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A matter for debate: the risk of bovine spongiform encephalopathy to humans posed by blood transfusion in the UK

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SUMMARY. If human infection with bovine spongiform encephalopathy (BSE) were to occur, donated peripheral blood from humans that might have become infected from eating adequate quantities of food containing BSE should, until evidence is available to the contrary, be assumed to contain the human form of the disease. The chance of disease transfer to a blood recipient in 1995, which might in turn cause clinical disease with an incubation period of 20 years, is calculated. Transfusion is calculated to be a potential cause of a maximum of only 0·2% of clinical cases of Creutzfeldt–Jakob disease (CJD) in the UK population if the BSE epidemic were to spread to humans. Prospective epidemiological techniques would be unlikely to demonstrate any such minor contribution that blood transfusion might make to CJD incidence.

Key words: bovine, BSE, encephalopathy, Creutzfeldt–Jakob, transfusion, spongiform.

Transmissible spongiform encephalopathies (TSEs), of which bovine spongiform encephalopathy (BSE) is one, are fatal, untreatable diseases of mammals with very long incubation periods. They can be transmitted from one species to another by the ingestion of infected tissue and the agents are not destroyed by domestic cooking. At this time BSE has been transmitted to 18 species, 16 of them by ingestion (Patterson & Dealler, 1995). Although much of the bovine tissue considered to be infective was removed from human food in November 1989 (Matthews, 1992) it must be considered possible that, if BSE is like other TSEs, the agent has been present in the human diet before and after that time (Dealler, 1993). Interspecies transfer of a TSE is generally more difficult than intraspecies transfer, a phenomenon called the 'species barrier'. It is partly because of this that the risk of human infection from eating BSE-infected bovine products is felt by some to be low. Should such oral infection of humans take place, however, its transmission to other humans through blood products, if this were to occur, would not have to overcome the 'species barrier'.

To calculate the potential for blood transfusion transmission it is first necessary to note that there is approximately a 70% chance that a TSE can be transmitted from one species to any other specific species (Dealler, 1993) and so it must be assumed that there is an underlying 30% chance that humans can never become infected with BSE. One then has to estimate the number of people that would be expected to receive adequate oral doses from their food for infection to take place (TSE infectivity in lymphoid tissues and blood is found early in the incubation period of the disease; Dealler, 1993). It is then assumed that, as most BSE-infected tissue that might have been eaten by humans during the BSE epidemic has already been consumed (Fraser & Foster, 1993), human peripheral blood donations might contain the agent in 1995. By using various possible scenarios for the amount of infectivity needed to infect a human by mouth, and the relative amount of infectivity present in the bovine tissue, it is possible to calculate the number of otherwise unexposed individuals that would receive blood transfusions from a human who was previously infected with BSE.

BSE TRANSMISSION TO HUMANS FROM FOOD

The minimum amount of infectivity needed to infect another animal of the same species with a TSE is called one infective unit (IU). Due to the 'species barrier', when an animal of another species is

inoculated a much larger amount, possibly between 10 and 10^4 times as much, is required for transmission. Currently the only experimental data that we have indicate that 3 mg of the various bovine tissues fed to humans does not contain enough infectivity to infect mice by intracerebral inoculation (i.e. contains less than one murine IU (MIU) (Fraser & Foster, 1993). This must mean that 1 g contains less than 300 MIU and 100 g, the average amount of meat in a human adult meal must contain less than 30 000 MIU. When the 'species barrier' between the cow and the mouse is taken into account, this tells us that a single human meal must contain less than 10^4 times this amount or 300 000 000 IU, and does not provide a workable indication of human risk. The amount of infectivity present in the tissues of other TSE-infected animals has been measured more accurately. This is currently all that is available for assessing human risks from BSE and these data are used here in calculations.

