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医薬品　研究報告 調査報告書

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研究報告の概要

英国で白血球除去が導入される前に赤血球製剤の輸血により、変異型クロイツフェルトーヤコブ病（vCJD）の伝播が3例報告されている。
げっ歯動物の伝染性海綿状脳症（TSE）の実験では、赤血球製剤の感染性は赤血球自体とは無関係であり、感染性は残留白血球や血漿中の他の成分と関連することが示された。
ハムスターの異常プリオンを添加した白血球除去ヒト赤血球の感染性は 0.01％まで除去されたと報告もあり、これは感染性が赤血球によるものではない、あるいは赤血球と感染物質が結合していてもその結合は緩く、ろ過プロセスによって除去されることを示している。
vCJD の原因物質がヒト赤血球と結合しないことを確認できたならば、血中の PRPsc の適切なスクリーニング検査がない現状においては、vCJD 発生国の輸血サービスは赤血球製剤を輸血する前に洗浄またはろ過処理して感染性除去を行うことが賢明である。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
英国における輸血による vCJD 感染例は白血球除去を行っていない赤血球製剤によるものであるが、赤血球自体には感染性はなく、ろ過により除去できるとの情報である。 現時点まで血漿分画製剤からの vCJD 伝播の報告はなく、血漿分画製剤の製造工程でプリオンが除去できるとの情報もある。	今後とも vCJD に関する安全性情報等に留意していく。

Prion protein and the red cell

David J. Anstee

Purpose of review
This review focuses on transfusion-transmission of variant Creutzfeldt-Jakob disease by red cell preparations.

Recent findings
Recently, three cases of probable transmission of variant Creutzfeldt-Jakob infectivity by transfusion of red cell preparations have been described in humans. Experiments on transmissible spongiform encephalopathies affecting rodents have led to the conclusion that infectivity in red cell preparations is not bound to the red cells themselves but contained within the suspending medium from which it can be removed by filtration.

Summary
Red cell preparations are the main transfusion product provided by blood services. If experiments demonstrating significant removal of rodent transmissible spongiform encephalopathy infections by filtration of red cell preparations are applicable to variant Creutzfeldt-Jakob in humans then a method for rendering human red cell preparations safe for transfusion is provided.

Keywords
bovine spongiform encephalopathy, normal prion protein, abnormal (infectious) prion protein, transmissible spongiform encephalopathy, variant Creutzfeldt-Jakob disease

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Abbreviations

BSE	bovine spongiform encephalopathy
GPI	glycosylphosphatidylinositol
PRPc	normal prion protein
PRPsc	abnormal (infectious) prion protein
TSE	transmissible spongiform encephalopathy
vCJD	variant Creutzfeldt-Jakob disease

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Introduction

Variant Creutzfeld-Jakob Disease (vCJD) was described in the UK in 1996 [1]. The emergence of this novel form of CJD is most probably related to the ingestion of food products obtained from cattle with bovine spongiform encephalopathy (BSE) [2,3]. From the outset the possibility was considered that passage of infectivity from the gut to the brain in affected individuals could involve blood. Therefore, transfusion services were alerted to the potential for transmission of vCJD to a patient by transfusion of blood components from a donor in the preclinical stages of disease. Consequently, precautionary measures were taken in the UK to minimize this risk, in particular leucodepletion, sourcing plasma for fractionation from non-UK donor populations, sourcing fresh frozen plasma for children born after 1 January 1996 (and therefore not exposed through diet) from non-UK donor populations and deferral of blood donors who had themselves been transfused [4]. Sourcing sufficient red cell and platelet components outside the UK is not feasible. The first cases of probable transfusion–transmission emerged in late 2003 and three probable transmissions, all linked to red cell preparations transfused before the introduction of leukodepletion, are now recorded [5,6,7*,8**].*

The infectious agent

There is a large body of evidence suggesting the infectious agent causing BSE and vCJD is an abnormal conformer of the prion protein [9]. Recently, evidence has emerged suggesting that retroviral infection can increase the release of infectious prions from cells and may be an important cofactor in the spread of infection [10*].

Normal prion protein (PRPc) is a glycosylphosphatidylinositol (GPI)-linked protein expressed at cell surfaces of many tissues. It is a glycoprotein rich in α-helix. The function of PRPc is unclear, although recent studies suggest a role in self-renewal of haemopoietic progenitor cells [11*]. The infectious prion protein (PRPsc) is an abnormal conformer of PRPc in which the α-helical regions become predominantly β sheet. This change in secondary structure alters the properties of the protein so that PRPsc has a greater propensity to aggregate. Aggregates of PRPsc accumulate within cells in the brain of

* Since this manuscript was submitted for publication a fourth case of probable transfusion-transmission of vCJD by non-leukodepleted red cell preparations has been reported in the UK (http://www.hpa.org.uk) and a further study demonstrating removal of endogenous TSE infectivity from leukodepleted scrapie-infected hamster whole blood by filtration through prion-specific affinity resins has been published (Gregori L, Gurgel PV, Lathrop JT *et al.*, 2006 Lancet 368;2226–2230).

affected individuals creating the toxic environment that ultimately results in spongiform encephalopathy. Size fractionation suggests the most infectious prion particles comprise aggregates of 14–28 molecules [12]. Once a small amount of PRPsc is ingested it can associate with PRPc from the affected individual and convert this PRPc to PRPsc creating an autocatalytic effect, which greatly increases the amount of PRPsc in the affected individual. This autocatalytic effect has been reproduced *in vitro* in a hamster model [13].

