

UK. Scientific evidence strongly supports the causal link between BSE and vCJD [30–33].

Prions as transmissible agents of TSEs

Today it is widely believed that TSEs develop when a host-encoded normal cell-surface glycoprotein, the prion protein (PrP^C, normal PrP) changes its conformation to a pathological isoform (PrP^{Sc}, abnormal PrP) that accumulates in the brain tissue of afflicted individuals [34]. Brain tissue of such individuals is highly infectious when introduced into susceptible species, especially by the intracerebral route of inoculation. The infectious agents responsible for the transmission of TSE disease are called prions. They are apparently devoid of nucleic acid and seem to be composed exclusively of a conformationally modified abnormal PrP [34], in which the α -helical content diminishes and the amount of β -sheet increases [35]. It is not understood how this conversion occurs, but studies using transgenic mice have suggested that another unknown factor is required [36], and the quest for the discovery of the nature of this unknown factor continues.

The physiological function of normal PrP has not been yet elucidated but several important observations imply a possible role in copper metabolism [37]. Normal PrP is widely expressed in most tissues throughout the body, including organs of the lymphoreticular system and blood cells [38–45]. In human blood, the highest level of normal PrP expression has been found in mononuclear cells and platelets [41–46], but a significant amount of cell-free PrP has also been detected in plasma [47].

TSEs and blood safety

During the past decade, CJD has been the object of considerable attention from the blood, plasma and fractionation industries. Initially, concern about the safety of blood products arose when it became apparent that donor pools contained plasma from patients who later developed CJD. However, several observations mitigated the possible risk associated with the use of such plasma pools. These included: (1) absence of epidemiological evidence for blood-related TSE transmission; (2) absence of definite evidence of transmission from experiments when human blood or blood components were inoculated into experimental animals (including chimpanzees); (3) very low levels of TSE infectivity in blood, compared to the brain, of rodents experimentally infected with various strains of prions; and (4) efficient reduction of TSE infectivity during valid-

ation studies of various steps used in the manufacture of plasma-derived products. However, new concerns about the safety of blood and plasma-derived products emerged when vCJD was identified in the UK [48], based upon the fact that the abnormal PrP was detected in lymphoreticular tissues, including tonsils, spleen and lymph nodes in vCJD patients [49–52], but not in sCJD patients, and in the appendix of a preclinical patient who eight months later developed vCJD [53]; in addition, spleens and tonsils of vCJD patients are infectious [54]. It has been argued that blood of vCJD patients interacting with lymphoreticular organs might contain the abnormal PrP and/or infectious prions. Concern is further heightened by the following observations: (1) BSE, causally linked to vCJD, has spread through many European countries; (2) the extent of exposure to BSE, the source and route of transmission, and transmissibility of different bovine tissues to humans have not been definitely established, and few epidemiological data are available to date; (3) the number of vCJD cases is increasing, and it is impossible to predict accurately the number of people who may have been infected with BSE and might develop vCJD in the future, because the incubation period may vary from 4 to 20 or even 40 years, as found with kuru; (4) epidemiological data are scarce concerning the risk of blood-related transmission of vCJD; (5) disease transmission by transfusion of blood from experimentally BSE-infected sheep has been reported [55]; (6) information is incomplete about the distinctive physico-chemical and biological properties of the vCJD agent in comparison to the other well-studied laboratory strains of TSEs; (7) there is no test available for early diagnosis of infected individuals; and (8) validation studies on the removal of TSE agents (including vCJD) during the manufacturing of plasma-derived products have not been completed and verified by different laboratories.

Experimental blood-related transmission studies

Animal-to-animal transmission

TSE infectivity has never been found in blood from animals with naturally occurring infections (scrapie in sheep, BSE in cattle) when inoculated into mice [56–58]. However, early TSE blood-related transmission studies were not extensive, and employed only a small number of donor and recipient animals (Table 1). The low susceptibility of conventional mice in these studies can be explained by the existence of an interspecies barrier. In addition, it is

Table 1. Transmission studies to detect infectivity in the blood of animals with TSE.