The number of cases of BSE in cattle in the UK and their individual ages of onset are published annually by the Ministry of Agriculture Fisheries and Food (MAFF). The case population is large enough that, using official data for the age distribution of *all* the cattle in the UK, it is possible, using standard techniques, to calculate the number of infected cattle that would have been eaten before showing clinical signs of BSE. It is also possible to calculate the point in their incubation period at which they were slaughtered (Dealler, 1993). Using relatively accurate data for the level of TSE infectivity found in the liver, kidney, muscle and peripheral nerves of other species, and using information concerning the relative changes in levels of infectivity that take place during the incubation period, it is possible to estimate the infectious load that people in the UK may have eaten by 1995 (method fully published; Dealler, 1993, 1996; Dealler & Kent 1995).

Unfortunately it is not known how much BSE infectivity is needed to infect a human by mouth and we must assume a 70% chance that this is possible at all (Dealler, 1993). In mice 10^4 IU of scrapie (from another mouse) appears to be orally infective (Kimberlin & Walker, 1989), but few data such as this are available. As such it is necessary to calculate the number of people who might become infected if various possible infective doses for humans are considered (Table 1). The lowest of these, 10^3 IU, is probably unrealistically low, just as the highest, 10^9 IU, which may well represent the infectivity present in 10 g of bovine brain from a cow dying of BSE, is unrealistically high. From Table 1 it is clear that nobody could have become infected if bovine tissues carry a low level of infectivity and 10^7 IU are needed to infect a human by mouth. However, everyone might potentially be at risk if bovine tissues are highly infective and if only 10^5 IU are required. Currently we have no way to decide which of the scenarios, if any, of Table 1 is the most likely to be correct.

CHANCE OF BSE INFECTION BY TRANSFUSION IN UK: ASSUMPTIONS AND CALCULATIONS

It is assumed that the mean transfusion per recipient in the UK, 2·1 units, is derived from only two donors. Just over 2·08 million units of whole blood are used in the UK annually with a national wastage of under 5% (National Blood Transfusion data, 1994). It is assumed here that imported or exported human blood products are not involved and that, although there is evidence (which requires proper confirmation) that the buffy coat may be the fraction of the blood that contains the infectivity, recipients of components that may be richer in white cells or of platelets are either not at risk or unlikely to live for 20 years. It is likely that 50% of blood derivatives are transfused to recipients who die within 1 year and it is assumed that the rest will have a similar life expectancy to non-transfused members of the population. Age distributions used for recipients are: < 2 years, 3%; 2–12 years, 4%; 13–40 years, 15%; 41–50 years, 10%; 51–60 years, 11%; > 60 years, 56% (De Silva & Wajayatilake, 1994). For the purposes of calculation of potential risks, we will assume that, if transmissible, 1 donor unit would be adequate to transmit BSE to another person (by this time it would have crossed the species barrier and would be Creutzfeldt–Jakob disease, CJD) and to produce a clinical disease with an incubation period of 20 years.

Clearly someone already infected by BSE will not be further infected by transfusion. Also, someone who will die of other causes will not be affected by an infection that may have an incubation period of 20 years. The proportion of total adults (and hence potential donors) that would be infected with BSE is taken from Table 1, and this is taken as the proportion of blood donations that would be infected. The chance that a recipient with a life expectancy of 20 years will receive one unit from an infected donor can then be calculated. The proportion of these recipients that would not otherwise have become infected can then be calculated by assuming that the chance of a person in any of the population groups of contracting BSE from food is similar to that of an adult (in Table 1). Each of the figures in Table 1 gives rise to a separate figure for the people who would become

Table 1. UK population (millions) expected to have eaten a potentially infective dose of BSE by 1999 for given levels of infectivity that may be required to infect humans by mouth

Dose of BSE infective to humans (IU)	Relative infectivity of dietary beef tissue for BSE compared with other species infected with a TSE*		
	Low	Medium	High
10^3	33·74† (33·37–33·76)†	33·76 (33·76–33·76)	33·76 (33·76–33·76)
10^4	30·77 (22·58–32·53)	33·37 (32·76–33·76)	33·76 (33·76–33·76)
10^5	0·46 (0·13–1·09)	20·28 (18·38–22·12)	33·76 (31·5–33·76)
10^6	0	17·32 (17·32–17·35)	32·56 (23·16–32·64)
10^7	0	0·133 (0·036–0·137)	17·42 (17·35–17·66)
10^8	0	0	17·34 (8·82–17·34)
10^9	0	0	0·036 (0·036–0·13)

* Using known levels of infectivity found in the tissues of other species infected with TSEs as references.

