AMERICAN ASSOCIATION OF BLOOD BANKS

ASSOCIATION BULLETIN

#96-4

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To: AABB Institutional Members

From: Roger Svoboda, MBA, MS, MT(ASCP)SBB, President
Karen Shoos Lipton, JD, Chief Executive Officer

Re: Guidance on Notifying Recipients of Blood Components from a Donor Who Subsequently Was Diagnosed as Having Creutzfeldt-Jakob Disease (CJD) and/or CJD Risk Factors

The purpose of this bulletin is to provide Association members guidance concerning the notification of recipients of blood components from a donor who has subsequently been diagnosed as having Creutzfeldt-Jakob disease (CJD), has received human pituitary-derived growth hormone, has been found to have a family history of CJD or has received a dura mater transplant. The bulletin is composed of three sections. The first section is a summary of CJD and the associated issues. Although the summary highlights the known information, a review article prepared by Celso Bianco, MD, has been included in the second section. This article, which was presented at the December 1995 American Society of Hematology meeting and is printed in *Hematology 1995, The Education Program of the American Society of Hematology*, can be used as guidance in the preparation of medical staff. The third section of this bulletin proposes a possible approach for an establishment to follow when developing its policy with regard to notification of recipients of implicated components.

I. Summary

CJD is a rapidly fatal dementing illness characterized by spongiform degeneration of the central nervous system. Although CJD is not a reportable disease in the United States, CJD occurs at an estimated annual incidence of one case per million persons. The disease may have an incubation period of many years in humans. Transmission of this disease through intracranial inoculation has been documented in certain animal model systems. In addition, although most cases of CJD in humans are sporadic, iatrogenic transmission of this disease from corneal transplant, neurosurgical procedures, EEG depth electrodes, cadaveric dura mater and non-recombinant human growth hormone has been reported. In addition, a small number of cases are familial.

No case of transmission of CJD through blood transfusion or blood derivative has been documented. Still, transmission of CJD through blood components remains a theoretical possibility. Since 1995, the Centers for Disease Control and Prevention (CDC), the American Red Cross (ARC) and the New York Blood Center (NYBC) have had in progress a study to determine the risk, if any, of transmission of CJD by blood components from donors who subsequently develop CJD. To date, review of the cause of death of 35 recipients of these units indicates that none had developed CJD or other central nervous system disease. However, the low incidence of CJD, coupled with the long incubation period, suggest that definitive answers to the question of transmissibility will not be available in the near future.

The issue of the transmissibility of CJD by blood transfusion was first addressed by the federal Food and Drug Administration's (FDA) Blood Products Advisory Committee in December 1994. That review resulted in the recommendation that in-date cellular components of blood from donors who later develop CJD be withdrawn from distribution. The Committee further recommended that physicians and recipients be notified if such units had been transfused. The Committee recommended against recall of manufactured components. Concern from the hemophilia community over that recommendation led the FDA to convene a Special Advisory Committee constituted to review the possibility of transmission of CJD through plasma derivatives. At its meeting on June 22, 1995, the Special Advisory Committee recommended that all plasma products containing plasma from individuals who later developed CJD be withdrawn from the market. The Special Advisory Committee recommendation resulted in the issuance of the FDA's directive in August 1995, "Precautionary Measures to Further Reduce the Possible Risk of Transmission of CJD by Blood and Blood Products." This memorandum recommended notification of consignees of the potentially contaminated units. The purpose of this notification is to enable consignees to inform the recipient's physician to permit counseling of the recipient of product from a high risk donor "as deemed medically appropriate."

