

Guidance for Industry and/or for FDA
Reviewers/Staff and/or Compliance

Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater

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**This document supercedes the “Guide for 510(k) Review of Processed
Human Dura Mater” dated June 26, 1990**



**U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Plastic and Reconstructive Surgery Devices Branch
Division of General and Restorative Devices
Office of Device Evaluation**

Preface

Public Comment

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Such comments will be considered when determining whether to amend the current guidance.

After 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions may be submitted at any time for Agency consideration to the Plastic and Reconstructive Surgery Devices Branch (PRSB), HFZ-410, 9200 Corporate Blvd., Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact PRSB at 301-594-3090.

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Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater*

Preface:

Processed human dura mater is an unclassified medical device (Procode 84LEM) and should not be confused with dura mater substitutes (Procode 84GXQ) which are classified at 21 CFR 882.5910. This guidance document provides a brief background on the regulation of processed human dura mater and is intended to replace the guidance document “Guide for 510(k) Review of Processed Human Dura Mater,” dated June 26, 1990. It should be noted that a primary motivation for providing this updated Guidance is to offer additional insight into methods and procedures for preventing the transmission of communicable disease that could be associated with the use of processed human dura mater.

As stated in the “Proposed Approach to the Regulation of Cellular and Tissue-Based Products,” published on February 28, 1997 (Ref. 1), FDA may, in the future, redesignate human dura mater to regulation under the human tissue regulation under the legal authority of Section 361 of the Public Health Service Act. The preamble to the proposed rule entitled “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products,” published in the Federal Register on May 14, 1998, further discusses and requests comments on this proposal (63 FR 26744, at 26747). The Agency believes that human dura mater that meets the criteria proposed in “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products,” may be appropriately and effectively regulated under section 361 by controlling the potential infectious disease risks posed by transplantation. However, because dura mater products are currently regulated as medical devices, the information described below is requested to ensure the safety and effectiveness of these devices as described in 21 CFR 860.7(g)(2) (Ref. 2).

Background:

Regulation of Processed Human Dura Mater - Processed human dura mater was in commercial distribution before the enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act of 1976. While a classification recommendation was discussed at the February 2, 1990 meeting of the Neurological Devices Advisory Panel, product classification was not finalized. As of the date of issuing this guidance, processed human dura mater products continue to be regulated as unclassified medical devices via premarket notification.

Processed Human Dura and Creutzfeldt Jakob Disease - In February 1987, the Center for Disease Control (CDC) reported the first U.S. case of Creutzfeldt Jakob Disease (CJD) in an individual who had received a processed human dura mater graft. In 1996, a nationwide CJD survey in Japan identified 43 cases associated with implantation of processed human dura mater. This increased the worldwide total of published cases of CJD associated with processed human dura mater use to 62. The great majority of these cases (59 out of 62) were related to the use of Lyodura, a particular brand of processed human dura mater manufactured in Germany. In March 1997, the World Health Organization (WHO) recommended that processed human dura mater grafts no longer be used, especially in neurosurgery, unless no alternative was available. At the same time, the Japanese Health and Welfare Ministry banned the use of processed human dura mater in brain surgery in Japan.

* This document is intended to provide guidance. It represents the Agency’s current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Because FDA established safeguards and guidelines in 1990 to minimize the possibility of CJD transmission by processed human dura mater implantation, and because there were no confirmed cases of CJD transmission related to the use of processed human dura mater in the United States as of March 1997, the FDA did not restrict the distribution of processed human dura mater in the United States. However, the decision was made to hold public meetings of the FDA Transmissible Spongiform Encephalopathies Advisory Committee (FDA TSE Advisory Committee) to re-evaluate the safety of processed human dura mater grafts with respect to surgical use and CJD transmission.

