN: No, the total. Excuse me, the total number of grafts added in the bovine pericardium plus maybe 5,000 grafts of dura mater. So I don't think there are more than maybe 10,000 at most of the dura mater, and the bovine, I do have a figure from the company as of last week that they were selling about 7,000 per year, and they expected that number to go up considerably.

DR. BROWN: So in round figures, about 10,000 dura mater allografts, about 7,000 pericardial --

DR. PENN: No, I would think there are more pericardial than there are dura mater right now. Since we are guessing --

DR. BROWN: Let's talk about bovine pericardium, human dura mater, and miscellaneous synthetics, a proportion.

DR. PENN: I would think in the United States that we have reasonable numbers on the bovine. That is a fairly solid 7,000 per year.

DR. BROWN: Dura.

DR. PENN: Dura, I would guess --

DR. BROWN: That's bovine.

DR. PENN: That's bovine. Dura, human dura prepared in one of these two ways, we have at least with the

two companies present in the room, at least 3,500 per year that we know about, and there are certainly more than that. So if we say 5,000, that would be a reasonable estimate.

For the others, I don't think we have numbers yet, and I suspect in the United States it is relatively small whereas in other countries it may be much higher.

DR. TRAMONT: So you are saying 20,000.

DR. PENN: You are saying that it's about 20,000.

DR. TRAMONT: Is that what you are saying?

DR. PENN: I am saying that and I am not going to be able to prove it to you exactly. 20,000 plus or minus 10,000.

DR. BROWN: What we come away with is that bovine pericardium is a very significant alternative in use in this country. Whether it slightly more, slightly less, but it is a large proportion of grafting in this country uses bovine pericardium as an alternative to dura.

Dura remains also a very significant player in the use, and that synthetics in this country play a comparatively minor role. Is that fair?

DR. PENN: Right, and I should also say I didn't talk about reporting. I forgot to say that the reporting is about what you hear, that is, very poor, about 40 percent, and I have heard it is as high as 60 percent of the grafts

are reported back to the company, so that is leaving out a significant number of patients for followup.

DR. BROWN: Do you have any personal feeling about what we are going to be asked as a second question to answer, are there any special categories of neurosurgical procedures for which there is a consensus that a dural graft is superior?

DR. PENN: Yes. I think actually it is not fair to my other colleagues for them not to have their chance to show situations in which large amounts of dura are needed for a proper repair for the patient's safety, and there is no question that what we have in mind is closure of major areas that if not closed would produce clearly infection CSF leak and adhesion to the other underlying tissue.

DR. BROWN: So that what you are saying is that as a category, the size of the repair necessary would favor the use of a dura graft because it's a better graft?

DR. PENN: Right, but I didn't say that about -- bovine pericardium is another issue, and that we don't have an answer on because there are no studies. I mean there is one study of 35 patients in the published literature, so we don't know long term how that is going to work, but that is certainly a possibility down the line that we could replace, for example, all of the human dura with bovine, but we just

don't have the information to assert that.

DR. BROWN: Of course, the unstated concern of everybody in the room, and no one is saying it, so I will, then, you will run across FDA approval to prevent bovine spongiform encephalopathy from being introduced to the human brain.

DR. PENN: Of course.

DR. BROWN: Yes. Questions.

MR. FAITEK: Dr. Penn mentioned that there are approximately twice as many bovine replacements as human replacements that are used.

If there are only a study of 35 patients, on what basis are these 7,000 bovine tissues being sold and bought and used by the medical community?

DR. PENN: Well, I think there are a lot of reasons, and it is something that each individual neurosurgeon makes his mind up about, but also there are people promoting it, that's one thing, that there is a shortage of the human dura. It's not really available easily, and that it's expensive. Bovine is much less expensive. Autopsies are not done on the sources, they don't discuss the history with the animal, and, you know, it is just a cheap substitute that may be as good or better, and the issue has not been resolved yet.

DR. BROWN: It is a good place to ask the question here. What is the cost of a dura graft?

DR. PENN: I brought some dura grafts for you, but I won't sell them, because I am not in that business. A dural graft, a human dural graft will be about \$800 compared to I think about \$400 for the bovine, and the synthetics vary. You could probably tell me to the penny what it is. It depends on the size, of course.

DR. MALININ: The charge for a dural graft is \$400.

DR. PENN: Is now 400? Okay.

DR. MALININ: It has been for years.

DR. PENN: Okay. Texas is a little more expensive? Okay. And how much is the --

MS. OSTER: We range anywhere from 200 to over 1,000.

DR. PENN: It is the large sheets that, of course, are concerned.

DR. BROWN: So average \$400 or \$500 a graft. Average.

Yes, Sidney, you had a question.

DR. WOLFE: Either in your own experience or to the extent that you know the experience of other neurosurgeons, tell me a little bit about the circumstances

in which fascia lata or temporalis fascia could be used, and do you know places in this country that particularly in the last few years, have moved more in the direction of using those autologous substitutes more than cadaver dura?

DR. PENN: I think people who were using cadaver dura are more likely to have switched to the bovine if they had concerns about disease transmission, and that some people who plan out their operations well beforehand, for example, I have a partner who always closes his pituitary tumor cavities with fascia lata, so he plans for it.

DR. WOLFE: And he has been doing that for a long time.

DR. PENN: He has been doing that for 20 years. So a lot of it has to do with how you were taught to do it and what you consider to be an extra operation. The situation often is that we don't know how large an area of dura that we are going to have to replace until we do, and then to reprep the patient in a totally different area where we don't normally operate is time-consuming, raises the possibility of an infection, and that we will not be as happy with as just taking the material rapidly, having it ready for us, of the right size, and not having to do a lot in terms of preparation.

DR. WOLFE: But your point is that planning and

training could certainly increase the number of circumstances where autologous tissue, such as fascia lata or temporalis fascias could be used.

DR. PENN: For some cases, but it is not a perfect material by any means.

MR. FAITEK: Doctor, I am still a little confused. From the numbers that you just gave us, it seems that the bovine product is used twice as often as the dura product.

DR. PENN: It is my impression talking to companies that it is used at least as much as and maybe more, but I can't be sure of those solid figures because I didn't survey each and every place that is providing dura.

MR. FAITEK: In your personal experience or your knowledge, is there any reason why bovine product can't be used to totally replace the dura mater product?

DR. PENN: I think you would have to ask the companies whether they would be able to provide enough of it to do so.

MR. FAITEK: But as for the user, which you would be, do you see any reason why you can't switch completely to bovine product?

DR. PENN: I can put Silastic in, too. I mean there are things I can do as a neurosurgeon that are legal and there is a history to doing it, but I would like to have

some reassurance that that material is going to be good long term, and there is no way of getting that information right now because it hasn't been used extensively until the last three years, and we don't have any major reports on that material yet.

DR. BROWN: We are going to have to move on to the next speaker, but before you leave, since we as a committee are going to have to be polled individually, let me just ask you a final question.

Would it make you unhappy as a neurosurgeon not to have dura mater grafts available as a choice?

DR. PENN: Yes.

DR. BROWN: And the reason for that?

DR. PENN: I want to have the choice.

DR. BROWN: Because?

DR. PENN: I want to, as an individual neurosurgeon, want to look at all the information available and provide for my individual patient what I think is best, and I think that sometimes an overall ruling on this will take away a valuable material for me in some situations, that it would be foolhardy for me not to think that the future won't produce a better material for us, but I think that there are situations in which we still need it, and so I would at this point, unless the conversation convinces me

otherwise, that it is still a necessary material to be used like anything else in medicine that has some dangers to it.

DR. BROWN: If down the line bovine pericardium did prove to be a satisfactory alternative -- by "satisfactory" I mean proved to be a long-term survivor -- that would modify your opinion?

DR. PENN: Absolutely, as would a synthetic. I would be much more enthusiastic if we had a synthetic where we didn't have to worry about it so much.

DR. BROWN: So what I am hearing is that right now as we speak, dura mater is far and away the most satisfactory grafting material now, it may well be or it may not be that down the line, bovine pericardium will be as good, or some presently manufactured or yet to be manufactured synthetic, but as we speak, the human dura mater has advantages in your judgment.

DR. PENN: Right, and I should mention the allodurum, which I said we have no experience with, but might very well be a good material.

DR. BROWN: Thank you very much.

The next speaker is Dr. Raymond Sawaya from the University of Texas In Houston.

Dr. Sawaya.

Raymond Sawaya, M.D.

DR. SAWAYA: I would like to thank the committee and the FDA for inviting me to talk to you today. I had not considered myself an expert in this field and as far as I know, I have not won a Nobel Prize, so I hope I can contribute to the discussion today.

The second comment I would like to make is in particular congratulating Dr. Penn for an excellent presentation. This is not an easy topic. The data and the literature is very confusing, and studies cannot be easily done in this field, as I will try and highlight.

[Slide.]

With that introduction, I will not be as kind to your emotions as Dr. Penn was. He showed atlas pictures without blood in them. As a practitioner, I thought I need to show you the real thing. So those of you who dislike those pictures, you are prewarned.

[Slide.]

This is an example of a patient, a young male with a malignant tumor, and you could see easily this tumor on an MRI scan, which incidentally, is potentially a way to study graft in the future. MRI scans, as you know, were not available for a long time, but now they are and they are routinely used, so it is something we may want to keep in mind.

At any rate, the tumor is readily visible here. Although one does not know where the healthy dura in this patient is, we know that dura covers the brain, so it is likely to be here, but we have no idea where the dura is there. As it turns out, you will see the dura in this patient was pushed way down and infiltrated by tumor.

[Slide.]

There is at surgery, as the bone is cut, and there is the craniotomy, the bone is cut. We are looking at a hemorrhagic tumor, which was a malignant tumor. We do not see the dura until we scrape the tumor out, and now we are looking at dura which is infiltrated. This is the patient's own dura infiltrated with tumor.

So clearly, as a neurosurgeon trying to solve this problem, we needed to cut the dura along with the tumor, so that we have what we call a "gross total resection." This was accomplished.

[Slide.]

I will show you the bone because the bone itself, this is the outside of the bone and the inside of the bone was all infiltrated with the tumor, so the bone was removed, as well.

[Slide.]

But the key is now as the dura is being cut, you

could see there was tumor that has grown right through the dura in the subdural space, and now we are looking at normal brain that was pushed down.

[Slide.]

The dura is resected, and this is what you end up with. When you have to resect the dura, you end up with a defect, and I will say more about the defect later because the size of the defect, Dr. Penn alluded to this, is very important. In this case, it was extreme. This is a very large defect.

Again you are looking at healthy brain that needs to be protected. If the brain is not protected, if adhesions occur, scar occurs, seizures will develop. So again one of the reasons to protect the brain is to minimize some of these complications afterward.

[Slide.]

Typically, one needs to reach a healthy border of dura, so that as you are repairing it, you can suture it to the surrounding dura, and that is exactly what we have done using -- I borrowed this slide from Dr. Malinin -- and you see here a good-size, what is termed large allograft. This is one of those duras obtained for a cadaver, and it is readily available in the operating room, so there is no time wasted.

We know the size of the defect and we request the size from the circulating nurse.

[Slide.]

The sample is provided, and the dura is sutured, sutured in what we call watertight -- they are not always watertight, and that is a problem, that is a clinical practice -- we try to do the best we can.

There are CSF leaks that still will occur because the stitch may rip a small hole in the dura, but what one tries to do, one tries to minimize the problems, and that is one way -- that is a good way to minimize the problem is to obtain a good quality graft and to suture it as carefully or as meticulously as possible, so now we have the brain as protected as it can be in this particular patient.

Once this is done, cranioplasty is created because the bone has to be thrown out, the skin closed, and the healing normally proceeds well.

[Slide.]

This is after surgery where you see the dural graft. Again, we don't always see the dural graft, but this is one way I suppose one could look at the dural graft. Spinal fluid has accumulated here and the brain, which was pushed way down, is gradually working its way up there.

The brain is like a sponge. It doesn't just open

up right away, it will take time. This is an immediate post-op scan within 24 hours. Cranioplasty there, the skin is closed, and this patient has recovered well.

This patient had cancer. Eventually, he died from his cancer.

[Slide.]

The next example is again just another example of a tumor that has, in this case, protruded right through the skull into the soft issues under the skin.

[Slide.]

Similarly, there was a big lump.

[Slide.]

Similarly, it had to be removed, and I will not dwell too much on here other than to show you that here, the dura was thickened with the tumor.

[Slide.]

Again it was resected. The brain was healthy and had to be protected. Again, a large defect.

[Slide.]

And there is a dural graft that is providing that kind of protection. Cranioplasty was done and patient recovered.

[Slide.]

Another example of a patient who had a benign

tumor. It was not a meningioma, but it is a cousin of meningioma, hemangiopericytoma, that was growing slowly, had prior surgery somewhere else. At any rate the tumor was not removed and finally when we saw the patient, we elected to do what needed to be done, and that is to remove the sinus, there is a large venous sinus here, and the whole tumor, and repair that.

[Slide.]

I don't have an intraoperative picture, but again to show you that we end up with a big defect, removing the whole tumor. This patient now is several years post-resection, and she is essentially cured of her tumor, it has not recurred in the last three to four years.

So the point here is that although some patients have cancer and will die quickly, many others do not have cancer, they have benign tumors, or no tumors at all and require a graft, and they will live a long time, and therefore any solution to this problem has to be durable.

[Slide.]

Again, Dr. Penn did an outstanding job in reviewing the subject and any overlap I will try and use it for advantage here.

The indications very simply, clearly one, by reviewing the history of duraplasty, you have to go back to

the times of war, because that is when neurosurgeons were confronted with formidable problems of hundreds and hundreds, if not thousands, of soldiers with gunshot wounds to their brains, and need debridement and repair, and this is something we currently in civilian practice, as well, gunshot wound, car wrecks, and so on.

I put surgery, which is interesting, because anytime we do surgery and open the dura, we have altered the patient's dura. Dura is vascular. We have to coagulate blood vessels. As you do that, you shrink the dura, and frequently the dura cannot be approximated properly.

It happens daily, in every operating room, but as neurosurgeons we tend to repair small defects with what Dr. Penn alluded to, pericranium or temporalis fascia. Those are small repairs that we do routinely, and it will never be reported. You will never count those numbers, but they are by the thousands.

So surgery itself will lead to defects even though there may not have been a process like a tumor. Congenital malformation, Dr. Penn alluded to meningomyoceles or a defect over the spinal cord in newborn babies.

There are some indications that using dura there to cover this area is protective and reduces the amount of adhesions of the nerves under the dura. Infection

certainly, this is a very interesting problem, as a matter of fact. If you have infection, just like with gunshot wound or open wounds of the head, what material you put in there is critical.

If you going to put a synthetic, then clearly you are going to have bigger problems than putting biologic tissue that is going to be revascularized and will withstand the infection that is present there.

So this is a very rough summary of indications. What the numbers are, obviously, it is impossible to guess, but clearly there are needs throughout those various procedures for some kind of graft.

[Slide.]

Again, Dr. Penn was much more detailed in his summary. I will use this to remind us that many of things that have been tried, were tried with the idea that let's have something readily available and not very costly, that's good, but the practicalities of it turn out to be very limited.

As you go back and read the papers over the decades, you see what went on with these types of grafts that were tried and then a few years later one discovers that they created more problems than they solved, and that is particularly important to us as practitioners, because as

you close the dura or don't close the dura, put the bone back in there, and close the skin, you don't see what goes on.

Let's say adhesions occur. The patient has seizures. Well, brain tumor patients have seizures. How can we link what happened to the patient with the graft itself? It is almost impossible. That is why one needs to be cognizant that problems might occur and find ways to follow these patients if possible, although sometimes it is really not possible.

[Slide.]

Problems with xenografts. The perspective I have is, for one thing, they are now being subjected to the aspects that dura mater seems to be subjected to as far as safety is concerned, not that it is not good to subject dura mater allografts to scrutiny, absolutely, it is a must, but it is surprising that the other side is not being looked at as carefully, and that is really not acceptable when I view it from my perspective.

Autograft has been talked about and we use them all the time, they are very good, but good for small defects, not for large defects.

[Slide.]

So the perspective that I am hoping to bring to

this committee is summarized here, is that there are really physical and physiologic properties. We cannot look at the dura only as a barrier, as a mechanical or physical barrier. There is more to it, and as one goes through some 500 papers and literature that tries to deal with these problems over the last many decades, one really gets this appreciation of the healing process of dura.

Pliability is a physical matter that is important. We want something we can use, play with, fashion during the operating room. Size is very critical. Again, a small defect is not as difficult to deal with as large defects. The larger the defect, the more it is important that the material being used is biologic and is going to survive.

Tensile strength is important. The dura mater is created for that purpose and clearly has the best tensile strength in all directions if it is studied properly.

The watertight barrier, as I said, is an attempt and we don't always succeed, but that is what we try to do.

Low adhesivity is very difficult to study. There are many, many studies in animal models showing that the dura is what provides the best protection, but in humans, how can you do a study like this? We are not going to reoperate on patients looking for adhesions, so clearly that is a problem.

Physiologic healing. What I mean by this is revascularization, cells moving back into the dura, and that is best provided with human dura mater.

Low reactivity and finally durability are things that relate to what happens down the road. Silicon, we have heard examples with that. Patients are coming back with big lumps of fibrocytes that have formed around the synthetic or the silicon-made product. So those are things that we must keep in mind as we follow patients.

[Slide.]

My personal summary is that human dura mater is the only product that provides all the required physical and physiologic properties. You certainly can get away with using something else, there is no question about it. It is being done daily.

The question is as you look at cumulative data, which is likely to provide the properties that are required. I go back and see human dura mater is the best, and it is in fact the standard against which all other products are tested. All animal models that you look at, they have put human dura on one side of the animal's brain and the other product on the other side.

So they go back, use dura as the standard. So if you have dura, that is clearly the best.

[Slide.]

In summary or finally, I just want to mention, in the opening remarks this morning, it was alluded to, my association with the Transplantation Research Foundation from Houston, Texas.

I just want to mention that this association came as a result of wanting and needing dura, and not having it and being convinced that this is the right thing to do. I have therefore volunteered my services to help procure dura or make it available, and I must say I am impressed with the kind of work that went in providing allograft to neurosurgeons, and so that is the base of my association with this company.

Again, I think the committee for inviting me to speak to you today.

DR. BROWN: Thank you.

Would you agree with Dr. Penn -- well, you do agree with him that you would like to have human dura mater available --

DR. SAWAYA: Yes, I do.

DR. BROWN: That is clear. Would you also agree that at the moment there is really insufficient data to know whether any of the synthetics or bovine pericardium will turn out to be a satisfactory alternative?

DR. SAWAYA: I have concerns. One example, for instance, from a physiologic standpoint, is when as I look up at the data published about glutaraldehyde-processed tissue, that tissue is not allowing cells to regenerate and grow back into this graft, and that is what bovine pericardium is being processed with.

So again thinking about what is going to maximize the viability of this graft and therefore the durability of it, if you are preventing cells to get reintegrated into this graft, then clearly we are not putting a product that is likely to survive in the long term.

DR. BROWN: These are again very valid but still theoretical arguments. That is, no one is going to argue with you that a natural tissue stands to reason to be the best substitute, but there is still absolutely not enough data to know whether, in spite of these theoretical considerations, one or more of the alternatives will turn out in fact to be satisfactory.

DR. SAWAYA: I agree 100 percent.

DR. BROWN: Questions?

