Bovine Spongiform Encephalopathy (BSE): Causes and Consequences of a Common Source Epidemic

Neal Nathanson,1 John Wilesmith,2 and Christian Griot3

Bovine spongiform encephalopathy (BSE) is a transmissible spongiform encephalopathy (TSE) or prion disease of cattle first recognized in 1986 in the United Kingdom, where it produced a common source epidemic that peaked in January 1993 and has subsided markedly since that time. The epidemic began simultaneously at many geographic locations and was traced to contamination of meat and bone meal (MBM), a dietary supplement prepared from rendering of slaughterhouse offal. It appears that the epidemic was initiated by the presence of the agent of scrapie (a long-standing TSE of sheep) that was first transmitted to cattle, beginning in the early 1980s, when most rendering plants abandoned the use of organic solvents in the preparation of MBM. The epidemic was probably accelerated by the recycling of infected bovine tissues prior to the recognition of BSE. To terminate the epidemic, a prohibition on the feeding of ruminant-derived protein to ruminants was introduced in the United Kingdom in July 1988. The ruminant feed ban accounts for the decline of the epidemic after an interval of about 5 years, approximately equivalent to the average incubation period of BSE. Relatively few cases of BSE have occurred in cattle born after 1993, and it is predicted that the epidemic will terminate about the year 2000 based on an extrapolation of the present declining curve. A comparison of data from the United Kingdom with data from relatively low incidence countries, such as Switzerland, indicates that this epidemic has been mainly confined to the United Kingdom because of a unique concatenation of risk factors, including: 1) a high ratio of sheep to cattle; 2) a relatively high rate of endemic scrapie; 3) the heavy feeding of MBM to dairy cattle; and 4) changes in the rendering process used to prepare MBM. Recently, cases of a variant form of Creutzfeldt-Jakob disease (a TSE of humans) have been reported in the United Kingdom. These cases, at least 10 of which had onset in 1994–1995, are distinguished by their occurrence in subjects under age 40 years, by their clinical presentation, and by their neurohistopathologic picture. The appearance of this novel disease and its concentration in the United Kingdom have raised the question that it might represent the transmission of BSE to humans. However, the cases gave no history indicating an unusual exposure to live cattle, to the preparation of beef products, or of dietary exposure to bovine tissues, and it remains to be determined whether they are associated with BSE. Am J Epidemiol 1997; 145:959–69.

Creutzfeldt-Jakob syndrome; disease outbreaks; encephalopathy, bovine spongiform; prion diseases

THE EPIDEMIC

The United Kingdom

A previously unrecognized neurologic disease in cattle was first identified in the United Kingdom in 1986, on the basis of a constellation of symptoms associated with characteristic pathologic lesions in the brain (1). Clinically, there was the insidious onset of altered behavior (either fear or aggressive responses), ataxia (incoordinated gait, falling, tremors), and dys-
esthesia (abnormal responses to touch and sound). The relentless progression of these symptoms made it impossible to handle animals, and required that the cows be slaughtered within 1–6 months (2). Histologically, the brain exhibited spongiform lesions, astrogliosis, and neuronal fallout (1). It was immediately recognized (1) that the lesions were similar to those characteristic of transmissible spongiform encephalopathies (TSEs) or prion diseases in other species, specifically scrapie of sheep, the prototype of the TSEs. In retrospect, it was found that cases of BSE had been seen in England as early as 1985 but probably not before that year. This new disease was made statutorily notifiable (3, 4), and the numbers of cases continued to increase each month, indicating the onset of a major epidemic (figure 1).

The advent of a new prion disease in epidemic form led to a detailed investigation of its possible cause. An important clue was offered by mapping of the cases that occurred within the first 18 months of the outbreak (figure 2), which showed that they were widely distributed throughout much of England. This is the classical pattern of a common source epidemic rather than a propagated epidemic (figure 1).

The rapid spread of BSE cases in the United Kingdom exasperated the scientific and lay communities. The government implemented a series of stringent measures to control the disease: feed bans, slaughter restrictions, increased testing, and changes in the regulatory framework. The diagnosis and surveillance systems were strengthened, and the government took steps to mitigate the economic impact of the disease on the agricultural sector.

The epizootic of BSE was a major public health crisis. The disease had significant implications for the livestock industry, food safety, and public health. The discovery of BSE highlighted the importance of monitoring and reporting animal diseases to prevent the spread of zoonotic diseases to humans. It also emphasized the need for international collaboration in disease surveillance and control.