On October 6, 1997, the FDA TSE Advisory Committee met to consider information provided by the FDA, industry, CDC, National Institutes of Health (NIH), the neurology medical community, and other internationally recognized experts concerning the clinical benefits and risks of CJD transmission associated with processed human dura mater grafts. At the conclusion of this meeting, the committee recommended unanimously that neurosurgeons should avoid the use of processed human dura mater whenever possible. The committee concluded, however, that the final decision regarding use of processed human dura mater should be left to the discretion of the treating neurosurgeon, as long as the human dura mater is procured and processed following certain safety measures.

To improve the safety of processed human dura mater, and based upon the committee's recommendations, on March 6, 1998, FDA sent letters to providers of processed human dura mater requesting that they implement specific measures that may be beyond their standard operating procedures. On April 16, 1998, FDA presented to the FDA TSE Advisory Committee proposed revisions in the committee recommendations from the October 6, 1997 meeting. These revisions took into consideration the responses from the processed human dura mater suppliers to the FDA letter of March 6, 1998. The recommendations of the April 16, 1998, FDA TSE Advisory Committee have been incorporated into this guidance.

This guidance refers to recommendations and regulations issued under the Premarket Notification Procedures Regulation (21 CFR 807), the Quality System Regulations (21 CFR 820), and Medical Device Tracking Requirements (21 CFR 821). Manufacturers of processed human dura mater are advised to meet all of the requirements in these regulations. The information presented in this guidance document should not be perceived as a waiver of any of the above-cited requirements for device premarket submission, manufacture, and tracking.

A summary of information to be contained in a premarket notification (510(k)) submission:

Manufacturers who seek permission to market processed human dura mater must demonstrate the substantial equivalence of their product to a device that is legally marketed in the United States. To obtain marketing clearance for processed human dura mater, a manufacturer should supply the following information:

- I. Introductory information
 - A. The trade or proprietary name of the device.
 - B. The common or usual name or classification name of the device.
 - C. The establishment registration number, if applicable, of the owner or operator submitting the premarket notification submission.
 - D. The class in which the device has been placed under section 513 of the Act and the panel. (Currently, these products are unclassified.)
 - E. The name, address, and telephone number of the contact person responsible for the submission.

- II. Table of Contents
- III. Summary of information regarding safety and effectiveness upon which an equivalence determination can be made, or a statement that such information will be made available to interested persons upon request.
- IV. Statement of intended use for the device. The indications for use for the device should comply with the labeling described in Section XI of this document.
- V. A truthful and accuracy statement.
- VI. Description of the device.

An application should provide a complete description of the device, including the physical dimensions, materials, and physical properties of the device. A table comparing the similarities and differences in these parameters between the proposed device and predicate devices should also be presented.

- VII. Specification of all material components of the device.

- A. Donor Qualification

- 1. **Serology Testing**

A blood specimen from all potential donors should be tested and found negative for antibodies to pathogens of concern using FDA licensed screening tests. Today that list includes the human immunodeficiency virus, Type 1 and Type 2 (anti-HIV-1 and anti-HIV-2), hepatitis B surface antigen (HBsAg), and antibodies to the hepatitis C virus (anti-HCV). Screening tests that have been licensed for testing cadaveric blood should be used, when such tests become available.

- 2. **Evaluating risk factors for, and clinical evidence of, neurological and infectious diseases through medical record review and donor history interviews**

Each 510(k) application should describe the methods for evaluating the possible presence of risk factors for, and clinical or physical evidence of, neurologic or infectious disease. For example:

All available information including a donor's medical records, autopsy reports or any physical assessment reports (e.g., medical examiner report, police records), should be reviewed to determine donor suitability. These records should be evaluated by an individual who is qualified by profession, education, and training and who is familiar with the intended use of the device.

Interviews should also be performed with one or more individuals who can provide reliable information (e.g., a donor's next of kin, a relative, a member of the donor's household, an individual with an affinity relationship with the donor, or the donor's primary treating physician) concerning the donor's medical history and relevant social behavior. Such an interview should determine whether the donor had signs or symptoms of neurologic disease or engaged in certain activities or behaviors that place a donor at a high risk for HIV or hepatitis infection.