Implicit in the FDA's recommendation is the recognition that physicians will have to make a determination whether or not to notify a transfusion recipient about the risks inherent in the receipt of a unit of blood collected from a donor who was diagnosed with CJD, received human pituitary-derived growth hormone, received a dura mater transplant or was found to have a family history of CJD. Institutions and physicians making decisions whether or not to inform a patient about the risk of CJD should make that decision after consideration of the ethical and legal issues surrounding such a decision. Institutions may want to consider the following information. Prior to the August 8 directive, the three Institutional Review Boards controlling the collaboration between the CDC, ARC and NYBC had expressly disallowed the direct notification of recipients of blood components from donors who subsequently developed CJD based on the extremely low risk of CJD transmission, the tremendous stress that could be associated with receipt of the information and the absence of a screening test. It was expressly stipulated that recipient notification would be required if a treatment or test is developed for CJD, or if CJD is definitively shown to be transmissible by transfusion of blood components or products.

Although not directly applicable, case law in the area of informed consent suggests that a physician has a duty to disclose to his or her patient any information that is "material," as that standard is defined in each jurisdiction. The specific decision to withhold information from a patient, however, is a professional privilege that belongs not to the institution, but uniquely to the physician. Physicians and institutions may find it useful to seek guidance concerning the need or obligation to notify recipients from currently existing institutional review boards or institutional ethics committees. The circumstances in which it may be advisable or allowable not to inform a patient may be arrived at by consensus in these venues, which may be valuable for physicians in their decision-making. Information attached to this bulletin is provided in an effort to facilitate those discussions.

II. Creutzfeldt-Jakob Disease
By Celso Bianco, MD

[Note: An earlier version of this summary was printed in Hematology 1995, The Education Program of the American Society of Hematology. This article is reprinted with permission from the American Society of Hematology and Dr. Bianco.]

Creutzfeldt-Jakob disease (CJD) is a fatal, rapidly developing degenerative disease of the central nervous system characterized by dementia, multifocal myoclonus, and periodic triphasic discharges on electroencephalogram. Approximately 10% of the cases are manifest as ataxic illnesses. Most affected individuals die within one year of onset of symptoms (reviewed in 1,2). CJD was first described in 1920-21. Over 85% of the cases are sporadic, appearing in individuals without family history. About 10% of the cases are familial. About 80 cases of iatrogenic transmission have also been reported. CJD is related to a number of other dementias in humans and in animals, including the Gerstmann-Sträussler-Scheiker disease, fatal familial insomnia, kuru, scrapie of sheep and goats, and the bovine spongiform encephalopathy (mad cow disease) of cattle. Transmissibility of these diseases was initially evidenced by the epidemic of kuru among the Fore people living in the highlands of New Guinea. Transmission was traced to ritualistic cannibalism and has virtually disappeared since the practice was abandoned.

Starting in 1985, CJD was identified among seven of 6,284 recipients of human pituitary derived growth hormone (3). Concerned about the theoretical possibility of transmission by transfusion, the FDA recommended as a precautionary measure that individuals who received human pituitary derived growth hormone be deferred from donating blood (November 25, 1987). In Europe, development of CJD among recipients of human pituitary derived growth hormone was also a serious problem. By November 1994, there were 11 cases reported in the US, 14 in the UK, and 32 in France (Lawrence Schonberger, CDC, presented at the Blood Products Advisory Committee on December 15, 1994). Iatrogenic transmission of CJD has also been documented among some recipients of human dura mater transplants (4) and in cases where electro-encephalogram electrodes were used in multiple patients without appropriate sterilization (1). A single case associated with corneal transplant has also been associated with transmission of CJD. The period of incubation for manifestation of disease has varied from one year to more than 20 years.

The incidence of CJD has been studied by Schonberger, et al, from the CDC, and was estimated at 1:1,000,000 in the US. There have been 2,614 cases in 12 years with an average of 218/year. The incidence is zero among 5-19 year olds, and reaches 6:1,000,000 among individuals over 60 years of age. The incidence has remained constant over the years, and is the same in all states. There are no reports of transmission of CJD by sexual or casual contact.

