



## **UPDATE ON THE 'TRANSFUSION' vCJD CASE**

### **Issue**

1. In December 2003 the Secretary of State for Health informed Parliament of the death of a patient who died of vCJD 6.5 years after receiving a blood transfusion donated by an individual who subsequently developed the disease. SEAC will be updated on this case.

### **Background**

#### **Blood transfusion vCJD case**

2. The recipient was transfused blood in 1996 from a donor who was, at the time of donation, free of clinical signs of vCJD. The donor developed vCJD in 1999. The recipient died of vCJD in the autumn of 2003. A case report has recently been published in the *Lancet* by Llewelyn *et al* 2004 (Annex 1).
3. It is possible that the disease was transmitted from donor to recipient by blood transfusion, in circumstances where the blood of the donor was infectious, three years before the donor himself or herself developed vCJD, and where the recipient developed vCJD after a six and a half year incubation period. This is a possibility not a proven causal connection, as it is also possible that this patient acquired vCJD by eating BSE-infected meat or meat products.
4. This development is not entirely unexpected, and over the last 7 years, SEAC have worked on the assumption that blood may be infective and based on precautionary risk assessments, measures have already been put in place by the Department of Health and the National Blood Service to protect the blood supply. Additionally, experimental research in animals has shown that prion diseases can be transmitted via blood transfusion.

#### **Parliamentary questions on the case**

5. The statement made by the Secretary of State and supplementary Parliamentary questions and answers relating to the vCJD transfusion case are presented in Annex 2.

## **Measures already in place to protect the blood supply**

6. In view of the possibility of transmission of CJD from transfused blood, exclusion criteria have been put in place to prevent people “at risk” from CJD donating blood ([Annex 3](#)). The precautionary measures that have been put in place in the UK are as follows:
  - All blood for transfusion has been leucodepleted (white cells removed by filtration) since 31 October 1999.
  - From the end of 1999, plasma for blood products has been sourced from outside the UK.
  - Since December 2002, fresh frozen plasma for those born after 1<sup>st</sup> January 1996 has been sourced from the USA.
7. In June 2003, the Advisory Committee on Dangerous Pathogens (ACDP) published revised guidance on safe working and prevention of infection for transmissible spongiform encephalopathy agents, see web link: <http://www.doh.gov.uk/cjd/tseguidance/>. The ACDP guidance assumes that blood can be infective but that the level of infectivity in blood from sCJD or vCJD infected humans is low. This guidance is based on previous SEAC advice and advice from a joint ACDP/SEAC working group.

## **Previous SEAC opinions**

8. SEAC considered the possibility that blood may be infective in October 1997 when they initially advised leucodepletion of blood and that assessments be carried out on the risk of transmission of vCJD by blood transfusion, which would help inform decisions on any measures that may be necessary to protect blood transfusion recipients. In 1999 SEAC considered a report on the assessment of the risk of exposure to vCJD infectivity in blood and blood products by Det Norske Veritas (DNV). Following this assessment, SEAC identified several measures that might provide significant reduction in risk of transmission via blood, in particular leucodepletion and elimination of UK plasma products.
9. In June 2002 SEAC were informed of several research projects which were in progress and where results might necessitate revision of the assessment at a later date.

## **Experimental research evidence for transmission of TSEs by blood transfusion**

10. Houston *et al.*, 2000<sup>a</sup> and Hunter *et al.*, 2002 (Annex 4) transfused blood (400-450mL) or buffy coat (1 unit, equivalent to 400-450mL blood) from sheep experimentally infected with BSE or natural scrapie to scrapie-susceptible recipient sheep. Two out of 17 recipients of whole blood showed clinical signs typical of TSE in sheep. Both these recipients were transfused with whole blood taken during the preclinical stage of donor BSE infection. Although still incomplete at the time of publication, this study indicated a frequency of transmission of BSE in at least 8% of the 24 recipients transfused with either whole blood or buffy coat. This would rise to 17% if a further 2 suspected cases transfused with whole blood taken during the clinical stage of donor BSE infection were to be confirmed.
11. One positive transmission occurred in a sheep transfused with buffy coat taken at the clinical end-point from the donor, no other transmissions from the 7 buffy coat donations were seen at the time of reporting.
12. Of the 21 sheep transfused with whole blood taken from natural scrapie-infected animals, 4 animals have shown clinical signs of scrapie at the time of publication, indicating a frequency of transmission of scrapie in at least 21% of the recipients.
13. Hunter *et al* 2002 comment that infectivity may not be confined to the buffy coat fraction and there may also be significant levels of infectivity in the plasma and/or red cell fractions.
14. Previous studies on the infectivity of blood from animals with TSE have been reviewed by Brown *et al* (2001), see Annex 5. In the experimental models it was clear that blood or its components can be infectious during both the incubation and clinical phases of TSE disease. On the weight of the available data the authors considered that transmission of the disease by the intravenous route required 5-7 times more whole blood, buffy coat or plasma than transmission by the intracerebral route.

