**Review** article

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# Variant CJD (vCJD) and Bovine Spongiform Encephalopathy (BSE): 10 and 20 years on: part 1

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**Abstract**

*From 1986 more than 184,000 cattle in the UK and islands (of which >1,880 have been detected by active surveillance using rapid tests) and approaching 5,500 elsewhere have been confirmed with BSE. The original 1988 ban on the use of ruminant-derived protein in ruminant feed has been upgraded and now prohibits the use of any processed animal protein in feed for any farmed food animal. As a result of rigorous enforcement this reinforced ban is now regarded as fully effective from 1 Aug. 1996. Reasons are given for the substantial slippage that occurred initially and for the small but diminishing number of cases that have occurred in cattle born after 1 Aug. 1996. The 1989 offal ban, initially introduced to protect public health, has likewise been progressively strengthened and since 1995 has been effectively enforced by the Meat Hygiene Service, thus protecting the consumer. It is now extended as the specified risk material (SRM) ban throughout the EU. BSE continues to decline towards elimination in the UK and is being dealt with effectively in other Member States of the European Union (EU) and Switzerland with an extensive (and very expensive) range of edicts. The improving situation in the EU has encouraged the EC to draft a TSE Roadmap outlining possible reduction in control measures whilst still protecting the consumer. The situation on a global basis still causes concern as, although cases are less frequent than in the UK, surveillance, legislation and enforcement are not clearly as extensive and effective as in the EU. The risk of primary transmission of BSE to man from cattle to cause variant CJD (vCJD) is examined with reference to up-to-date assessments of bovine tissue infectivity and is now regarded as unlikely in the EU and Switzerland.*

***Key words:*** *BSE, vCJD, active surveillance, rapid testing for $PrP^{Sc}$, TSE Roadmap*

## Perspective

Reports in *The Lancet* in 1997 summarised what was known about BSE and speculated on possible risks to human health [7,8]. At that time, the bovine epidemic had accounted for more than 165,000 cattle in British herds. In the present report, two decades after BSE was first recognised and one decade after the first cases of vCJD in human patients were announced in the UK, we re-examine important developments that may relate to human health.

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## The source of BSE

The true origin of BSE, first recognised in British cattle in 1985-86, may remain a mystery. It is virtually certain that the vehicle of infection was meat-and-bone-meal (MBM) fed as a dietary supplement predominantly to dairy calves [2,23]. MBM, and its associated by-product tallow, were derived mainly from the carcases of fallen stock and other animal and poultry material rejected or unwanted for human consumption. The starting materials were subjected to "rendering", a cooking process in which water was extracted, fat was separated as tallow, and the remaining protein-rich material ("greaves") was ground to make MBM for animal feed or agricultural and plant fertilizer. MBM was marketed primarily in the UK, but considerable amounts went abroad.

The infective agent of BSE (see below) has remarkable resistance to physical and chemical destruction including dry heat, even up to 600°C [3]. Research has shown that some of the rendering procedures in use in the years leading up to the onset of BSE in the mid-1980s would not have reduced the titre of the causative agent to undetectable levels in the final MBM product. For one process the residual titre in the MBM was comparable to that of the untreated raw materials [32]. Residual BSE infectivity has not been detected in the tallow fraction after rendering, but the case against MBM as the vehicle of BSE in cows is convincing. The ineffective rendering processes have now been abandoned. There is just one approved world standard rendering process for use on ruminant materials that may carry a TSE risk and this demands exposure of particles ≤50 mm diameter to 133°C, at a pressure of 3 bar, for 20 min (often referred to as "pressure cooking") [28].

## Preventive measures

In late 1987, when MBM was identified as the likely vehicle of BSE [36], protective legislation was quickly introduced in the UK. The use of ruminant-derived protein in feed destined for ruminant animals was prohibited in July 1988 [2,14]. If this feed-ban had been effectively enforced and rigorously obeyed, it would have eliminated recycling of the agent in infected feed supplements, not only in cattle but also in various captive wild ruminants in zoos and wildlife parks. Sadly, it was not. Moreover, it did not restrict the use at that time of MBM in feed for pigs and poultry. In retrospect, we now see the many problems of cross-contamination that were to haunt us for many years to come.