The causative agent of CJD is controversial. Initially, CJD was thought to be caused by a slow virus. Later, transmission studies performed in the scrapie

model indicated that the infective material was devoid of measurable amounts of nucleic acid. The evidence for an infectious protein, the prion, is carefully presented in a recent review (1). Essentially, the prion is a conformationally altered form of a normal plasma membrane protein called PrP^c. Abnormal PrP, or PrP^{Sc} can induce conformational changes in normal PrP^c and is consequently "infectious." This conformational change may require co-factors. PrP^{Sc}, the altered form, is highly resistant to proteases, and can form rod-shaped multimers which precipitate as amyloid. The spongiform alterations in the brain of CJD patients have been attributed to the deposition of PrP^{Sc} amyloid (2).

Some authors still favor a viral etiology for CJD, or believe that the co-factor for the alterations of PrP is a virus (5). However, the majority of investigators in the area accept the prion etiology for CJD.

CJD and Blood Transfusion

On October 18, 1994, the American Red Cross (ARC) reported to the FDA that a 64-year-old blood donor who had donated more than 90 times over more than 30 years had died with a clinical diagnosis of CJD. Plasma from his donations was often pooled for further manufacture of plasma derivatives. On October 27, 1994, ARC voluntarily recalled components of the last four donations made by the donor. On November 17, 1994, Baxter and ARC initiated voluntary market withdrawal of implicated lots of IVIG, Factor VIII AHF, Albumin, and Plasma Protein Fraction. Soon, Miles withdrew Alpha 1 proteinase inhibitor lots and Sandoz withdrew IVIG that contained donations made by this donor. In November 1994, hemophilia treaters in New York initiated notification of patients who received implicated lots of Factor VIII AHF that they had received products which contained plasma from a donor who later developed CJD.

The initial concerns about transmissibility of CJD by transfusion were raised by Manuelidis, et al (6). These investigators inoculated buffy coat cells from the peripheral blood of two CJD patients into the brains of rodents. After 200-500 days, these animals showed spongiform degeneration of the brain, while control experiments "never resulted in CJD." More recently, these investigators (7) inoculated buffy coat cells from normal volunteers with no family history of dementia into the brains of hamsters. After a long period of observation, 26/30 buffy coats (86.7%) induced CJD-like changes in the animals' brains. The investigators concluded that the CJD agent "endemically infects humans but only infrequently produces dementia." This interpretation is highly controversial, because these experiments constitute the logical control for the early experiments performed with CJD buffy coats, and raise serious questions about assay specificity. Furthermore, these experiments could not be replicated in rodents or in primates (P. Brown, presented at the June 22, 1995 meeting of the FDA Special Advisory Committee on Creutzfeldt-Jakob Disease). In experimental models, transmission of CJD by routes other than the intracerebral route has not been achieved.

The theoretical possibility of CJD transmission by transfusion has been examined by other investigators. A study of transfusion histories of 202 definite and probable cases of CJD which had been part of prospective studies performed in England and Wales between 1980-84 and 1990-92, showed that 21 of the patients had received blood transfusions and 29 had donated blood (8). The frequency of blood transfusions or donations did not differ between CJD cases and matched controls, leading the investigators to conclude that the evidence did not suggest that transfusion was a major risk factor for development of CJD (8). No cases of CJD among hemophiliacs have been reported in the medical literature. The Medline database contains 1,485 references on CJD and 6,385 references on hemophilia between January 1976 and October 1994. None of these references links CJD and hemophilia. An extensive review of mortality data performed by L. Schonberger from the CDC did not identify a single CJD death in individuals with a clotting disorder or hemoglobinopathy.