---

<sup>a</sup> Houston F., Foster J.D., Chong A., Hunter N. and Bostock C.J. (2000) Transmission of BSE by blood transfusion in sheep. *Lancet* 356, 999-1000

15. From the review by Brown *et al* (2001) attempts to detect infectivity in the blood of humans with CJD have centred largely on sporadic CJD, with isolated studies using blood from iatrogenic CJD and familial CJD, with infectivity demonstrated in buffy coat, whole blood or plasma in some studies using rodent bioassays but not in monkey or chimpanzee bioassays. With vCJD, no infectivity was detected in blood from 2 patients using mouse bioassays (Bruce *et al* 2001)<sup>b</sup> however sensitivity could be limited by the species barrier.
16. Herzog *et al* 2004 (see paper SEAC INF/81/6) reported that, on the basis of primate data, the intravenous route should be considered as efficient as the intracerebral route for the transmission of BSE, indicating that blood can carry infectivity round the body.

### **SEAC opinion on transmission of prion diseases by blood transfusion**

17. In September 2002 SEAC considered the Hunter *et al* 2002 transfusion study in sheep and concluded that the work did not directly inform about the level of risk but there remained a theoretical risk for human health from the transfusion of blood or blood products. SEAC recommended that more targeted fractionation studies should be performed to determine which fractions contained infectivity and whether this varies according to the stage in the incubation period, and should include testing for infectivity in leucodepleted sheep blood.

### **EC Scientific Steering Committee (SSC) Opinion**

18. The SSC reviewed the studies on transmission of BSE by blood transfusion in sheep by Hunter *et al* 2002 in their Opinion issued in September 2002 (Annex 6). The SSC concluded that “these results support already published SSC, SCMPMD and EMEA opinions and recommendations on blood safety”. (These opinions are summarised on pages 7 and 8 of the SSC opinion in Annex 6). The SSC also stated that “although the transmission of infectivity through blood in vCJD urgently needs further study, the data presented in this paper neither justify nor add arguments for the introduction of new methods or approaches to the assessment of blood safety.”

---

<sup>b</sup> Bruce M.E., McConnell I., Will R.G., and Ironside J.W. (2001) Detection of variant Creutzfeld-Jakob disease infectivity in extraneural tissues. *Lancet* 358, 208-209

## List of accompanying material

### Annex 1

Llewelyn C.A., Hewitt P.E., Knight R.S.G., Amar K., Cousens S., Mackenzie J and Will R.G. (2004) Possible transmission of variant Creutzfeld-Jakob disease by blood transfusion. *Lancet* **363**; 417-421

### Annex 2

The 17 December 2003 Statement by the Secretary of State for Health and related Parliamentary Questions

### [Annex 3](#)

ACDP/SEAC guidelines on Transmissible Spongiform Encephalopathy Agents: Safe working and the prevention of infection.

Extract from Part 4: Infection control of CJD and related disorders in the healthcare setting

Annex A.1 Distribution of TSE infectivity in human tissues and body fluids

### Annex 4

Hunter N., Foster J., Chong A., McCutcheon S., Parnham D., Eaton S., Mackenzie C and Houston F. (2002) Transmission of prion diseases by blood transfusion. *J. Gen. Virol.* **83**; 2897-2905

### Annex 5

Brown P., Cervenáková L. and Diringer H. (2001) Blood infectivity and the prospects for a diagnostic screening test in Creutzfeld-Jakob disease. *J. Lab. Clin. Med.* **137**; 5-13