BSE mainly affects adult cattle in the 4-6 years age range, with a mean incubation period of 60 months. Accordingly, the entry of infected but clinically healthy animals into the food chain, and eventually into the animal feed chain, would occur both during and before the onset of the epidemic. Preclinical animals could not be recognized until appropriate tests were developed and even then only after death. Even with the ruminant feed ban in place, cattle could be carrying the infection for some years before going down. Therefore in 1989, in order to immediately protect public health it was decided to prohibit the use in human food of certain specified bovine offal (SBO) that, in an infected animal, might carry the BSE agent. The selection of the offal to be banned was based on existing knowledge on the pathogenesis of the natural analogous disease of sheep and goats known as scrapie.

In 1990 a case of feline spongiform encephalopathy was reported in a domestic cat [38] and BSE was experimentally transmitted to a pig [34]. The SBO ban was therefore extended to protect all species of mammals and birds, and it was successively extended during the 1990s so that the whole head (except the tongue) of cattle more than six months old was banned, and sheep and goat heads were also removed from the human food chain. In time, the concept of specified animal materials that might carry a risk of BSE infection was developed. The full agreement of the EC in these matters was slowly achieved and a Specified Risk Material (SRM) ban became European law from 2000 [16], with subsequent amendment to take account of new knowledge and improvement in the general European BSE situation.

## BSE in cows born after the ban

It was hoped that the feed ban of 1988 would have progressively reduced the number of infected cattle born after the ban (BAB) in the UK, which indeed it did, but it was not fully effective. Alternative mechanisms of infection such as maternal, horizontal or environmental transmission could not account for the extra cases. Sporadic BSE equivalent to sporadic CJD is not known to occur though a small number of cases of bovine amyloidotic spongiform encephalopathy (BASE) have been reported in Italy that may be different from BSE or merely reflect a different pathogenesis or phenotype [6]. No other sources were found, so it was concluded that continuing exposure of cattle to feed

somehow contaminated with infected MBM must be the cause.

By January 2006, more than 180,000 cases of BSE have been confirmed in British cattle, of which more than 44,000 were born after the 1988 feed ban [13]. This massive leakage is now attributed to cross-contamination of ruminant rations, mostly with those intended or prepared for pigs and poultry that were legally permitted to contain MBM until 29 Mar. 1996. A contribution was also made by inadequate separation and processing of SBO that permitted MBM prepared from SBO to enter non-ruminant feed and thus be a source for cross-contamination of cattle rations. To deal with contaminated feed 'in the pipeline' a feed recall scheme was introduced to remove and destroy it. The reinforced feed ban is regarded as effective from 1 Aug. 1996.

When these deficits were appreciated and research determined that much less than 1g (now known to be about 1 mg) of BSE-infected brain was sufficient to provide an oral infecting dose for cattle, the feed ban was reinforced by testing feed for prohibited protein and it was more strenuously policed. Following a recommendation of the British Government's Spongiform Encephalopathy Advisory Committee (SEAC), it was prohibited from 29 Mar 1996 to feed mammalian protein to any species of farmed food animal or bird, including horses and fish. This is known as the reinforced feed ban and is regarded as being fully effective from 1 Aug. 1996 due to rigorous enforcement following the feed recall period. Despite this, as at May 2006, 131 cattle born subsequently have been confirmed to have BSE (BARB cases), (DEFRA unpublished data). The first BARB cases were believed