Then, we shall go on to the third speaker who comes to us from Scotland and the United Kingdom, Dr. James Steers, himself a neurosurgeon and I am assured that he will provide us a representative viewpoint from the United

Kingdom neurosurgical community.

Dr. Steers.

James Steers, M.B.B.S.

DR. STEERS: Mr. Chairman, members of the committee, ladies and gentlemen: I shall do my very best just to do that.

I should perhaps explain at the beginning that somebody who appears in the typewritten program as Mr. James Steers, M.B.B.S., in the United Kingdom is a properly qualified doctor. M.B.B.S. is equivalent to your M.D., and the reason our surgeons are referred to as Mister is in the 16th Century, in Scotland, James the IV, and in England, Henry the VIII, granted charters to the barber surgeons. We have held onto that tradition ever since.

I am also very conscious that I am really here in my colleague, Dr. Will's suitcase. Dr. Will in Edinburgh has set up the BSE surveillance unit within the United Kingdom, and I happened to be a handy neurosurgeon to come along, too.

I am also going to be brief because a lot of what has been said already applies to my talk, but I will point out differences between United Kingdom practice and the United States, and the first important point to make is that we have lived without any form of human cadaver dura since

1989, so we start from a different perspective at this stage, nor do we have bovine pericardial implant although it is just beginning potentially to come into the United Kingdom.

So I am talking from the perspective of dealing with fascia lata or natural tissue taken from the patient and donated to be a dural replacement or synthetic graft.

[Slides.]

Our indications for duraplasty are essentially those that have been outlined already, tumor removal, essentially meningioma or other process involving the meninges, and as Dr. Penn said, and Dr. Sawaya alluded to, in elderly patients where the dura and the pericranium is intensely adherent to the bone, it is very easy to damage the dura at the time of operative procedure, and it may become a necessity that perhaps had not been quite as planned, some other tumors, for instance, where this would be very much something that I would perhaps plan to have the facility to take a graft if necessary.

In head injury, depressed fracture, anterior fossa fracture, and Dr. Penn again showed a very nice picture of the fracture and the dural tear associated with it, the problem of CSF coming down the nose, and the potential for meningitis and cerebral abscess.

Something that we don't see so much of, gunshot injury in the United Kingdom of yet, although it is slowly increasing despite our new legislation about handguns. And in the spine and craniospinal junction there is a place for consideration of duraplasty, particularly with the congenital anomalies where, if you like, you need almost to put a gusset in the dura to make it a larger space for displaced cranial tissue.

If you have, as here, an extensive compound depressed fracture, it may be difficult in fact to get sufficient pericranium or temporalis fascia from the other side to be able to carry out the necessary repair, and I will just show a few examples of the sort of injuries and situations that we deal with.

[Slides.]

Here is a large meningioma, and you could anticipate, if I was operating on this patient, I would prepare the patient's thigh as part of the workup in the operating room before starting my craniotomy, anticipating that I would need to take some fascia lata, this very convenient layer of tissue to be found in the thigh easily accessible.

The problem with it -- as I will talk a little later on -- is principally cosmetics and postoperative pain.

Here is an example of a congenital anomaly in which the cerebellar hemisphere is prolapsing down, and it is causing an obstruction at the foramen magnum, the junction between skull and spinal canal, and to deal with this, you need to enlarge the space and to sew in a dural patch here.

You can use here, in a larger child, cervical fascia, but in the very small child -- I will come to it in a minute.

[Slides.]

Here is an example again of a meningioma. That is the tumor bed. This is the dural side. This is the margin of the dura. You can never get enough natural tissue from around here to be able to recreate this space, and the way I would close this would be with a fascia lata graft.

Now, if for one reason or another there is fascia lata available, I would have to sew in some form of modern synthetic material that I will talk about a little later on.

[Slide.]

This is a child with a compound depressed fracture. Again, I had to harvest tissue from the thigh to make up this very sizable dural defect here.

[Slides.]

Here is an example of two spinal problems, a complex spinal anomaly here, at which it would be impossible

to close the dura over this without compressing the underlying structures, and this is perhaps the most difficult thing for us in the U.K. at the moment.

A small child who will have a lipomeningocele, this white tissue here is misplaced fat, it also happens to have a syrinx, as well, but to recreate the dura at the bottom here, because there is no dura, the fat goes straight through onto the skin, can be a very difficult problem, and in very small children, there isn't sufficient fascia to be able to cope with this, so we have to use an artificial dural patch.

[Slide.]

Again, our requirements for duraplasty are those that have been said before. It needs to be effective and as the real two reasons for doing a duraplasty -- well, I suppose there are three -- it is to keep things in the right place, so if you have got herniated tissue that might fall out, like nerve roots in the spinal canal, you would want to keep them in.

It is to keep the CSF in the right place. CSF is in fact truly kept in the subarachnoid space, but you can't repair the arachnoid, it is far too filmy and nothing would hold in the way of sutures. So, you have to repair the dura to make it effectively CSF-proof, and the dura in depressed

fractures and trauma is said to be the great barrier to infection. So it is under certain circumstances a very important thing to have an effective duraplasty.

It has got to be easy to use. Some of the tissues that you are using are very delicate and they are down a hole, and if you are having to use quite a bit of push to get your needle through your artificial dura, and then you have only got a very tiny force to get your needle through the dura itself, it is difficult to manipulate the tissues, it is difficult to pull the suture tight. It will tear out of the dura and stay in the graft.

It needs to be able to conform to the shape. It has got to be free of complication, and obviously easily available. The complications that have been associated -- and this particularly important for us -- with the earlier synthetic implants, particularly the Silastic implants, they were associated with delayed hemorrhage.

They were not necessarily CSF-proof. They were difficult to get to conform to the shape that you were taking out. They were associated with infection. They had this huge fibrous reaction sometimes. It was absolutely enormous. If you rescanned the patients, you almost thought their tumor had regrown, but in fact this was just exuberant fibrous reaction to the graft that had been in, and then

there is the question of immune response and CJD.

[Slide.]

So we use in I would think 90 percent or more of cases, where we can, the patient's own tissue, fascia lata from the thigh, and there is an awful lot of it to be had. You have got two thighs, and certainly you could replace I think the whole calvarial dura if you had to.

If you are operating on the back in an adolescent or adult or perhaps a four-year-old or more, you could use adjacent spinal fascia, but it would be difficult in a neonate or a year-old, and then there is pericranium and temporalis fascia, the tissue actually around the head.

It has got advantages. It is accessible. It is a homograft, the patient's own tissue. It conforms very well to the shape of the defect. It is very easy to use. It has the same resistance as the tissue you are sewing it to. It is CSF-proof.

You can suture it, and I am not sure tomorrow whether you are going to be discussing tissue glues and fibrant sealants as blood products, as part of your second discussion, but that would be of particular import to neurosurgeons, too.

It's a fresh-on process tissue. You can implant it under a skin graft. It is minimal effective risk. Low

cost. Now, it is low cost in the U.K., and one of the really interesting things that I read in the article that I think we alluded to 35 cases of bovine implant, is that in fact it is not low cost as far as the theater economy of U.S. hospitals are concerned, because operating time costs more in terms of dollars than the graft. The time taken to harvest the graft and the additional incision is in fact more expensive than actually having a graft and sewing it in. So it might be low cost to us, I am not sure that that argument applies across the board.

I haven't named my name because I wasn't certain whether I was going to be allowed to or not. The synthetic grafts that we use apparently in the U.K., or we use in Edinburgh, but there is a polyester urethane which we have been using for the last two years, which obviously we can't talk about long term problems with, but in the short term, does actually give us a lot of these things.

It is easy to use, it is CSF-proof. You have minimal infective risk, it isn't expensive, but obviously, it is not human tissue and it may not stand the longer test of time, and there are other tissues that we have also -- or implants that we have used that are synthetic, that aren't so successful, and are not really CSF-proof, and don't go along.

So, we do have perhaps a disadvantage, and I would agree entirely with Dr. Penn and Dr. Sawaya with the difficulties that you can have with synthetic implants.

[Slides.]

Now just to close and really just to say what has been said before, this is John Hunter, who in 1700 became really the - or 1700s became the founder of the science of surgery within the United Kingdom, and was very instrumental in the Royal College of Surgeons in London, and he was really a very important figure. He would have been really interested in what we are talking about today, and he would have been disappointed in us modern surgeons because we actually don't know do we have to close the dura.

I was bought up by Professor Gillingham as my teacher, and he never closed the dura, and I am certainly not aware of huge or major problems that occurred with his patients, but hospital stay was not a major problem in those days, but in this day and age where you have to perhaps think about how fast a patient can through a hospital process, you can't afford to have CSF problems and repeated lumbar punctures, which might have solved the problem very well here, but wouldn't be acceptable today.

There is a huge amount of anecdotal evidence in the literature. I mean there are lots and lots of papers

that talk about complications with this and that. They talk about technical ability to implant something and how well it does, but there is very, very little in the way of anything that could be called a controlled trial.

I think that actually if you have done absolutely nothing else for me -- and I hope that I have done something to help your committee -- you have certainly made me rethink where we stand surgically as far as duraplasty is concerned.

Thank you for your attention.

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

Are there questions for Dr. Steers? Yes.

DR. WOLFE: Dr. Steers, could you tell us a little bit about the basis back in 1989 for the U.K.'s decision to stop using human dura (a), and (b) what your own personal attitude is towards its unavailability?

I think you mentioned the figure that in 90 percent of the cases -- I assume you were talking about all neurosurgical procedures -- in which you needed to do something, you were able to do with autologous tissue, and that is something that probably grew since 1989.

Can you give us a little bit of look into that process in the last eight years?

DR. STEERS: I would have to refer Question 1 to Dr. Will, who would talk to you much more authoritatively

about the nonlicensing Niagera [ph] within the U.K. than I can.

I have to say there has been no, if you like, rebound phenomena amongst the United Kingdom neurosurgeons bemoaning or saying that we are now having a very difficult and uncomfortable time, that we should not have because this dura was -- we were stopped from using this tissue. That would certainly be my own view.

DR. WOLFE: So you have been able to get along well enough -- Dr. Brown earlier made the point that we hear about complications from Silastic, not surprisingly causing all the fibrous tissue reaction, and some delayed hemorrhagic complications from other tissue, but the point was made that there aren't comparable data from operations where cadaver dura is used.

I mean in your experience, having switched, I presume you were operating before 1989, as well?

DR. STEERS: I think I go back to 1974.

DR. WOLFE: In your experience -- and again this is going to be your anecdote -- but do you have the impression that the number and/or nature of the postoperative complications that you have experienced has changed once you were disallowed, so to speak, from using the human cadaver source of dura mater?

DR. STEERS: I think I would have to say nay to that. I mean I have removed cellophane from a patient who was operated on by Professor Dott in the fifties. I have removed Silastic on at least half a dozen occasions from various sites with huge difficulty. I mean we just would not use that again.

But beyond that, I have to say no, I do not think that the complication rate or difficulty rate has so significantly increased that there is an outcry, if you like, amongst British neurosurgeons.

DR. WOLFE: So dura as opposed to autologous tissue seems to have the same kind of scope and amount of complication rates in your experience?

DR. STEERS: I think that would be true, but I have to say again -- because I think Dr. Penn's difficulty is absolutely correct -- how often is this done. I think that we would some form of duraplasty, probably 20, 25 times a year in Edinburgh, once every other week, of which, if I am saying, you know, we are talking about two synthetic implants, if we are talking less than 10 percent, I mean we are not talking large numbers, and if each unit more or less operating on somewhere approaching -- well, we would operate on 1,000 patients between the childrens and the adult hospital in Edinburgh, that gives you our perspective of the

level.

DR. WOLFE: That is on the synthetic, but let me just focus the question a little bit more. Presumably, before '89, a much larger proportion of the cases were being done with human cadaver dura.

DR. STEERS: Presumably. I mean one of the earliest papers suggesting this actually came from the National Hospital, Queens Square. I think Lindsay Simon and McFarland published. I mean yes, the answer to your question is that certainly lyophilized dura was used.

I don't think its withdrawal has created a huge problem.

DR. WOLFE: Thank you.

DR. PENN: When you state the whole problem, I think you are proper to emphasize how few patients overall any particular individual will have. That is the first thing.

DR. STEERS: That is correct.

DR. PENN: The second thing is that you still seem to require in some cases a dural substitute.

DR. STEERS: That is absolutely right.

DR. PENN: Are you confident now that this dural substitute that you are using is something that we all could use and therefore not have this problem?

DR. STEERS: Again, the answer to that obviously has to be no on the generalization, but you would have to say that the majority of problems that turned up with Silastic turned up within 12 or 24 months.

Now, patients have been doing that period of time without the problems that occurred with, say, for example, that particular synthetic, do you see what I mean?

So, I don't think necessarily we are going to be dealing with the same long term problems. There is also experimental evidence from the Mayfield Group in Cincinnati, who have done implant work in animals, looking at a comparison between a synthetic implant and I think it was Lyodura implant, and there again, you know, there wasn't a huge difference between the level of adhesions and the complication rate, but over a much shorter period of time.

So I think, you know, it is not necessarily total doom and gloom for all synthetics, but as yet the perfect one I think we would all admit isn't there.

DR. BROWN: Dr. Sawaya, is there anything that you would like to say that perhaps you didn't agree with that Dr. Steers presented? You guys are the experts. Why don't you get into some arguments?

DR. SAWAYA: I think the points were made, and you have emphasized those points, that we don't know how far

down the road one needs to go to define whether there is a problem or not.

I think the literature has taught us that the problems can be delayed. Silicon, you mentioned it, Jim, is a good example. In fact, Ongiko in the Mayfield Group reported cases 10 years later with big masses occurring. So I think we need to keep that perspective in mind. I think the whole point I am making here is that history has given us that lesson - don't close your eyes because things could happen down the road.

DR. BROWN: Thank you very much. I think this set of three presentations has been an education for me and probably for the committee, as well.

What we are going to do now is conclude this morning with an epidemiologic paper by Dr. Robert Will. As we are running a bit late, I think it wise to hold over the experimental study papers for after lunch, and so immediately after lunch we will hear from Drs. Diring and Tateishi.

Now we will hear from Dr. Will.

Epidemiological Assessment of CJD Transmission

Through Use of Processed Human Dura Mater Products

DR. WILL: I am very grateful for the invitation to come and speak at this meeting. I personally am quite

concerned about the issue of human dura mater grafts and I hope to explain why in a relatively short presentation.

[Slide.]

Iatrogenic CJD is a medical tragedy, the transmission of an untreatable and uniformly fatal disease from one individual to the other, and this is a relatively recent updated graph of the numbers showing there has been neurosurgical transmission historically many, many years ago in the early 1950s, transmission through depth electrodes through a corneal transplant, and most recently the numbers of dura mater grafts affecting transmission presumptively from one person to another is now 69 cases including some cases recently reported by Professor Tateishi from Japan.

Of course, this is also the tragedy of the human growth hormone recipients of whom there are now more than 90 victims, and in Australia, four cases of individuals who developed CJD following treatment with human pituitary gonadotropin.

The mean incubation period is approximately six years in the individuals who have received dura mater, although I do not have full information from the Japanese cases, and I am sure Professor Tateishi may be discussing this later, but it is also the case that I think there is at least one case with a minimum incubation period of about 12

years who received a dura mater graft.

[Slide.]

In the United Kingdom, we have been studying Creutzfeldt-Jacob disease systematically since about 1979, the date in England and Wales going back to 1970, so we believe we do have fairly good ascertainment of Creutzfeldt-Jacob disease. During that time, we have identified a number of patients who have received dura mater grafts, human dura mater grafts, and have then developed Creutzfeldt-Jacob disease, and there are six of these patients.

This illustrates the delay between the operation date and the development of CJD. This is just listed here, I won't read them off. What I should say in this is that we believe that five of these cases received the product Lyodura, but one of these individuals almost certainly did not receive Lyodura, and this relates to this individual who was treated in 1969 with a dura mater graft and then developed CJD in 1978 and died in 1979.

I am not sure if it is appropriate in this type of meeting, but I would just like to discuss this one individual case here, age 24 with a cerebellar astrocytoma, operated on in 1986, developed CJD in 1994, and died about a month ago.

The reason I am mentioning this particular case is that during this meeting, it has not been apparent I don't think or stated what a dreadful business CJD is, and particularly iatrogenic CJD. This individual was actually eight months pregnant when she developed her illness, and the whole disastrous development of this disease has been appallingly difficult for her family, and I think that is true of many of these cases of iatrogenic CJD with an onset sometimes relatively early in life. It is certainly something that should be avoided if at all possible.

[Slide.]

Now, this is a relatively old slide and I apologize about the nature of it, but this listed at that stage the known cases of dura mater related CJD, and this is the country of origin of the case, the year of the operation, date of death, and the material that was used, and there are a number of things that are fairly apparent from this.

First of all, the great majority of individuals who have developed Creutzfeldt-Jacob disease following dura mater graft had received the product Lyodura. What is also very striking, if you look at the year of operation, the great majority of patients received a Lyodura graft within a relatively short period perhaps 1982 to '87, and this

strongly suggested there was some form of cross-contamination and potential contamination of lots of Lyodura.

Professor Tateishi has very kindly allowed me to say something about the Japanese data which is an addition to this, often as one case, and there have now been 43 cases of dura mater related CJD in Japan, of which 35 were treated between 1982 and 1987, but there are patients who have developed CJD following dural graft after those dates, and of course prior to those dates, and there is at least one case where the dura mater was locally produced.

An important question looking at this sort of graph is do we know that this is complete, are there cases that are missing. Well, I think we have to be quite cautious about suggesting that this is complete because it depends to a certain extent upon surveillance of CJD and indeed there has been cases described, which may be coincidental, of CJD following other procedures in neurosurgical, one following an eardrum repair, tympanoplasty and we have recently identified a second case with tympanoplasty using human dura, who developed CJD.

The origin of the dura of this case is still under investigation, but it was certainly not Lyodura.

There is also a report, fairly recently, of CJD

developing in individuals who had been treated with embolization using material produced from human dura. The case is in France suggesting that there may be other unexpected routes of transmission that have not yet fully been investigated. So I do not know that this is a complete list.

[Slide.]

One of the problems with iatrogenic CJD -- which I come back to at the end -- relates to the relatively recent occurrence of these cases. This is data actually from Australia. It is very similar to the data we have in the United Kingdom. This is from Colin Master's report, looking at the subtypes of CJD, and here is iatrogenic CJD, in Australia first occurring around 1987, and cases are continuing to occur now.

It is a relatively new phenomena, and this is one of the problems with this, is that the risk that was taken to produce these cases was taking place many years ago.

[Slide.]

Just to reiterate, this is a graft from Dr. Brown's paper, looking at human growth hormone recipients. This shows at that stage the total number of cases, U.S.A., England, France, et cetera.

Just in brief, the issue of whether there was a

risk from human pituitary hormones in relation to CJD was initially discussed in the United Kingdom in the late 1970s, around here, and at that stage there was a great deal of reassurance taken I think from the fact that human pituitary growth hormone had been used probably from about 1960 in the United Kingdom, and at that stage 18 years later there had never been a case of CJD related disease.

I think that you have to be cautious on using the fact that there has not been a case, being reassured that there will not be a case in the future.

