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# An Epidemiologist's View of Bovine Spongiform Encephalopathy

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# An epidemiologist's view of bovine spongiform encephalopathy

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**SUMMARY**

Bovine spongiform encephalopathy was first recognized in Great Britain in 1986 and was the result of infection with a scrapie-like agent surviving in meat and bone meal used in feedstuffs. This effective exposure commenced in 1981–82 and was associated with a reduction in the use of hydrocarbon solvents in the manufacture of meat and bone meal. The epidemiological features are consistent with sheep scrapie as the original source, but the epidemic was amplified by the recycling of infected cattle tissue resulting in a marked increase in incidence from 1989. The food borne source was eliminated by legislation introduced in July 1988. The first effects of this became apparent during 1991 and these have become more obvious during 1993 with a reduction in the national incidence. Specific studies are still in progress to determine whether other means of transmission can occur, but none capable of maintaining the epidemic have been detected.

## 1. INTRODUCTION

A great deal of mystery and intrigue followed the recognition of a novel neurological disease of cattle, in 1986, in which the lesions in the brain were reminiscent of those in sheep affected with scrapie (Wells *et al.* 1987). Conclusive evidence that this disease, bovine spongiform encephalopathy (BSE), was a member of the transmissible spongiform encephalopathy was acquired relatively quickly (Wells *et al.* 1987; Fraser *et al.* 1988; Hope *et al.* 1988). This greatly assisted the formulation of the later epidemiological studies, but the uniqueness of the disease, being confined to Great Britain in the early years, presented an additional degree of difficulty.

This paper summarizes completed epidemiological studies, gives an overview of the important features of the epidemic, and discusses the possible origins of the epidemic and current knowledge relevant to its future.

## 2. INITIAL STUDIES ON THE AETIOLOGY

Although there was histological evidence that BSE was a scrapie-like disease, a degree of uncertainty was necessary in designing the initial study because of the then inexplicable reason for its occurrence. It therefore considered a wide spectrum of potential aetiologies ranging from intoxication to possible sources and vehicles of a scrapie-like agent (Wilesmith *et al.* 1988). In summary, this study provided compelling evidence that meat and bone meal, incorporated in cattle feedstuffs as a source of protein, was the vehicle of infection. No evidence of any other major contributory risk factors for the development of the disease was found and the feeding of ruminant-derived protein to ruminants was statutorily prohibited on 18 July 1988.

As soon as was possible, in the first half of 1988, the process of identifying appropriate and potentially useful neighbourhood controls for inclusion in case-control studies to investigate this initial finding was started. The completion of these studies was possible in 1991 and they substantiated the original hypothesis that BSE occurred as a result of exposure to a scrapie-like agent via meat and bone meal (Wilesmith *et al.* 1992). Experimental studies to directly investigate this hypothesis were clearly impossible because of the large numbers of animals required to preclude an equivocal result.

## 3. STUDIES TO INVESTIGATE WHEN AND WHY EXPOSURE OF CATTLE STARTED

An initial consideration was whether BSE was a truly new disease. This was a component of the initial epidemiological study accompanied by a histopathological review of archival material and indicated that the epidemic commenced around April 1985 (Wells *et al.* 1992; Wilesmith *et al.* 1988; Wilesmith 1993). Having some confidence of the time of the start of the epidemic enabled analyses to estimate the most probable time when effective exposure of the cattle population commenced. This was originally estimated by simulation studies and revealed that this occurred in the winter of 1981/82. The other conclusion was that exposure must have started suddenly such that the probability of exposure of cattle changed from zero, or an ineffective level, to a constant, effective exposure over a relatively short period of time.