Donor species	Recipient species	Inoculum ¹	Route of inoculation	Positive/total donors
Scrapie (natural)				
Goat	Mouse	Blood clot/serum	i.c.	0/3
Sheep	Mouse	Blood clot/serum	i.c.	0/18
BSE (natural)				
Cow	Mouse	Blood clot/serum	i.c. + i.p.	0/2
Cow	Mouse	Buffy coat	i.c. + i.p.	0/2
Scrapie (experimental)				
Goat	Goat	Whole blood	i.c.	0/14
Mouse	Mouse	Whole blood	i.c.	0/39
Goat	Mouse	Blood clot	i.c. or s.c.	0/20
Sheep	Mouse	Serum	i.c.	1/1
Rat	Rat	Serum	i.c.	1/1 (pool)
Mouse	Mouse	Serum	i.c.	1/1 (pool)
Mouse	Mouse	Whole blood	i.c.	3/13
Hamster	Hamster	Whole blood	i.c.	0/9
Hamster	Hamster	Blood extract	i.c.	5/5 (pools)
Hamster	Hamster	Blood extract	i.c.	10/11 (pools)
Hamster	Hamster ²	All blood components	i.c.	1/1 (large pool)
		Whole blood	i.c.	2.5–50%
		Whole blood	i.v.	< 1%
Mink encephalopathy (experimental)				
Mink	Mink	Serum	i.c.	0/1
Mink	Mink	Whole blood, plasma, red cells, white cells, platelets	i.c.	0/8 (pools)
BSE (experimental)				
Cow	Mouse	Buffy coat	i.c. + i.p.	0/11 (pools)
	Cow ²	Buffy coat	i.c.	0/4 (pools)
Mouse	Mouse	Plasma	i.c.	4/48
Sheep	Sheep ²	Whole blood	i.v.	1/19
CJD (experimental)				
Guinea pig	Guinea pig	Buffy coat	i.c., s.c., i.m., i.p.	10/28
GSS (experimental)				
Mouse	Mouse	Buffy coat	ip	4/7 (pools)
Mouse	Mouse	Buffy coat/plasma	i.c.	5/5 (pools)
		Buffy coat/plasma	i.v.	2/2 (pools)
		Whole blood	i.v.	1/20 ³

¹In several of the studies, assays were conducted on serial specimens obtained during both the incubation and clinical phases of disease.

²Ongoing experiments. Citations for the original studies can be found in [76]. ³Brown P & Cervenakova L, unpublished data. i.c., intracerebral; i.m., intramuscular; i.p., intraperitoneal; i.v., intravenous.

possible that animals with natural disease might have extremely low levels of TSE infectivity in blood that are not detectable in inbred mice, and more sensitive transgenic mice should therefore be used for the studies.

In contrast to the negative results observed in most transmission studies using human blood and the blood of animals with natural disease, transmissions have been consistently achieved when blood or blood components from experimentally TSE-infected animals, primarily rodents, were used for the

studies (Table 1). Infectivity has been found in blood and blood components during both the incubation phase of the disease and in clinically ill animals [59–71]. More recent studies employing large numbers of animals have reported extremely low levels of infectivity in blood, and blood components of mice < 100 infectious U mL⁻¹, that is 10⁴ times less than in the brain) infected with mouse-adapted GSS strain of human TSEs [66,67] and hamsters infected with hamster-adapted 263K strain of scrapie [68–70]. The intravenous route of

Table 2. Transmission studies to detect infectivity in the blood of humans with CJD.

Diagnosis	Pos./total subjects	Animal assay	Inoculum	Route of Inoculation	Pos./total animals	Reference
Sporadic CJD	1/1	Guinea pig	Buffy coat	i.c.	2/2	73
Sporadic CJD	1/1	Guinea pig	Buffy coat	i.c.	0/5	
		Hamster	Buffy coat	i.c.	2/2	
Sporadic CJD	1/3	Mouse	Whole blood	i.c.	2/13	71
Sporadic CJD	1/1	Mouse	Leukocytes	i.c.	0/10	74
		Mouse	Plasma conc. x3	i.c.	3/8	
Sporadic CJD	0/3	Chimpanzee	Whole blood units	i.v.	0/3	75
Sporadic CJD	0/1	Guinea pig	Whole blood	i.c., i.p.	0/2	
Sporadic CJD	0/1	Spider monkey	Whole blood	i.c., i.v., i.p.	0/3	
Sporadic CJD	0/1	Squirrel monkey	Whole blood	i.c., i.p., i.m.	0/1	
Sporadic CJD	0/4	Squirrel monkey	Buffy coat	i.c., i.v.	0/4	
hGH iatro. CJD	1/1	Hamster	Whole blood	i.c.	1/4	72
Sporadic CJD	0/13	Transgenic mouse	Buffy coat	i.c.	0/106	Safar <i>et al.</i> 2000 ¹
			Plasma	i.c.	0/56	
Variant CJD	0/7	R111 mouse	Buffy coat	i.c.	0/34	54
			Plasma	i.c.	0/47	

¹The transgenic mouse data has not been published [76]. Pos., positive; conc., concentrate.

inoculation was shown to be less efficient than the intracerebral route of the disease transmission for both buffy coat and plasma [67], and very low transmission rates were achieved by transfusion of whole blood [70; P. Brown and L. Cervenakova, unpublished data].