What could explain the date of initial transmission of BSE and how does this relate to the possible incrimination of MBM? MBM is manufactured in rendering plants, of which there were about 45 in the United Kingdom in the early 1980s. These plants convert slaughterhouse refuse (offal) into two products, tallow (fat) and a defatted mixture of MBM. The process involves mixing, heating with steam, milling, and extraction with hydrocarbon organic compounds that act as fat solvents while precipitating the protein. The organic solvent extraction process demanded a high energy input, and the increase in fuel prices during the 1970s made this process inefficient. This,
together with a loss of the differential price between tallow and MBM, meant that extracting tallow from greaves (partially rendered offal), resulting in a fat content of about 1 percent in the MBM, was uneconomic. Other factors responsible for the decline in the use of the organic solvent extraction process were the increase in energy density provided by residual fat in MBM, and the introduction of more stringent health and safety measures in industrial processes. The proportion of MBM processed with fat solvents fell from about 70 percent in the mid-1970s to around 10 percent in the early 1980s, concurrent with the postulated first transmissions of BSE to cattle (2, 8).

At this point, it is necessary to note the physical properties of prions, the agents of the TSE, mainly based on studies of scrapie of sheep (10–12). Prions consist of a single protein, designated PrP (prion protein or protease resistant protein), which is attached to cellular lipid membranes by a glycosyl phosphatidylinositol (GPI) anchor. The infectivity of prions is notoriously resistant to heat (including steam under pressure) and treatment with some harsh denaturing agents, such as formaldehyde, but can be inactivated by lipid solvents (12). It may be postulated that if petroleum distillates are used in preparing MBM, they would substantially reduce the infectivity of any prions in the raw tissues used by rendering plants (13).

Another critical fact is that there is a large sheep population in the United Kingdom, so that ovine waste
TABLE 1. Risk factors among 169 early cases of bovine spongiform encephalopathy (BSE), United Kingdom, 1986*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of cases</th>
</tr>
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<tbody>
<tr>
<td>Meat and bone meal (MBM) dietary supplement</td>
<td>169</td>
</tr>
<tr>
<td>Dictocaulus viviparus vaccine</td>
<td>82</td>
</tr>
<tr>
<td>Leptospira hardjo vaccine</td>
<td>8</td>
</tr>
<tr>
<td>Salmonella dublin vaccine</td>
<td>5</td>
</tr>
<tr>
<td>Clostridia species vaccine</td>
<td>18</td>
</tr>
<tr>
<td>Viral respiratory vaccines</td>
<td>5</td>
</tr>
<tr>
<td>Bacterial antisera</td>
<td>9</td>
</tr>
<tr>
<td>Hormones</td>
<td>49</td>
</tr>
<tr>
<td>Pyrethroid insecticides</td>
<td>6</td>
</tr>
<tr>
<td>Organophosphorus insecticides</td>
<td>121</td>
</tr>
</tbody>
</table>

* Data from Wilesmith et al., 1991 (8).

constitutes a substantial part of the offal treated by rendering plants. Furthermore, in the United Kingdom, scrapie is enzootic in the ovine population at a relatively high prevalence, roughly estimated at about 2 cases per 1,000 sheep (14). These considerations led to the hypothesis that the scrapie agent had always been present in slaughterhouse offal but was inactivated during the production of MBM. With the change in rendering practices in the late 1970s, it is postulated that inactivation became less effective, leading to the contamination of some batches of MBM beginning about 1980 (13, 15, 16).

Circumstantial evidence in support of this hypothesis is provided by studies of the geographic distribution of BSE in the United Kingdom (table 3). There was a marked gradient, with highest cumulative incidence in southern England and a decrease toward the north, with the lowest rates in Scotland. The MBM produced in the approximately 45 rendering plants in the United Kingdom was mostly distributed locally. A survey revealed (8) that in the late 1980s rendering practices differed in different regions, with the use of petroleum solvents and reprocessing of greaves inversely related to BSE incidence (table 3).