† Figures relate only to people aged 16–64 years (34·6 million) in the UK as data are not adequately available for younger or older age groups. Figures represent the numbers of UK people who would have eaten a specific *cumulative* infective dose (*y* axis) by 1999 given the infectivity of bovine tissue as related to other species with a TSE (*x* axis). Calculated using MAFF data at December 1993 and published methods (Dealler, 1993). If the infective dose is not cumulative then these figures should be calculated in a separate manner (Dealler & Kent, 1995); this is, however, felt unlikely. These calculations assume that only 10% of peripheral nerve reaches the human diet and that no 'specified offals' (brain, spleen, thymus, gut, etc.), which were banned from the human diet in November 1989, were ever eaten. They assume that all clinically infected cattle are reported to MAFF, that all diagnoses are accepted by their veterinary officers, that all are correctly diagnosed by histology and that no cattle born after 1991 ever develop BSE. Upper and lower limits of 95% confidence interval.

infected from blood transfusion but would not otherwise catch BSE and these are shown in Table 2.

RESULTS AND DISCUSSIONS

Currently we have inadequate information to state which of the possible values in Table 1, and its corresponding value in Table 2, are the ones that will prove to be relevant as we do not know how infective the tissues are, or what the oral infective dose is for humans. It is clear, however, that the risk from blood transfusion is 2–3 orders of magnitude lower than that from food and hence may be exceedingly difficult to demonstrate by prospective epidemiological studies. Tables 1 and 2 show a maximum possibility of 60·6 thousand blood transfusions transmitting CJD, but this would give rise to 0·2% of the clinical cases of the disease. It should be noted that in 12 out of 21 possible values in Table 2 transfusion was irrelevant to the transmission of CJD and in a further four it was very low.

Scrapie, the TSE of sheep, has been found in the bloodstream of animals affected with the disease; in mice (Clarke & Haig, 1967; Field, 1967; Field *et al.*, 1968); in rats (Clarke & Haig, 1967), in hamsters (Casaccia *et al.*, 1989) and in sheep (Gibbs *et al.*, 1985). CJD has been found in the blood of infected mice (Kuroda *et al.*, 1983), guinea-pigs (Manuelidis *et al.*, 1978) and humans (Manuelidis *et al.*, 1978, 1985; Tateishi *et al.*, 1980; Tateishi, 1985) and with persistent viraemia demonstrated in the buffy coat (Manuelidis *et al.*, 1978). No infection was found, however, in the blood of scrapie-infected goats (Hadlow *et al.*, 1974), similarly infected mice (Dickinson *et al.*, 1969; Eklund *et al.*, 1967) and CJD or kuru sufferers when the disease was inoculated into mice (Gibbs & Gadjusek, 1972; Gajdusek, 1977). Mink inoculated with blood from a mink suffering from transmissible

Table 2. UK population (thousands) expected to have been transfused blood from a postulated BSE infected person in 1995 and for this transfusion to affect the recipients' life expectancy

Original oral dose of BSE postulated to have infected the blood donor (IU)	Relative infectivity of dietary beef tissue for BSE compared to other species infected with a TSE*		
	Low	Medium	High
10^3	0*	0	0
10^4	14·1 (5·6-48·0)	0	0
10^5	4·3 (1·2–10)	54·7 (49·5–58·9)	0 (0–10·6)
10^6	0	60·6 (60·6–60·7)	5·6 (5·4–46)
10^7	0	1·3 (0·3–1·3)	60·5 (60·5–60·6)
10^8	0	0	60·6 (54·8–60·6)
10^9	0	0	0·3 (0·3–1·3)