The manufacturer should establish donor selection criteria and develop standardized methods for reviewing medical records and performing interviews. Such procedures should

draw upon the appropriate standards of voluntary organizations (e.g., American Association of Tissue Banks, Eye Bank Association of America) as well as the recommendations, Guidelines, and Regulations published by agencies within the Public Health Service (Refs. 3-12). Exclusion criteria based on, but not specifically limited to, the criteria below should be identified:

Regarding neurological screening:

- (1) donors diagnosed with Creutzfeldt-Jakob Disease or a known family history (blood relative) of a person with non-iatrogenic Creutzfeldt-Jakob Disease;
- (2) donors who received injections of human pituitary-derived growth hormone (pit-hGH);
- (3) donors who received transplants of dura mater;
- (4) donors diagnosed with any degenerative or demyelinating disease of the CNS (e.g., multiple sclerosis) or other neurologic diseases (e.g., senile dementia, Alzheimer's disease);
- (5) donors who died in a neurological/psychiatric hospital;

Regarding other exclusion criteria:

- (6) donors who meet the exclusion criteria for potential infectious disease described in the "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation" (Ref. 10);
- (7) donors diagnosed with active infections at the time of death, e.g., rheumatic fever, generalized septicemia or systemic infection, mycosis, tuberculosis;
- (8) donors diagnosed with diseases of unknown etiology; and
- (9) donors without adequate documentation of medical history;

3. Physical Assessment

The application should identify standardized donor selection criteria for physically assessing a cadaver in a general autopsy. Exclusion criteria based on clinical evidence of possible infectious or neurologic diseases should include, but not specifically limited to, evidence of:

- (1) physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis;
- (2) physical evidence of anal intercourse including perianal condyloma;
- (3) physical evidence of non-medical percutaneous drug use such as needle tracks;
- (4) disseminated lymphadenopathy;
- (5) oral thrush;
- (6) blue or purple spots consistent with Kaposi's sarcoma;

- (7) needle tracks, including examination of tattoos which may be covering needle tracks;
- (8) unexplained jaundice, hepatomegaly, or icterus; or
- (9) if the body was rejected for routine autopsy due to infectious criteria or if the autopsy was done in an infectious disease control room or under any special precautions and the reasons for these procedures.

4. Gross and Histological Examination of Brain

The application should describe the procedures for performing a full autopsy on each donor's brain. Following fresh examination, the brain should be fixed, sliced, gross examination of the entire brain conducted (including multiple cross sections), and multiple samples of tissue obtained (from different parts of the brain) for histologic examination. This examination should be performed by a qualified neuropathologist after dura mater collection. Potential donors should be excluded when any possible evidence of TSE-related changes is observed during gross and histological examination of the brain (Refs. 13-16).

5. Archiving of Donor Brain and Dura Mater Tissue

FDA recommends that frozen (at a temperature equal to or less than -70°C) and fixed samples of both donor brain and dura mater tissues should be archived. The donor brain samples should include at least 5 grams of the frontotemporal region. These samples should be retained for 10 years based on the current state-of-scientific knowledge regarding the development of screening tests and our expectation that as the science evolves, screening tests may become available within that time.

While archiving samples of donor brain and dura mater may not immediately increase the assurance of dura mater graft safety, comprehensive collection and storage of such tissues would permit subsequent testing for TSE-induced changes when improved or new test methods become available. In the event that a dura mater-graft recipient becomes ill with CJD, testing of archival donor material might assist in determining whether the dura mater graft was the source of infection.

6. PrP-RES (Proteinase-Resistant Prion Protein) Testing of Brain Tissue

While reagents for PrP-RES testing are available from certain research laboratories, testing is currently a research/investigational-use tool (Ref. 13). Because there is no approved or validated PrP-RES test that is marketed for the screening of CJD in brain tissue, the FDA is not requiring its use at this time. However, when either a validated test becomes available or evaluation of available data demonstrate the utility of PrP-RES testing as an aid in determining that brain and dura mater tissues are not contaminated with CJD, incorporating PrP-RES testing into standard operating procedures will be recommended.