Taken together, these observations permit a confident statement that TSE infectivity occurs in the blood of experimentally infected animals, however, the relevance of these data to humans remains the subject of ongoing scientific debate.

Human-to-animal transmission

Attempts to transmit disease from human blood to animals are summarized in Table 2. Transmission of human CJD to rodents by intracerebral inoculation of whole blood [71,72], buffy coat [73] and plasma [74] has been reported. However, all these studies have been questioned on scientific grounds. In contrast, a number of attempts to transmit the disease have been made at the National Institutes of Health (NIH) Laboratory of Central Nervous System Studies [75] with negative results. Blood from 13 CJD patients, inoculated into either primates or rodents, including transfusion of units of blood from three sporadic CJD patients into three chimpanzees, did not transmit the disease. Another large study conducted recently using transgenic mice highly susceptible to human disease failed to record any positive transmissions from buffy coat and

plasma collected from 12 sporadic patients and one patient with familial CJD [76]. In addition, no transmissions resulted from intracerebral inoculation of mice with buffy coat and plasma from four vCJD patients [54]. More experimental studies using transgenic mice and nonhuman primates have been initiated to explore the transmissibility of the vCJD through blood transfusion and the use of plasma-derived products. The results of these ongoing studies will help us better evaluate the risk of transmitting vCJD through blood and blood components.

Epidemiological blood-related Creutzfeldt-Jakob disease transmission studies

A number of epidemiological studies have evaluated the risk of TSE transmission by blood or plasma-derived products. None of these studies has provided evidence that classical sporadic, familial or iatrogenic TSE are transmitted via blood transfusion or via plasma-derived products. Two systematic reviews of case-control studies [77,78] have analysed data from Japan [79], the UK [80-82], Europe [83], and Australia [84] and found no association with risk of developing sporadic CJD from blood transfusion.

Three studies investigating the possibility of human-to-human CJD blood-related transmission among the most frequently exposed individuals with genetic bleeding disorders were performed in the US

[85,86] and UK [87]. In the US study [85], neuropathological examinations of brain tissue from the few available autopsied patients with haemophilia A (22 cases), haemophilia B (one case) and von Willebrand disease (one case) revealed no features of CJD. All examined individuals, except one, received clotting factor concentrates for more than 10 years; one patient received cryoprecipitate. Most of the patients (21 cases) were HIV positive and the majority (15 cases) had clinical evidence of CNS involvement. Brain tissue from two cases was also evaluated for the presence of abnormal PrP; neither was positive by immunohistochemistry. Analysis of national mortality data in the US from 1979 to 1994 showed no evidence of CJD in patients with increased exposure to blood or blood products, specifically, patients with haemophilia A, haemophilia B, thalassemia and sickle cell disease [86]. In response to the emerging concern over vCJD, a retrospective neuropathological examination was conducted on 35 HIV positive UK haemophilic cases who were treated with clotting factor concentrates derived from predominantly UK donors during the years 1962–95 [87]. No evidence of spongiform encephalopathy was found and immunohistochemical analysis was negative in all cases. It was concluded that, at present, there is no evidence of the transmission of vCJD via clotting factor concentrates to patients with haemophilia.

An investigational retrospective study has been conducted by the US National Blood Data Resource Center since 1995 [88; personal communication from M. Sullivan]. Only the classical form of CJD has been under investigation because no cases of vCJD have occurred in the US. The study found no evidence of CJD transmission in 332 transfusion recipients of blood components from 23 CJD-implicated donors. None of the 212 (66%) deceased recipients for whom the cause of death was known died from CJD, and a subgroup of 120 surviving recipients (34%) continue to be followed. In addition, a subgroup of 42 long-term survivors have lived a minimum of 5 years after transfusion with no signs of neurological disease; some recipients were transfused as many as 28 years ago, and 17 of these survivors received components prepared from blood donated less than 1 year prior to the onset of disease in the donor. A report from Germany [89] identified one CJD patient who donated 55 units of blood during a 20-year period to 27 individuals. None of 18 deceased individuals died from dementia or neurological causes; nine patients were still alive 4–20 years after receiving transfusions from this patient, without any sign of mental deterioration.