**BSE in Europe**

Although BSE has occurred in a number of European countries, the reported incidence has been much lower than that in the United Kingdom. It is likely that...
the higher incidence in the United Kingdom was due to the concatenation of several circumstances, all of which occurred only in the United Kingdom. These include: a high ratio of sheep to cattle; a high enzootic prevalence of scrapie in sheep; the intensive feeding of MBM to dairy cattle; and the changes in rendering practices used to prepare MBM. A comparison of BSE in the United Kingdom and Switzerland illustrates these differences. Table 4 shows that the cumulative incidence of BSE in Switzerland is about 100-fold lower than in the United Kingdom. There are three rendering plants in Switzerland that supply MBM to the feedmill industry. A comparison was made of the relative risk of scrapie contamination of slaughterhouse waste produced in the two countries, based on the ratio of sheep/cattle and the relative prevalence of scrapie in sheep (17). As shown in table 4, if this relative ratio is normalized to 1 for the United Kingdom, it is estimated at 0.002 for Switzerland, indicating that the likelihood of scrapie entering rendering plants was much lower in Switzerland. Figure 5 shows that the BSE outbreak in Switzerland occurred about 3 years later than the outbreak in the United Kingdom. Because the Swiss imported considerable amounts of MBM from other countries, it is likely that most of the BSE cases were due to imported rather than domestically manufactured protein supplement (19, 20).

**Possible vertical transmission from cow to calf**

The question of whether BSE could be transmitted horizontally from cow to cow or vertically from cow to calf has been considered from the beginning of the epidemic (21). Because all animals in each age group in a herd would be exposed to the same dietary supplements, it could be difficult to distinguish horizontal from common source transmission. However, the low frequency of BSE in affected herds (overall < 5 percent cumulative incidence) suggests that horizontal transmission was not occurring, and detailed studies of selected herds has provided no evidence of cow-to-cow transmission (Wilesmith, 1996, unpublished observations).

It has long been suggested that scrapie in sheep is transmitted from ewe to lamb, perhaps via the placenta from which the scrapie agent has been isolated, although a recent critical review (22) concluded that vertical transmission may be more myth than fact. In 1994, a case-control study (21) was conducted in the United Kingdom of cases of BSE in animals born after the ban on feeding ruminant-derived protein was introduced in July 1988 (see below). This study provided no evidence that maternal transmission would sustain the epidemic or prolong it significantly. It indicated that maternal transmission—if it occurred—would be at a very low rate and would not explain the occurrence of cases of BSE in animals born after the feed ban.

Another study was initiated in 1989 to examine the question of maternal transmission or of a maternally associated risk factor, based on a long-term follow-up of selected cohorts of animals. This cohort study is now nearing completion, and interim analyses have been completed (table 5). The observations indicate an as-yet-unexplained declining risk in successive birth cohorts and a major change in this statistic for animals born after the 1988 feed ban. These results may indicate a very low maternally associated risk for offspring.

**Fitting Table 3**

<table>
<thead>
<tr>
<th>Region</th>
<th>% of dairy herds with BSE</th>
<th>Use of solvents to process MBM†</th>
<th>% of MBM from graves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southern England</td>
<td>12.6</td>
<td>No</td>
<td>0.2</td>
</tr>
<tr>
<td>Midlands</td>
<td>3.9</td>
<td>No</td>
<td>8.6</td>
</tr>
<tr>
<td>Northern England</td>
<td>2.8</td>
<td>No</td>
<td>25.5</td>
</tr>
<tr>
<td>Scotland</td>
<td>1.8</td>
<td>Yes</td>
<td>39.0</td>
</tr>
</tbody>
</table>

* Data from Wilesmith et al., 1991 (8).
† MBM, meat and bone meal.

**Fitting Table 4**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>United Kingdom</th>
<th>Switzerland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle population</td>
<td>-12,000,000</td>
<td>-1,700,000</td>
</tr>
<tr>
<td>Cumulative BSE reported</td>
<td>-160,000</td>
<td>-213</td>
</tr>
<tr>
<td>through May, 1996</td>
<td>-13,300</td>
<td>-125</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>1,000,000†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>relative ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheep population</td>
<td>-29,000,000</td>
<td>450,000</td>
</tr>
<tr>
<td>Ratio: sheep/cattle</td>
<td>2.4</td>
<td>0.26</td>
</tr>
<tr>
<td>Estimated prevalence of</td>
<td>2,250</td>
<td>40</td>
</tr>
<tr>
<td>scrapie per 1,000,000 sheep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated scrapie</td>
<td>1</td>
<td>0.002</td>
</tr>
<tr>
<td>contamination of offal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>relative ratio‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† This estimate does not take account of the turnover of the population.
‡ Relative ratio calculated as the product of the ratio of sheep/cattle multiplied by the estimated prevalence of scrapie, normalized to 1 for the United Kingdom.
of cows that developed BSE, and analyses of the completed study are designed to determine whether this effect is the result of maternal transmission, genetic risk (23, 24), differential exposure to contaminated MBM, or a combination of these possible factors.