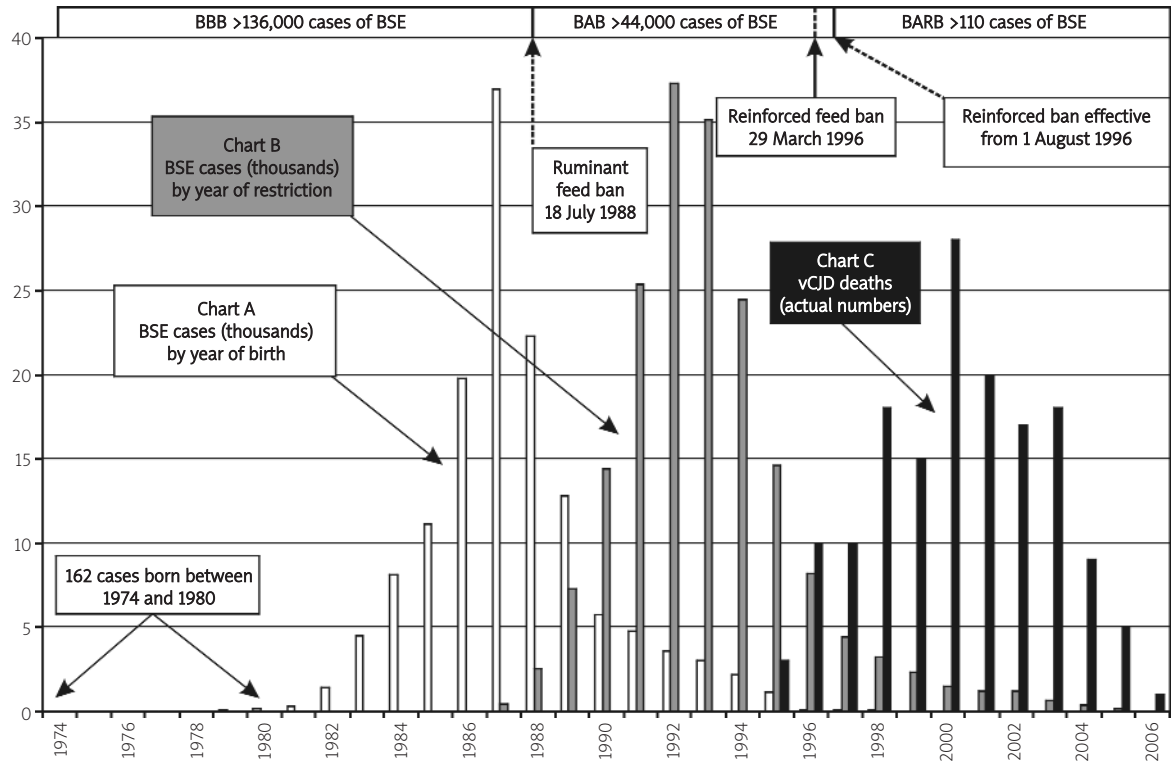


**Fig. 1.** Temporal occurrence of BSE cases in Great Britain/UK born before or after various feed bans

Three overlapping charts show: A - BSE confirmed cases in Great Britain by date of birth where known (it was not known for 43,332 animals). The case with the earliest date of birth was born in 1974. Increasing, but small numbers of cases (invisible on the chart) occurred in the 'invisible period' until 1981. Also shown are time periods for three populations of cattle (BBB = Born before the July 1988 ruminant feed ban; BAB = Born after the 1988 feed ban and before the March 1996 reinforced feed ban was effective (1 Aug 1996); and BARB = Born after the reinforced feed ban was effective (from 1 Aug 1996)) [13,14]. B - BSE cases in the UK and islands by year of restriction [26]. (Date of restriction = date on which a State Veterinary Officer examines the animal and has the opinion that BSE is suspected on clinical grounds and serves a restriction notice to prohibit movement off the premises and to require isolation of the animal if due to calve). C - vCJD deaths in the UK to 18 Feb 2006 [25]

to result from feeding imported ruminant feed or feed ingredients contaminated with infected MBM. The contamination was suggested to have occurred during marine transport from the continent, *e.g.*, if a vegetable feed cargo immediately followed a cargo of MBM. This is understandable because a ban prohibiting the feeding of processed animal protein to all farmed animals in the rest of the EU was not in place until 1 Jan. 2001. It is not even clear that this latter ban was totally effective from the date of its introduction; for example, ten new countries acceded to the EU in 2004 were not all operating completely to the new standard. A more recent detailed epidemiological investigation has shown that an important source of infection for BARB cases has been persistence of contamination in on-farm feed bins that had not been adequately cleaned and disinfected before the 1 Aug. 1996 deadline. A review by Professor William Hill of the evidence for the occurrence of BARB BSE cases in cattle has been published [10]. The BSE epidemic in Northern Ireland has followed a similar sequence of events and legislation as in GB. For example, of about 2150 cases of BSE there, almost 600 were BAB cases and 16 were BARB cases, as at August 2005.