B. Qualification of Other Device Components

The source and purity of all other device components (e.g., preservatives, cross linking reagents) should be identified. Such information may be supplied by reference to a Master File(s) if a letter

of cross-reference is included which authorizes FDA review of the appropriate documents. Submission of a Certificate(s) of Analysis (CoA) and/or a Materials Safety Data Sheet(s) (MSDS) for each device component can also greatly simplify application review.

VIII. Device manufacturing.

A. Processing Methods

1. **Manufacturing Reagents**

The application should contain information about all reagents (e.g., organic solvents) and processing methods used in device manufacture. Information similar to that discussed above for device components (i.e., reagent source, purity, CoA and/or MSDS) can be very helpful in evaluating the substantial equivalence of the proposed and legally marketed devices. The application should also identify the concentration in the final device of any manufacturing reagent that is potentially toxic.

2. **Viral inactivation and CJD disinfection**

Careful control of donor selection and dura mater retrieval procedures constitute critical safety practices for processed human dura mater. While histological examination of the brain may detect most infected tissues, it may not identify all CJD-infected grafts. Therefore, treatment of each product with a generally accepted disinfection technique should be performed to provide an additional assurance of device safety. The FDA TSE Advisory Committee recommended treating processed human dura mater with 1.0 N sodium hydroxide (NaOH). This recommendation was based on a study in an animal model in which 1.0 N NaOH treatment reduced CJD infectivity (Ref. 14). Each application should provide information about the methods for disinfection with NaOH or another procedure that has been validated to significantly reduce CJD infectivity. Such data should also demonstrate that subsequent rinsing steps are sufficient to reduce the concentration of residual NaOH (or other disinfectant) to a non-cytotoxic level and that the processed human dura mater retains its clinical utility (see Section IX.B. below.)

B. Manufacturing Controls

Because product specifications and end-product testing are insufficient alone to control critical characteristics of this product, the manufacturer should carefully monitor donor selection, tissue collection procedures, device processing, packaging, and distribution to achieve a reasonable assurance of product safety. The application should provide evidence that sufficient controls for device manufacture are in place to assure the safety of the final product. The sponsor should provide the following information about manufacturing controls:

1. **Excision Procedures**

Written procedures should require aseptic conditions for handling of all tissues. Tissue recovery should be performed within 24 hours of death and with sufficient temperature control to limit the effects of autolysis.

2. **Excision Facilities**

The manufacturer should provide information concerning the excision facility (morgue) and how it meets the minimum standards of a surgical operating room. Such information

should describe, but is not limited to, whether the excisional facility has:

- a. air filtration;
- b. stainless steel furniture;
- c. washable walls;
- d. refrigeration for cadaver storage;
- e. hypothermia blankets to cool the cadaver during the procedure; and
- f. single use or disposable instruments and processing aids for each donor.

3. Batch Processing

Processed human dura mater grafts from different donors should not be co-mingled during tissue collecting or product manufacture. The application should describe efforts to eliminate opportunities for cross-contamination during tissue collection and processing as well as the procedures employed to prohibit batch processing of material from different donors. For example, procedures should require the use of only disposable processing materials and surgical instruments during the recovery and processing of dura mater allografts. Because FDA is unaware of any procedure or reagent that is validated to totally inactivate the CJD-causing agent, FDA would welcome any information that justifies an alternative approach for the sole use of disposable processing materials and surgical instruments.