It is also important to assess the potential impact of maternal transmission. For calves born after the ruminant feed ban of July 1988, it appears that maternal BSE may elevate lifetime risk of BSE by no more than 5 percent. Thus, each 100 cases of MBM-transmitted BSE would give rise to no more than five cases of vertically transmitted BSE. This suggests that maternal transmission, if it occurs, would have a negligible impact on the waning epidemic.

**Control of the epidemic and future projections**

The recognition that BSE was a common source epidemic and the identification of contaminated MBM as the putative cause led to a decision to ban ruminant offal as a raw material in the preparation of dietary supplements destined for feeding to cattle. The "ruminant feed ban" of July 1988 represented a decisive administrative action to control the problem, as well as the ultimate test of the hypothesis that MBM was the source of the outbreak. In the United Kingdom, the epidemic peaked in January 1993 and has undergone a dramatic decline so that in mid-1996 incidence was about one-quarter of maximal levels (figure 1). The waning of the epidemic has followed a path that was roughly predicted at the time of the feed ban (25), providing strong support for the MBM causal hypothesis.

A recent elegant mathematical and statistical study of the BSE epidemic by Anderson et al. (6) has used back calculation to reconstruct the dynamics of the outbreak, including the probable numbers of infected animals. This analysis indicates that infections did not cease in July 1988 immediately following the feed ban, but continued in substantial but declining numbers in animals born through 1991 (estimated new infections: >300,000 in 1988 and around 30,000 in 1991). This is consistent with observations on the occurrence of BSE cases in birth cohorts (table 2) that show that cases occurred in animals born in 1989 through 1991, but in sharply decreasing numbers (5). The continued occurrence of new infections immediately after the feed ban can be ascribed to contaminated feedstuffs manufactured before July 1988, which were already in the feed supply chain. In addition, there is evidence after 1988 of accidental cross-contamination in feed mills of rations produced for consumption by monogastric animals (poultry and pigs) and ruminants (cattle and sheep), and of the
TABLE 5. Frequency of bovine spongiform encephalopathy (BSE) in calves born of cows with and without BSE, United Kingdom, 1987–1989*

<table>
<thead>
<tr>
<th>Birth date</th>
<th>BSE status of mothers</th>
<th>No. of offspring studied</th>
<th>No. of offspring with BSE</th>
<th>% of offspring with BSE</th>
<th>% difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>With BSE</td>
<td>11</td>
<td>8</td>
<td>73</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Without BSE</td>
<td>10</td>
<td>2</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Jan.–June 1988</td>
<td>With BSE</td>
<td>12</td>
<td>5</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Without BSE</td>
<td>14</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without BSE</td>
<td>205</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>With BSE</td>
<td>36</td>
<td>4</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Without BSE</td>
<td>44</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1987–1989</td>
<td>With BSE</td>
<td>273</td>
<td>42</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Without BSE</td>
<td>273</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Both groups</td>
<td>546</td>
<td>55</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Calves born to mothers with BSE were compared to calves born to mothers without BSE in the same herds and birth years. All study animals were followed until they had reached age 7 years (unless BSE or another disease had intervened), and BSE was confirmed by histologic examination. There are 63 additional animals in this study that are still alive or where histologic examination is pending. Data from Wilesmith et al., unpublished, 1995, based on an incomplete study conducted by the Central Veterinary Laboratory, Weybridge (9).

possible feeding of cattle with rations produced for monogastric animals (26). The risks of accidental contamination were greatest in the northern and eastern regions of England where pig and poultry populations are concentrated, and this has resulted in a change in the geographic variation in risk for animals born since the feed ban.

The study by Anderson et al. (6) has also provided a sound basis to predict the remaining course of the epidemic (plotted in figure 1) and has confirmed that maternal transmission, if it has occurred, will have only a minor influence on the decline of the epidemic.