The inference from these findings was that there

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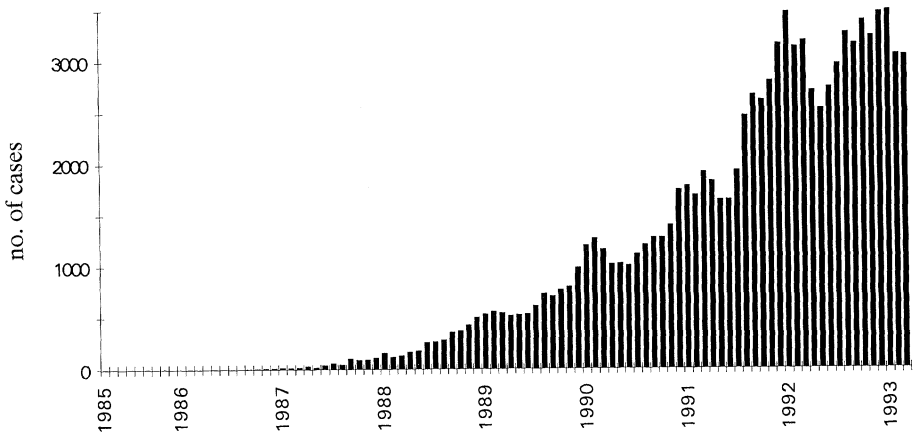


Figure 1. Epidemic curve of cases by month and year of onset of clinical signs.

had been a change in a single factor or, perhaps more inconceivably, coincidental changes in a number of factors which could have increased the risk of exposure. A number of potentially significant factors were identified (Wilesmith *et al.* 1988). The most obvious of these, the novel inclusion of meat and bone meal in cattle feedstuffs, was not a factor. Meat and bone meal, containing both ovine- and bovine-derived tissues, had been used for several decades before the putative start of exposure and there had been no change in its rate of inclusion. However, on investigation, there had been a reduction, over a relatively short period, in the use of solvent extraction in the manufacture of meat and bone meal (Wilesmith *et al.* 1991). Organic solvents were used to maximize the yield of the other product of rendering, tallow (animal fat). In this process there were two components which could have reduced the titre of a scrapie-like agent, given its physico-chemical properties (Millson *et al.* 1976). The first was the direct application of the solvent at high temperature (70–80°C) for up to 8 h. The second was the application of superheated steam to remove the final traces of solvent. As this change in the rendering process was coincident with the estimated onset of exposure and the distinct likelihood that the solvent extraction component could have prevented a sufficient concentration of a scrapie-like agent surviving, it has been suggested as the working hypothesis to explain the onset of exposure sufficient to cause the expression of disease, and therefore the epidemic. This change also explained, in part at least, the geographical variation in risk, which has persisted throughout the epidemic, with cattle in Scotland having the lowest risk of disease. The only two rendering plants which continued using solvent extraction were both in Scotland and produced most of the meat and bone meal for this part of Great Britain.

As the epidemic has progressed it has been possible to re-assess the validity of the original estimate for the onset of exposure. The early indications, in 1988, from descriptive epidemiological analyses were that the full extent of the incubation period had not yet been observed. The continued monitoring of the epidemic has supported this in that it is only in the later years that a more complete understanding of the incubation period distribution, notably the 'tail', has been possible. The evidence is therefore entirely against the apparent first detection of the disease at some considerable time after its initial occurrence and certainly not after the occurrence of the disease had become well established.

## 4. OBSERVATIONS ON THE BSE EPIDEMIC (1986–1992)

The epidemiological features of the disease are consistent with a food-borne source and in particular with meat and bone meal as the vehicle of infection. The initially detected cases occurred simultaneously throughout Great Britain (Wilesmith 1992), but with a marked geographical variation in risk, with the greatest incidence in the southern counties of England and the lowest in Scotland. These are explicable by the geographical variation in risk of exposure from meat and bone meal (Wilesmith *et al.* 1991). The other marked variation in risk has been that between the two production types of herds with adult breeding animals. The cumulative proportion of affected dairy herds in Great Britain was 46% compared with 10% of beef suckler herds affected by August 1993. The risk for animals born in beef suckler herds is even lower than suggested by the crude incidence as only 1.4% of beef suckler herds have experienced a case of BSE in a homebred animal. Most beef suckler herds affected have experienced a case as a result of the purchase of cross bred animals from dairy herds. This lower risk is simply explained by the difference in exposure from the food-borne source as a result of the different nutritional requirements between the two herd types resulting in a much lower level of feeding concentrate rations in suckler herds.