The other issue is that in the late 1970s, a study was carried out in Edinburgh, in the Neuropathogenesis Unit, in order to try and mimic the production mechanism of human pituitary hormones. This study was negative, suggesting that these hormones might be safe, and I think again there is a caution in overinterpreting perhaps experimental studies that do not fully mimic what is happening in reality.

In relation to dura mater, I personally would have concerns about small rodent studies which look at decontamination with very thin dura mater, unnecessarily applying that data to human dura mater, which is a different thickness and may be less permeable.

[Slide.]

So if there is a risk to transmission in iatrogenic CJD, what are the major determinants? Well, the major determinants are the route of exposure, the species barrier, and the dosage.

The route of exposure very likely within-species transmissions, but the intracerebral route is by far the most efficient route of transmission of these diseases. It maximizes the risk of transmission.

Trying to transmit from one species to another often introduces a barrier to transmission. This of course does not apply within within-species transmission in which there is no barrier of the transmission of a host-adapted agent to that host. Human-to-human transmission is the greatest risk.

Finally, the dosage, and this is a major determinant to the efficacy of transmission, and certainly in relation to human-to-human transmission, the last thing you want to use are brain titers of infectivity.

As you may have gathered from the implications of what I am saying, my concern about human dura mater grafts is that all three of these factors maximize the risk.

[Slide.]

Now, in relation to using safe sourcing of material, an important question is how accurate is the

diagnosis of Creutzfeldt-Jacob disease in the community, and of course it is very difficult to get direct data on this.

What I have used here is a slide from the United Kingdom study of about a 12-year period, in which we looked to see how accurate the diagnosis of CJD was at least on death certificates.

What we know from the surveillance data, which is systematic, is that we get a set number of cases per annum. We can then find out how those patients were certified on the death certificate as to what the cause of death was, and as you can see, in recent years, about 28 percent of cases of CJD were not certified as dying of this condition.

Now, a great proportion of this error relates to individuals who are writing the death certificate in a hurry on a Monday morning, and it may be that these cases actually were diagnosed as CJD, but nonetheless, within this group, there are a proportion of patients in whom the diagnosis of CJD was never suspected.

[Slide.]

This is my last slide. The question is, is it possible to achieve safe sourcing of human tissue for medicinal products? Guidelines have been utilized in a number of areas, for example, in human pituitary hormone production in relation to sourcing of hormones, and I am

afraid to say that they failed, and one of the problems with this is the great latency to recognition failure. That is, the decisions are made on what seems to be entirely reasonable grounds perhaps, but it is only 10 or 15 years later that it is realized that that decision was in fact an error.

The other problem with the guidelines is whether they are adhered to, and this has been an issue in the United Kingdom. For example, there has been one individual who received a corneal graft from a patient who died of CJD some years after the official guidelines were introduced. Fortunately, this did not result in disease because the corneal graft was removed almost immediately, but I think there is a risk in putting too much faith in guidelines unless they are absolutely rigidly adhered to.

There is also the possibility of trying to obtain material from individuals who do not have a significant medical history, who may not even have any neuropathology, but who may, nonetheless, have infectivity in their brain in relation to prion disease.

There is this issue of the pericardial graft, which was obtained from someone who probably did not suffer from a neurological disorder, and it is presumptive that this was the cause of the subsequent CJD.

Dr. Brown published some years ago subclinical CJD in an individual who had received human growth hormone, who died of intercurrent illness, and I believe the facts are that the initial neuropathology did not show any abnormality, and it was only subsequently when detailed immunocytochemical staining was done that this individual was discovered to have high levels of PrP in the thalamus.

So there is a risk that even with histological examination that you cannot guarantee the absence of infectivity albeit rarely.

I have mentioned decontamination already. So I well understand the possibility of minimizing the risk of human dura transmission - by selecting donors who are young, by ensuring that they do not have neuropathological changes of CJD, et cetera, by using decontamination procedures which minimize infectivity during the production process.

But my concern is that even if all those were adhered to strictly, you can never minimize or remove all risk, and the problem with human dura mater, which is distinct from many other issues in relation to potential case-to-case transmission of CJD, is that this involves intracerebral placement of a tissue that potentially contains brain titers of infectivity.

In my opinion, if there is a failure, then, it is

highly likely that the use of this material would subsequently result of disease.

So, of course, the crucial issue is the risk-benefit analysis which has already been discussed by my neurosurgical colleagues.

Thank you for your attention.

DR. BROWN: Thank you, Dr. Will.

Do we have questions from the committee for Dr. Will? Yes.

DR. WOLFE: Thank you for your excellent presentation. I would just ask the same question that I asked Dr. Steers before, which is back in '89, when the decision was made, what were the major factors in reaching the decision to stop using -- I mean Lyodura was the number one culprit, but you pointed out, and others have alluded this morning to the possibility, if not certainty, that non-Lyodura products have been the genesis of some cases.

So, what was the thinking in '89 (a); and (b) knowing what you know now, would you recommend or have you recommended for the U.K. that the policy be changed?

DR. WILL: Well, I have to state quite clearly that I was not directly involved with the decisions that were made, although I was involved with this sort of meeting where information was produced, but my understanding is that

after the initial description of CJD in dura mater recipients, I think in MMWR, and then a subsequent discovery of further cases, I think the decision was made that this product, without specifying which type of product, human dura mater as a whole was potentially a risk factor for iatrogenic CJD, and in view of that, particularly in view of previous experience of what had happened with human growth hormone, that this material should be withdrawn from use, although I think what happened was that import certificates were probably withdrawn. That is my understanding.

If I were asked now my opinion as to whether human dura mater grafts should be reintroduced into the United Kingdom, my answer would be I do not think they should unless there were clear evidence from neurosurgical colleagues that it was essential to use this material in individual patients for their benefit because there was no other alternative that is likely to result in them suffering from some neurological damage or deficit.

I do not think from what I have gathered from my colleagues including Mr. Steers and other neurosurgeons from Britain that the situation in the United Kingdom is that it is felt that this is essential material to use. As Mr. Steers has said, we in the United Kingdom are not using this material for nine years, and I believe the same situation

has occurred in Australia.

DR. WOLFE: It is not used in Australia either?

Are you aware of other countries, I mean aside from the recent WHO recommendation that it not be used, and Japan's decision not to use it, are you aware of other countries, either recently or during the same interval of time, that have taken the position of the U.K. and Australia?

DR. WILL: I am not, but that doesn't mean there aren't because I can't say that I am fully informed about other countries.

DR. WOLFE: Do you think it would be useful to do such a survey and just find out what the policies are?

DR. WILL: Yes. I think it would be a very interesting thing to do.

DR. WOLFE: Thank you

DR. BROWN: Other questions for Dr. Will?

DR. LESSIN: You alluded to genetic factors. Can you give us an update on the status of genetic predisposition to this disease in terms of any specific genes or gene linkages that place individuals at risk?

DR. WILL: In the U.K. study, sporadic classical CJD, the great majority of individuals have a particular genotype, the polymorphic region in the prion protein gene

codon 129, a great majority are defining homozygotes.

In central inoculations of iatrogenic CJD or effective central inoculation, such as Lyodura graft, the situation again is that there is an excess of methionine and zygotes rather similar to classical CJD.

The data on which I base this was published by Dr. Brown, and he may well be able to give far better informed comment that I have just made.

DR. BROWN: That is essentially correct. The polymorphic genotype is overwhelmingly homozygous in the dura mater cases that have been tested as it is in sporadic CJD.

Larry, did you have a question?

DR. SCHONBERGER: I was wondering, have you done any numerator and denominator type of analyses, and specifically breaking it down by the Lyodura situation, which was the group processing and poor recordkeeping and poor screening, and so on, versus, say, non-Lyodura product? Has anything been done in that realm?

DR. WILL: No. It is an extremely important question, but I am afraid I cannot answer it because I do not have denominator information. In fact, I have learned more about the denominator here today than I had known about it before. I am not sure if that investigator is widely

available or readily available.

Clearly, dura mater has been used extensively around the world, and there have been a relatively small number of cases overall. I would be very interested in relation to this issue to hear from Professor Tateishi who I think may have very much better information, for example, on the data in Japan where there has seemed to be so many of these cases, as to whether this necessarily reflects a greater usage of this material, but I am afraid I cannot give you hard data on denominators.

DR. SCHONBERGER: You did present the numerator data, and I was wondering, when you showed like seven cases, you said five were from known Lyodura and one was known not to be Lyodura, and one was unknown, is that right?

DR. WILL: There were six on that slide, and five of the U.K. cases were Lyodura related, but one almost certainly was not, and there is this case in Italy which was locally produced, and of course there is the case, the suspect case that you described today.

DR. SCHONBERGER: Right.

DR. WILL: But it is quite correct that the great majority, the vast majority of cases of dura mater related CJD received the product Lyodura.

My argument is that even though that is the case,

there are theoretical reasons for having to be very careful about using Lyodura of any source.

DR. BROWN: Dr. Tateishi, anticipating part of your presentation, but to answer the specific question here, my recollection from what you told me was that in Japan, approximately 20,000 dural grafts were performed each year, and you have, let us say in rough figures, 40 to 50 cases, and that occurred in patients, again in rough figures, between about 1982 and 1987 with one or two trailing cases.

So, you have got a five-year period roughly with 100,000 grafts and roughly 50 patients. I mean that is a numerator and a denominator for Japan subject to a little revision when Dr. Tateishi presents his material.

DR. SCHONBERGER: What I was hoping that we might get a sense of would be the difference between this product Lyodura, which seems to account even in Japan, for virtually all of their risk with this product of dura mater grafts versus what that comparable numerator and denominator might be for non-Lyodura.

DR. BROWN: The numbers there are so small that your feeling has to go down to zero. You have got one case from Britain, you have got one case from Italy. Nobody knows what the denominators are there.

DR. SCHONBERGER: And one case from ourselves.

DR. BROWN: And possibly one case from Japan. We will hear it, but in no case, more than one case, four different sources, and what can you say more than that? I don't think really a denominator is going to help you a whole lot.

DR. SCHONBERGER: Well, I wanted to get a sense whether -- clearly, we have a tremendous magnitude of difference of risk from looking at the numerators alone between this one product Lyodura --

DR. BROWN: Yes, no question.

DR. SCHONBERGER: -- versus the non-Lyodura product. Now that Lyodura product, presumably the production technique has been changed, and so we are going to continue to get cases because of the long incubation period from this disease, and that we will continue to show that that Lyodura product was a problem.

In fact, I think that 41 or 42 of the 43 cases that were reported from Japan all related back to the outbreak from the Lyodura problem that was identified back in 1987.

DR. BROWN: They all went back to that period - '82, '85, '87, where the Lyodura was produced and distributed.

DR. SCHONBERGER: What I was concerned about is

that we overreact to one situation where we know there was a problem and that that problem is now corrected. What I am trying to get a better feel for are the three or four cases that don't fall into that category, that is, the one from England, the one from Italy, maybe our own case, and so on, whether the denominator explains the difference or whether in fact we are dealing with a totally different risk, and I was wondering if anybody could help us with that.

DR. BROWN: Only what I said. You are never going to get that feeling because the denominator in England just ain't available, the denominator in Italy isn't available. We don't even know where the Italian case material was prepared, not do we know that about the English -- correct me if I am wrong, Bob -- and our case is very dicey as being a case.

DR. WHITE: But Larry brings up a point that maybe needs to be brought out at some point in time. I am not sure what the right time is, but we are hearing a lot about Lyodura, but we don't know much about Lyodura. We don't know how it was prepared, the material that has caused these cases, we don't know how it has been prepared and how products that are currently being used compare with that product.

DR. BROWN: Actually, we do, but I had hoped that

would be distributed in the packet that you got. That is known in detail, and it involved I think possibly hydrogen peroxide, on the one hand. I know it involved radiation. It did not involve any step that damages the infectious agent, not until 1987.

DR. SCHONBERGER: One of the reasons we reacted to the first case, there was only one case at the time that we thought that there was a problem, and the reason we thought that there was a problem was precisely because of the comparison of the processes used by this producer of Lyodura versus what we could discover was being used by the Miami Tissue Bank and other banks that we interviewed, and we were struck with the differences in safety, and one of the major things was sort of laissez faire attitude in a way towards commingling product and keeping product separated during the course of production, and so on. They tended to group the materials all together at various processes and also, as I say, did not or we couldn't get from them a clear sense of selection of the source material with much confidence that they were using that.

DR. BROWN: It is now 12:30. We will have a break for lunch. We will reconvene at 1:30.

Before lunch, the members of the committee, a sheet has been supplied to us by the FDA which does include

ajh

the relevant processing steps used by the Tutoplast Company about which we inquired this morning. That will be distributed -- it is a single sheet -- to everybody on the committee. It is confidential. It should not be shown to the general public.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m. the same day.]

AFTERNOON PROCEEDINGS

[1:30 p.m.]

DR. BROWN: We are now having the final two presentations, each of which will relate an experience with experimental decontamination of dura mater. In addition, Dr. Tateishi I am sure will bring us to speed on the Japanese experience with human CJD in that country as a consequence of dura mater implantation.

I turn the microphone over now to Dr. Heino Diringer from the Robert Koch Institute in Berlin.

Experimental Studies on Decontamination Procedures**Processed Human Dura Mater****Heino Diringer, Ph.D.**

DR. DIRINGER: The Robert Koch Institute is a governmental institute for infectious diseases, and you all are aware that in early 1987, there was the first association between a case of Creutzfeldt-Jacob disease and possibly dura mater implant caused by a product of a dura mater company.

A couple of weeks later I got a telephone call by another German company. We discuss whether this could actually be possible. So I asked the German governmental institute, which is responsible for drugs and for medical

products, the Bundesinstitute Institute, whether this is an interesting drug and whether we should do something about this, and I looked up into the literature, and there was nothing known about any transmissible agent associated with dura mater so far.

So, of course, after asking the head of the institute whether it would be useful for us also to do such cooperative work, and we decided to study the method by which the company Frimmer and Viggio purify their dura maters.

[Slide.]

We normally work and we always work with animal model systems, and the animal we work with is this little animal. It is a hamster, and there is a strain of scrapie agent which actually causes disease in sheep, but it is an identical disease which we use in these animals.

So the first question we asked is there infectivity associated with dura mater, and for this we took animals at the final stage of the disease, and we removed the dura mater from this guy, which in the beginning was not very easy, but if you keep it one day in water, in distilled water, you can easily remove it, then you wash it, and what you then do is you put it into a buffer, you homogenize it by ultrasonication, and you inject it back in other animals,

and you see whether they come up with the disease.

[Slide.]

The first of the two tables I am going to show you is this one. The first line, it is just to see that we can show infectivity in brain. There is no problem with that, of course. The incidence was four out of four animals, and the incubation date is from infection of the animals to clinical symptoms, is 72 days, and from this one can calculate the amount of infectivity per gram of wet brain, so it is between 10^9 and 10^{10} IC LD50.

Now we took the dura mater and treat it. Ten out of 10 animals came down with the disease. Incubation period is about 10 days longer, telling us that in between 10^6 to 10^8 infectious units are indeed in dura mater.

So the association between dura mater implant and Creutzfeldt-Jacob disease in man was already quite likely. Then, we ran such material through the procedure by that company, which is actually washing it with various buffers using hydrogen peroxide for inactivation of conventional viruses and using organic extraction procedures and doing irradiation with x-rays.

Under the standard condition you see again all the animals came down with the disease. Again, the incubation period was a bit longer. This tells us that we lose about

roughly between 90 percent and 99 percent of the infectivity, but still after this procedure, the material is infectious.

In the material, the dura mater of the hamster is a very tiny, very delicate piece of material, different from that in humans. So I suggested, because it is collagen, and collagen is a very rigid material that one might treat it with sodium hydroxide to see what happens, and as you can see, if you use the standard procedure, and then you use in addition sodium hydroxide at 0.1 molar or at 1 molar, the animal came down in this particular experiment.

We stopped the experiment after 350 days. After this, we never had any animal coming down. The latest animals we ever, ever experienced was around 320 days. So, the estimated titer per gram was less than 10 LD50. So, it is quite an efficient method to destroy these kind of agents.

Well, after we knew this, we were interested in the question, well, at the end of the disease, we know that there is infectivity in the brain, of course, and also in the dura mater, as we can show here, but what about in the incubation period.

[Slide.]

So, we infected animals by a intraperitoneal

route, in this particular experiment, by an intraperitoneal injection, and then at four days after infection, up to 78 days after infection, we took some of the animals, took brain material from these, and dura mater, and looked for infectivity.

I must tell you that after intraperitoneal infection, up to this time, you can't see any clinical symptoms in these animals. Clinical symptoms appeared at about 90 days.

Here, we find for the first time infectivity after about 50 days, and 10 animals came down, and you see it varies quite a bit, but it tells you also that in this particular period of time, the titer in the brain is low. At the same time, you can also see that already in the dura mater some animals came down with the disease.

[Slide.]

So, you can calculate again by the incubation period and by the low incidence that in between less than 10^4 LD50 must have been in the dura mater during the incubation period, and in between 10^2 to 10^8 LD50 within the brain material.

That's all that I can tell you about the contamination of dura mater with this kind of agent.

Thank you.

DR. BROWN: Thank you very much, Heino.

Are there questions for Dr. Diringer from the committee? Yes, Ray.

DR. ROOS: Did you look at protease resistant PrP in any of this tissue especially untreated or treated?

DR. DIRINGER: No, not in this particular experiment, but it is so clear-cut by the incubation period there is no doubt that -- and, of course, by the clinical symptoms.

DR. ROOS: I guess I was more concerned about the animals that are over 350 days and what that really means, and that is why I thought it might be of interest. When you inactivate these, and you say they are inactivated, what happens to PrP and protease resistance?

DR. DIRINGER: We have done this in a lot of other experiments. The very moment, over 350 days, you won't find PrP in an animal which doesn't show any clinical symptoms, at least not in our hands.

Normally, these animals come down at 250 days, so this is more than double the usual incubation period.

DR. ROOS: I was concerned about PrP in the inoculum that you have treated.

DR. DIRINGER: No.

DR. WOLFE: When we were being shown data earlier

this year from researchers concerning decontamination of gel, one of the problems was that a lot of these studies involved small numbers of animals, and I guess the question is aside -- I mean let's assume that if it doesn't show up in 350 days, it won't show up, but there is also the artifact of the small number of animals.

I mean did you do any kind of calculations as to what number of animals you might have needed to show --

DR. DIRINGER: Yes. We published this in the Lancet. We described that these were single experiments I showed you, but in this article we write that out of 40 animals treated with sodium hydroxide, 1 came down with the disease and a very long incubation period of about 230 days.

DR. WOLFE: So 1 out of 40.

DR. DIRINGER: Came out. It must have been contaminated with an extremely low amount of infectivity.

DR. WOLFE: Thank you.

DR. BROWN: And the treatment was an hour?

DR. DIRINGER: The treatment with the alkali was one hour at room temperature.

DR. BROWN: And the animal that came down was tenth normal or 1 normal sodium hydroxide?

DR. DIRINGER: It was the 1 normal.

DR. BROWN: One normal.

DR. DIRINGER: Yes.

DR. BROWN: Are you at liberty to tell us what company contracted you to carry out these experiments?

DR. DIRINGER: Yes. It was Frimmer/Viggio. I think it is now Biodynamics situated in Erlanger in Germany.

DR. BROWN: That is interesting because we heard this morning that Biodynamics had included the sodium hydroxide step from the beginning of their manufacturing period, which went back, as I recall, to 1972, and unless I am mistaken, what this implies is that that is not the case and that sodium hydroxide would not have been added until after your experiment had been completed in 1988.

