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## Transmission of BSE by blood transfusion in sheep

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We have shown that it is possible to transmit bovine spongiform encephalopathy (BSE) to a sheep by transfusion with whole blood taken from another sheep during the symptom-free phase of an experimental BSE infection. BSE and variant Creutzfeldt-Jakob disease (vCJD) in human beings are caused by the same infectious agent, and the sheep-BSE experimental model has a similar pathogenesis to that of human vCJD. Although UK blood transfusions are leucodepleted—a possible protective measure against any risk from blood transmission—this report suggests that blood donated by symptom-free vCJD-infected human beings may represent a risk of spread of vCJD infection among the human population of the UK.

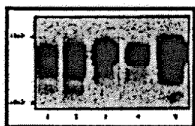
The demonstration that the new variant of Creutzfeldt-Jakob disease (vCJD) is caused by the same agent that causes bovine spongiform encephalopathy (BSE) in cattle<sup>1</sup> has raised concerns that blood from human beings in the symptom-free stages of vCJD could transmit infection to recipients of blood transfusions. There is no evidence that iatrogenic CJD has ever occurred as a result of the use of blood or blood products, but vCJD has a different pathogenesis and could present different risks. CJD is one of the transmissible spongiform encephalopathies (TSEs) characterised by the deposition of an abnormal form of a host protein, PrP<sup>Sc</sup>; the normal isoform (PrP<sup>C</sup>) is expressed in many body tissues. Available evidence, based on detection of infectivity in blood in rodent models, and absence of infectivity in naturally occurring TSEs, adds to the uncertainty in risk assessments of the safety of human blood. PrP<sup>Sc</sup> has been reported in blood taken from preclinical TSE-infected sheep,<sup>2</sup> but it does not follow that blood is infectious. Bioassays of human blood can only be carried out in non-human species, limiting the sensitivity of the test. One way of avoiding such a species barrier is to transfer blood by transfusion in an appropriate animal TSE model. BSE-infected sheep harbour infection in peripheral tissues<sup>3</sup> and are thus similar to humans infected with vCJD.<sup>4</sup> BSE infectivity in cattle does not have widespread tissue distribution.

We report preliminary data from a study involving blood taken from UK Cheviot sheep challenged orally with 5 g BSE-affected cattle brain and transfused into Cheviot sheep from a scrapie-free flock of New Zealand-derived animals (MAFF/SF flock). MAFF/SF sheep do not develop spontaneous TSE and the transfused animals are housed separately from other sheep. All sheep in the study have the PrP genotype AA<sub>136</sub>QQ<sub>171</sub> which has the shortest incubation period

of experimental BSE in sheep.<sup>5</sup> 19 transfusions from BSE-challenged sheep have been done, mostly with whole blood. Sheep have complex blood groups and only simple cross-matching can be done by mixing recipient serum and donor erythrocytes and vice versa. Therefore single transfusions only were made between sedated cross-matched animals to minimise the risk of severe reactions. Negative controls were MAFF/SF sheep transfused with blood from uninfected UK Cheviot sheep. As a positive control, MAFF/SF sheep were intravenously injected with homogenised BSE-affected cattle brain.

We have seen BSE clinical signs and pathological changes in one recipient of blood from a BSE-infected animal, and we regard this finding as sufficiently important to report now rather than after the study is completed, several years hence. The blood donation resulting in transmission of BSE to the recipient was 400 mL of whole blood taken from a healthy sheep 318 days after oral challenge with BSE. BSE subsequently developed in this donor animal 629 days after challenge, indicating that blood was taken roughly half way through the incubation period. 610 days after transfusion, the transfused sheep (D505) itself developed typical TSE signs: weight loss, moderate pruritus, trembling and licking of the lips, hind-limb ataxia, and proprioceptive abnormalities. This is the first experimental transmission of BSE from sheep to sheep and so we have nothing with which to compare this incubation period directly. In cross-species transmissions, bovine BSE injected intracerebrally gives incubation periods of about 450 days in these sheep,<sup>5</sup> and the donor animal had an oral BSE incubation period of 629 days (see above). There are no similar data available on other infection routes. Immunocytochemistry with the antibody BG4 on tissues taken from sheep D505 showed widespread PrP<sup>Sc</sup> deposition throughout the brain and periphery. Western blot analysis of brain tissue with the antibody 6H4 showed that the PrP<sup>Sc</sup> protein had a glycoform pattern similar to that of experimental BSE in sheep and unlike that of UK natural scrapie (figure), indicating that the TSE signs resulted from transmission of the BSE agent.

All other recipients of transfusions and positive and negative controls are alive and healthy. The positive controls, which involve a species barrier, are expected to have lengthy incubation periods. With one exception, all transfused animals are at earlier stages post-transfusion than was D505. The exception is a sheep which is healthy 635 days after transfusion with BSE-blood donated at less than 30% of the BSE incubation period of the donor sheep.



PrPSc (proteinase K treated) analysed by SDS-PAGE, immunoblotted with 6H4, and visualised with a chemiluminescent substrate

All lanes are from the same gel with different exposure times. Size markers are to the left of lane 1. Lane 1: natural scrapie sheep brain, 3 min exposure. Lane 2: as lane 1, 10 min exposure. Lane 3: sheep D505, blood-transfusion recipient, 10 min exposure. Lane 4: experimental BSE-affected sheep brain, 30 s exposure. Lane 5: as lane 4, 10 min exposure. Each lane loaded with amount of protein extracted from 0.1 g wet weight of brain, except lane 3 which was extracted from 0.2 g brain.

Although this result was in only one animal, it indicates that BSE can be transmitted between individuals of the same species by whole-blood transfusion. We have no data on blood fractions or on levels of infectivity in blood of preclinical vCJD cases, but whole blood is not now used in UK transfusions. The presence of BSE infectivity in sheep blood at an early stage in the incubation period suggests that it should be possible to identify which cells are infected, to test the effectiveness of leucodepletion, and to develop a diagnostic test based on a blood sample.

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