### [Annex 6](#)

EC Scientific Steering Committee Opinion on: "The implications of the recent papers on transmission of BSE by blood transfusion in sheep (Houston et al, 2000; Hunter et al, 2002)" adopted on 12-13 September 2002

**Guidance from the Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee**

***Extract from: Transmissible Spongiform Encephalopathy Agents: Safe working and the prevention of infection, Infection control of CJD and related disorders in the healthcare setting***

**Part 4**

**Infection Control of CJD and Related Disorders in the Healthcare Setting**

**Blood**

4.10 Ongoing epidemiological studies have not revealed any cases of CJD or vCJD being caused by blood or blood products. However, vCJD is a relatively new disease on which there are few data. There is experimental evidence that intracerebral inoculation of some blood components can occasionally transmit the CJD agent. Recent work (Bruce *et al* 2001, Wadsworth *et al* 2001) found no infectivity or PrP-res in buffy coat prepared from blood from vCJD patients. However, the transmission of experimental BSE from sheep-to-sheep *via* whole blood transfusion has been reported from ongoing experimental work (Hunter *et al* 2002).

4.11 In consideration of the possibility of transmission of CJD *via* transfused blood, exclusion criteria were put in place to prevent people “at risk” from CJD – see Table 4a, sections 2 and 3 - donating blood. In addition, in view of the uncertainties surrounding the risk of transmission of vCJD *via* blood or blood products, the following precautionary measures have been put in place in the UK:

- All blood destined for transfusion has been leucodepleted (white cells removed by filtration) since 31 October 1999;
- Plasma for blood products has been sourced from outside the UK since 1998;
- Fresh frozen plasma (FFP) for those born after 1 January 1996 has been sourced from the United States since 2002.

**Patient risk groups**

4.16 When considering measures to prevent transmission to patients or staff in the healthcare setting, it is useful to make a distinction between *symptomatic* patients, *i.e.* those who fulfil the diagnostic criteria for definite, probable or possible CJD or vCJD, and *asymptomatic* patients *i.e.* those with no clinical symptoms, but who are potentially *at risk* of developing one of these diseases, *i.e.* having a medical or family history which places them in one of the risk groups – see Annex B for diagnostic criteria.

Table 4a below details the classification of the risk status of symptomatic and asymptomatic patients.

**Table 4a: Categorisation of patients by risk**

4.17 Patients should be categorised as follows, in descending order of risk:

<p>1. Symptomatic patients</p>	<p>1.1 Patients who fulfil the diagnostic criteria for definite, probable or possible CJD or vCJD (see Annex B for diagnostic criteria).</p> <p>1.2 Patients with neurological disease of unknown aetiology who do not fit the criteria for possible CJD or vCJD, but where the diagnosis of CJD is being actively considered</p>
<p>2. Asymptomatic patients at risk from familial forms of CJD linked to genetic mutations</p>	<p>2.1 Individuals who have or have had two or more blood relatives affected by CJD or other prion disease, or a relative known to have a genetic mutation indicative of familial CJD.</p> <p>2.2 Individuals who have been shown by specific genetic testing to be at significant risk of developing CJD or other prion disease.</p>
<p>3. Asymptomatic patients potentially at risk from iatrogenic exposure##</p>	<p>3.1 Recipients of hormone derived from human pituitary glands, e.g. growth hormone, gonadotrophin.</p> <p>3.2 Individuals who have received a graft of <i>dura mater</i>. (People who underwent neurosurgical procedures or operations for a tumour or cyst of the spine before August 1992 may have received a graft of <i>dura mater</i>, and should be treated as <i>at risk</i>, unless evidence can be provided that <i>dura mater</i> was not used).</p> <p>3.3 Patients who have been contacted as potentially <i>at risk</i> because of exposure to instruments used on, or receipt of blood, plasma derivatives, organs or tissues donated by, a patient who went on to develop CJD or vCJD*.</p>

## NB: A decision on the inclusion of corneal graft recipients in the "iatrogenic at risk" category is pending completion of a risk assessment.

\* The CJD Incidents Panel, which gives advice to the local team on what action needs to be taken when a patient who is diagnosed as having CJD or vCJD underwent surgery or donated blood, organs or tissues before CJD/vCJD was identified, will identify contacts who are potentially at risk.