Would Biodynamics care to comment on that?

MS. OSTER: It is my understanding -- and I don't know the specific years -- but prior to the use of the 1 normal, they were using 0.1 normal, which was one of the original inclusions in the 510(k), and subsequent to review by FDA, the 0.1 normal was changed to 1 normal. So that would have been -- John, do you know when that was? '89 or '90, in that period.

DR. DIRINGER: But in the -- maybe it is different from the Germany company compared to the one here in the United States. In the convention method, I tested for them, there was no alkaline step at that time, because the samples

were prepared by the company, not by me. The samples of buffer, of hydrogen peroxide, inorganic materials came all from this company, and we put all materials in.

Then, we tested, and then they were sent back to irradiation, and then we tested, and in these cases, there was always still infectivity there. I cannot remember that I had samples with sodium hydroxide from that company.

DR. BROWN: Well, that is an historical point that can be perhaps made precise if it's important, and, of course, I assume the company was also aware that at least -- well, that one animal using 1 normal sodium hydroxide did in fact come down with the disease.

This does not surprise any of us in the field where we have an occasional breakthrough at the level of 1 animal in 40 or 1 animal in 100. That is apparently what is going to be happening with blood infectivity as well, which we will talk about tomorrow.

But the fact that sodium hydroxide is not totally sterilizing all the time is not a surprise. On the other hand, nearly complete sterilization or inactivation is not to be sneezed at, and it is certainly a whole lot better than not including it.

So I would warn everybody not to get too caught up in the idea of all or none. Anything that you can do to

minimize infectivity is a good thing even if it is not absolutely, totally complete.

Thank you very much, Heino.

The next speaker and last speaker to address this committee is Professor Jun Tateishi, who we are very pleased was able to come from Japan. His career was spent as a neuropathologist and experimentalist in Kyushu University in Fukuoka, Japan.

Dr. Tateishi.

Jun Tateishi, M.D.

DR. TATEISHI: Thank you, Mr. Chairman.

[Slide.]

I will talk about the decontamination experiment and then about newly discovered CJD after a dura mater graft in Japan.

[Slide.]

Disinfection experiments were done using mouse-adapted CJD strain. CJD-infected mouse strain were homogenized in saline and centrifuged. The supernatant was mixed with chemicals, then usually kept for two hours at room temperature and dialyzed against distilled water for 48 hours. Each sample was inoculated into mouse brains and the mice were observed as long as possible.

This slide shows the number of mice affected and

the total examined. This is the incubation period, the mean period in days. This is the calculated infectivity ID50 here. Disinfection effects of chemicals depend on the concentration of chemicals or the temperature of treatment.

One N sodium hydroxide lengthened the incubation period and 80 percent formic acid, or 7 molar guanidine hydrochloride, 3 molar trichloroacetate and 50 percent phenol could activate the infectivity. 3 percent SDS, sodium dodecyl sulfate, was not effective below 60 degrees centigrade but effective after three minutes of boiling. As SDS is not corrosive, not expensive and has clinical effects, we use it in daily practice.

[Slide.]

I have applied some treatments on formalin-fixed human dura mater. Dura was sectioned in the same size and, at the left, boiled for 10 minutes in 3 percent SDS which caused severe shrinkage and intermediate shrinkage, in the middle, after two hours dipping in 98 percent formic acid and no shrinkage after two hours dipping in 50 percent phenol.

For the decontamination of dura mater, formic acid and phenol are applicable.

[Slide.]

I will move on to the next topics. The nationwide

surveillance of CJD started in April of last year. A study group was organized by the Ministry of Health and Welfare of Japan and I was a member of the group. We sent questionnaires to many hospitals and personnel and got a high response. The answering rate reached 74 percent.

[Slide.]

The total number of patients reached 865 during 12 and a half years. The incidence of sporadic CJD and familiar CJD, including GSS, was similar to those in other countries; namely, one patient per 1 or 2 million population.

There was no case treated with native human growth hormone and no case resembling new-variant CJD reported in the United Kingdom, but 46 sporadic CJD patients had a past history of the graft of processed human dura-mater products.

[Slide.]

This slide shows years of dura graft in the horizontal line. This is the year of the dura graft. And the year of the disease onset in vertical line; disease onset is here. Especially many CJD patients were found among recipients grafted between 1983 and 1987. It is written in red figures -- most frequent.

Patients suddenly decreased after 1988 when new decontamination treatment using sodium hydroxide was

introduced in the manufacturing process of Lyodura. One of two patients grafted after 1988 received the old product which was not withdrawn by the manufacturer in this case. The other patient, grafted in 1991, remains unclarified. Except just one case, all patients were grafted with the old product of Lyodura.

[Slide.]

Latency between the graft and onset of CJD had two peaks, around three years and around nine years after the graft.

[Slide.]

Mean latency was a little longer in the Japanese cases than the reported cases by Dr. Brown. The mean incubation was 7.4 years.

[Slide.]

Duration of clinical illness was similar in both groups and usually longer than that in other countries.

[Slide.]

The time course of CJD infection through Lyodura in Japan is shown here. In 1973, Lyodura was imported in Japan at first. In 1984, maximal CJD infection occurred after dura graft in this year, ten victims out of 20,000 recipients in one year.

In 1987, the first case of dura-graft CJD was

reported in the USA. FDA issued safety alerts and ordered withdrawal of Lyodura. Manufacturers of Lyodura added sodium hydroxide treatment and dura-graft CJD stopped occurring from the recipients except two cases in 1989 and 1991.

If lower infectivity is left in the processed dura, new patients may be found in the future after the longer incubation period. Anyway, the Japanese Ministry totally banned the use of the processed dura at the end of March of the last year. Since then, Japanese neurosurgeons repair dural defects with autologous fascia lata, temporal fascia or synthetic substitutes such as gortex.

[Slide.]

Many new synthetic duras, such as the absorbable one shown here, are now being produced. This is reported in the Journal of Neurosurgery in this June issue.

[Slide.]

This is my summary. First, selection of donors and individual processing of dura mater is most important to prevent CJD infection. Two, formic acid and phenol applicable to dura like sodium hydroxide. Three, ten minutes boiling in 3 percent SDS is best for the instruments, hardware and glassware. Fourth, alternative use of autologous fascia or synthetic substitutes must be

considered.

Thank you for listening.

DR. BROWN: Thank you very much, Dr. Tateishi. I may have missed, again, what you said about those last two cases. My recollection is that you said that the case that occurred from a graft put in in 1991 was the single case which was not associated with Lyodura.

I wasn't sure what the date of distribution of either of those two grafts was; that is to say, is it possible or known that both of those grafts, in fact, were produced and distributed much earlier and simply were in storage until they were used in 1989 and 1991.

DR. TATEISHI: We are asking to the hospital, but they could not clarify the product.

DR. BROWN: Am I correct that the 1991 case was not Lyodura?

DR. TATEISHI: No. It is not clear Lyodura.

DR. BROWN: It is unknown. It could have been but it is not sure.

DR. TATEISHI: Not sure; yes.

DR. BROWN: Other questions?

DR. ROOS: Maybe I missed this. You showed a slide of inactivation. First, I wasn't exactly clear as to what agent you were using in what animal and, second, it

looked to me like the infectivity was spared when you used 1 normal NaOH in most of the animals, although the incubation period was prolonged.

I just wondered whether you or Paul or somebody might comment on that if I read that slide correctly.

DR. TATEISHI: I used mouse in my experiments, inoculating the CJD-infected mouse brain homogenate. So, at that time, I used various concentrations of sodium hydroxide, 1 N sodium hydroxide lengthened the incubation period, very long, but not completely disinfected even after using 2 N sodium hydroxide. I think complete decontamination is always very difficult using such a mouse model.

DR. BROWN: Were these final concentrations, Dr. Tateishi; that is to say, when you showed a concentration of 1 normal, was this the final concentration, meaning you added equal -- you added 2 normal --

DR. TATEISHI: 2 normal.

DR. BROWN: -- to the homogenate in equal amounts and the final concentration was 1 normal? That is the slide of inactivation, the concentrations of chemical that you showed, were those the final dilution concentrations of the chemical? To get 1 normal, did you add 2 normal to homogenate to get 1 normal?

DR. TATEISHI: I omitted some data in the slide. I reported in my article all of that, but I mentioned only 1 normal sodium data.

DR. BROWN: Let me try and rephrase it because I don't think I am making myself clear. Was the concentration of sodium hydroxide that actually was present in your mix of chemical and brain homogenate 1 normal when you showed 1 normal?

DR. TATEISHI: Yes; 1 normal.

DR. BROWN: That was the final concentration; that is, the concentration that was actually present in the homogenate. To get a final concentration of 1 normal if you mix equal volumes of chemical and brain, you need to add 2 normal to achieve a final concentration of 1 normal because it will be diluted 100 percent.

DR. TATEISHI: 1 normal is the initial concentration for two hours.

DR. BROWN: The reason I belabored that is because your results are at variance with most other results using 1 normal sodium hydroxide. I think the answer you gave us when you add 2 normal sodium hydroxide, you achieve a final concentration of 1 normal sodium hydroxide and that was effective when you used 2 normal, which I think you said you had no transmissions after adding 2 normal.

Most of us when we report the data use the final concentration. So your result with 2 normal as an initial is comparable to what we have found in the literature and in our experiments which is a final concentration of 1 normal. So they are not at variance. They are simply a different way of reporting the information.

DR. SCHONBERG: I was noticing that nine of your cases occurred within two years of the administration of the dura mater graft. You mentioned that since 1987, you have tried to reduce the use of the product that is implicated in 45 or 44 of the 46 cases. This means that you have only had one case, if I understood the data correctly, that has been associated with all the product that has been used in Japan since 1987 or since you stopped using the Lyodura product.

But I don't have a sense of the denominator that we are talking about. I was wondering if you have any idea of how much new Lyodura, or Tutoplast or non-old Lyodura has been used in Japan since the older Lyodura was ceased being used.

DR. TATEISHI: In Japan, two processes of dura product are imported. One is Lyodura and one is Tutoplast. The frequency of Lyodura was over 60 percent of all dura imported. So before 1987, the old product of Lyodura and also the old product of Tutoplast both were imported to

Japan but from the old product of Tutoplast, no case was reported to cause to infect CJD.

DR. SCHONBERG: You had talked about a figure like 20,000 as I recall, on one of your slides. That was for a given year or given several-year period in around the mid-eighties?

DR. TATEISHI: It is 20,000 grafts per year.

DR. SCHONBERG: Has that number stayed about the same except now you are using a different product, or has the number of dura mater grafts used in Japan since 1987 dropped substantially in that period 1988 to, say, 1994?

DR. TATEISHI: Neurosurgeons have annually almost similar --

DR. SCHONBERG: Similar. So we have, then, a period from 1988 to 1994 of a non-old Lyodura being used. You do this survey in 1996 and we have maybe this one case, is that correct?

DR. TATEISHI: Yes.

DR. SCHONBERG: Thank you.

DR. PRUSINER: I don't want to belabor this point because I don't think we will get the exact answer that you were searching for, Paul, but I think that maybe we can have a conversation later about this issue of 1 normal versus 2 normal sodium hydroxide because in our experience, if it

were the other way around, if he had, on his chart, the final concentration as he listed it instead of what he added, I could easily see these results.

The one thing that I was a little concerned about is what these titers mean, but I think this gets too technical to discuss this here. I think we can just take them with a grain of salt.

DR. BROWN: Yes. I think the bottom line is that 1 normal sodium hydroxide is not a guarantee of sterility. We have known that for a long time. I am a little surprised that there is this much breakthrough, but, according to Dr. Prusiner, that was his experience as well; 2 normal sodium hydroxide is better than 1 normal, is better than 0.1 normal and on down the line.

That, then, concludes the input of information for the committee. Now Dr. Hellman will charge us. I should add by way of introduction that Dr. Hellman is one of the anchors of this whole process and is in the Office of Science and Technology within the Food and Drug Administration.

Charge and Questions for the Committee

DR. HELLMAN: Thank you, Dr. Brown.

As you said, I am Dr. Kiki Hellman, senior scientist in the Office of Science and Technology in the

Center for Devices and Radiologic Health, FDA. That is quite a mouthful.

First of all, I would like to thank all of our invited guests and consultants, the speakers who have come from quite a long way to share their information with us. We have heard from the industry, we have heard from the surgical community, from the research community, and from the epidemiologists, and it is the first time in my experience that I have seen all of this expertise to bear on this issue, but it is a very important one at that.

This morning, Dr. Jacobson described the safeguards established by the FDA beginning in 1987 to minimize the possibility of iatrogenic CJD transmission from dura mater allograft.

We recognize the importance of evolving regulatory approaches as we have new scientific and clinical information becoming available in order to assure the safety of the products that we regulate.

To this end, and because of events earlier this year regarding reports of dura mater allograft related cases of CJD transmission that you heard about this morning, the TSE Advisory was convened in this open public forum to help us, the FDA, in its reevaluation of dura mater allograft use relevant to the risk of CJD transmission.

I might mention that although the FDA is not obligated to adopt the recommendations of international bodies, such as the World Health Organization, nevertheless, we regard them very seriously and we are committed to international efforts for protecting public health and for harmonizing appropriate regulatory approaches.

This afternoon I would like to present the charge and questions developed by the FDA Planning Group, colleagues in both the Center for Devices and the Center for Biologics Evaluation and Research to the FDA TSE Advisory Committee.

We consider the committee a very important resource and a vehicle for discussing the latest scientific information on TSEs and the potential risk of TSE transmission via FDA-regulated products.

The committee's charge as you see in the overhead is to assess the safety of processed human dura mater as an implant for surgical use with regard to the risk of CJD transmission considering its purported clinical benefits and the adequacy of alternative products.

In other words, we are looking for your thoughts with regard to the safety of using dura mater allograft for surgical procedures when one balances the clinical benefits, the adequacy of alternative products, and the risks of CJD

transmission.

In addressing this charge, the committee will be performing an invaluable function and contributing to the science-based approach for decisionmaking to assure the continued safety of medical products.

[Slide.]

In considering your charge, there are two questions that we would like the committee to address, and we ask that the members of the committee be polled on these questions.

[Slide.]

Question 1: Taking into consideration the clinical benefits of dura mater allograft and the adequacy of alternative products, for what surgical procedures is there a need for dura mater allograft?

[Slide.]

Question 2: What measures or safeguards should be used to minimize the risk of CJD transmission associated with the surgical use of dura mater allograft?

[Slide.]

To aid in your deliberations, the committee might consider certain points that were discussed in the topics covered by our speakers this morning.

[Slide.]

In addressing Question 1, you heard about how donors are being screened, the sourcing procedures, acceptance/rejection criteria, and the standards and guidelines that are being followed, and you also heard how dura mater allograft is being processed, that is, the testing of the tissue and its examination, and the different decontamination protocols.

Integral to the processing of dura mater allograft is the effectiveness of decontamination procedures for minimizing potential CJD infectivity, and you just heard from Dr. Diringier and Dr. Tateishi data from experimental studies on decontamination procedures using TSE animal models.

The use of such studies to evaluate and guide dura mater allograft decontamination protocols might be considered together with appropriate donor screening procedure.

[Slide.]

Regarding the use of dura mater in surgical procedures, the committee might consider the types of procedures for which dura mater allograft is indicated along with the extent of its use, the alternative products that are available, and the safety aspects of using dura mater allograft and the alternative products.

[Slide.]

Because of the reported cases of CJD in a limited number of recipients of dura mater allograft, the committee might consider the epidemiological data on the correlation of the use of dura mater allograft and CJD transmission, and the traceability of dura-related CJD to either a common source and/or common processing procedure.

[Slide.]

In addressing Question 2, that is, what measures or safeguards should be used to minimize the risk of CJD transmission associated with the surgical use of dura mater allograft, possible measures that the committee might consider, among others, are the use of stricter donor screening criteria including any testing that might be available for donor screening for CJD and the use of additional decontamination steps in the processing of dura mater allograft.

In closing, I would like to mention that in addition to addressing the questions posed, the committee should feel free to offer any other recommendation or suggestions on this issue, and to encourage open discussion we also welcome public comment on this issue, as well.

Thank you.

DR. BROWN: Thank you, Dr. Hellman.

Open Committee Discussion

DR. BROWN: Now the fun begins. The answer to Question 1, which we aren't going to actually poll the committee members on until there has been plenty of time for discussion, clearly could be none, it could also be some, it could also be left to the discretion of the neurosurgeon, so that even if the answer to the first question is none, the way it is worded, "for what surgical procedures is there a need for dura mater," even if it is decided by the committee that there is no surgical procedure for which there is a need for dura, we still want to discuss the second question, which concerns should it nonetheless be used, what kinds of safeguards would minimize the risk of CJD.

I have a feeling that the discussion now is perhaps going to wander, but I think we should probably let it wander for a little bit, and I open therefore this session by inviting anyone who has a comment to speak out, and we will see where the discussion goes before we have to vote on these two questions.

Would anybody like to open up the discussion?

Yes.

DR. WOLFE: I just want to open it up by reading from the FDA guidance which was handed out to us, and I think that what they said back then, in '91, is really not

refuted by anything now. Just two sentences.

"The consensus of experts indicates there is no practical and reliable method to sterilize human dura mater that is infected with slow virus, e.g., CJD virus, nor is there any practical test to detect the presence of the CJD prion."

It then went to say that, "Therefore, the emphasis needs to be put in screening donor selection," and so forth, and we have heard today again that given the fact that at least for one of the major companies, they are only doing brain histopathology on 5 percent of the cases, and secondly, that because of the latency during which at least if the animal model is to be believed, there is infectivity, there is no assurance that people who are clinically or histopathologically free of the disease are not infective, you have sort of cut off both of the routes for trying to do something.

I mean, on one hand, we have seen even in this experimental model that 1 out of 40 animals treated for an hour with 1 normal sodium hydroxide -- final concentration I assume -- have infectivity, and so I am very concerned and which is why I tend towards the British approach or the U.K. approach is that better safe than sorry.

We do not have accurate data, which is usually the

case except in a randomized trial on a drug, it is usually the case we don't have accurate data on the risk, and the benefit appears at least for the last eight years largely, if not entirely, to be replaced not so much by synthetic materials, but by autologous tissue, which obviates the whole issue of infectivity with CJD.

So I guess I am going back to the guidance that was put out, and I am wondering why the FDA seems to have phrased the question, and seems to be telling us, that the guidance is still applicable when the World Health Organization made what was no more than a recommendation, because that is all it can do, that the use of dura mater implants be ended, FDA said no, our policies and guidances, and so forth, are adequate even though, as we heard this morning, it is not regulated as a device, it's a human tissue.

So those are sort of my concerns, and I don't think we have learned anything today that minimizes the concerns I have in all of those areas.

DR. BROWN: Perhaps we could hear again from Dr. Hellman. The FDA here is asking for advice to either revise or leave intact a guidance, if I am correct. The FDA is not considering, shall we say, upgrading their involvement in the allograft field by issuing a directive, for example,

prohibiting the use of dura mater.

Is that correct, or are you in a position, if this committee decides to recommend that, to accept the recommendation, and actually prohibit the use of dura in this country, or are you just interested in a guidance statement?