Six years after the first identified case of vCJD, the CJD Surveillance Unit in the UK has identified several vCJD patients who received blood transfusions but none has been linked to a donor who later developed CJD or vCJD. Of 14 vCJD blood donors, eight were traced and had donated blood to 22 recipients. Transfused blood components included whole blood (two recipients), red blood cells (13 recipients), buffy-coat reduced red cells (two recipients), fresh-frozen plasma (three recipients), and cryo-depleted plasma and cryoprecipitate (one recipient for each component). Plasma donations from eight donors had entered plasma pools for the manufacturing of therapeutic proteins that were distributed to thousands of donors [personal communication from R. Will]. At least four blood donors who have developed vCJD in the UK have contributed to pools of plasma used to treat patients with haemophilia A and B. As a result there were two recalls of product in 1997 and 2000 [C. A. Lee, unpublished data].

Developments in diagnostic screening tests for Creutzfeldt–Jakob disease

Most of the uncertainties about the risk of transmission of CJD through blood or plasma-derived products could be resolved by an accurate test for the early detection of infected individuals or identification of contaminated blood or plasma pools, but abnormal prions have never been detected in blood of presymptomatic or symptomatic individuals, and the level of normal PrP in plasma of CJD patients is no greater than in patients with other neurological diseases or healthy control individuals [90]. Until recently, other body fluids (except the cerebrospinal fluid) have not been used for detection of PrP, but a promising discovery has recently been reported by Shaked *et al.* [91] who detected the presence of abnormal PrP in the urine of experimental hamsters infected with prions long before the appearance of clinical signs. Abnormal PrP was also detected in the urine of cattle with BSE and in symptomatic humans afflicted with a genetic form of CJD. The value of this technique as a diagnostic tool will need to be validated by other independent laboratories. Another encouraging observation was recently made [92] by the discovery that levels of an erythroid differentiation-related factor (EDRF) transcript was decreased in the spleens of scrapie-infected mice in both the preclinical and clinical phase of the disease and in the blood of terminally ill animals. A significant decrease in the expression level was also observed in the bone marrow of cattle with early

signs of BSE and in whole blood of sheep with scrapie. Further analysis of mouse bone marrow revealed that EDRF is expressed in maturing erythroid cells. Preliminary analysis of normal human blood revealed EDRF expression in the nonlymphocyte fraction, and future studies will be required to determine whether EDRF might be used as a diagnostic marker of human TSEs.

Extensive reviews have recently been published on progress in the development of diagnostic screening tests for CJD by different laboratories [76,93]. All assays were aimed at detecting the presence of abnormal PrP as an indicator of TSE infection, and all except one were based on an immunological approach using appropriate PrP-specific antibodies. The sensitivity of classical immunoblotting assays has been significantly improved [52,93,94], variations of dissociation-enhanced lanthanide fluoroimmunoassay (DELFLIA) have been introduced [95, 96], and new advanced technologies such as UV-fluorescence spectroscopy [97], capillary electrophoresis [98,99] and confocal laser spectroscopy [100] have been applied. None of these assays has yet achieved the required sensitivity to detect picogram levels of abnormal PrP equivalent to approximately $10\text{--}20\text{ IU mL}^{-1}$, the estimated maximum concentration of infectivity in buffy coat during the preclinical phase of disease in experimental transmission studies [76]. One group reported the detection of abnormal PrP in blood from scrapie-infected sheep [99], but we have not been able to identify the presence of abnormal PrP in the blood of CJD-infected chimpanzees or humans afflicted with TSEs using this approach [Cervenakova *et al.*, unpublished data]. A potentially important discovery has been made by Saborio *et al.* [101] who reported that pulse sonication could convert *in vitro* normal PrP into a protease-resistant, abnormal PrP-like isoform in the presence of tiny quantities of the abnormal PrP template. Conceptually this procedure is analogous to polymerase chain reaction amplification; the initial templates of abnormal PrP aggregate with normal PrP to form new abnormal aggregates that are then disrupted by sonication to form smaller abnormal PrP units for continued formation of new abnormal molecules. This method yielded approximately 30 times more abnormal PrP (250 pg or 8.3×10^{-15} mol) compared to the input amount (6–12 pg or $0.2\text{--}0.4 \times 10^{-15}$ mol). It may be possible by this novel approach to amplify a subthreshold amount of abnormal PrP from blood to detectable levels.