Breed and sex were not identified as risk factors with respect to susceptibility and there has been no indication of an effect of age at the time of initial exposure. These remain as inconsequential factors and the most significant change in the descriptive epidemiology is the increase in incidence from 1989 to 1992 (figure 1). The reasons for this increase have been investigated (Wilesmith 1991, 1992). The increase was certainly real and not due to an increase in the ascertainment rate. This is evident from figure 2 which depicts the epidemic curve of cases in herds




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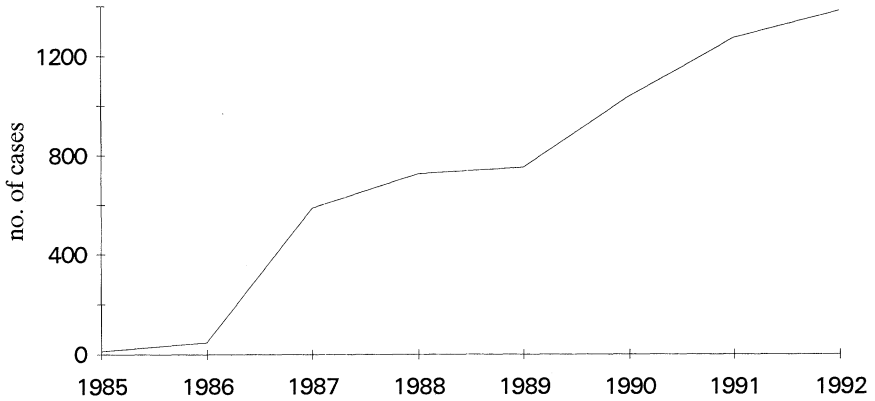


Figure 2. Epidemic curve of cases by year in herds from which cases were reported before June 1988.

from which cases were reported before the disease became statutorily notifiable in June 1988 and for which the ascertainment of cases is as complete as is possible.

The increase in incidence occurred uniformly throughout Great Britain (Wilesmith 1992). It was not associated with any marked change in the within-herd incidence (table 1), an increase which could have suggested the otherwise undetected occurrence of cattle to cattle transmission. Instead the increase resulted in an increase in the number of herds affected. This has been explained, and is entirely consistent with, an enhanced exposure from the inclusion of cattle tissue, from abattoir waste, in material used for the production of meat and bone meal (Wilesmith 1991). This would have commenced in 1984–85 and continued until the statutory ban on the inclusion of ruminant-derived protein in ruminant rations in July 1988. It has only been possible to model this process using general terms. During this period the probability of exposure for cattle would have increased as the proportion of infected cattle rose. An indication of this rate of increase is provided by the incidence in herds from which cases were reported before the disease became notifiable (figure 2). With the passage of time an improved understanding of this has been accumulated. It is now certain that at the time of the statutory ban the probability of exposure for cattle from the cattle source was still increasing and had not reached a constant maximum. The other aspect of interest in this analysis are the titres of the BSE agent in tissues and organs of cattle. This is gradually being obtained for terminal cases from infectivity studies in mouse bioassays (Barlow & Middleton 1990, 1991; Fraser *et al.* 1992; Middleton & Barlow 1993) and from pathogenesis studies of orally exposed cattle. Further analyses will be possible to examine this recycling process in more detail, but it is clear that the majority of affected animals has been the result of infection from cattle via meat and bone meal. This is important for other countries as if there is any risk of cattle becoming infected from indigenous sources, or as a result of the importation of sub-clinically infected cattle, and their tissues are included in meat and bone meal, there is a distinct possibility for the amplification of the prevalence of infection and therefore the occurrence of clinical disease.