DR. HELLMAN: It is the first, Dr. Brown. In view of the cases in Japan that were reported earlier this year, and the WHO recommendation, we are reevaluating the consideration for dura. We are primarily interested in the safety and considering both the epidemiological data and any other science-based data that we can bring to bear on this subject.

We are not only dealing with the guidance. What we are asking of the committee is science-based input to help us in reevaluating our position with regard to dura, to tell us for what procedures is there definitely a need for dura, to look at the safety of both dura and alternatives that are out there.

Whatever decision the committee comes up with, with regard to dura, whether it's stricter criteria, whether it's a restriction of the use of dura, we have different regulatory vehicles that we can put in place to address that whether it is regulated as a device -- which is how dura is

regulated now -- or whether it will be regulated as a tissue under the Center for Biologics.

So we can take care of the regulatory vehicle with regard to assessing safety, and what we would like from the committee is a judgment based on the science, both the experimental and the epidemiological, on the restriction of dura if that is appropriate, and also some discussion of alternatives and for what procedures either would be appropriate.

Does that help you? So it's not just guidance that we are looking at here.

DR. BROWN: In other words, the FDA has it within its power, should they choose to use it, to actually ban the use of dura in this country? Ban it outright, ban it, no dura shall be used? You could do that, that is a theoretical possibility --

DR. HELLMAN: Yes, it's a theoretical possibility.

DR. BROWN: -- all the way down to the other end by saying, well, it looks as though dura is no more dangerous now than it was back when we had our previous consultation several years ago.

So anything from one to the other and everything in between.

DR. HELLMAN: That's right. We haven't looked at

this issue, if you recall, since 1987, and you were present at the first meeting we had in '87.

Dr. Alpert, would you like to add to that or Dr. Jacobson?

DR. JACOBSON: Yes, I think we absolutely could ban the product if that is what we think is necessary to do. I think the concern we had was that we have a lot of variables that we are weighing here.

Certainly safety is very, very important, and effectiveness is also important, and one of the concerns that we were hearing was concern from the neurological community that in fact they didn't have adequate substitutes for the dura mater in the surgical procedures that they were using, and even in the discussions we have heard today, one of the things that keeps coming through is that there are a number of substitutes, they have all down sides and certainly the synthetics, we have very little experience with, so we really don't know.

We have a relatively well-described risk for the dura mater, but we really don't have very much of a described risk for some of the other alternatives, and that was what we wanted to get on the table here and wrestle with a little bit.

We thought that it was important in March when the

ban was announced in Japan that we have a discussion here in the United States.

DR. TRAMONT: Paul, why don't we start with that premise then?

DR. BROWN: Which basically is the first question, which is what I was going to suggest. Unfortunately, apart from our two neurosurgeons on the committee itself, none of us has the faintest idea how to answer that question because it is a question for the neurosurgeons to answer, what surgical procedures is there a need for dura mater.

We have three different neurosurgeons, and it seems to me that the conclusion that was reached is that if dura mater had no risk, it would be ideal. It does have a risk or at least under certain circumstances, and as we speak, there is not enough information to know whether any of the alternatives are as good. I don't know what more we can say. But let's throw that out. That is my proposition.

DR. TRAMONT: There is no harm in being honest and truthful with that statement, it's what it is.

DR. BROWN: Linda.

DR. DETWILER: For the neurosurgeons, if tomorrow you couldn't use dura mater, I mean give me some circumstances, a scenario, what would happen with patients, because, Dr. Penn, you mentioned, you said you just want the

choice, but I didn't really hear concrete, well, in this scenario I need to use it because.

DR. PENN: Well, first of all, there would be an outcry by neurosurgeons across the country about it, because it would take them by surprise. Second of all, we would all survive, and our patients would probably survive, but what we don't know is whether we would be putting them at greater risk for complications of using the substitutes, which we would immediately go to.

So it is a question of balancing risks here, and I should say that I think that the majority of neurosurgeons would feel that if there were an adequately proven substitute, that we would move to that rather rapidly. The marketplace would take care of the problem.

The way I see the problem in terms of the first question is that there are some cases where it clearly is very difficult to cover the area that we need to cover with anything, either a dural substitute or the human product, and that being the case, that -- well, we don't have to define each and every one of those operations, we can say that in circumstances that require dural coverage, that it is appropriate if the committee agrees not to ban it outright.

But I think it is very hard in the situation to

come down very solidly about it. What I think that we would feel much better in having is some control over how the dura is prepared, certainly the human dura is prepared, and some sense that there is some appropriate regulation for the substitutes.

Right now the situation is such that the FDA as a policy approved the use in selling of materials that we don't know how they will hold up over time. In other words, the situation has given us some substitutes, like gortex, for example, that has no literature behind it, or the human dermis prepared with glutaraldehyde, and it is the overall situation that isn't acceptable.

What I would like to see is us not ban it outright, but move to a policy that would allow us to, as rapidly as appropriate over a number of years, find substitutes.

DR. DETWILER: I have one more follow-up question. I guess it really struck me that the bovine pericardium is used almost in double the cases of the grafts, and why do you think that is, especially if there is no data? I mean people must have some success or maybe they are just unknowing have side effects on that?

DR. PENN: It is probably a very good substitute, but it has been used infrequently until the last three

years, and it will take us another six, 10 years to see that that may be even a better material than we have, but it will take some time.

DR. SAWAYA: The answer will be marketing. The answer could be marketing.

DR. DETWILER: You mean you would just use a product because it is marketed, and not really knowing if it would be --

DR. SAWAYA: Especially when the alternative may not be readily available.

DR. TRAMONT: The operative statement that you made, Dr. Penn, is you would be willing or the community would gladly substitute something else if it had a track record that showed it to be equal or better than the present dura mater.

The real issue is how do you get there, how do you get to fulfill your criteria? Will another committee be convened in five or six years, and a statement that Sidney read will be read again, which is we have got a status quo and we don't have any information, a little more information that we had before except we know that there are some questions and red flags around the edges.

So maybe we ought to make a proposal that we ought to suggest that the FDA maintain a registry of every kind of

material that is used in this kind of surgery, so that data can be real hard data, as hard as you can get it in this situation when you do these kinds of studies, can be looked at five or six or seven years hence, so that the question that you are raising can be addressed.

DR. PENN: And what I am saying is it has been undermined totally by allowing dural graft material and the substitutes to be out there in the field and be promoted without proper testing, which makes me feel uneasy, so there is nothing out there to enforce getting the type of data that will gradually resolve the issue.

DR. TRAMONT: And Kiki said we wanted to have scientific data.

DR. BROWN: That raises the issue that not only would it be useful to have -- and it will occur -- to have additional testing and information on alternatives, but it would be awfully nice, for example, if today already we had information that combined the data from both of the experimental studies done by Dr. Tateishi and Dr. Diringer.

For example, wouldn't it be nice to know that a dura mater in the hamster model, which is endogenous dura, that is, it is inherent infectivity, were sterilized by any one of the several chemicals that Dr. Tateishi mentioned, specifically with respect to shrinkage and perhaps

biological satisfactory performance, phenol, on the one hand, and formic acid, on the other.

Formic acid is extraordinary. You can put tissue sections that have been in formic acid, you can put a section of tissue into formic acid and then take it out of formic acid and it will still maintain its ability to be histologically read. On the other hand, it has to be put into formaldehyde, which probably wouldn't do the dura mater any good.

The point is that there are a number of inactivating chemicals and procedures to which dura mater has not been exposed, and it would be nice to know if there were such a chemical better than sodium hydroxide, which is already pretty good.

I have been asked, and will recognize, Dr. Susan Alpert from the FDA, and she would like to make a comment to us.

Yes, Dr. Alpert.

DR. ALPERT: I just think it would be useful for the committee to understand a little bit about how the alternatives that you are discussing have in fact come to market, and to do that, let me just run a little bit through how the Center for Devices and Radiological Health looks at nontissue alternatives or nontissue products that are used

in this type of an indication or in these types of indications.

It is important to know that many of the products that go to market, go to market based on general use as either patching or covering materials, and as such, the clinical data on which the approvals are based are broad spectrum and not specific for a given type of surgical procedure.

If a company wants to claim a very particular type of use, then, we do expect that there would be valid scientific evidence, generally in the form of clinical data, data from clinical trials, that support that claim, the claim of safety and efficacy in a very specific use.

However, it is also important to recognize, as I think came out in the discussions already today, that one can't wait long term to place such products in the market, and therefore the data on which or the time frame during which those decisions are being made are fairly early, for example, three years or maybe five years of experience, not 10 or 20, which would significantly delay those products reaching the marketplace.

So we have a situation where the majority of products currently being used as patches, went to market with very general claims. They don't carry a specific brain

covering claim. If that were to be developed, we would expect to see data.

Thirdly, it is true that they are out there with shorter duration evaluations because it makes little practical sense to wait 10 or 20 years for that data to come in before a product reaches the marketplace.

There are, however, safeguards and mechanisms to gather data during the marketing of products. One is that we have a tool that we can use to get postmarket surveillance studies. That is actual clinical data from trials of products that are legally marketed.

A second is, of course, are reporting systems for adverse events reporting.

Thirdly, if during the development of a product there is a need to look at a particular use in a broader community, we have something called the "treatment investigational device exemption," which allows availability of the product while data is being gathered, and I think that we have a number of tools of that sort that might help us to move forward on some of the alternatives that you were talking about this morning, and if I can answer any other questions about how these products, these alternatives might reach the marketplace, I would happy to answer them.

DR. TRAMONT: So it is not difficult to get

postmarketing data if you want it.

DR. ALPERT: If, in fact, it is determined that that is needed, we have the authority to ask for it.

DR. BROWN: Yes, Gil.

DR. WHITE: Paul, I wonder if it would be possible -- a lot of what we are discussing are cases that occurred a while ago with a particular product that was not treated in the way that current products are, and so in a sense what I hear is that we are comparing alternative products in a sense with that particular product -- I wonder if we can focus a little more on the dura mater products that are currently being prepared and what we think their risk is for transmission of CJD.

I don't think it is quite fair to compare those products with Lyodura is my bottom line here. They just aren't the same thing. And I am hearing that Silastic type membranes have a fairly uniform complication rate. We don't know what the risk is with bovine pericardium, but whatever the risk is with bovine pericardium, it probably is the same risk as human dura mater, that is, if it can occur, it can occur.

The other thing to factor in there is that I keep hearing that 1 normal sodium hydroxide does get rid of the transmissible agent for CJD, but it doesn't do it 100

percent of the time, but again the other products appear to be being treated with something that is equivalent to that and yet in a time of perhaps heightened observation, that is, if there were CJD occurring with these other products, we certainly would think we would be hearing about it. We are not hearing about it.

So the bottom line is can we focus perhaps on the products that are currently available and sort of throw the Lyodura out, because it isn't currently available.

DR. BROWN: I doubt that Lyodura -- well, it is not for me to say -- but I expect Lyodura is not likely any time soon to get an import permit issued.

DR. WHITE: Well, I didn't mean that. I meant figuratively, the old Lyodura is no longer available.

DR. BROWN: Right. On the other hand, as Dr. Malinin told us, the dural grafts that are being processed by the University of Miami do not include a sodium hydroxide processing step, so in a sense, you have one product that is on the market without this. Tutoplast includes it, and I don't know what Lifelink Tissue Bank includes or not. Does anybody know? This is the speaker that was not able to come today.

But the point is that despite the fact that there is nothing that will inactivate CJD in the protocol used by

Miami, to all intents and purposes, Miami has escaped problems at least one that has been detected in the occurrence of CJD.

Ray.

DR. ROOS: Just to follow up Gil's comments, I guess the risk if you didn't have any sodium hydroxide step would be one in a million dural transplants would transmit disease to another individual assuming that there was proper controls and no pooling and cross-contamination, and that doesn't sound too bad to me.

Of course, there is all kinds of problems with biological tissues. There may be viruses that we don't even know about, and I am certainly -- I would prefer myself to get my own fascia and a synthetic product if it worked.

So one question is, you know, how come three countries or two countries aren't using these dural grafts, and I think to a certain extent that it had to do maybe with the bovine spongiform encephalopathy problems and also the Lyodura problems, as well, and in fact I think those are significant pressures on us at the moment, as well as the WHO statement.

With those pressures and the fact that a lot of what is being used at present are synthetics, to me, that is probably going to be the future. I don't think of ourselves

under enormous pressure at the moment. On the other hand, I do think that the days of dura mater transplant are probably numbered and that it would behoove the FDA or appropriate groups to work with the neurosurgery community in the United States to take appropriate action about what tests should be done, how could you validate the synthetics, what is going to work best, and to put something in a time frame, so that we really move things along into an appropriate material to be used.

So that would be kind of my suggestion at this point.

DR. BROWN: Just an addendum. In looking through, it has been shown to me that the Lifelink presentation that would have been made -- this is a third Florida-based dura mater producer -- only include ethyl alcohol as a sterilant, so two of the three products that either made or would have made presentations this morning still have no step in the protocol that has any influence on the life of the CJD agent.

DR. ROOS: But despite that, Paul, you are still talking about a 1 in a million risk.

DR. BROWN: No, exactly.

DR. ROOS: I mean we are making it smaller than that, but we are starting off with something that is very

small unless it's a Lyodura situation or unless some manufacturing protocol breaks down, which is a danger, and that's why I think the synthetics and to move over to them would be important.

I am concerned, though, that if we don't have some kind of pressure on the neurosurgeons, that people will kind of continue to practice as they always have been and perhaps do things easy or else be in the prey of the HMO that is going to tell them how to do things in a most cost effective rather than particularly safe way necessarily.

DR. BROWN: Well, inertia counts for a great deal in daily life, but it seems to me that from what we have heard from the three neurosurgeons, there would be absolutely no objection at all to the statement that they themselves are looking for the ideal safe alternative.

I didn't get the feeling that they need pressure exerted on them, that they are themselves looking for these alternatives.

DR. ROOS: I must say I was concerned that bovine pericardium seems to be the popular alternative in this country, and I would have wondered about porcine pericardium or some other animal species or synthetic.

DR. PENN: Well, to put this in some perspective, this is not a topic that anyone in neurosurgery would be

excited about because, one, there is no possibility of getting an NIH grant on a topic like this realistically. It is not something that will promote anybody's future in academic neurosurgery.

It is a very dull topic to most neurosurgeons because a risk of 1 in a million is not the type of risk that we are trying to deal with in everyday life. Everyday life, we are trying to make risks of many percent change for the better for our patients.

So this does not have the urgency that this committee might feel it does, and it will only become an urgency when like there was a crisis with the availability of Silastic, that that would withdraw, for example, something that was very important to neurosurgical procedures, shunting procedures, that would affect our life enormously.

So if you want this done, you had better figure out a way that the FDA can either encourage getting that type of information and encourage the proper studies to be done. Otherwise, we will end up with either inertia or have to, if another crisis like Lyodura comes up, have another committee meeting and ban it.

I mean it seems to me there are some very practical considerations that you ought to go over to get

the type of data that you need to resolve this issue.

DR. TRAMONT: But it also seems to me that the FDA has tools already to begin to address that. They could ask for postmarketing information on any material that is used in place of and including dura mater.

DR. PENN: And right now the compliance for dura mater is less than 50 percent most likely.

DR. TRAMONT: Compliance?

DR. PENN: Compliance for even sending a simple postcard back to the company. And I can tell you that we do not have -- I haven't work in devices for a long period of time -- we do not have very good reporting back from the medical community on device failures. There are lots of them that happen, and you are asking to find something that is very rare.

DR. TRAMONT: So you don't think even a postmarketing tool is going to help at all.

DR. PENN: No. I can think of tools that would get the answer in a few years, but I don't think postmarketing will do that alone.

DR. BROWN: Barbara.

MS. HARRELL: Yes, I have a question. In the absence of CJD, what is the five-year survival rate for patients receiving the dura mater for a brain covering?

DR. PENN: It's unfair because we don't have those figures, but if a baby gets it with a meningomyelocele, that baby can have a normal life span. So that would be the longest case. Obviously, patients who have dura involved with tumors are going to have a very short period of time.

MS. HARRELL: I thought that was real important, you know, regarding the length of time they would be expected, because it would minimize the risk if there was a very, very short expectancy probably.

DR. PENN: Absolutely. That is a good question.

DR. SAWAYA: I am kind of discouraged with the way the discussion has been going. On one level it seems as neurosurgeons we may have failed to convey the potential problems that do occur without using dura.

Just CSF leaking infection alone is likely to be in greater numbers than what the remote likelihood of CJD transfection. That is one aspect.

The second aspect, as a practitioner, looking at the data published and what was presented here today, there was a problem, there was a crisis that was picked up fairly early on with Lyodura. Reaction in this country and others have occurred, and suddenly we see it coming under control.

So I stand back and I wonder why are we beating it any further if regulatory mechanisms or scientific

information has been transmitted, and we have learned from it, and we have done corrective measures, why is that not sufficient, why are we looking at banning dura for other products that have not been studied, whether it's in England or somewhere else? We don't know what happened to these patients. They have not been followed, there have been no series.

So, to go from one extreme to the other is extremely confusing to me.

DR. BROWN: Well, join the club. I can tell you why we are doing it. We are doing it -- well, we are doing it because we have been asked by the FDA to do it. They want good advice. The FDA is being asked to do it because the United States public is not satisfied with anything less than zero risk. It's as simple as that.

We know that zero risk doesn't exist, but they want it anyway. To give you a little broader context, in the past several years, partly because of guidances and advice from the FDA, millions and millions of dollars and product shortages in the blood field have occurred by virtue of recalling lots to which a CJD donor had contributed, and that at the moment is purely theoretical. There has never been a demonstrated case.

So we are destroying all kinds of things even when

something hasn't been shown to occur, and that is what I am calling zero risk.

DR. SAWAYA: I understand this, and that is why I raise the issue, is that we are talking about alternatives that are in no way zero risk, in fact, are in much greater risk.

DR. BROWN: Well, I think by alternatives, you mean alternatives to the dura. Well, this is not a point that came out to me in the discussion, particularly in view of the differences of opinion voiced by the United Kingdom representative and what you just said.

Correct me if I am wrong, but I didn't get the feeling from what we learned from the U.K., that the alternative risks were real and immediate.

DR. SAWAYA: Can I respond to this?

DR. BROWN: Surely.

DR. SAWAYA: You are willing to argue about the concentration of NaOH, and you haven't asked for data on those patients that were treated in the U.K. in terms of publications. We have not seen how many had complications that may be related to the implant, how many are likely to have in the future.

What I am saying here without being picky is that we don't have the data of the alternatives, so how can we

embrace the alternatives?

DR. BROWN: Well, this is why I said initially, join the group. The FDA is constantly put in the position, as are we, of providing a risk-benefit ratio for which we know neither the risk nor the benefit. We do the best we can.

Dr. Steers.

DR. STEERS: I have great sympathy with what you said. I have great sympathy with my American neurosurgical colleagues, and I think perhaps I would like to make two points. Firstly, harvesting of fascia lata graft could be construed as an additional operative procedure. Unfortunately, because it's something that I take for granted, and in the time scale that I had to prepare this talk, I didn't actually have to do a fascia lata graft, and so I was unable to provide photographs for us.

I think Dr. Penn made a very important point, that this isn't a procedure that thrills neurosurgeons and therefore you don't regularly take photographs of what you are doing under these circumstances, but it would have, for instance, cosmetic implication and perhaps I didn't make that clear this morning.

If you are harvesting directly from the tissue underneath the scalp that you are already operating, or from

the fascia of the spine where you are already operating through a current incision, that does not imply additional, if you like, operative procedure beyond that, that one might reasonably do.

