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Joan Claybrook, President

August 15, 2001



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Food and Drug Administration
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**Citizen Petition to Ban Human Cadaveric Dura Mater**

Dear Dr. Feigal:

Public Citizen, a nationwide consumer organization with 135,000 members, hereby petitions the Food and Drug Administration (FDA), pursuant to 21 USC § 360f and 360h(e) and 21 CFR § 10.30 to immediately ban as an unsafe medical device and recall all dura mater derived from human cadavers. Dura mater, a strong connective tissue surrounding the brain, can be obtained from deceased persons and transplanted into recipients who have suffered brain trauma or undergone neurosurgery for medical conditions such as cancer or bleeding in the brain. Worldwide, cadaveric dura mater has been found to have caused at least 114 human cases of always-fatal Creutzfeldt-Jakob disease (CJD), including three in the U.S., almost as many as the 139 CJD cases due to contaminated growth hormone.[1] The devices were banned in Britain in 1989 and in Japan in 1997, without apparent problems. Also in 1997, the World Health Organization (WHO) recommended against the use of cadaveric dura mater.[2] Because there are safer alternatives, such as synthetic dura mater, grafts from the patient's own fascia lata (connective tissue from the lateral aspect of the thigh) and bovine pericardium, there is no reason for this product to remain on the market.

A. ACTIONS REQUESTED

1. A ban on the sale of human cadaveric dura mater
2. A recall of all unimplanted human cadaveric dura mater from hospitals and all other channels of commerce



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01P-0354

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B. STATEMENT OF GROUNDS

*Evidence of harm*

CJD is one of a family of diseases known collectively as the Transmissible Spongiform Encephalopathies (TSEs). The major human disease in this category is CJD, but others include kuru and Gerstmann-Straussler-Scheinker syndrome. In animals the best known TSEs are scrapie among sheep and now Bovine Spongiform Encephalopathy (BSE or "mad cow disease") among cows. When BSE is transmitted to humans it is known as variant CJD (vCJD). Any of the human TSEs could potentially be transmitted by a cadaveric dura mater implant.

The first case of CJD due to a cadaveric human dura mater implant was reported in 1987.[3] The patient was a 28-year-old woman who had received a graft of a dura mater product named Lyodura, imported into the U.S. via Canada, for surgery to remove a tumor of the ear canal. (Lyodura was never approved for sale in the U.S.) In a 1987 update on this case, the Centers for Disease Control and Prevention (CDC) stated that

> [C]urrent [1987] procedures used to sterilize human dura mater are not adequate to inactivate the CJD agent, and even the most stringent donor screening cannot exclude asymptomatic prepatent carriers of CJD. Thus the use of any human dura mater product carries some risk of transmission of CJD, and procedures that minimize the risk are important. Alternatives to these products, such as autologous fascia or synthetic materials, are available.[4]

A case in New Zealand[5] and four cases in Spain[6] were subsequently reported. All of these six initial cases involved Lyodura. Lyodura was manufactured using a process that permitted the commingling of dura mater from multiple donors and used 0.1 N sodium hydroxide, rather than the currently recommended 1 N sodium hydroxide, which is ten times stronger.

A second U.S. case of CJD associated with a Lyodura graft was reported in 1994.[7] More recently, a third U.S. case of CJD apparently due to cadaveric dura mater was reported. It followed a neurosurgical procedure conducted in 1992, before the current FDA Guidance (see below) and before the manufacturer, Biodynamics of Alachua, Florida, switched from 0.1 N to 1 N sodium hydroxide. However, there was no commingling of tissue during the production phase. The company, rather belatedly, recalled all unimplanted product. The CDC authors conclude in an article published this year:

> However, even the most stringent donor screening and dura mater processing practices may not totally eliminate the potential for an infectious graft. Because

> of this inherent, albeit small, risk of CJD transmission by dura mater grafts, surgeons may want to consider the alternative use of autologous fascia lata, temporalis fascia [from the side of the patient's face], or synthetic substitutes.[8]

By far the largest outbreak of dura mater-associated CJD occurred in Japan from 1985 onward.[9,10,11] At least 65 patients developed CJD following neurosurgery and receipt of a dura mater graft. At least 54 of them involved the use of Lyodura. With incubation periods as long as 15 years, this epidemic may have not yet ended. It has been estimated that patients who received dura mater between 1979 and 1991 were at 29.2 to 104.9 times the risk of getting CJD than the average person in Japan.[12,13]

Reacting to the Japanese outbreak, the WHO recommended in 1997 that cadaveric dura mater not be used:

> Because over 50 cases of CJD have resulted from cadaveric dura mater grafts, it was strongly recommended that dura mater no longer be used, especially for neurosurgery, unless no other alternative is available. If, nevertheless, dura mater is to be used, only material should be considered that is from non-pooled sources originating from carefully screened donors and subjected to valid inactivation treatment.[2]

There have now been at least 114 cases of CJD related to cadaveric dura mater reported worldwide.[1] This epidemic is probably not yet over. At present, the mean interval in the Japanese cases (which represent 59% of cases to date)[1] is 103.1 months (8.6 years) with the longest latent period being 218 months (18.2 years) and cases still occurring.[11] Most of the dura mater used in the U.S. is produced by Biodynamics and the University of Miami Tissue Bank. Roughly 20,000 grafts take place each year in the U.S., of which approximately 5,000 to 10,000 involve human cadaveric dura mater.[14]