## The hazard for man

An early assumption that the agent of BSE in cows was a variant of the agent of scrapie in sheep led us to believe that transmission of BSE to man was unlikely. BSE might have come from cows or sheep [36]. We have no clear evidence of which, but we know that BSE has many puzzling characteristics and that strain typing studies indicated that the agent that causes BSE is biologically and molecularly different from the agents of scrapie and other transmissible encephalopathies except the vCJD agent [23] from which it is biologically indistinguishable [4]. Human cases of the disease, now called vCJD, began to be recognised in 1995 in the UK [37]. The most likely danger period for human ingestion of the BSE agent in meat and meat products is thought to be the years 1984-89 when public health protection was limited and before the SBO ban was in place to protect consumers. The "period of hazard" for humans could theoretically extend back into the 1970s if there has always been a low undetected level of BSE infection in cows. However, there is some evidence that a degree of protection was afforded to cattle until the late 1970s and early 1980s by the use of hydrocarbon solvents in the rendering process to extract tallow. During this period, the rendering industry progressively ceased to use these solvents. Whatever the reason, it is clear that a level of BSE agent sufficient to cause disease 5 years later was present in MBM fed to calves at least from 1980/81, and that a degree of recycling had occurred from 1984 (thus boosting the exposure) even before the first case of BSE in cattle was confirmed at the end of 1986. Thus, 1984 is taken as the start of the major hazard period for the consumption of contaminated beef and meat products in the UK. In view of the lack of adequate and effective control measures until 1995-6, the hazard period for possible human infection might extend forward until the use of mechanically recovered meat (MRM) and head meat was controlled.

Some cheaper processed products such as burgers, pies, beef sausages and mince could have contained MRM and head meat that may have been contaminated with potentially infective tissues such as residues of bovine brain, spinal cord and dorsal root ganglia until controls were in place and the Meat Hygiene Service (MHS) was set up to monitor and enforce them in 1995. In regard to MRM, the Food Standards Agency reported a historical study on the uses of MRM in the period 1980-1995 [22]. Some 5,000 tonnes of bovine MRM was used annually, mostly in catering and retail economy foods such as burgers (40%), frozen and dried mince (40%), but not in burgers from major fast food outlets. Frozen mince was used in some hospitals and schools with the rest being exported or having minor uses.

In regard to imported beef and sheep meat, the Food Standards authority records 144 breaches of the SRM regulations until Dec. 2005 [20]. The meat was almost entirely derived from BSE-infected countries in the EU [20]. The usual outcome has been destruction of the offending consignment [21].

There have been 17 breaches of the SRM regulations in the UK until Dec 2005, two of which were from imported animals or material [21]. SRM was removed and destroyed. In addition, there has been a small number of breaches of the regulation prohibiting the slaughter for human consumption of cattle over 30 months old. Most have related to slaughter (and usually consumption) of cattle over the prescribed age limit by just a few days, though a few were substantially older [21]. Any risk to the consumer from these collective events is regarded as low since either, the SRM was removed, or the whole consignment was destroyed.

## BSE worldwide

BSE is known to have been spread widely, along cattle trade routes and where bovine products and by-products, including rendered animal proteins and compound animal feed containing MBM, are imported and marketed. Countries with cases reported to the Office International des Epizooties (OIE) are listed in Table I along with the date of the first report of BSE. The total number of cases outside the UK is currently around 5,400. Cases of vCJD have occurred in several countries with BSE and one that has not reported BSE.

In a classification of perceived Geographical BSE Risk (GBR), the Scientific Steering Committee of the European Commission has proposed four categories ranging from I (BSE highly unlikely) to IV (BSE confirmed at a higher level) [29]. The UK and Portugal previously in Category IV, now satisfy the conditions for Category III and are currently so classified. Thus they align with all other EU Member States, Canada and the USA. The UK (since 3 May 2006) and Portugal now adopt the less stringent SRM regulations applying to EU Member States in Category III. They are also permitted to export live cattle and beef again, which in the UK was denied in 1996 by a world-wide ban, though a small volume of beef exports under the strict conditions of a date-based export scheme was subsequently introduced.