VARIANT CREUTZFELDT-JAKOB DISEASE AND ITS POSSIBLE ASSOCIATION WITH BSE

The potential transmission of BSE to humans by the consumption of beef or beef products prepared from cattle with the disease had been considered from the outset of the epidemic (27). There were several reasons to discount this possibility. Perhaps the most persuasive was a number of carefully conducted epidemiologic studies that failed to demonstrate an association between sporadic cases of Creutzfeldt-Jakob disease (CJD) (or other human prion diseases) and consumption of lamb, mutton, or other sheep tissues including brain (27–29). It was reasonable to argue that, if scrapie of sheep had never been transmitted to humans, then it would be unlikely that a closely related spongiform encephalopathy, arising by transmission of scrapie to another ruminant species, would pose a risk. Another relevant biologic observation was the relatively low infectivity of scrapie, when administered by feeding, in contrast to intracerebral injection (30, 31); in one study using mice, 10^5 intracerebral LD50 were required to produce one intragastric LD50 (32). In particular, the failure to transmit kuru to chimpanzees by feeding of material shown to have high titer by intracerebral and other routes of injection (33–35) suggested that transmission of BSE to humans would be unlikely. Nevertheless, early in the BSE epidemic, some workers (36) expressed concern about the potential transmission of BSE to humans.

Several actions were taken to minimize the theoretical risk of BSE transmission (3, 4). First, BSE was made a reportable disease, with compensation to farmers for animals destroyed because of the disease. In the United Kingdom, a diagnostic service was established to screen all suspected cases by neurohistologic examination of the brain; since 1987, about 200,000 suspect animals have been examined, of which about 80 percent have been confirmed as positive for BSE (3). Also, in 1989, a “ban on specified bovine offals” was imposed, forbidding entry into the food chain of certain bovine tissues (including brain and spleen) that might contain the BSE agent (4).

In April 1996, a new variant form of CJD (vCJD) was reported (37) in 10 patients resident in the United Kingdom with onsets of illness between February 1994 and October 1995 (the number of probable cases was around 15 by December 1996). There are three
types of CJD, sporadic (about 85 percent of cases), familial (about 15 percent of cases), and transmitted (<1 percent of cases). Variant CJD was distinguished from sporadic CJD by four major characteristics: 1) the cases were mainly under age 40 years at onset, in contrast to CJD where <1 percent of cases are this young; 2) the clinical picture of vCJD, in which behavioral changes, dysesthesia, and ataxia were prominent early symptoms, contrasted with that of CJD, in which dementia is usually seen early in the illness; 3) the absence of triphasic slow waves on the electroencephalogram in cases of vCJD differed from the pattern that is seen in most cases of CJD; and 4) vCJD exhibited certain neuropathologic features, most notably plaques staining for the prion protein (PrP), which are rarely seen in CJD, although they are common in other spongiform encephalopathies of humans, such as kuru and Gerstmann-Straussler-Scheinker syndrome (33).

Two circumstantial aspects of vCJD, its appearance in 1994 and its localization in the United Kingdom, raised the question whether vCJD could be related to BSE. Both of these points deserve careful consideration. First, is vCJD a truly new entity or only one that is newly recognized? To date (December 1996), there are no reports of cases similar to vCJD occurring prior to 1994. Second, is vCJD a worldwide phenomenon or is it mainly confined to the United Kingdom? One case has been reported from France (38), but at this time there are no reports of vCJD from other countries. Recent studies in the United States (39, 40) confirm that there are very few CJD cases with onsets under age 45 years, and there has been no evidence of an increase of younger cases in the last few years (table 6), nor has intensive surveillance at a number of neurologic centers identified individual cases of vCJD (40).

Genetic studies of vCJD provide additional pertinent data (table 7). Among normal persons, there is a polymorphism of the PrP gene at codon 129 (45). Cases of CJD usually are homozygous at codon 129, either for methionine or valine in the sporadic form of the disease (46), but predominantly valine in the cases transmitted by injection of cadaver-derived growth hormone (47). All of the 10 cases of vCJD that have been tested were homozygous for methionine at codon 129 of the PrP gene (41). This codon 129 methionine homozygosity bolsters the grouping of cases of vCJD as a distinct prion disease of humans. However, it does not help to distinguish between different hypotheses about its origin.

The original 10 cases of vCJD gave no family history of prion diseases. More pertinent, there was no indication of exposure to growth hormone or other risk factors (e.g., brain surgery and tissue transplants) that have been associated with the transmission of CJD (33). Nor did these cases give a history of unusual consumption of beef or calf brains, or any occupational or casual exposure to cattle, slaughterhouses, or rendering plants. To date, this line of inquiry has failed to demonstrate any link to BSE.