If you are harvesting fascia lata, you are making a separate incision from the primary incision through which you are carrying out your procedure, and although that would be an extremely low risk because you are already under anesthetics, and that sort of risk is accounted for, the risk of anesthesia, the risk of prolonged postoperative pain of infection is very, very small from this sort of incision. Nevertheless, it is an additional incision with a cosmetic implication which might have very significant implications depending on the potential career of the individual involved.

I think the other point that is extremely difficult, and I think that it is a point that the committee perhaps will have huge difficulty coming to terms with this afternoon is the current state of research and properly controlled trials on the available synthetic materials, and I think that this point is well made.

I think that there is scope for significant work to be done in this direction, and I think that the point of exchange of which carries the most risk at the moment, the

risk of CJD or a risk of synthetic implant, is an unresolved question, and I think that is a perfectly valid point for Dr. Sawaya to make. I hope that is helped.

DR. BROWN: Right. I agree and what we said before we need additional information, not only on the ability of alternatives to be safe and satisfactory, we also need more information on the risks to human beings from CJD contamination, and we don't have full information on either side, which is unfortunate, but it is almost the rule rather than the exception.

Yes, Leon.

MR. FAITEK: We have heard various manufacturing operations having various techniques for either decontaminating or harvesting or producing the dura mater. We have heard things like lack of a brain biopsy of the cadaver, decontamination, the issue of pooling, and does the FDA have any position on any of these items, and are there regulations regarding pooling of harvested tissue, are there regulations regarding requirements for a brain biopsy for dura mater, and are there requirements and/or specific instructions for donor screening in the FDA, that don't leave it up to the individual manufacturer, but makes it a requirement that they follow this procedure?

DR. CIARKOWSKI: Art Ciarkowski, Center for

Devices.

The control of this at this time consists of the guidance which you have in your packet, which we distributed in 1990, which really stays away from pooling. I mean pooling was identified as a problem, and the guidance pretty much comes close from prohibiting that type of practice.

In terms of the other aspects, we do not require autopsy. I think it is recommended, but it is not a requirement. I think if recommendations were given on that, we would consider upgrading our guidance to include the recommendations of the panel in that regard.

DR. BROWN: The way this was phrased, Question 1 and 2, this is really Question 2 now. I would like to actually get beyond Question 1, which I think has now reached a spinning wheels point.

DR. WHITE: Paul, could I ask two questions that I think aren't spinning wheels?

DR. BROWN: Yes.

DR. WHITE: One, with Silastic, when you do get a fibrous complication from such a membrane, what is the consequence to the patient of that, reoperation, otherwise benign, or is there some other complication?

DR. PENN: No, there can be a complication from the reoperation if there is a big fibrous structure, it can

act like a tumor pressing on the brain, and you can get any number of symptoms from that, that could be due to the damage created by that. It is also very hard to repair because of the fibrous scar.

The other thing is that hemorrhage has occurred with Silastic because of the new membrane that was forming around it, and those were unpredictable stroke-like symptoms.

DR. WHITE: And in the experience of all three of you, could you give us some kind of percentage or prevalence of the various complications of those membranes?

DR. SAWAYA: I avoid using anything that is inert absolutely.

DR. WHITE: So no experience. And your experience?

DR. PENN: My experience is not large enough to really comment. Maybe I have used Silastic about 10 times, but I stopped using it because of other reports of other neurosurgeons, but we do not have the numbers to say that this is any better or worse, say, than a hemorrhage after we do a tumor resection and use normal human dura.

DR. WHITE: And you have no experience?

DR. STEERS: I stopped using Silastic and did a number of years ago when the first reports began to come out

of complications with it, and I have turned to fascia lata graft. Very occasionally, I use a new polyester urethane based synthetic material, which has yet to stand the test of time I think would be the correct way to say it, so I can't give you a list of complications at this time.

DR. WHITE: So will you all guess, I mean is it 50 percent, 25 percent, 10 percent, 75 percent?

DR. PENN: For Silastic, I would think it was in the 5 to 10 percent range, possibly higher, but all the other agents, it may be much smaller than that.

DR. WHITE: Paul, my second question was more to you. If there are some materials that are currently being used that don't have sodium hydroxide treatment, if the risk without sodium hydroxide treatment is 1 in a million, could you put an estimate on what you think the risk would be with the sodium hydroxide treatment? Assuming that it is not zero, it is going to be something less than 1 in a million, do you want to guess at that?

DR. BROWN: I don't think anybody would have a number. All I would say was that it's too small to be worried about.

DR. SCHONBERGER: I have heard the number 1 in a million bantered around a bit, and I assume that you get that 1 in a million because that is the incidence of the

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disease in the United States, but don't forget, dura comes from people who are dead, and if you look at the proportion of the people who are dead who have CJD, you are closer to 1 in 10,000.

What it strikes me about in terms of -- and I agreed with your point that in this discussion we need to make the distinction between what happened with Lyodura and what is happening with the post-Lyodura products, I think that is an excellent point because one way of looking at the data from Japan is that it was very dramatically presented to the world, and we suddenly had 43 dura mater cases, and I suspect from the timing of the World Health Organization decision and the timing of the banning in Japan, that one can't help but think maybe that that publication of 43 cases had something to do with those actions, but in fact, we in a more settled situation can reflect that those 43 cases basically, you know, really reflect the same problem that we had identified in 1987.

The other issue is that it may not be just the sodium hydroxide that is the key preventative step. There is some evidence that I am hearing that there are several companies that don't use sodium hydroxide are not having the problem.

That suggests to me that maybe the problem with

Lyodura has been their rather sloppy -- I don't know what the word is -- that their lack of attention to selecting donors and the fact that they pooled everything together, so if you had one hit, you may contaminate a whole batch.

DR. BROWN: This again is moving into the second question and I really want to get rid of the first one. Frankly, I don't like the first question.

I would say, judging from what we have heard, that most -- we will poll right now -- but my guess is that most people around this table will say none. We haven't been presented with the need, an absolute need for a dura mater allograft under any circumstances. But I think a more reasonable solution to the first question is to say that the choice of whether to use a dura or not is a matter of professional neurosurgical discretion and that the neurosurgeons are urged to use alternatives whenever it is possible to do so. Then, we can get to the second question and find out what the committee feels about minimizing the risk to dura, but that is my prediction.

Is it reasonable to take a poll now on the first question just as it is asked? You may abstain, you may qualify, or you may answer with a simple yes or no.

Question again. For what surgical procedures is there a need for dura mater allograft?

We will start with you, Linda.

DR. DETWILER: You summed it up very well, so that is exactly how I feel. None that I have been presented, but I wouldn't want to take that away because I don't think the experience here, I don't have that experience.

DR. BROWN: Ray.

DR. ROOS: I guess no absolute need, but it seems like it is in use in this country and is beneficial at the moment as far as its use. I agree with your suggestion about an urge to the neuroscience community. I would also urge that we do get data about the alternatives and also that perhaps there be some funding opportunities for individuals in the neurosurgical community to give them a little incentive with respect to these investigations.

DR. BROWN: Gil.

DR. WHITE: Well, I agree none except that I think if we can adequately deal with the second question, that is, if we can minimize the risks, I might say that I would prefer personally to have a dura mater graft rather than some of the alternatives. So I think the two questions, as always, are intertwined, but I would clearly say I am not hearing there are any procedures for which we absolutely have to use dura mater.

DR. BROWN: Barbara.

MS. HARRELL: Ditto.

DR. BROWN: Ed.

DR. TRAMONT: I disagree with none, but I don't think there is any data to be able to answer that question that has been presented to us or that anyone knows about it in this meeting.

DR. BROWN: So abstain?

DR. TRAMONT: Abstain.

DR. BROWN: Leon.

MR. FAITEK: I haven't heard anything here today that would persuade me if I were a patient to take that decision, if I needed the surgery, out of Dr. Penn's and Dr. Sawaya's hands.

Question No. 1 is really not a fair question especially since we haven't done anything or haven't discussed about doing something to minimize the risk in the first place, and those are those various procedures and pooling and deactivation, all of that.

So I am not sure whether my answer is yes or no on this question, but I think my answer would be I would leave it up, at this point, providing all safety issues that can be taken, are taken, that the decision be left to the surgeon.

DR. BROWN: We are going to re-poll on exactly

this. I think, in retrospect, what we should do is poll exactly on this question, for what surgical procedures is there a need for dura mater allograft, and we are going to get some nones, and then re-poll as to whether or not we feel that that decision should be left up to the individual surgeon. Those are two very specific possibilities.

And you have decided that it should be left up to the individual surgeon.

MR. FAITEK: On Question No. 1.

DR. BROWN: Right.

DR. PENN: But you haven't answered yes or no, is that right? As phrased.

MR. FAITEK: I don't know how to answer it.

DR. BROWN: We will just say abstain on that one. Richard.

DR. PENN: I think there are absolute indications for doing it at this stage. And I think that the question that you are asking is ambiguous until it is defined what we are dealing with and what are the regulations we put in.

DR. LESSIN: Do you say there were or were not?

DR. PENN: I said they are absolute.

DR. LESSIN: Could you enumerate those for us?

DR. PENN: Those indications are when the neurosurgeon feels that it is necessary to use that tissue

rather than other tissue available. I am not being --

DR. BROWN: Exactly. That is really not funny.

DR. PENN: I mean that is the point.

DR. BROWN: There aren't categorical situations where you could predict for us that you must use it under these circumstances. I mean it is perfectly understandable. You are the captain of the ship. You are doing the operation, and something happens, and you say we have to use dura.

DR. PENN: I don't want somebody to say, well, it's only if you have a large malignant tumor and you have X number of square inches or feet worth to cover. I mean that is a surgical decision that should remain that way.

DR. BROWN: Sidney.

DR. WOLFE: I would say none mainly just instructed by the experience of eight years in the U.K. where it has been in a sense taken out of the hands. I mean I don't know and we probably don't have any data as to whether occasionally, a British neurosurgeon reached the point where he or she felt that it was absolutely necessary and they somehow or other got ahold of some dura, but I think that the instruction by the government to the neurosurgeons has been don't use it, they haven't, there is no evidence at least in response to a question I asked this

morning that harm has occurred to people as a result of that.

DR. BROWN: I abstain on this question.

Lawrence.

DR. LESSIN: I think there has been substantial underreporting of cases based on what we heard from Dr. Schonberger, and just my clinical experience in epidemiologic reporting, one wonders what the real case frequency or incidence is, if one were able to dig down to the data, autopsy cases, 1 in 10,000, how many patients are being seen in their older years and being called Alzheimer's disease or something else, so I am concerned about that.

I also would echo what Dr. Tramont said earlier, and that is, is this committee going to meet again in five years or some successor to it, again trying to make decisions without data. I have been involved in previous meetings of this type, urged that outcomes analyses and databases be amassed, and they are not. We are back in the same situation that we would find ourselves in time and again, and somehow we should link whatever advice we give to the FDA to an absolute, if not requirement, at least strong, take a very strong position that both retrospective data be obtained, perhaps study the British database, perhaps using HCFA. One question I would ask is when you bill a

neurosurgical procedure, is a dura graft billed as a separate ICD-9 code?

DR. SAWAYA: Duraplasty is, yes.

DR. LESSIN: So HCFA has a big database on this. You could pull out names and numbers and track down these people and find out what has happened to it. So that, you know, a smart epidemiologist -- and I am certainly not one of those, I am just a country doctor -- would be able to get us better information than we have got at the present time.

Absolute need for dura mater allograft? I don't think I am convinced by any neurosurgeons that there is an absolute need.

DR. BROWN: Lawrence.

DR. SCHONBERGER: I will abstain.

DR. BROWN: Raymond.

DR. SAWAYA: Again, I don't know that I have conveyed enough, the continuum that there is between a small defect and a large defect in terms of the physiologic healing process, in terms of if you have infections. That is why we cannot break it down into one procedure can get a dura, another cannot, because it is a continuum.

Overall, I cannot see how dura can not be made available, so clearly my answer is that it has to be made available.

The second part of your --

DR. BROWN: We are going to come on around again.
Bill.

DR. HUESTON: It is an interesting proceeding,
isn't it?

DR. BROWN: Isn't it.

DR. HUESTON: I am fascinated by how quickly we are in one sense willing to throw out the evil we know for things that we don't, and I am concerned to an extent that we had sufficient information whereby we can further manage risks that we increasingly understand with the ideal material, and if one, for instance, says there is no indication for dura mater and bans it, there will be a rash of new applications of completely untested materials, as we have already heard that have a general approval to use as patches being put in a fair number of patients across the United States in which we will listen and watch as CDC and others count up the cases just as with the Silastic, and I am not convinced. I think that there are indications with dura mater, still indicated, and I think in part that is based on what we will talk about. I believe we can further reduce or manage the risk associated with dura mater transplants.

DR. BROWN: The tally for this specific question

is 6 say none, 3 say some, and 4 abstained.

Now we are going to have an opportunity to qualify that on a question that I am including because I want it included, and that is would you prefer to recommend that neurosurgeons avoid the use of dura mater whenever possible, but that the choice should be left to the neurosurgeon, yes or no to that question.

DR. DETWILER: Yes.

DR. BROWN: Ray.

DR. ROOS: There are actually two parts to that question.

DR. BROWN: We are not going to break it down any more. Go ahead.

DR. ROOS: Repeat the question, would you?

DR. BROWN: We recommend that the FDA recommends, all we are doing is recommending to the FDA, that neurosurgeons be urged, whenever possible, to avoid the use of dura mater allografts, but that the decision will be left to individual neurosurgeons.

DR. ROOS: I certainly think that they should be urged to avoid this in the sense that they have the possibility of fascial transplants getting around synthetics that I think would be preferable to this allograft that we are talking about, and if that alternative could be acted

on, I think it would be better.

On the other hand, I think at the moment that I would leave things in the hands of the neurosurgeons to kind of get their field in order and get appropriate assessments to what the alternatives are, how well do they work, and if the work well, to carry on with the alternatives and synthetics, so I guess a yes to both.

DR. BROWN: Gilbert.

DR. WHITE: I would say no to that, and I guess my reason for saying no is that again I think what we ultimately say depends on what we would like to see done to ourselves I suppose. I guess if a neurosurgeon came in to me and say we are going to have to do a dura mater repair on you using an unpooled, untreated human-derived dura mater, I would rather have Silastic.

DR. BROWN: So would I.

DR. WHITE: On the other hand, if it were a treated, nonpooled dura mater, I would rather have dura mater than silastic or bovine pericardium or whatever. So my answer is no. I mean I am just explaining my "no" answer.

DR. BROWN: That is exactly what we should have done, which was to discuss the second question before the first one. Barbara.

MS. HARRELL: Yes.

DR. BROWN: Ed.

DR. TRAMONT: Yes.

DR. BROWN: Dr. Faitek.

MR. FAITEK: I would have to say no for the same reason that Dr. Gilbert said.

DR. BROWN: Richard.

DR. PENN: Yes.

DR. BROWN: Dr. Wolfe.

DR. WOLFE: I would say no for I guess the different reason is that one way of interpreting that would be mainly a copout on leaving it all to the neurosurgeons. I mean we obviously have evidence that the neurosurgeons can be convinced to move more towards using autologous tissue if told to do so, and if the interpretation, which I can easily see it being, of this yes vote is the neurosurgeon is the final arbiter and will take it on a case-by-case basis, it is entirely possible that there will be no shift in the proportion of cases in which dura mater is used.

That is why I am really asking a question. Do you think that if the FDA were to make a recommendation to neurosurgeons in this country, use alternatives, primarily autologous alternatives whenever possible, but if you really think you need to use dura from cadaver, use it, do you

think that would in fact have or not have an impact on the practice of neurosurgery in this area, what do you think?

DR. PENN: I think it depends how it is done.

DR. WOLFE: How what is done?

DR. PENN: How that type of announcement is made and with what factual basis. If, for example, the FDA wrote an editorial in a neurosurgical journal on these issues, I think it would affect behavior to some degree. It wouldn't completely affect behavior, but it would have some effect, and it would also have medical-legal implications which will affect behavior.

So I don't think that it's a hopeless situation with changing our behavior, but I do think that we all sit around this table disagreeing about odds for things, and that as long as that is the case, it may be hard to affect behavior.

DR. WOLFE: The addendum on this is the FDA is fond of saying, and legally it's correct, we don't regulate doctors, we regulate drugs, or in this case, we don't regulate doctors, we regulate medical devices. So in the absence of any FDA regulatory authority on the device itself, FDA has no sway from a legal perspective, from regulatory perspective over what the neurosurgeon does in that instance, and can only rely on the good faith or you

will raise the issue of the possible malpractice implications to change behavior.

So I guess I am concerned about the way in which it would be done. I mean if it were a strong exhortation that even though we do not have authority to regulate neurosurgeons' behavior, we strongly recommend that whenever possible, a neurosurgeon uses an alternative, preferably autologous, until such time as synthetics have been shown to have more evidence than they do right now, it will be different, but I don't think that is how things work.

DR. BROWN: So you would vote against.

DR. WOLFE: Right.

DR. BROWN: I vote for mainly because I already have an idea what I would like to see Question 2 wind up as, so I pass on again to Lawrence.

DR. LESSIN: If the American Academy of Neurological Surgery or some similar august body of professors could come up with a series of guidelines that would answer the question that understandably Dr. Penn wouldn't answer for us here today, but at least printed guidelines on what are the appropriate situations in which to use treated dura -- and from what I have heard today, it ought to be 1 normal sodium hydroxide treated dura, and not open to the manufacturing process of choice -- then, I would

vote yes, I would leave it up to surgeons, but all the neurosurgeons that practice in this country are not of the same of the same caliber as the professors that are sitting around this table, and I think in most cases, judgment is good, but not in all cases.

So in the presence of guidelines, I would vote yes; in the absence of guidelines, simply giving a free hand to the neurosurgical community under any circumstances to make these decisions as they wish, I would have to vote no.

DR. BROWN: I am counting that as a negative.

Larry.

DR. SCHONBERGER: I vote no, as well. I agree with the way Dr. White expressed it earlier, and I would like for the decision -- we should express that the decision be made by the neurosurgeon with the knowledge of what we are talking about here, that there really is no absolute safe product, that all these products are going to come with some risk, although they would not have to be a risk of the magnitude that we have seen with Lyodura.

They also should understand that just because FDA allows this product to be used, that it isn't necessarily totally risk free, and finally, because of the issues of the need for information, given that we have put this in the hands of the neurosurgical community, it would be nice if

some organized effort could be made to gather better data on the complications of these products.

DR. BROWN: So I count you as a negative.

DR. SCHONBERGER: Correct.

DR. BROWN: Raymond.

DR. SAWAYA: I have a problem with the questions because half of it my answer is yes to, the other half is no. The "yes to" is that the surgeon has to decide, and I am glad that there is some support for that position. The "no to" is that we are collectively giving a recommendation for an "alternative," quote, end quote. We don't know what the alternative is. So it is going to come out as a very confusing recommendation that I cannot endorse.

So if I say no to your vote, then, I am voting against the surgeon having the choice of choosing what is right, and if I say yes, then, I am condoning something else that I have a problem with. So I wonder if you are going to be able to break it in two.

DR. BROWN: Yes, you get a half.

DR. BROWN: Bill.

DR. HUESTON: Given additional risk management procedures that will answer Question No. 2, I vote yes.