A similar approach to GBR by the OIE specifies three levels of risk within its Code which gives recommendations for safe international trading in cattle and cattle products [28]. The OIE and EC rules are proposed to be aligned by 1 Jul. 2007 [19].

## Preventive strategies

Such schemes depend heavily on reliable updating of information and upon the quality of animal identification, record keeping, notification and surveillance. Until 2001 in the EU, surveillance relied mainly on passive clinical detection and reporting of suspect cases for further investigation by the appropriate state veterinary services. In the latter years of the 1990s, various 'rapid' tests for BSE were developed for use on brain material and approved for use in the EU [24] and more have been approved since. These are applied rigorously throughout the EU and in some other countries, notably Japan [33] to detect the presence of $PrP^{Sc}$, which is an indicator of TSE infection and is the disease-specific structurally modified form of the normal host membrane protein $PrP^{C}$ (see below). The rapid tests were first applied to cattle and subsequently to sheep and goats (and a few other species), and they revealed many more unsuspected BSE cases because they could detect infected cattle 3-6 months before clinical onset.

An Over Thirty Months (OTM) Rule was introduced in the UK in 1996 whereby cattle more than 30 months old were excluded from all food and feed chains and meat from them was prohibited for export. They were essentially dealt with as SRM and destroyed. This was based on the fact that the minimum age of occurrence of BSE was increasing and cases in animals less than 30 months old had been rare. In fact, none has been recorded in slaughter animals since 1996. In the rest of the EU from 2001, all cattle for human consumption >30 months old are compulsorily tested and if positive the whole carcase is destroyed, as well as closely proximate carcases on the slaughter line. All organs including hides and blood from these cattle are also destroyed. On 7 November 2005, the UK formally relinquished the OTM rule and adopted the same testing regimen as other Member States except that any cow born before 1 Aug. 1996 would forever be excluded for human consumption.

Compulsory rapid testing was targeted not only at slaughter cattle >30 months of age but also "risk animals" >24 months of age. These include: fallen cattle stock (dead animals), casualty animals, animals found abnormal at *ante mortem* inspection, offspring of cases, feed cohorts of cases, and those slaughtered as part of a BSE elimination programme. Positive cases are confirmed by traditional methods. The diminishing number of cases confirmed each year in both the slaughter and risk populations and the continuously rising age at onset indicates good enforcement of the various measures [18,19]. The fallen stock and casualty slaughter populations are yielding the largest numbers and highest proportion of positives and this endorses the importance of targeting active surveillance. The proportion of cases detected by active surveillance using the rapid tests now exceeds that detected by passive surveillance. More than 10 million are completed each year in the EU. The cost is enormous and now probably out of proportion to the risk, especially in slaughter animals and in the 30-35 month age group and younger (Table II) [19].

It is important to note that in the early years of the epidemic and particularly before the SBO ban was

**Table I.** Confirmed cases of BSE in native-born and imported cattle and definite or probable cases of vCJD by country and date of first report of BSE

| Country | Total BSE cases | Number Imported* | vCJD cases** | First BSE report*** |
|---|---|---|---|---|
| Great Britain | 180,892# | 2 | UK – 160 | 1986 |
| Northern Ireland | 2,160# | | 154 + 6 alive | 1988 |
| Other British Isles | 1,290 | | | 1987/8 |
| Republic of Ireland | 1,558 | 12 | 3** | 1989/1989 |
| France | 969 | 1 | 16 | 1991 |
| Portugal | 988 | 7 | 1 | 1990/1994 |
| Spain | 590 | 1 | 1 | 2000 |
| Switzerland | 460 | 1 | | 1999 |
| Germany | 389 | 6 | | 1992/2000 |
| Belgium | 131 | | | 1997 |
| Italy | 131 | 2 | 1 | 1994/2001 |
| Netherlands | 78 | | 1 | 1997 |
| Poland | 38 | | | 2002 |
| Slovakia | 20 | | | 2001 |
| Japan | 22 | | 1** | 2001 |
| Czech Republic | 23 | 1 | | 2001 |
| Denmark | 14 | 1 | | 1992/2000 |
| Slovenia | 6 | 1 | | 2001 |
| Canada | 6 | 1 | 1** | 1993/2003 |
| Austria | 2 | | | 2001 |
| Liechtenstein | 2 | | | 1998 |
| Luxembourg | 3 | | | 1997 |
| USA | 2 | 1 | 2** | 2004/2005 |
| Sultanate of Oman | 2 | 2 | | 1989 |
| Azores | 1 | 1 | | 2000 |
| Falkland Islands | 1 | 1 | | 1989 |
| Finland | 1 | | | 2001 |
| Greece | 1 | | | 2001 |
| Israel | 1 | | | 2002 |
| Sweden | 1 | | | 2006 |
| Saudi Arabia | 0 | | 1 | |
| Total | 189,527 | 41 | 188 | |

