

World Federation of Hemophilia
1425 René Lévesque Blvd. W. Suite 1010
Montréal, Québec
H3G 1T7 Canada
Tel.: +1 (514) 875-7944
Fax: +1 (514) 875-8916



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The paper by Hunter et al (Transmission of prion diseases by blood transfusion - *Journal of General Virology* (2002), 83, 2897–2905. Published ahead of print -16 July 2002) offers valuable data on the potential transmission of transmissible spongiform encephalopathies (TSE's) through blood. In this work, transmission of bovine spongiform encephalopathy (BSE) in sheep from blood from other sheep infected orally with this disease is described, furthering work earlier reported by this group¹. In addition, this paper reports the first description of a naturally occurring TSE – sheep scrapie – being transmitted through blood. However, the authors' comment that "...that measures taken to safeguard the blood supply in the UK are fully justified" (p 15) bears further comment.

As a result of the uncertainty surrounding the potential transmission of variant Creutzfeldt Jakob Disease (vCJD) by blood, in 1998 the United Kingdom authorities took two decisions:

- i. Plasma for fractionation into large pool plasma derivatives was not to be sourced from donors resident in the United Kingdom. This measure was restricted to the plasma for fractionation; other blood products, including cellular components and plasma for transfusion, has continued to be sourced from UK donors².
- ii. Other blood products sourced from UK donors were to be submitted to leucocyte depletion to remove white blood cells from the product prior to their clinical use³.

Since the decision to not use plasma from UK-sourced donors, a range of studies⁴ have demonstrated that plasma fractionation processes have the capacity to eliminate high levels of contaminating prion agents. This capacity does not seem to depend on the strain of agent studied⁵. Hunter et al's paper does not address the issue of the transmission of disease through contaminated plasma fractions, as their studies were limited to whole blood or buffy coat transmissions. The sheep data do not allow the computation of the potential infectivity levels in human blood, but an approximation derived from data on tissue prionic contamination in vCJD patients⁶ suggests that the demonstrated capacity of fractionation processes to eliminate prions would be sufficient to render plasma derivatives non-infectious.

¹ Houston F et al (2000) Transmission of BSE by blood transfusion in sheep. *Lancet* 356:999-100000

² Press release UK Department of Health 98-182 - 13 May 1998. Committee on safety of medicines completes review of blood products. On <http://www.doh.gov.uk/cjd/press/blood.htm>

³ Press release UK Department of Health 98/295 - 17 July 1998. Government accepts advice on leucodepletion from spongiform encephalopathy advisory committee. On <http://www.doh.gov.uk/cjd/press/advice.htm>

⁴ Farrugia A (2002) Risk of variant Creutzfeldt Jakob disease from factor concentrates: current perspectives. *Haemophilia* 8:230-235

⁵ Stenland CJ et al (2002) Partitioning of Human and Sheep Forms of the Pathogenic Prion Protein During the Purification of Therapeutic Proteins from Human Plasma. *Transfusion* in press.

⁶ Wadsworth JDF et al (2001) Tissue distribution of protease resistant prion protein in variant Creutzfeldt-Jakob disease using a highly sensitive immunoblotting assay. *Lancet* 358: 171-180

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The initial studies suggesting that TSE infectivity may be concentrated in peripheral leucocytes⁷ have now been updated through other studies indicating that this is not the case⁸, and Hunter et al's study also quotes work indicating that pathological prion is not found on peripheral sheep leucocytes. Therefore, while targeted use of leucocyte reduction in blood products continues to be a legitimate option in transfusion practice⁹, the UK decision to introduce this measure in order to decrease any unknown vCJD blood risk is not supported by evidence, including Hunter et al's data. Indeed, Hunter et al's demonstration that buffy coat as well as whole blood transmitted disease in their sheep scrapie experiments does not allow any conclusions regarding the possible differential distribution of infectivity in blood, as both these products show a similar composition. Infectivity in cell-free plasma has been shown by previous studies in a rodent model of blood infectivity¹⁰, and again, these infectivity levels have been shown to be eliminated from therapeutic plasma fractions.

Hunter et al's paper necessarily raises the question of the relevance of these findings in sheep to the human situation. The heightened concern of vCJD blood transmission relative to the risk of classical CJD (cCJD) lies primarily in the higher level of extra-neural involvement, primarily in the lymphoreticular system (LRS) in the variant disease. Such a high LRS involvement has been demonstrated and confirmed by Hunter et al for sheep infected orally with BSE and sheep with natural scrapie. It does not appear to result in a similar level of peripheral LRS involvement in recipient sheep infected with BSE through blood, and equivalent data in humans is lacking as no human patients have had blood vCJD transmission. However, the relatively short incubation periods, albeit in genetically susceptible sheep, reported by Hunter et al for blood transmission of TSE's suggests that this high level of LRS involvement may result in heightened blood infectivity relative to TSE's where such involvement is not evident, such as human cCJD. In this regard it is interesting that Hunter et al report a low level of LRS involvement in sheep inoculated intracranially with BSE, and transfusion studies using such sheep as donors might prove insightful. In the meantime, ongoing studies on recipients of blood components from donors who developed vCJD should allow, in time, a better assessment as to whether the high transmission rates observed in sheep are to be expected in humans. Twenty two such recipients are under observation with no cases of vCJD observed up to now. Further data on the vCJD cases, to define time interval between blood donation and development of disease are being accumulated.

Hunter et al's paper is stimulating active consideration of further precautionary measures in minimising blood vCJD risk. While such measures need to be kept under constant review,

⁷ Klein MA et al (1997) A crucial role for B cells in neuroinvasive scrapie. *Nature* 390, 387-90

⁸ Shlomchik K et al (2001) Neuroinvasion by a Creutzfeldt-Jakob disease agent in the absence of B cells and follicular dendritic cells. *PNAS*;98:9289-9294.

⁹ Vamvakas EC & Blajchman MA(2001) Universal WBC reduction: the case for and against. *Transfusion*; 41:691-712.

¹⁰ Brown P et al (1999) Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfeldt-Jakob disease in humans. *Transfusion* 39:1169-1178.

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there appears to be little justification for countries to further donor deferral measures beyond those already announced for donors with a history of residence in the United Kingdom, or to consider further the leucodepletion option, at least in terms of vCJD risk. Another option under active consideration – the deferral of donors who are previous transfusion recipients, is known to have a potentially severe effect on the blood supply¹¹, and such effects need to be carefully considered before this and similar measures are introduced. However, Hunter et al's other statement “that the measures taken to restrict the use of blood in the UK have been fully justified” merits support. Numerous studies continue to document the inappropriate use of blood in various clinical situations,¹² a situation demanding as active an approach as the measures taken to minimise vCJD through supply interventions. Furthermore, in an era of increasing availability of substitutes for blood – derived pharmaceuticals, authorities continue to be hesitant in providing the infrastructure required for, for example, the provision of recombinant coagulation products for people with haemophilia. It is through comprehensive strategies like these that blood related infectivity risks can best be minimised.

Albert Farrugia PhD
Blood Safety Adviser, World Federation of Hemophilia
On behalf of the TSE Task Force of the World Federation of Hemophilia

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¹¹ Giangrande P (2002) Summary of EMEA Meeting on TSEs London, June 19th/20th, 2002. On http://www.wfh.org/Content_Documents/Blood_Safety/EMEA_rpt_June02.pdf

¹²The Sanguis Study Group (1994) Use of blood products for elective surgery in 43 European hospitals. *Transfusion Medicine* 4:251-268