4. Record Keeping/Tissue Tracking

As described in 21 CFR 820.60 subpart F, each manufacturer should establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and application. The 510(k) application should describe the methods and record keeping procedures for tracking each lot of final product directly back to the tissue donor. Such information should include, but is not limited to:

- a. donor medical records, e.g.,
 - (1) including the record of the time of death and certification of the time of tissue recovery;
 - (2) the results of post-mortem examination and serological studies sufficient to evaluate the potential of communicating infectious, malignant, and/or neurological disease or to detect diseases of unknown etiology;
 - (3) a record of compliance with the written procedures for recovery;
- b. device manufacturing records as defined in 21 CFR 820 subpart M (Quality System Regulations); and
- c. information about how the sponsor complies with the tracking regulations for dura mater (see 21 CFR 821 and Section 519(e) of the Federal Food, Drug, and Cosmetic Act), which were enacted on December 14, 1998. Please refer to “Guidance Document on Medical Device Tracking (1999)” for additional insight into the procedures for accurately tracking medical devices.

C. Final Product Sterilization

For devices labeled as sterile, in general, a SAL of 10^{-6} is recommended for all devices unless there

is substantial justification for not being able to achieve this level. Such data can be obtained by determining the viral inactivation properties of scaled down versions of specific production techniques and the sterilization methods using appropriate model viruses. Review of the ICH Draft Guideline on Viral Safety Evaluation of Biotechnology Products from Cell Lines of Human or Animal Origin is recommended with regard to the design of such studies and the selection of model viruses. The final results of these studies should demonstrate that the sum of the log clearance of virus from the selected manufacturing steps and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material.

Regarding terminal sterilization procedures, the application should describe:

1. the method of sterilization;
2. the validation method for the sterilization cycle;
3. the sterility assurance level (SAL) to be achieved; and
4. the method for monitoring the sterility of each production lot.

If radiation sterilization is used, the sterilizing dose and methods for monitoring exposure level should be specified. If ethylene oxide (EtO) sterilization is performed, the application should describe the methods by which residual levels of ethylene oxide, ethylene chlorohydrin, and ethylene glycol are determined and the amount of EtO and residues remaining on/in the device. Because EtO and its decomposition products may be very neurotoxic, specifications for EtO residuals should be set at a non-cytotoxic level. Review of "Guidance for ANSI/AAMI/ISO 10993-7: 1995, Biological evaluation of medical devices-Part 7: Ethylene oxide sterilization residuals" is recommended.

IX. Product Characterization

All applications should address issues concerning biocompatibility, final tissue structure, and device performance. Examples of these issues are:

A. Device Biocompatibility

The biocompatibility of processed human dura mater should be determined in accordance with the Blue Book Guidance G95-1, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." Standard protocols such as those identified by the USP or ASTM should be used when assessing device biocompatibility. Such tests should also be performed on devices ready for surgical use (i.e., after manufacture, sterilization and packaging for commercial distribution). The application should provided the test results for the following analyses:

- Cytotoxicity
- Sensitization Assay
- Irritation or Intracutaneous reactivity
- Acute Systemic toxicity
- Mutagenicity or Genotoxicity
- Hemolysis
- Pyrogenicity

Regarding device pyrogenicity, FDA recommends a limit of 2.15 EU/device (i.e., 0.06 EU/ml based on a standard extract volume of 40 ml/device). Implantation studies at the intended anatomical site of use should examine the histology of the device and surrounding tissue as a function of time. In addition, such studies should evaluate the possibility of cerebral spinal fluid leakage, the formation of adhesions to the device or surrounding tissue, whether the device

increases the incidence of infection, hydrocephalus, foreign body reactions, or other tissue reactions.

For products that remain in the body for greater than 30 days, the following additional tests are recommended:

Subchronic toxicity - 90 days (with histology of the surrounding tissue)

Chronic toxicity - 180 days (with histology of the surrounding tissue)

Long term carcinogenicity studies should be performed with any device in which a positive genotoxicity test result was obtained.

B. Product Structure and Performance

Information about the product structure is critical in determining the equivalence of proposed and legally marketed devices. For processed human dura mater, such data should include the following information:

Product Description

Photographs

Product Overview

Physical/Mechanical Properties

Device thickness

Tensile strength

Suture retention strength

Suture hole properties (e.g., reapproximation, resealing and CSF leakage).