*Source: vCJD data [25,31]; Cattle data OIE [26,27] and DEFRA [12]*

*Note: Figures may vary depending on the source of information and the date of central reporting.*

** Imported animals were mostly exported from the UK but some were exported from other European countries.*

*** Cases are ascribed to countries where clinical signs commenced. The country of exposure is rarely known with certainty (except for cases of secondary human to human transmission). If from food, exposure could be from imported contaminated products. Nevertheless, it is most likely that at least one case in Ireland, both cases in the USA and 1 case each in Canada and Japan were exposed in the UK.*

**** In countries where BSE has occurred in imported and native-born cattle and the first case of the former preceded the latter, two dates are given. The first is the date of report of the first imported case and the second the date of the first native-born case.*

*# Of the total BSE cases, 1679 in Great Britain (at 20 Jan 2006) and 203 (at 31 Oct. 2005) in Northern Ireland were detected by active surveillance (rapid testing) [9,12] – see Preventive strategies below. Active surveillance in the EU commenced formally in 2001 and cases reported from the end of 2000 were increasingly detected by this method rather than by passive surveillance.*

**Table II.** Cost (M€) of BSE monitoring healthy slaughter and risk animals and cost (M€) per BSE case detected from Jan. 2001 - Dec. 2004 by age group

| Age group | Monitoring cost (M€) | | Cost (M€) per positive case detected | |
|---|---|---|---|---|
| | healthy slaughter animals | risk animals | healthy slaughter animals | risk animals |
| < 24 months (m) | 152 | 3 | no cases | no cases |
| 24-29 m | 137 | 20 | no cases | 10.2 |
| 30-35 m | 302 | 29 | 302 | 29.5 |
| 36-41 | 138 | 18 | 69 | 17.8 |
| 42-47 | 108 | 15 | 11 | 0.9 |
| All ages | 1.612 | 223 | 1.56 | 0.07 |

*Source: EC.[28] [19]*

*Note: The mean cost of each test is taken as €45.*
*The total cost of monitoring in the period is 1,835 M€.*
*Total number of tests in the period >44.6 M and in 2004 >10 M [18,19].*

introduced in GB in 1989 (and long before active surveillance became possible in the new millennium), pre-clinical and any sub-clinical cases of BSE that might have occurred could have been consumed undetected. The astonishing number of cattle, most of which were consumed in this way, has been estimated using modelling, to be between 1 and 3 millions [30].

The improving situation in the EU has resulted in the EC publishing a TSE Roadmap that lays out a proposed reduced programme for BSE control and elimination in the short, medium and long term [19]. The key piece of EC legislation to protect human and animal health from the hazard of any TSE was adopted on 22 May 2001 and is known as the TSE Regulation [15] laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies. The Roadmap acknowledges the progressively and continuously reducing numbers of confirmed BSE cases throughout the EU, coupled with an increasing age of peak occurrence, and proposes a reciprocal risk-based relaxation of some of the measures whilst assuring a high level of food safety and thus continuing protection of the consumer. An example, to show the start of the process, is that, as from 1 Jan. 2006, the age at which the vertebral column of cattle has to be removed as SRM in the whole EU is 24 months instead of 12 months. Since the vertebral column has not been removed for some years from UK cattle until 30 months of age as the BSE risk is so low, this is disappointing for the UK, but it is likely to be adopted on the grounds that rules should be harmonised. It is a pity that this rule applies to UK beef destined for domestic consumption as well as that for export, for there is no scientific justification for such action. However, now that the UK is a GBR Category III country, it benefits from the less strict SRM rules by not having to split bovine carcases from 6 to 12 months of age in order to remove the spinal cord, which previously was only exempt for cattle under 6 months of age.