One problem that the field faces today is the absence of a high-affinity reagent that would specifically recognize only abnormal PrP. Recently, plasmi-

nogen, a protein of the fibrinolytic system present in blood, which has also been implicated in neuronal excitotoxicity, has been identified as the first naturally occurring protein that may specifically bind full-length native abnormal PrP from brain tissue of multiple species [102, 103]. Earlier, a protocadherin-2 was identified as a cellular receptor of high affinity ($K_d < 25\text{ nmol}$) for both normal and abnormal forms of PrP [104; personal communication from N. Cashman]. Ideally, the use of these or other reagents with similar properties, in combination with various approaches such as *in vitro* amplification, may achieve a concentration of abnormal PrP to levels that could be detected by presently available methods, and also find use in the removal of infectious TSE agents from blood and plasma-derived products.

Removal of TSE agents/prions during the manufacturing process of plasma-derived Products

To define the risk of vCJD being transmitted by plasma-derived therapeutic products, it is first necessary to define the partition of infectivity through the various separation steps used in the manufacture of plasma products. Two approaches are possible for validation studies: (1) use of plasma of experimentally infected animals (endogenous infected plasma) containing low levels of infectivity that can be detected only in bioassays; and (2) use of brain tissue (or tissue extract) from infected animals or humans as an infectivity 'spike' to evaluate the clearance of TSE infectivity in bioassays, or of abnormal PrP by an immunological method, for example Western blot [94,105,106] or conformation-dependent immunoassay (CDI) [95].

Two experiments have evaluated partitioning of endogenous TSE infectivity in plasma collected from clinically ill mice infected with mouse-adapted human TSE during Cohn fractionation, modified for small volumes [66,67]. The TSE infectivity was partitioned into various fractions using cold precipitation and different ethanol concentrations and pH. Even though some of the infectivity partitioned into cryoprecipitate, used by most manufacturers to produce FVIII, the level of infectivity was more than 10-fold lower than in plasma, and several log orders lower than levels in the brains of clinically ill animals. These very low levels of infectivity did not allow an evaluation of the removal capability of various steps. Therefore, most validation studies have been performed using the 'spiking' approach, which has documented a significant degree of

abnormal PrP removal during precipitation, adsorption/desorption steps, including anion and cation exchange chromatography, hydrophobic interaction chromatography, nonspecific adsorption, and multiple ion-exchange procedures [106, 107].

Brown *et al.* [66] studied the partitioning of TSE infectivity during the modified Cohn fractionation of plasma separated from human blood 'spiked' with hamster-adapted 263K scrapie strain. Only a small proportion of the infectivity (3%) was recovered in plasma and only 0.71% and 0.86% in cryoprecipitate and fraction I + II + III. Table 3 shows the efficiency of TSE infectivity and prion removal by various steps used for manufacture of FVIII. Lee *et al.* [94,105] performed validation studies of certain plasma-purification steps used by Bayer for the manufacture of plasma-derived therapeutic proteins. Their principle purification steps for manufacture of FVIII (Koate DVI) employ multiple precipitations and size exclusion chromatography [106]. Two validated manufacture steps, cryo-precipitation and PEG precipitation, together removed 2.2 log₁₀ ID₅₀ from FVIII [105]. Foster [107] calculated the cumulative removal efficiency of multiple steps employed by SNBT Protein Fractionation Centre (Edinburgh, UK) during the manufacture of plasma products, by analysing published data on the removal capacity of various steps. A 4 log₁₀ ID₅₀ reduction of TSE infectivity during the manufacturing of the FVIII concentrate, Liberate[®] was shown. In a subsequent large experimental study Foster *et al.* [108] showed a 6.8 log₁₀

cumulative reduction of abnormal PrP by four main steps (cryoprecipitation, precipitation and adsorption of cryoprecipitate extract, ion exchange chromatography and membrane filtration) used in the production of FVIII.