Although this amplification has contributed to the cumulative total of just over 100 000 cases from 1986 to August 1993, the risk of cattle becoming affected has been notably low. This is especially so given the uniform susceptibility, and incubation period, of cattle experimentally infected with BSE (Dawson *et al.* 1991). All cattle inoculated intracerebrally developed disease and is in contrast to the variable susceptibility of sheep following injection with scrapie which is attributed to the variation in genotype (Hunter *et al.* 1992). Variations in the nucleotide sequence of the bovine PrP gene have been detected (Goldmann *et al.* 1991) and differences in the prevalence of the 5- and 6-copy alleles of the octarepeat polymorphism between breeds have been found (M. Dawson, personal communication). However, no association between genotype and BSE has been found. The low risk for cattle is therefore unlikely to be due to a low prevalence of a susceptible genotype. The most probable explanation is that the average exposure to infection has been very low (Kimberlin & Wilesmith 1994). The recycling of infection in cattle would have resulted in an increased number of packets of infection rather than an increase

Table 1. *Within herd incidences (%) of* BSE *in herds affected in 6 month time periods 1988 to 1992*

| 1988 | | 1989 | | 1990 | | 1991 | | 1992 | |
|---|---|---|---|---|---|---|---|---|---|
| Jan–Jun | Jul–Dec | Jan–Jun | Jul–Dec | Jan–Jun | Jul–Dec | Jan–Jun | Jul–Dec | Jan–Jun | Jul–Dec |
| *all herds* | | | | | | | | | |
| 1.8 | 1.8 | 2.0 | 1.9 | 2.1 | 2.2 | 2.3 | 2.5 | 2.7 | 2.7 |
| *herds in which a case was reported before June 1988* | | | | | | | | | |
| 1.7 | 1.5 | 1.5 | 1.6 | 1.8 | 1.8 | 1.9 | 2.1 | 2.0 | 2.0 |




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in the average titre of infection within them and therefore not resulted in an increase in the mean within herd incidence.

## 5. THE ORIGIN OF THE EPIDEMIC

Scrapie has been endemic in the sheep population of Great Britain for several centuries and this species is recognized as the natural reservoir of scrapie-like agents in animals. Cattle are susceptible to scrapie when experimentally exposed by both oral and parenteral routes (Gibbs *et al.* 1990). Two ways in which the BSE epidemic may have originated from sheep scrapie have been suggested (Wilesmith *et al.* 1988, 1991).

The first is that a novel spontaneous mutation arose in sheep which was pathogenic for cattle. The sudden onset of exposure of the cattle population and the simultaneous occurrence of BSE initially throughout Great Britain provides evidence against this hypothesis. Such a mutant strain would have had either to arise in a large proportion of infected sheep across the country or spread rapidly from one focus. Both of these are highly improbable.

The second is that cattle have always been susceptible to sheep scrapie, but had never been sufficiently exposed to cause disease. Considering the species barrier effect, the absence of any genetic control of BSE would suggest that there was a uniform selection effect throughout the cattle population. Bioassay of isolates of BSE from cases occurring early in the epidemic indicate that cattle have succumbed to a single strain of agent which is different from any known strain isolated from sheep scrapie (Fraser *et al.* 1992). There is, however, only one contemporary isolate of scrapie and cattle have not been experimentally exposed to native sheep scrapie. It is therefore not known whether the BSE strain exists in natural sheep scrapie.