Burst strength

Histological and EM studies (to determine if collagen/tissue degradation occurred)

Clinical experience

The application should provide a summary of any clinical experience obtained with the device in dural repair or other indications. Reference should be made to the appropriate 510(k), PMA, or IDE number as well as reference to any overseas experience.

The above tests may not be relevant or necessary in all cases, such as when a manufacturer submits a marketing application for a device which has the exact same material specifications as a previously marketed product, and for which the tradename and device claims are the only changes being made.

C. Product Specifications

The sponsor should provide information about product release specifications. Such data should identify the test method, release specification and when during manufacture the test is performed. Examples of final product release specifications can include:

Device Thickness

Pore Size

Bursting Strength

Residual levels of manufacturing reagents (leachables)

Residual levels of heavy metals

Pyrogen levels
Sterility

D. Product Expiration Dating

Data supporting the expiration date for the product should be submitted. Such data should be collected from at least three production lots. Stability studies should monitor the critical safety and effectiveness parameters of device performance during the entire proposed shelf-life.

X. A description of the packaging to be used to maintain the sterility of the device.

XI. Labeling

As a medical device, the labeling for processed human dura mater should conform to 21 CFR 801.109. The application should contain all labeling information for processed human dura mater, including individual package labeling, package inserts, and available promotional literature. The labeling should specify the intended use of the device, contraindications, warnings, precautions, and directions for use, as well as any additional product claims. The labeling should also include information so that the graft recipient is notified in writing that she/he has received a processed human dura mater graft implant. Finally, product labeling should permit information on tissue sourcing to be maintained in the recipient's hospital record.

References

1. "Proposed Approach to the Regulation of Cellular and Tissue-Based Products" (2/28/97), available at <http://www.fda.gov/cber/guidelines.htm>
2. "The Commissioner may require that a manufacturer, importer, or distributor make reports or provide other information bearing on the classification of a device and indicating whether there is reasonable assurance of the safety and effectiveness of the device or whether it is adulterated or misbranded under the act."
3. FDA Recommendations to Blood Establishments for "The Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg)," 12/2/87.
4. FDA Recommendations to Blood Establishments for "Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis," 12/22/93.
5. PHS Guideline for Preventing Transmission of HIV through Transplantation of Human Tissue and Organs, *MMWR* 1994:43, 1-17.
6. PHS Guideline for Screening Donors of Blood, Plasma, Organs, Tissue and Semen for Evidence of Hepatitis B and Hepatitis C, *MMWR* 1991:40, 1-17.
7. FDA Recommendations to Blood Establishments for "Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma," 6/8/95.
8. FDA Recommendations to Blood Establishments for "Precautionary Measures to Further Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease by Blood and Blood Products," 8/8/95.
9. FDA Recommendations to Blood Establishments for "Deferral of Blood and Plasma Donors based on Medications," 7/28/93.
10. FDA Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation, July, 1997.
11. FDA Revised Recommendations to Blood Establishments for "Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)," 4/23/92.
12. FDA Revised Recommendations to Blood Establishments for "The Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," 4/23/92.
13. Kretschmar H.A., Ironside J.W., DeArmond S.J., Tateishi J. Diagnostic Criteria for Sporadic Creutzfeldt-Jakob Disease. *Arch. Neurol.* 1996; **53**:913-920.
14. Diringer H., Braig HR. Infectivity of Unconventional Viruses in Dura Mater. *The Lancet*, 1989:439-440.
15. R. T. Johnson and C.L. Gibbs, "Creutzfeldt-Jakob Disease and related Transmissible Spongiform Encephalopathies," *NEJM*, **339**, 1994-2004 (1998).
16. P.L. Lantos, et. al., "Is the neuropathology of new variant Creutzfeldt-Jakob disease and kuru similar?", *The Lancet*, **350**, 187-188 (1997).