* Figures relate to UK transfusion recipients (thousands) in 1995 under 51 years of age who would otherwise not be at risk of BSE but who would have received blood from UK donors shown in Table 1 (i.e. donors who would have eaten a specific (cumulative) infective dose of BSE (*y* axis) by 1999 and with consideration of the relative infectivity of bovine tissue as compared with other species with a TSE (*x* axis). Calculations: (Blood units used −wastage)/2·1) × (proportion of donors infected by 1995) × (proportion of recipients not infected orally by 1999) × (proportion under 50 years) × 0·5 − (half the number of transfusions in which 2 potentially infective units were used). This is statistically organized to give an indication of the number of people who would receive a transfusion of 1 unit of blood from a person infected with BSE by 1995 and would themselves be expected to live another 20 years. Upper and lower limits of 95% confidence interval.

mink encephalopathy showed no sign of disease (Marsh *et al.*, 1973) nor was scrapie in the goat transmitted by peripheral inoculation into a separate goat (Pattison & Millson, 1979). These findings suggest that viraemia is present at such low levels as to sometimes prevent disease transfer across a 'species barrier' or when inoculated in small amounts (Casaccia *et al.*, 1989).

The dose of infectivity that has been shown to be infective by i.v. transmission in mice is only 9 IU (Kimberlin & Wilesmith, 1994) and the amount of infectivity expected to be present in 300 mL of human blood would, if similar to that found in the hamster, be greater than 10^4 IU throughout the incubation period (Casaccia *et al.*, 1989). However, the peripheral transfusion of 300 mL of whole blood from a patient suffering from CJD to a chimpanzee has not led to disease after 8 years (Gajdusek, 1990) but the 'species barrier' and the long incubation period that is expected may rule this out as a helpful indicator. It is suspected that, as CJD derived from pituitary hormone inocula may lead to a spongiform encephalopathy similar to kuru, so might that derived from blood transfusion (Esmonde *et al.*, 1993), but few cases (about 5%) are of this clinical form. Of 202 patients identified as having CJD, 16 had a definite history of blood transfusion and this was found to be similar to a matched control group (Esmonde *et al.*, 1993). The sporadic CJD symptoms were also found to be similar to those in individuals who had received a blood transfusion. This would suggest that blood transfusion is currently an unlikely cause of their CJD. The model calculated used here agrees with this; with fewer than 25 cases of CJD annually (as there have been prior to 1990) fewer than two people would be expected to have received infected blood by transfusion and to have survived 20 years (data not shown). This inoculation would, however, have taken place 20 years ago and CJD incidence data from this period are poorly available. Four Australians died of CJD (with symptoms similar to kuru) 5 years after receiving a blood transfusion (Klein & Dumble, 1993) but inadequate statistical data are available to demonstrate a relationship with transfusion. The report of a man dying of CJD who had donated blood between 1971 and 1991 shows that 18 recipients had died – none

from CJD – that one had reached 22 years without signs of CJD and nine were still alive, the oldest being 21 years and healthy (Heye, 1994). These findings, although they are the only ones published, may suggest that intravenous transmission of CJD through blood may indeed need a very long incubation period or not take place at all. The possibility that CJD is present only in the cellular fraction may mean that noncellular recipients are not at any risk, but further research is required.

The general population and the medical profession of the UK are mindful of the risks of CJD transmission by transfusion (Arya, 1991; Contreras & Barbara, 1991; Contreras *et al.*, 1991; Watkins, 1991). If indeed there does prove to be a risk of BSE being transmitted to humans via the food chain, then the potential opportunity for secondary transmission by transfusion of blood and its components would appear to be far outweighed by the potential of transmission via food.

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