This second hypothesis cannot be dismissed and is favoured by the epidemic curve of cases in the herds in which cases were reported before June 1988. This subset of herds provides the best indication of the true form of the epidemic by virtue of the more complete ascertainment of cases from these herds. It provides a strong indication of two stages. The first, up to 1989, appears akin to an extended common source epidemic with a constant exposure. The second is typical of a propagative epidemic which is consistent with the effects of recycling of cattle tissue from an ever increasing, until July 1988, prevalence of infected cattle. In contrast, the probability of infection for cattle from sheep, via meat and bone meal, would have remained constant. The first stage is therefore consistent with the epidemic arising directly from sheep, without any intermediary stage. A variant of this hypothesis could, however, include the selection of the most heat resistant strains in the rendering process.

In summary, the original risk factors identified for the occurrence of BSE in Great Britain are still relevant. These are: a large sheep population in relation to that of cattle; a sheep population with endemic scrapie; the use of ruminant-derived protein in cattle feedstuffs; and conditions of rendering that allowed a significant survival of the scrapie agent. At present, a major epidemic has not occurred outside the British Isles and it appears that the same combination of risk factors is not present elsewhere. However, further experimental studies would be of assistance in testing the most likely hypothesis that cattle became infected from sheep, via meat and bone meal, and would aid veterinary authorities in other countries conduct risk assessments for the occurrence of BSE.

## 6. INDICATORS OF THE FUTURE COURSE OF THE EPIDEMIC

A number of aspects of the descriptive epidemiological features are being monitored in detail together with specific analytical studies to determine the likely future course of the epidemic and, should any occur, to identify means of transmission other than from the food borne source at the earliest opportunity.

Recent changes in the age-specific incidences have occurred (Wilesmith & Ryan 1992, 1993; Wilesmith 1994). The first was in 1991, with a reduction in the two year old age class. This was followed by a reduction in 3–4 year old animals in 1992. These were expected given the time of the ban to prevent the food borne source in July 1988 and the incubation period, resulting in a modal age at onset of 4 to 5 years, and the absence of any other source.

These changes have been reflected in the number of suspect cases reported under the legislation during 1993, the epidemic curve of cases and the epidemic curve of newly affected herds (Wilesmith 1994). The last of these indicated a reduction in the rate of new herds becoming affected from July 1992.

A cohort study to specifically investigate the possible occurrence of maternal transmission is in progress, but definitive results will not be available for some time. In the meantime, the data arising from the epidemic are used to estimate any excess risk for the offspring of confirmed cases. None has been observed to date (Wilesmith 1993), but maternal transmission on its own would not sustain the disease in the cattle population (Wilesmith & Wells 1991). Other potential means of transmission such as from semen have also been examined from the epidemiological data, again with no evidence of a risk from this source (Wilesmith 1993).

Cases of disease in animals born after 18 July 1988 have occurred. At the end of July 1993 there were 3103 such cases of which 2737 were born in 1988. These cases are not entirely unexpected as there would have been several months supply of finished feedstuffs within the food marketing chain and on farm and because these animals would have been subjected to the greatest probability of exposure. The incidence of these cases do not signify a significant prolongation of the epidemic or an important means of transmission other than the food borne source. Cases born in 1989 are the subject of a current case-control study to assess the relative risk of infection from the food source. Although there is no evidence of excretion of the BSE agent from cattle, such as from placenta, the relative risks of maternal transmission and horizontally acquired infection from affected animals calving at the




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time of the birth of these cases will be studied. This is necessary as it is impossible to assess the risk of food borne infection for individual cases as we do not have a complete knowledge of the probability of infected feedstuffs persisting in the food chain for prolonged periods, or the chances of true accidental inclusion of ruminant-derived meat and bone meal in proprietary cattle rations.

In summary, the current evidence is that the effects of preventing the food borne source are apparent. A convincing finding is the difference between the observed number of reported suspect cases and that expected given no ban on the feeding of ruminant-derived protein which amounted to a reduction of 20 000 cases in the financial year 1992–93 (Wilesmith 1994). At present there is no evidence of a source or means of infection to maintain the epidemic in the cattle population. However, the detailed monitoring of the epidemic continues in order to detect any circumstances under which transmission between cattle can occur.

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