A related question is whether infected cattle entered the human food chain, providing a potential source of exposure. During the period 1985–1995, a cumulative

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<tbody>
<tr>
<td></td>
<td>No. of deaths</td>
<td>Death rate</td>
<td>No. of deaths</td>
<td>Death rate</td>
</tr>
<tr>
<td>0–44</td>
<td>22</td>
<td>0.04</td>
<td>18</td>
<td>0.02</td>
</tr>
<tr>
<td>45–59</td>
<td>160</td>
<td>1.17</td>
<td>170</td>
<td>1.26</td>
</tr>
<tr>
<td>60+</td>
<td>564</td>
<td>4.04</td>
<td>703</td>
<td>4.52</td>
</tr>
</tbody>
</table>

* Based on an analysis of death certificates. After Holman et al., 1996 (39).

total of >150,000 cases of BSE were confirmed (table 2). These cases were distributed over about 32,000 affected herds (with one or more cases of BSE), or about five cases per herd (9). Because the mean size of affected herds was about 100 cattle (figure 3), in affected herds the incidence of diagnosed cases was around 5 percent of animals. This suggests that, in such affected herds, the approximately 95 percent of cattle that were apparently normal included some animals that were incubating BSE. Anderson et al. (6) estimated, using back calculation methods, that >700,000 animals incubating BSE entered the human food chain during the period 1985–1995, in addition to the >150,000 diagnosed with BSE that did not enter the food chain. If >2.5 million cattle are slaughtered annually, the >700,000 animals represent <3 percent of the >25 million animals that entered the human food chain in the United Kingdom during 1985–1995. Furthermore, the majority of these subclinically infected animals would have been slaughtered for prime beef at <30 months of age, at a time when they would have been less than halfway through the incubation period (around 60 months); this appears to be significant because infectivity has not been detected in the central nervous system 30 months after infection in an ongoing study of the pathogenesis of BSE following oral exposure (50).

Other relevant information is provided by experimental studies of BSE transmission to primates. It was recently reported (51) that a single pool of bovine BSE, injected intracerebrally into three rhesus macaques, produced a disease (after a 3-year incubation period) that resembled vCJD both clinically and pathologically. This finding stands in contrast to the transmission of sporadic CJD to primates, which produces a syndrome similar to human CJD (52–56). It is noteworthy that cynomolgus macaques are homozygous for methionine at codon 129 of the PrP gene (52). Collinge et al. have provided further important evidence in a recent study (41; see comment in 48). In that study, Collinge et al. utilized the approach of Parchi et al. (49) to compare the patterns of pathologic prion proteins (PrPSc or PrPSc*) in polyacrylamide gel electrophoresis (PAGE). PrPSc shows microheterogeneity due to different glycosylation patterns that produce several discrete bands on PAGE, and differences in the banding pattern of PrPSc from different prion diseases provide a biochemical "signature" (57). Strikingly, the signature of PrPSc from vCJD is similar to that of PrPSc extracted from cattle with BSE and macaques or mice to whom BSE has been transmitted, and this pattern is distinct from that of CJD that has been transmitted from human to human (table 7).

Transgenic mice have also been used to determine the potential for transmission of BSE to humans. Collinge et al. (58) have employed mice in which the native mouse PrP gene was "knocked out" and a transgene for human PrP was introduced. When injected intracerebrally, these mice are susceptible to CJD prions but have failed to exhibit evidence of spongiform encephalopathy 500 days after injection of BSE prions (Collinge et al., personal communication, 1996). However, the mouse transgene carried valine at codon 129 (59), and it remains to be determined whether the result would be different if the experiment was repeated with mouse bearing a transgene carrying methionine at codon 129.

COMMENT

The question of the relation between BSE and vCJD has been the subject of much debate (52, 60–62). In our view, the evidence available at this time precludes any final conclusion whether or not there is a significant relation between vCJD and BSE, although the recent description (41) of a distinctive glycoform signature of prions in cattle with BSE and humans with vCJD has strengthened the argument for a potential association. Answers to the following questions would shed light on this enigma. Does ongoing surveillance confirm that variant CJD is a new prion disease and that it is occurring mainly in the United Kingdom? Is there significant prion infectivity in beef products prepared from cows that are incubating BSE, and are the titers adequate to infect primates by the oral or any other route? If the evidence continues to support an association, it will still leave residual questions, such as the following. Do cases of vCJD have specific risk factors, in addition to homozygosity at codon 129, or is transmission a rare event governed only by the laws of chance? Why are there no cases of vCJD in persons over age 40 years? How many cases of vCJD may be predicted (62, 63)?

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REFERENCES