DR. BROWN: All right. Perhaps it wasn't the best question and we may have to come back to it, but I think it

ajh

is time to come to grips with Question 2 for which I assume there is going to be much clearer alternatives.

The tally, incidently, on that was 7 in favor -- 6 1/2 actually, 6 1/2, and 4 1/2 for disagreement, and no abstainers.

As I said, don't despair, we may come back and formulate a question that everyone on the committee will be comfortable with, with respect to the first question.

But the second question, let's just assume that dura is used, what measures or safeguards should be used to minimize the risk of CJD transmission. I am going to focus this discussion fairly tightly, and up to the first issue is the source. We are going to deal with the source as a means of minimizing, that is to say, donor selection and criteria used for donation of dura mater.

Barbara.

MS. HARRELL: The question that I have is since Lyodura products have been banned, have any of the infected donors come from the U.S.?

DR. BROWN: Any of the?

MS. HARRELL: Infected donors.

DR. BROWN: Infected donors.

MS. HARRELL: Have any of the infected donors, the donors who have donated the dura mater, who have infected

other recipients?

DR. BROWN: As far as I know, the answer is no, there is no case in which a U.S. donor, processed either here or elsewhere, has caused the transmission of disease.

What would the committee like to see as criteria for donor selection or exclusion?

DR. TRAMONT: I will start that one. I would say no dura should be used without a concomitant biopsy of the brain. After all, to get the dura, you have got to open up the cranium.

DR. BROWN: Right.

DR. TRAMONT: Biopsy of the brain is just a little needle punched into the brain.

DR. BROWN: Good. I am glad you brought that up, and I personally couldn't agree more. I think it is appalling that a dura mater should be removed from a brain without someone having taken a thumbnail size piece of tissue and looked at it, so I agree that is one of my own rock-hard, absolute criteria for the future.

Linda.

DR. DETWILER: How about testing for the abnormal, the protease-resistant PrP?

DR. BROWN: I think that is an excellent idea, and I would also vote in favor of that. There, we may get into

a little more problem, but we can discuss that, but again, these now are two very specific procedures that we can either highly recommend or require, or discuss, but we will have time to discuss them.

Sidney

DR. WOLFE: I mentioned this earlier, the great variability in competence of those looking at the slides in terms of neuropathology. The number of cases we are talking about isn't so huge that somehow or other we should at least put in the idea that someone who has some good knowledge of neuropathology look at it, because it is possible that the average pathologist looking at slides might blow it even if you did a brain biopsy.

DR. BROWN: I think most average neuropathologists would not, but I think agree for the third point that this should be reviewed and examined by a neuropathologist with the approval, let us say, an FDA-approved neuropathologist.

A neuropathologist would already be far along, but yes.

MR. FAITEK: Dr. Brown, could you explain what that second procedure was?

DR. BROWN: Leon asked what the immunologic procedure was. That is most simply a procedure in which a section of tissue is fixed and then stained with an antibody

that detects the prion protein. The presence of prion protein is, to all intents and purposes, pathognomonic of the disease and a little less secure, but still pretty good. Its absence will give you very strong presumption that the disease doesn't exist. A combination of a negative test for that and a negative neuropathology will minimize the possibility of CJD being present in the brain to virtually nothing.

Ray.

DR. ROOS: I don't think we should deemphasize at all the importance of an appropriate interview and to the history of individuals with respect to whether they are demented or have some neurological signs, or whether there is a family history of neurological disease.

I am concerned about sourcing from foreign countries especially the quality of the interview process and medical records in foreign countries, and I think we should be cautious about that and have high standards with respect to that.

I am a little concerned about the issues related to pathology because --

DR. BROWN: Could we stop a second for the point, because the pathology and the interview -- and this is another, as far as I am concerned, major point. I don't

think anything would be lost if we simply specified that all donor material -- maybe I will get a reaction to this -- but so far it looks as though U.S. donors are close to being adequate to demand.

And I agree with you, when we get outside the confines of this country, quality control -- which is not to say the other countries don't have quality control -- but our problems of getting that quality control to our satisfaction become very much larger. So I am just not sure that we really need dura mater from Ukrainian cadavers.

DR. ROOS: At least I think at a minimum there should be an evaluation with respect to where the sourcing has come from and the quality control with respect to that. Maybe we are going to end up with the same answer.

I am a little concerned about the histopathology issue because I kind of get bogged down in my mind as to who these neuropathologists are and how much tissue do you want to have screened, and it concerns me just a little bit.

In other words, do you want one piece of the cortex and what cortex and how big and how many slides?

DR. BROWN: I am trying to make it in my own mind as easy on the companies as possible and still be secure, and based on our 300 cases of sporadic CJD at the NIH, a small piece of frontotemporal cortex is 99 percent secure.

That's pretty good. That is 1. Two, I would estimate or I would suggest that a neuropathologist, or two, or three, perhaps one for each company.

I don't anticipate neuropathologists from all over the country making judgments on this. I assume that a company would have the ability to contract for not a huge amount of money these kinds of examinations. We are going to probably get into money a little bit later, but that would be my idea, that there be a small number of neuropathologists, perhaps one for each company that wanted to use dura, and they would be looking at brain after brain after brain, but not a full-scale autopsy, just one piece, a postmortem biopsy.

DR. ROOS: My only other concern, which really has to do with the next step here, is the collection of the dura and what comes first, and I like the idea about sampling on the brain. We should watch out about the sequence of how things are taken from the cranial cavity, because I would feel very badly if the same instrument that was used to take a piece of the brain then removed the rest of the dura.

DR. BROWN: Yes, I would think the dura would have to come first.

DR. ROOS: I think that kind of the next step -- just to jump ahead -- is I think there should be a protocol

in the same way that the slaughterhouses perhaps now have a protocol about how you take tissue from an animal, and if you leave the central nervous system for last or you don't take it.

DR. BROWN: You are suggesting basically an autopsy or tissue protocol, right, an autopsy protocol for getting tissue. We also have mentioned it, but have not used it so far, and that is I think everyone would agree that individual donors have to be processed in their entirety as individuals, that is, there can be no opportunity for one donor tissue to touch another, which is what the Tutoplast people now do, and I would suggest that be an absolute criterion also to be met for dura to be acceptable.

The interview, it seems to me, we ought to -- I mean the FDA is all over the blood industry in terms of, you know, the questions that are asked, and so forth, and so on, but the allograft industry pretty much goes on their own, and it seems to me there ought to be a satisfactory standardized interview protocol also, so that we know a set of questions is being asked and answered.

DR. SCHONBERGER: At least the questions that were used for the blood probably would be an appropriate --

DR. BROWN: Yes, exactly, at least as thorough as

it is for blood donation. I mean you ask somebody -- I mean you know what a problem is, you have all kinds of people asking questions, and they say, oh, do you have any dementia in the family, and someone says no. Well, you go on, that's fine, I don't have to ask anymore questions. Well, you ask a different question, has anybody had any mental problems or any nervous problems in the family, and they say yes.

So interviews are important, and they can probably be very good excluding, a basis for exclusion and selection, but they have to be done right.

Yes, Gil.

DR. WHITE: I agree rock hard on the biopsy. I mean I think that is crucial, and I agree with making sure we are asking the right questions although I think a lot of people will not answer a question, and I don't think that questionnaires are great ways of screening.

DR. BROWN: Oh, nothing is absolute. All you are doing is accumulating minimizing steps.

DR. WHITE: I understand, I agree with it. I guess I would wonder, I would like to throw something out and just see the response of the committee. I wonder how the committee would feel about recommending donors less than the age of 50 or excluding donors over the age of 50.

DR. BROWN: Actually, you know, it would be much

safer the other way around. If you excluded donors under the age of 80, everybody who is going to get CJD would have already died.

DR. WHITE: Well, okay, throw that out.

DR. BROWN: We will put it down for discussion, age brackets.

DR. WHITE: You may want to modify the age. I don't know if that is the right age.

DR. BROWN: The problem with the age is we still don't know, in a patient that dies at the age of 60 of sporadic CJD, how long before his brain is going to be infectious. I am afraid it is a question that we will not be able to answer, but there is indication from experimental work and a little bit of indication from human work that that incubation period can extend, not the incubation period, but the period at which infectivity is present can extend for several years before the onset of clinical disease.

DR. WHITE: For several or seven?

DR. BROWN: Several. If you judge by iatrogenic disease, it may be -- experimental evidence suggests about halfway through an incubation period, and we know that the incubation period for growth hormone iatrogenic disease is 15 to 20 years. Half of that is about 10 years. That is a

speculation. There isn't any hard evidence. It's analogy. But it is certainly infectious before a patient becomes ill for sure.

DR. WHITE: I mean 80 percent, what we heard was that 80 percent of donors currently from the first company were over the age of 50.

DR. BROWN: Right.

DR. WHITE: So this would obviously have some implications, but I would still be interested in opinions from the --

DR. BROWN: Are there any other criteria that people have thought of at the donor level, where it all begins? Linda.

DR. DETWILER: I guess I have a question. I think there is some now evidence or accumulating evidence in animals that perhaps there is some kind of genetic makeup of the animal that might even preclude them from showing clinical signs, yet, there is evidence of the protease-resistant prion in the brain.

Do you think that is theoretically possible?

DR. BROWN: I think at this point, on molecular genetic test will help us, period. I mean we could go on and on, but I think that is a fair statement.

Other criteria that people might want to talk

about?

DR. WHITE: I assume the questions not only include mental health, and dementia and those sort of things, but also should include previous administration of growth hormone.

DR. BROWN: Sure, right, the same sort of thing that blood donors are subjected to. I have never understood actually how allograft people had flexibility more than the blood donation people, but that is the case, and I don't think it should last.

A little arithmetic tells you that each donor is worth about \$2,000 to the company, \$2,000 a head, roughly 4- or \$500 per graft, roughly four or five grafts per dura.

So a company is selling the product harvested from each individual for about \$2,000. I would guess that if done properly, the neuropath examination, and even an immunostain would probably not add more than a couple of hundred dollars to each donor. So instead of a couple of thousand, you might be talking -- well, let's make it terrible -- let's say 2,500, which would, divided by 4, the extra 500 would make those grafts about \$100 more expensive. They are already 4- to \$500.

I am not sure that would put companies out of business, I doubt it, especially if the cost were passed

along to the recipient. I mean that is a very practical matter, but we are not talking about an extra thousand or \$2,000 to make these examinations.

A single piece of brain tissue put through an automatic processor, fixed for standard hemotoxylin and eosin examination, a pathologist wouldn't have to spend more than five minutes looking at that, and if they charge more than 100 or \$200, they are grossly overpaid.

So I think it is a practical thing. We are not talking an ivory tower here.

Yes, Linda.

DR. DETWILER: The immunostain for us -- and we do those on routine -- it is \$8.00 a slide.

DR. BROWN: Bingo.

DR. WHITE: Another possible thing would be paid donors. I don't think any company currently uses paid donors, but we may want to make a statement about that, as well, that paid donors should be excluded or there should be no whatever.

DR. BROWN: And as I understand it from this morning, I think the question was, and the Tutoplast people said that their donors were not paid, as I recall.

DR. WHITE: That is correct.

DR. BROWN: So I will put down here no paid

donors.

Yes, there is a Tutoplast question.

MS. OSTER: First of all, the PrP test, is that an FDA-approved reagent or kit, since we are required to have our testing done by CLIA laboratories for infectious disease?

DR. BROWN: I suspect it is not an FDA-approved kit, but I suspect that it could be very quickly approved under the circumstances.

The question is there are antibodies around. It is not a single antibody. There are any number of antibodies that can be used, and any number of laboratories has them, and they in fact are commercially available.

DR. CIARKOWSKI: The kit wouldn't necessarily need to be FDA approved since it wouldn't be in interstate commerce.

DR. BROWN: I am sorry?

DR. CIARKOWSKI: The test wouldn't need to be approved by FDA. I mean if a laboratory is doing it as a service for the company, it wouldn't need FDA clearance.

DR. BROWN: What about if the company itself did it?

DR. CIARKOWSKI: FDA only distributes those kits that are distributed, you know, for doing tests. If the

company decides to do it themselves, or if another company provides a service, where they are doing a test, FDA does not clear those products.

DR. BROWN: The FDA does not what?

DR. CIARKOWSKI: Approve those products.

DR. BROWN: They don't approve them.

DR. CIARKOWSKI: That's right.

DR. BROWN: Does that mean they disapprove them? They don't regulate them.

DR. CIARKOWSKI: We don't regulate them.

DR. BROWN: So you could pay attention to it even though it's an unregulated reagent, I mean you could say that's good, right? What you are telling me is that you would like to send a kit if we decide that an immunostain is a good thing, the preferable procedure would be to have an FDA-approved reagent, which would then be distributed to the company?

DR. CIARKOWSKI: I am just saying that for these tests, FDA does not actively regulate all laboratory tests. We only regulate those specific tests that are distributed by manufacturers. If it is a service or if a company doesn't sell, FDA is not getting involved in regulation of those.

DR. BROWN: So in the context of today's

discussion or subject, you would be comfortable if the company used a widely recognized satisfactory reagent.

DR. CIARKOWSKI: That is correct.

DR. BROWN: Without having to come through the kit mechanism.

MS. OSTER: And briefly on the issue of paid donors, right now that is currently illegal in the United States according to the UNOS Act that was enacted a few years ago, and thirdly, on the donor screening, Biodynamics feels that that is a very "regulated," quote regulated practice that we and several tissue banks across the United States use through the intervention of the AATB and the standards that they provide.

There may be some small mom and pop organizations out there that are doing things that could be questioned, and I think Ted can attest to this -- we are very proud of the fact that we have piggybacked on many of the elements of the bloodbanking industry, and we practice those as thoroughly as we possibly can.

DR. BROWN: Thank you.

Are there any other suggestions about criteria to be used for donor sourcing? Anybody on the committee first. Yes, Leon.

MR. FAITEK: There may be a case where a donor

received an implant, but the history can't be traced. There might be a criteria involved that the time of the implant is at least 20, 25 years before.

DR. BROWN: That is, for example, the hypothetical situation where a patient who had received a dural graft is now donating?

MR. FAITEK: Or a dural transplant or something else.

DR. BROWN: I don't think the Red Cross has any duration criteria. That is to say, if you have been given growth hormone at the moment, it doesn't matter whether it was 5, 10, or 30 years ago, you are excluded. It is a blanket exclusion.

MR. FAITEK: Automatic exclusion.

DR. BROWN: I mean in time that will probably be relaxed, 40 years or 20 years from now, when we have had no cases in 10 years, then, I would guess that when you got it would be important, but at the moment we are still finding cases.

DR. LESSIN: Did I understand that currently, dura is used in 20 percent of neurosurgical procedures?

DR. PENN: No, 1 percent.

DR. LESSIN: One percent.

DR. PENN: In Japan, there was a very high figure,

but I think 1 percent would be a fairly high number.

DR. LESSIN: So people that have had a laminectomy or cervical disk operation, it is unlikely that they --

DR. PENN: No, that is the bulk of neurosurgery practiced now, about two-thirds, that is not used for that situation.

DR. BROWN: Well, what we have at the moment are the following criteria, and if everyone on the committee agrees, we can poll for whether or not these would be satisfactory criteria, and these -- actually, we won't poll it now because we have a second issue to deal with, which is inactivation procedures, but at the moment what we have ideally is: an individual who is unpaid, for whom an interview has been conducted using an FDA-approved protocol, an autopsy in which the dura is removed before a piece of brain is removed, a small piece of frontotemporal tissue fixed and examined for the presence of spongiform encephalopathy by a qualified pathologist, an immunostain for PrP on the same tissue -- that is the beauty of the fixation, you can do this on the same piece of tissue that has been looked at by the pathologist -- and that the individual specimen should never be in contact with any other specimen.

Those are the source criteria.

Barbara.

MS. HARRELL: Would you want to add to that, that the individual specimen would not come in contact with any fomite also?

DR. BROWN: With any?

MS. HARRELL: Fomite.

DR. BROWN: As far as we know, fomites don't have anything to do with the transmission of CJD.

MS. HARRELL: Indirect surface instrument used on another specimen?

DR. BROWN: Okay. That, I understood when I said individually handled, that there would be no possibility of cross-contamination. Maybe that is a better way to put it.

I would propose that set of requirements as being an absolute minimum for the use of human dura mater.

MS. HARRELL: Were you not going to include the country of origin of the donor?

DR. BROWN: Oh, yes, we also put that, U.S. donors, unpaid U.S. donor.

DR. SCHONBERGER: Maybe we should modify that to allow FDA some flexibility to add some other countries depending on some process -- I mean certainly Canada or the U.K. might not be in the same category.

DR. ROOS: There may be somewhere in the United

States that isn't acceptable from a quality point of view, so you want the source institution to have appropriate standards, to meet those standards.

DR. BROWN: How would you want to phrase that for advice to the FDA?

DR. DETWILER: Countries that have equivalent standards?

DR. BROWN: Ray was just saying he thinks maybe some places in the U.S. don't have standards as high as Romania, so we have to deal with that.

DR. ROOS: How about just appropriate, that the interview and collection process would meet appropriate standards as seen fit by the FDA?

DR. PENN: I think that leaves too much wiggle room.

DR. ROOS: I mean the FDA is going to make it specific probably and look over -- I mean they have to look over the sources from the pharmaceutical companies that have this material.

DR. PENN: But if it's in the country or maybe Canada, too, they can inspect. If it's foreign, really foreign, it is not going to be a practical thing that they can do, and it leaves it open for companies to get those sources, and not have them inspected in a practical way.

DR. BROWN: Can I ask the FDA itself, someone who is present, how they would -- you get the sense of what we want -- how would you like it phrased? That is to say we would like the selection of the donor, the interview, all of these things which have to be quality controlled, we would like that to be done. Is there any way that you would like that suggested?

DR. HELLMAN: I was going to suggest that we have appropriate criteria, but perhaps Art Ciarkowski can give you specifics.

DR. CIARKOWSKI: We do have the authority to do inspections in foreign countries. If a certain threshold were established, we could obtain information from those countries in which we can do inspections.

DR. WOLFE: The fact is that there are lots of data showing that for companies manufacturing prescription drugs, and so forth, that the odds of being inspected are much lower in a foreign country because of budgetary reasons. So you have the authority, yes, but the budget precludes that from actually happening, so I think that is a risky thing to do.

DR. BROWN: Shall we say an unpaid U.S. donor with exceptions if necessary?

DR. HELLMAN: It might be helpful if the committee

could draft some appropriate criteria that would allow use of donors outside the U.S. In other words, if there were standard criteria that could be developed, but because in the last analysis, compliance might be difficult.

DR. BROWN: I would suggest that the committee not be given that responsibility, but that we charge the FDA to establish, okay --

DR. HELLMAN: That's fine.

DR. BROWN: -- a group that will draw up such criteria.

DR. WHITE: Paul, don't forget donors over 100.

DR. BROWN: Right, donors over 100.

DR. SAWAYA: How about the term equally verifiable?

DR. BROWN: I am sorry?

DR. SAWAYA: Equally verifiable.

DR. BROWN: With respect to what?

DR. SAWAYA: To history and histology, and so on.

DR. BROWN: Equally verifiable, that is to say, no matter what the source country, whatever.

DR. SAWAYA: In terms of the data.