*Safer alternatives*

A number of dura mater substitutes have been approved for marketing in the U.S. For convenience, we have divided these into the synthetic, those obtained from the patient's own tissues and those obtained from another patient or animal. Synthetic dura mater implants may be made from reabsorbable materials.[15,16] They work by allowing the infiltration of a synthetic mesh by connective tissue as the mesh dissolves. Grafts from the patient's own fascia lata or temporalis fascia are also viable alternatives, although for fascia lata this requires a second incision and a modest increase in operative time.[17,18] Finally, one can use tissues from another patient or animal. Positive reports for both ovine[19] and bovine[20] pericardium have been

published. Acellular human dermis (human skin does not appear to carry infectivity for CJD or other TSEs)[21,22] and a collagen sponge produced from bovine tendons have also been used.[23] Of the nine currently FDA-approved dura substitutes, four are synthetic, four are manufactured from bovine pericardium and one is derived from bovine achilles tendon.[24] In the U.S., bovine pericardium from BSE-free countries is probably used more often than cadaveric dura mater,[25] indicating that a ban on dura mater grafts would not have a major impact on the conduct of neurosurgery in this country.

Two studies have sought to compare the safety and effectiveness of various graft materials. In a non-randomized study, the researchers found approximately equally low complication rates between the patient's own fascia lata, bovine pericardium and cadaveric dura mater.[18] A randomized comparison between bovine pericardium and dura mater published in 1990 showed comparably low complication rates.[26] However, surgeons considered the bovine pericardium to be more workable and less likely to be of an inconvenient thickness than dura mater. The cutting characteristics, suturability and water-tightness of the two materials were considered to be about equal. While we recognize that some materials may be preferable to others for particular purposes, the wide array of FDA-approved dural substitutes gives neurosurgeons sufficient flexibility without presenting the unnecessary risk of CJD or vCJD.

Dr. James Steers, a neurosurgeon from Britain, where cadaveric dura mater has now been banned for 12 years, testified before an FDA Advisory Committee that British surgeons have managed well without cadaveric dura mater:

> I have to say that there has been no ... 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.[27]

Moreover, when he was asked whether the switch from cadaveric dura mater had led to increases in the number or severity of postoperative complications, he answered:

> I think I would have to say nay to that ... 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.[28]

*Inadequacy of FDA regulation to date*

Unfortunately, the FDA elected not to follow the WHO guidelines. FDA's TSE Advisory Committee met on October 7, 1997 to discuss TSE transmission by human dura mater and voted

6 to 3 (with 4 abstentions) that there were no surgical procedures for which there is a need for cadaveric dura mater (Dr. Wolfe was in the majority).[29] Unfortunately, the Committee then voted 6 ½ to 4 ½ to recommend that cadaveric dura mater be avoided whenever possible, and that the operating neurosurgeon should decide whether to use human dura mater (Dr. Wolfe was in the minority).[30] (The possibility of banning the material was not voted on explicitly.) The FDA went on to develop a voluntary Guidance on the use of cadaveric dura mater.[31] That guidance expanded the need for evaluating risk factors for neurological and infectious diseases, suggested a full autopsy of the donor's brain, recommended treatment with 1 N sodium hydroxide and stated that tissues should not be commingled during processing.

While these processes are likely to reduce the probability of CJD transmission, compliance remains voluntary. Even if current manufacturers are willing to comply with these guidelines, future manufacturers may not be. More fundamentally, there is simply no guarantee that these processes will eliminate CJD risk. Even the stronger 1 N sodium hydroxide does not completely remove infectivity from dura mater; in one study, one of 40 hamsters became infected with scrapie (a disease related to CJD) following intracerebral inoculation of brain tissue that had been treated for one hour with 1 N sodium hydroxide.[32] In another, infectivity was also retained after treatment with 1 N sodium hydroxide; four out of five mice inoculated intracerebrally with sodium hydroxide-treated brain tissue became infected in the study.[33] In a third study, seven out of nine mice exposed intracerebrally to brain homogenates treated with 2 N sodium hydroxide became infected.[34] Other investigators have reported similar results.[35] Moreover, the long latent period between implantation and disease (up to 18 years[11]) makes it difficult to use physical examination or history to reliably exclude potentially infectious donors.

C. ENVIRONMENTAL IMPACT

Nothing requested in this petition will have an impact on the environment.

D. ECONOMIC IMPACT

The only potential loss of income is to the companies currently producing human cadaveric dura mater. Sales of alternative materials can be expected to increase.

E. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

*Conclusion*

At the TSE Advisory Committee meeting on January 18, 2001, the Committee (on which Dr. Lurie now sits) was asked to consider whether potential tissue donors, including dura mater transplant donors, who had spent a significant amount of time in Britain should be precluded from donating. This was based on fear of vCJD transmission from those currently incubating the disease in Britain, where over 95% of vCJD cases have occurred. We find it ironic that the FDA would ask the Committee to consider such a restriction based on concern about vCJD when even in Britain the number of vCJD cases (97 definite and probable cases since 1996 or about 20 per year[36]) is substantially less than the number of British CJD cases (about 60 per year given the standard assumption that the incidence of CJD is one per million per year[37] and a British population of 59.5 million in 1999[38]). Why are we considering action against the disease (vCJD) that, at least to date, represents the lower risk, when we haven't adequately reduced the dangers from the more common form of this disease?

There is strong evidence that cadaveric dura mater represents a completely unnecessary risk of CJD to the public. The disease in question is fatal, the risks cannot be reliably eliminated and there are clear alternatives. Yet the FDA has not opted to ban the material, even though two other countries, Japan and Britain, have done so without evident problems, and the WHO recommends this course of action. Ironically, the U.S. still permits the import of dura mater sourced from the very countries (Japan and Britain) where the material is no longer used. We hope that the recent attention to BSE will induce the FDA to finally take action to adequately protect the public.

Yours sincerely,

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cc: Dockets Management Branch

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