As at 1 January 2006 the UK still reports the largest annual number of cases of BSE, but the majority are cattle born before 1 Aug. 1996. None of these will ever enter the food or feed chain and the situation improves year on year. The peak age of onset of BSE in the UK cases is older (10 years) than in other countries, so that the UK (understandably) can look earlier towards the day of complete elimination of the disease particularly as an Older Cow Disposal Scheme for cattle born before 1 August 1996 was introduced by DEFRA in January 2006. This scheme will last three years with reducing compensation payments each year. This has the effect of making cattle over 13 years old on 1 January 2009 valueless and should stimulate their voluntary slaughter for destruction by this date [11]. From 2001 to 2004 the mean age at onset of BSE cases in slaughter animals in the 15 EU Member States increased from 76.2 to 95 months (say, 8 years). Ireland and Switzerland and then the other European countries follow the UK progress towards elimination.

Outside of Europe the number of reported cases is low (Table I) but it is too early yet to be certain of progress towards universal elimination, as there is some worrying variation in the measures employed. At present, we can be sure that neither pigs nor poultry present a TSE risk to man, but sheep and goats might. One case of suspect BSE in a goat in France has been confirmed. The goat did not enter the food chain. The remainder of the herd was destroyed and tested and no goat was positive. No case has yet been reported in sheep and although maternal transmission of experimental BSE in sheep has recently been confirmed [1] it seems that no small ruminant species presents more than a negligible risk.

## Tissue infectivity in BSE

Research into the tissue distribution of infectivity in natural and experimental BSE in cattle is being extensively studied in the UK using conventional mice or cattle as the bioassay animals [35] and in Germany using highly BSE-sensitive transgenic mice [5]. The use of cattle to detect infectivity eliminates the species barrier to transmission and maximises test sensitivity. In studies of the natural bovine disease, infectivity in cattle tissues (using conventional mice and/or cattle for detection) was found only in the brain, spinal cord, the retina and the third eyelid (nictitating membrane).

The experimental disease was induced by oral challenge of cattle with BSE-infected brain material followed by sequential killing of small groups of animals enabling the pathogenesis of the disease to be determined. In these studies infectivity has been found (using conventional mice and/or cattle) in the tonsil at 10 months post-challenge [35]. This resulted in a change in the legislation to include tonsil from all ages of cattle as specified risk material (SRM) for destruction instead of from those over 12 months of age [17] and modification of the method used to harvest tongues for human consumption. In addition, infectivity was found in the distal ileum from cattle groups killed at 6-18 months and from 36 months post-challenge. Dorsal root ganglia (DRG) were also infected in groups killed from 32 months post-challenge (about 3 months before clinical onset in the experiment, *i.e.*, at 35 months post-challenge) [35].

Most recently, using transgenic mice, infectivity has been found in some peripheral nerves and in a single muscle from a single German cow with natural, clinically-advanced BSE, but at low titre compared with that in the brain [5]. These studies have also confirmed that the bovine lymphoreticular system (other than the tonsil and ileum, which are officially classed as SRM) is not significantly involved. This contrasts with the pathogenesis of scrapie in sheep and vCJD in man. Thus, to date, our most recently developed techniques confirm that BSE infectivity in slaughter cattle that have passed a rapid test is likely to be confined to the ileum and perhaps the tonsil. In more advanced cases of BSE, high levels of infectivity are likely to be confined for practical purposes to the CNS and its associated ganglia.

## Concluding remarks

Careful collection and analysis of epidemiological data have enabled identification of the important factors responsible for the transmission and distribution of BSE. This led to the introduction, and later strengthening, of the measures introduced to reduce or eliminate the risk to cattle and other animals via feed. Effective research into the distribution of tissue infectivity in cattle with BSE, similarly has led to endorsement of the 1989 SBO ban and to later extensions on a wider geographic basis, thus providing protection for the consumer. The consequences of the transmission of the BSE agent to produce human cases of variant Creutzfeldt-Jakob disease (vCJD) will be considered in PART 2 of this Review.

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