DR. BROWN: I think we are going to have to trust the FDA to act responsibly given their -- we are re-charging the FDA. The FDA is charging us, and now we are charging

the FDA, and there is no reason why members of the committee, for example, in the field couldn't be asked by the FDA to participate in that kind of protocol for donors, but the sense, in any case, is that the donor has to have exclusion criteria that are not less rigid than those used currently by the Red Cross. I think that is a sort of fair minimum.

Let's move on to things that we can do to grafts that will make them even safer, assuming they are infectious.

Who wants to start that? We have all heard about sodium hydroxide. Do we want to stipulate, for example, that exposure to 1 normal sodium hydroxide for an hour be included as a mandatory step, or any other chemical, or how do you want to deal with that?

DR. WHITE: I would agree with that. I think we heard this morning also that maybe peroxide is useful for something else, but peroxide is not going to be useful for this, and shouldn't be --

DR. BROWN: No, peroxide, we already know is not a chemical that has much effect on these diseases.

DR. WHITE: I wholeheartedly support an hour's worth of sodium hydroxide, 1 normal.

DR. BROWN: Have the neurosurgeons present, are

they aware of having used sodium hydroxide treated grafts, and are they as satisfactory as grafts that have not been treated with sodium hydroxide?

DR. SAWAYA: The one I have used were not treated.

DR. PENN: And I haven't, so I can't help you with that.

DR. BROWN: You have not used any treated ones, neither one of you have used a --

DR. PENN: No.

DR. BROWN: -- have used a Tutoplast graft in the past seven years?

Where are you selling those things?

MS. OSTER: Where do they live?

DR. BROWN: Are they all in quarantine?

MS. OSTER: Across the United States.

DR. BROWN: So two out of two -- zero for two present have not used Tutoplast grafts.

That is actually a question I assume that the Lyodura people now elsewhere in the world, and Tutoplast, have not had massive complaints about the usability of sodium hydroxide treated grafts. I mean there have been no feedback that these really are a little brittle or they don't work quite as well?

MS. OSTER: No.

DR. BROWN: Well, that's good.

DR. DETWILER: Paul, I don't know about the suggestion, maybe wording that sodium hydroxide or if a company can show that another process is equivalent in inactivation, so that if something comes down the road, it is not locked in?

DR. BROWN: I think we can add this as a kind of postscript. It seems to me that sodium hydroxide is demonstrable, it doesn't hurt the graft evidently, and it works. I think in this discussion, which is all being transcribed, we open the door to continuing experimentation to see whether or not other chemicals would be as satisfactory or even better as we heard today.

DR. ROOS: Another point about this material -- and I am not exactly sure how I feel about this, I would love to see it, but I don't know whether it's feasible -- and that is I was attracted by the first company's presentation that they actually save a small amount of tissue and bank that as a sample.

From a public health point of view, it is certainly very valuable in the sense that if Larry wanted to know whether that transplant back some years ago really caused disease, we could go back to that source.

I don't know whether that is unusual practices in

the implant and transplant world, and I just raise that up for discussion.

DR. BROWN: It was certainly standard practice for growth hormone. I would ask the Tutoplast representatives whether that would pose a problem too quickly to store a little sarsted [ph] vial with a fragment of dura mater in it, or perhaps you already do that. I guess you said you did. Would that pose an industrywide problem to require archiving a fragment of all the duras that left?

MS. OSTER: It is certainly not a problem for us because we currently do it. We have since we started here. I would think it would not impose a problem because they are probably doing sterility testing or something on small portions that they are removing to represent the tissue through the process.

DR. BROWN: So we will add archival storage. It probably wouldn't have to be each graft. It should be each donor.

DR. WOLFE: FDA has the authority now, and has exercised it a few times, to require a patient registry. It is one thing that as described, only about 50 percent of the implanting surgeons wind up sending stuff back to the company, but there is no reason why there shouldn't be a registry of every patient in whom this is implanted. It

could be used for a whole number of reasons, not simply the notification of some poor person that they had gotten a piece of dura from someone who turned out to be contaminated, just in terms of followup, epidemiology, and so forth. The number is not so staggering that that should be avoided. I think it is important for FDA and everyone else to know.

DR. BROWN: So a registry of recipients.

DR. WOLFE: Recipient, patients, not doctors, because things previously have gotten back to the level we know who we sold this to, but then the doctors don't --

DR. BROWN: Who should keep this registry?

DR. WOLFE: The company.

DR. BROWN: Does that pose a problem? I mean the company is not going to have access to the individual patients. That will require that each time a graft is used, that the neurosurgeon make a note and see that the company itself is notified. Is that a problem for neurosurgeons, is that gilding the lily?

DR. PENN: It probably won't get done unless you have some enforcement mechanism attached to it.

DR. BROWN: It's like a reportable disease, measles, for example.

DR. PENN: If they couldn't sell it without

getting that back or get reimbursed without getting it back, they will get it back through the nurses, not the neurosurgeons.

DR. SAWAYA: I agree. In addition, you know, the company sells the graft to the hospital, they don't see it to a specific patient, so it is really more the hospital and the physician's responsibility more than the company.

DR. WOLFE: Right, but they still can get the data. I mean they know who was the recipient.

DR. BROWN: The growth hormone also was distributed to clinics rather than to -- often the individual doctor's name was on it, but he wasn't necessarily the one that gave it. I mean there would be a whole clinic full of doctors.

So, yes, certainly it is desirable. Maybe we should put that in as a desirable rather than a mandatory. It has less to do with safety than with assessing and analysis after the fact.

DR. SCHONBERGER: You might even want to go further and ask that at some point, you know, that a periodic survey of the vital status of these patients to make sure they haven't died of CJD would be indicated.

DR. BROWN: Well, among other things, CJD is not a reportable disease in this country.

DR. WOLFE: That's all the more reason to do that.

DR. SCHONBERGER: That is why I am suggesting that it be done in part, because it would be a way of specifically going after --

DR. BROWN: Maybe the CDC could make a major push and get CJD to be a reportable disease.

DR. HUESTON: That might decrease reporting.

DR. BROWN: Sorry?

DR. HUESTON: Making it a reportable disease might decrease reporting.

DR. BROWN: Is that what generally happens when you require a disease to be reported, it is not reported as much?

DR. HUESTON: There are multiple examples from around the world.

DR. BROWN: How about this country?

DR. SCHONBERGER: I think a focused study on the specific group that you know have received the product, and you want to know what happened to them, is perhaps more appropriate than to, because of this problem, to suddenly make the disease reportable throughout the U.S., which of course gets reported frequently to CDC, as you know, through death certificates.

It does not handle this particular problem. There

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is really no ongoing surveillance in an active way, which is what I am making the suggestion, in the United States for dura mater associated cases to be reported. It seems to me that the entire process is dependent on passive reporting for surgeons and neurologists to recognize the problem and report it.

Now, they did do that in Connecticut for that first case that you showed, but there is no systematic way of getting at this problem, and that is why I was indicating that industry has a list of the people who have received their product. If we can perhaps throw in there some point where you can check what happened to those people, and in fact CDC would be very happy to help with that process if the names were available.

DR. BROWN: Can we still leave as the desirability for --

DR. SCHONBERGER: Certainly.

DR. BROWN: -- a registry to be available?

DR. SCHONBERGER: I am basically agreeing with Sid on this. I think it is the way to go.

DR. BROWN: Is there a consensus on these measures that we have suggested? Will.

DR. HUESTON: May I just add one other thing, and that is that the compliance is extremely important. I think

that was pointed out by several of our people here.

DR. BROWN: Yes, enforcement and compliance.

DR. HUESTON: So a compliance plan needs to be part of this, and that doesn't necessarily mean that -- obviously, the manufacturers are part of that, and I think we had some presentations of some of the quality control in place. We also had some evidence of some -- I think they were just referred to as mom and pop organizations for which we know very little about their recordkeeping, and I think at times we leave giving a massive recommendation, but without recognizing that if there is no compliance, it essentially is ineffectual.

DR. BROWN: Yes, and this again I think will be -- yes, that is a word that of course it's a buzz word, I don't use it very much, but the FDA I guess uses it quite a lot, and yes, of course, anything that is recommended, if it is simply recommended and forgotten about, it is pointless, so yes, to the degree the compliance can be achieved, it should be. Again, I guess we could probably use the example of the Red Cross where compliance is checked on and surveyed, as I understand it, on a fairly regular basis.

DR. WOLFE: Could I comment on that? I mean the current guidance does not have the force of a regulation, and it states right in it this is not a regulation, which

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means in a sense if you are the compliance people, you have a harder time doing something for violation of a guidance than of a regulation, so I guess I would just urge that to whatever extent is possible, that the decision that FDA makes on this is turned into the form of a regulation, so that compliance is more likely as opposed to less likely.

DR. BROWN: I agree and that was my viewpoint, that this be a mandatory regulation, and not just a recommendation.

Given these regulations, shall we re-poll on Question 1 or is that necessary?

DR. PENN: Are we absolutely clear on which of these recommendations you are putting down as regulatory that we are asking for?

DR. BROWN: All of them.

DR. PENN: But we had some that had question mark, about other countries, some that -- to make the record absolutely clear, could you say that the committee wants these following regulations, and just list them quickly for us, if you would?

DR. BROWN: I will try. The first regulation is that an individual donor not be paid. The second regulation is that there be an interview with specific protocol questions to be designated by the FDA, and not to be less

rigorous than those already in effect for the Red Cross; that the criteria for the donor selection, if from another country, be made equally verifiable by the FDA; that in the course of the autopsy, the dura should be removed before the brain is cut, that a piece of frontotemporal cortex about the size of the -- well, about a centimeter by centimeter, centimeter cubed, should be removed and fixed for neuropathology examination and immunostaining by a qualified pathologist; that from the beginning of the first touch of the dura, that the dura will be handled individually with due regard to the avoidance of cross-contamination including cross-contamination by instruments; that there be an archival storage of a small fragment of dura from each donor, and that the dura in the course of processing be exposed for one hour to a concentration of 1 normal sodium hydroxide with an option for the use of other chemicals in the future if they should be found as or more satisfactory; and that all of this is subject to compliance.

Yes, we have an FDA representative.

DR. ALPERT: Yes. This is Dr. Alpert from the Center for Devices, Office of Device Evaluation.

I think that there are two mechanisms that might be useful for the committee to consider. I am not sure that regulation is exactly what you are looking for in the sense

of how to get the controls in place that you are concerned about for donors.

For example, in the newly proposed tissue program, there are in fact both donor screening suggestions, as well as Good Laboratory Practice and Good Clinical Practice type considerations where recommendations of this sort can be considered as the appropriate laboratory pieces for certain kinds of products.

If the dura mater were to remain a device, we have another mechanism which we call "special controls," where we can specify the kinds of testing and the way in which a product needs to be evaluated and prepared that can be part of the oversight of a premarketing authorization or a marketing authorization.

DR. BROWN: Can I cut you a little short, Dr. Alpert?

DR. ALPERT: Yes.

DR. BROWN: I think that is useful to know, but what we want you to know is that no dura should be used in this country without these criteria having been fulfilled and we leave it to the FDA to accomplish that in any way it sees fit.

DR. ALPERT: That's great because what I was responding to was the consideration that there would be a

regulation necessity. I think we have other tools.

DR. BROWN: Okay. Good.

DR. WHITE: Paul, one other comment. I looked at a couple of these. It looks like some of them have lot numbers, but some of them don't. I think if we are going to talk about tracing, we have to make sure. It's a minor point and I am sure addressable, but we need to make sure that these things are identified by some identifier number.

DR. BROWN: Right. So each donor shall have an individual lot number, and the archival storage of a fragment of it.

DR. WOLFE: Can I just make a comment? In reinventing the regulation of human tissue, the document that FDA put out, it says, "Thus, some products, such as dura mater, will be subject to lesser regulatory requirements than applied currently."

So I am concerned about what that means.

DR. ALPERT: I actually can answer that. The issue is whether or not a premarket submission with a specific authorization on a company by company or tissue bank by tissue bank process needs to be in place in order to assure safety and appropriate use of product, so whether there are other mechanisms other than what is currently the 510(k) or premarket notification procedure that is gone

through. It is not to lessen the science, but to change the regulatory burden, and it doesn't change the authority the Agency has to enforce against whatever is the appropriate science.

DR. WOLFE: So you are just saying that they wouldn't have to submit a premarket application, but they would be subject to FDA regulations requiring all of the above that Paul just read off.

DR. ALPERT: That is the kind of mechanism that we are looking at.

DR. SCHONBERGER: Somebody mentioned lot number. It clearly is a problem from our standpoint when we investigate these cases, that in many instances, and in fact in most that I am aware of, the lot number is not written on the chart.

Now, I don't know whether this group has any way of encouraging the manufacturer to encourage the physicians, and so on, to put such lot numbers on. I can point out that in Japan -- it is a problem internationally -- they didn't have one lot number recorded on the 43 cases I knew about before, and although we did have a lot number on the first case in the United States, there were whole groups internationally, when we tried to link the various cases that had been reported to the lot number that we knew about,

that New Zealand and other countries, Spain, did not have the lot number, so it is an international problem and maybe the companies can help us with that in some way.

DR. BROWN: Well, we can specify the lot number be place on a container, but of course, after the lot number is placed on a container, if the container is thrown out without the lot number having been transferred to the surgical record, you are not going to know what it is anyway.

I think we are approaching questions that we just don't have any control over.

DR. SCHONBERGER: That is what I suspect.

DR. BROWN: The package that I hope I don't have to stipulate again, I would like to poll the committee on.

Linda.

DR. DETWILER: Yes.

DR. BROWN: Ray.

DR. ROOS: Yes.

DR. BROWN: Gil.

DR. WHITE: Yes.

DR. BROWN: Barbara.

MS. HARRELL: Yes.

DR. BROWN: Edmund.

DR. TRAMONT: Yes.

DR. BROWN: Leon.

MR. FAITEK: Yes.

DR. BROWN: Richard.

DR. PENN: Yes.

DR. WOLFE: Yes.

DR. BROWN: I vote yes.

Lawrence.

DR. LESSIN: Yes.

DR. BROWN: Lawrence 2.

DR. HUESTON: Yes.

DR. BROWN: Raymond.

DR. SAWAYA: Yes.

DR. BROWN: William.

DR. HUESTON: Yes.

DR. BROWN: Fantastic.

Unless anybody has other things to say --

DR. PENN: Oh, I do. A neurosurgeon gets the last word -- well, I hope it isn't the last word.

I would like to say that we could still have a meeting five years or 10 years from now, and not know whether there is a substitute material that we can use in case something else happens and we end up with some unpredicted cases of CJD.

So one of the reasons we have that is we don't

have regulations for other materials being used in neurosurgery as substitutes, and if the FDA simply approves a use of a material that has been used for other things, for use in the brain, then, we are going to -- without any pretesting in humans -- then, we are going to be in this situation again.

So I would also put in a recommendation that guidelines for testing of dural substitutes should be worked on.

DR. WOLFE: Could I respond to that? Some legislation that passed, unfortunately, 98 to 2 in the Senate, would allow for the first time the promotion of unapproved uses of devices, drugs, and other FDA regulated products, which really creates the kind of problem that you are talking about. In other words, all someone has to do is come up with some sort of "peer-reviewed" article somewhere that says, hey, it's good to use this in the brain even though there really aren't well-controlled studies supporting it, and you are going to encourage more of this kind of use, and in our view, discourage the kind of testing that you are asking for.

DR. PENN: But the FDA allowed this on these other materials even before the Senate voted.

DR. WOLFE: They didn't allow the promotion. All

I am saying is that the widespread use of it increases once a company is able to promote something that is put off-label use.

DR. PENN: But there is promotion going on of the other uses of this patch material and legally, they can promote the use, because as you have just heard --

DR. WOLFE: They can use it, but not promote it.

DR. PENN: No, they can promote it because -- well, they are promoting it, and I think that they told me, their legal people told me that they are allowed to do that because it is under slightly different regulatory rules as a tissue.

So we need some plan to get from here to there, because we would like potentially to get to zero transmission by not using this material if there is a better one available, and I don't see that we have accomplished that. Now, that is a lot to ask for from this committee, but maybe a suggestion in that direction would be useful.

DR. BROWN: What suggestion would you make?

DR. PENN: The one that the FDA should review materials that are being placed in contact with brain tissue, and not just, you know, as a policy.

DR. BROWN: But for example, a material placed in contact with brain tissue.

DR. PENN: Yes, that if it's a natural material that has the potential of infection, that the rules for that should be clear. I don't know exactly how to phrase it, I haven't worked that out in my mind, but maybe the FDA people can tell us how to manage this problem.

DR. BROWN: I am a little confused and have also been asked, as this committee was charged with answering a particular charge and the questions, not to expand beyond this.

DR. PENN: That is fair.

DR. BROWN: So it is an issue that we, as a committee, have not been asked to consider. It is a good issue.

DR. TRAMONT: Under the category of measures and safeguards, it would seem to me that asking the leadership of neurosurgery to come up with guidelines for the use of properly processed dura mater would be appropriate, the guidelines for use of many other products, drugs, a variety of factors. There seem to be no published guidelines.

DR. BROWN: I think we heard today from the neurosurgeons that, try their best, they wouldn't be able to give you a priority list for the use of dura mater versus any other tissue with the single exception perhaps, or two exceptions, of older people for whom the fascial alternative

is no longer viable, and for very large grafts.

It seems to me I got the sense that in both instances, the dura mater was preferable, but other than that, I think they will continue to tell you that they just can't generalize and that in a given situation, something may happen that tells them a dura mater graft is the best choice. Is that true?

DR. SAWAYA: Yes, but I think it is fair to say that it is good to look at what happens regardless of whether you use human dura or nonhuman dura. There is nothing wrong in saying attempt to get answers, attempt to follow these patients, and that is what guidelines do.

Perhaps, not a recommendation, but to bring it to the attention of our society, I don't think is a bad thing. Now, whether it can be done and can be done well, that is a different issue.

DR. LESSIN: Another issue might be an individual recipient or patient who has a short life expectancy of less than five years, where the latency of the development of the clinical syndrome is not likely to be overcome.

DR. BROWN: Ray.

DR. ROOS: I heard what you said about sticking to the charge, but I just have to mention one thing, and that is somebody talked about the similarity between the dural

plan situation, brought up a slide of the growth hormones, but really I think this reminds me much more of the corneal transplant, because we have tissue that is unpooled here, which comes from CNSoid type material.

Certainly the optic nerve is associated and gets implanted right into the cranial cavity, and I just wondered whether guidelines with respect to corneal transplants exist, are they very different from what we have decided on today? I can understand that it is not going to be inactivated by 1 normal NaOH. And if those guidelines are more vague, should the committee address that just to be consistent since, to me, it seems like a very analogous situation.

DR. BROWN: I think in the future, as I guess I implied, it seems to me that the FDA has a good deal more interaction with blood producers and plasma fractionators than they do with the allograft industry, and it would be a good idea to standardize the kinds of criteria and methods that are used all across the board. There is certainly no reason to suppose that grafts ought to be dealt with in any other way than a transfusion, which is, after all, a graft also. Blood is a tissue.

So, yes, in general, it seems to me you are right, that there ought to be a standard that is adhered to by all

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companies which traffic in the transfer of human tissue and fluids from one person to another, and perhaps that will slowly come.

Thank you very much. We will met tomorrow at 8:30 in the morning.

[Whereupon, at 4:30 p.m., the proceedings were recessed, to be resumed at 8:30 a.m., October 7, 1997.]