Some of these same issues have been addressed in an extensive study conducted recently by Aventis Behring [109]. The company uses multiple precipitation steps during the manufacture of Haemate P (equivalent to Haemate HS), and ion-exchange chromatography for the manufacture of Beriate P (equivalent to Beriate HS) [106]. The study evaluated the efficiency of TSE removal by various precipitation steps, using four different spikes prepared from the brain tissue of hamsters infected with Sc237 strain of scrapie, and compared the partitioning of various prion strains, including vCJD. The question of proper spiking material for inactivation/removal experiments is important because the physico-chemical state of the agent, should one exist in human blood, is not known. Removal of less than 1 log₁₀ of PrP was achieved by cryoprecipitation and a precipitation step utilizing 8% ethanol when plasma was spiked with any of three different materials, brain homogenate, microsomal membranes and caveolae-like domains. However, significantly more removal was achieved for cryoprecipitate (2.4 log₁₀) and 8% ethanol precipitate (3.1 log₁₀) when purified abnormal PrP was used as a 'spike' [109].

Removal of TSE infectivity has also been documented in a validation study of the American Red Cross/Baxter manufacturing process used for preparation of coagulation factor VIII concentrates (Red Cross'

Table 3. Efficiency of prion protein and/or TSE infectivity removal by various steps used in manufacture of plasma-derived factor VIII.

Validated manufacturing steps	Spiking material: hamster scrapie ¹	Detection method	PrP ^{Sc} or infectivity reduction factor	Company
Cryoprecipitation, precipitation and adsorption, SD treatment and ion-exchange chromatography, membrane filtration	263K: microsomal fraction	Western blot	6.8 ³ log ₁₀	SNBTS Protein Fractionation Centre [108]
Cryoprecipitation and cryoprecipitate/PEG separation	263K: brain homogenate	Western blot Bioassay	2.2 ³ log ₁₀ mL ⁻¹ 3.0 log LD ₅₀ mL ⁻¹	Bayer [105]
Cryoprecipitation	Sc237: brain homogenate, microsomal fraction, CLDs ² Sc237: Purified PrP ^{Sc}	Conformation-dependent immunoassay	< 1 log ₁₀ 2.4 log ₁₀	Aventis-Behring [109]
Ethanol precipitation 8%	Sc237: Brain homogenate, microsomal fraction, CLDs Sc237: Purified PrP ^{Sc}		< 1 log ₁₀ 3.1 log ₁₀	
FVIII immunoaffinity column ion-exchange chromatography [109]	263K: Brain homogenate	Bioassay	4.57 log LD ₅₀ mL ⁻¹ 3.47 log LD ₅₀ mL ⁻¹	American Red Cross/Baxter [110]

¹Hamster-adapted scrapie (263K or Sc237); ²CLD, caveola-like domains; ³sum of all steps tested.

MONARC-M™ and Baxter's Hemofil M). For validation of the efficiency of two main manufacturing steps (monoclonal antibody affinity chromatography and ion exchange chromatography), cryoprecipitate suspension and fresh eluate from the immunoaffinity column were spiked with 263 K scrapie strain [106]. The results showed removal of 4.57 log₁₀ ID₅₀ by the anti-FVIII immunoaffinity chromatography, and of 3.47 log₁₀ ID₅₀ by Q-Sepharose chromatography, for a total removal of 8.04 log₁₀ ID₅₀ by the complete process [110].

Taken together, accumulated data provide strong evidence that a substantial amount of TSE infectivity could be removed by the steps used during the manufacturing of coagulation factors. These data agree with the failure of epidemiological studies to identify iatrogenic blood-related transmission of TSEs. More studies are under way to address the safety issues associated with vCJD, not only for coagulation factors, but also for other plasma-derived therapeutics. Hopefully, the combination of different approaches and new developments in detection and/or removal methodologies for TSE infectivity will lead to even greater safety in regard to the still theoretical risk of iatrogenic transmission of vCJD through blood transfusion and plasma-derived products.

Conclusion

Treatment of haemophilic patients with high-quality therapeutics, and the elimination of risks associated with blood-transmitted diseases, deserves our highest priority. The emergence of vCJD in the UK has produced a new, albeit hypothetical, risk of infection for haemophilic patients treated with coagulation factors, and some evidence suggests that the TSE agent causing vCJD might be more invasive to lymphoreticular tissue than classical CJD. Without a reliable diagnostic test for selection of donors and testing of blood products, a donor deferral policy will remain the main preventive measure. Producers of plasma-derived therapeutics, including FVIII, are working toward the development of appropriate methods to assure the removal of the vCJD agent/infectivity, if present in human blood. Treatment of haemophilic patients with recombinant FVIII may further decrease the possible risk of human-to-human vCJD transmission. However, in the absence of available recombinant products, the hypothetical risk of vCJD from plasma products is surely outweighed by the real risk of inadequate medical treatment.

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