Normal prion protein is essential for the disease process

PRPc must be available for prion disease to occur [14,15,16•]. Furthermore, mice engineered to translate PRPc without a GPI anchor accumulate PRPsc in the brain, blood and heart but do not develop clinical scrapie [17,18]. These results indicate that membrane tethering of PRPc is essential for disease progression. GPI-linked proteins frequently occupy lipid rafts in the plasma membrane. In cultured adult sensory neurones PRPc leaves lipid rafts to recycle between the cell surface and recycling endosomes in a time scale of minutes [19]. The mechanism whereby PRPc is converted to PRPsc is not fully understood but may occur at the cell surface when PRPc leaves its lipid raft prior to endocytosis [20]. After endocytosis, PRPc goes to recycling endosomes [21] while PRPsc trafficks to lysosomes [22]. Passage of PRPsc to lysosomes can be via multivesicular bodies from which small vesicles 40–100 nm in diameter (exosomes) rich in GPI-linked proteins bud off and are released from the cell. These exosomes can contain PRPsc and have the potential to transfer infectivity from one cell/tissue to another [23].

Transfer of infectious prion protein from gut to brain

After peripheral infection, PRPsc accumulates and replicates in the lymphoreticular system, particularly the spleen and lymph nodes, prior to neuroinvasion and disease. The process by which PRPsc travels from gut to the lymphoid organs may occur via the blood through bone marrow-derived dendritic cells, which pick up PRPsc in the gut and transport it directly to the lymphoid tissues [24]. In rodents, follicular dendritic cells (FDCs) found in the germinal centres of lymphoid organs are major sites of PRPsc accumulation and the rate of transfer of PRPsc from lymphoid tissue to sympathetic nerves is likely determined by the relative positioning of FDCs and sympathetic nerve endings [9,25].

Infectious prion protein in blood

The foregoing discussion describes a process whereby infectivity (PRPsc) in the gut passes via the blood to the spleen and lymphoid cells and thence to the brain by way of antigen-presenting cells capable of taking up and replicating PRPsc. If the antigen-presenting cells come into contact with other blood cells whilst in transit from gut to lymphoid tissues or process PRPsc in a manner which results in the generation of exosomes containing PRPsc it is possible infectivity could transfer to other cells in blood. The cycle of PRPsc replication could continue within those other blood cells that have the necessary intracellular organelles, and those cells without the necessary machinery for recycling PRPsc like red cells may act as passive carriers of infectivity. There is considerable evidence for the occurrence of exosomes in human blood [26] and that they can derive from platelets [27] and reticulocytes [28] as well as from circulating dendritic cells [29]. Furthermore, transfer of GPI-linked proteins CD55 and CD59 from transfused red cells to the red cells of a patient with paroxysmal nocturnal hemoglobinuria has been demonstrated *in vivo* [30]. In this context it is interesting to note that exosomes containing HIV-1 released from immature dendritic cells were found to be 10 times more infective of CD4+ T cells than cell-free virus particles [31].

Exosomes do not provide the only hydrophobic environment in plasma. Recently, evidence has been presented [32•] showing that brain-derived PRPsc binds with high affinity to apolipoprotein B, the major component of very low density and low-density lipoproteins (VLDL and LDL) in plasma.

Infectivity in red cell preparations used for transfusion

There is persuasive evidence [8••] that transfusion of red cell preparations from donors who subsequently developed vCJD has transmitted the disease to three recipients. In each of these cases, the transfusions took place before leucodepletion of red cell preparations was introduced in the UK. Leucodepletion of 450 ml whole blood collected from scrapie-infected hamsters removed 42% of the total infectivity [33]. Whether or not a similar reduction in infectivity is achieved by leucodepletion of human blood is unknown. More relevant is whether or not leucodepletion of human blood is sufficient to prevent transfusion–transmission of vCJD. The follow-up of recipients of leucodepleted red cell preparations from donors who subsequently developed vCJD will provide information of relevance to this question [8••]. The leucodepletion process itself does not appear to result in increased numbers of leucocyte microvesicles that may carry infectivity [34] but would probably not remove exosomes. Given the uncertainty concerning the effectiveness of leucodepletion in removing infectivity from human blood, attention has turned to the possibility of employing filters, which selectively remove PRPsc. Sowemimo-Coker *et al.* [35] filtered 300 ml red cells from 500 ml anticoagulated whole blood collected from scrapie-infected hamsters. They report transmission of