On December 15, 1994, the issue of CJD and transfusion was reviewed by the FDA Blood Products Advisory Committee. After extensive discussion, the Committee recommended that in-date cellular products of blood from donors who later develop CJD should be withdrawn from distribution. In case these products were transfused, the Committee recommended that physicians and recipients be notified. In the case of plasma pooled for further manufacture, the Committee recommended against recall of manufactured products, because of the lack of evidence for transmission. The hemophilia community appeared to be quite dissatisfied with this recommendation, leading the FDA to convene a new Advisory Committee to review the possibility of transmission of CJD by plasma derivatives. The Special Advisory Committee met on June 22, 1995, and recommended that all plasma products containing plasma from individuals who later died of CJD, including albumin, should be withdrawn from the market, despite the lack of evidence for transmissibility of CJD by these products. The FDA issued a memorandum to blood establishments on August 8, 1995 mandating quarantine of these products. In case these products must be released because of shortages, they must bear a warning indicating that the product was made from plasma from a donor later found to have CJD or to be at high risk of CJD. The warning also states that the risk is theoretical and should be balanced against the known medical benefits of the products. An accompanying memorandum determines that individuals who have a family history of CJD or have received dura mater transplants should be deferred from donating blood or plasma. The definition of family history was clarified by the FDA on December 14, 1995. Blood donors with one "blood relative" with history of CJD must be deferred and the collected unit discarded. If there are two or more "blood relatives," the family is considered a family at risk of CJD, and in-date products from prior donations must be placed in quarantine.

Lookback studies have been organized around blood donors who later developed CJD. These studies involve identification of recipients and review of their health status. So far, review of the cause of death of 35 recipients of these units indicated that none had developed CJD or other central nervous system disease. One case of potential transmission to a liver transplant recipient who also received transfusions of albumin has recently been reported. One of the albumin donors died three years later from a dementia clinically characterized as CJD (9). Obviously, the liver transplant recipient was exposed to a variety of drugs and biologics, making it difficult to determine the exact source of disease. Unfortunately, because of the very low incidence of CJD and the long incubation period, there will be a long period of time before more definitive answers become available. In the interim, CJD is being approached as a disease which can theoretically be transmitted by blood and blood products.

References

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III. Policy and Procedure for Recipient Notification of Components or Derivatives Made from Donors with CJD Implications

Blood collection facilities should notify blood transfusing facilities of the implicated units. Each notification should include Association Bulletin #96-4, containing suggested procedures and materials to facilitate a decision on the part of a recipient's physician whether to notify.

A) The medical director of the blood bank would initiate deliberations by the appropriate body at their institution (eg, institutional review board, ethics committee, medical staff executive committee, medical staff at large). The group might, at a minimum, include a risk manager, lawyer, clinician who transfuses, blood bank medical director, a patient who has been a blood or component recipient and others identified as appropriate by the facility. The convened entity may want to define criteria for notification based on the following factors B, C, and D.

B) The medical director of the blood bank would provide the group with the current state of relevant knowledge with regard to CJD and transmission (eg, the lack of an available test or treatment) and the risk (theoretical and reported) of CJD transmission by transfusion. The medical director can prepare further by reading "The Prion Diseases," Prusiner, S.B. *Scientific American* 272:48-57 (1995), for a more comprehensive explanation of the nature of the putative causative agent of CJD.

C) The medical director would also inform the group of the categories of donors at theoretical risk (eg, donors actually diagnosed with CJD or who received dura mater transplants or non-recombinant human growth hormone, donors who have a history of only one or of two or more family members with CJD) and help assess the significance of the level of documentation in each case (eg, autopsy, death certificate diagnosis, family folklore).

D) Recipient information that may be of relevance would also be elaborated (eg, closeness of patient-physician relationship, recipient's medical history and diagnosis, recipient's age, recipient's ability to understand/cope with this information).

With the above information, the group can deliberate and develop criteria for informing patients that they have received a component or derivative from a donor with a CJD risk and criteria for electing to withhold such information. The criteria would allow physicians to individualize decisions so that it would be most applicable to individual patients.

The result would be a policy and procedure for that facility. This would be distributed to the medical staff. Then, when a blood bank notifies a recipient's physician of transfusion of an implicated unit, that physician will know the policy and procedure or can be directed to it. ◆