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Bovine Spongiform Encephalopathy

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The first case of bovine spongiform encephalopathy (BSE) was diagnosed in England in 1986 and was regarded as little more than a curiosity. Since that time, the spread of the disease in the United Kingdom (UK) has been extensive and the effect on the cattle industry in that country catastrophic. In part, the paranoia associated with this disease stems from the fact that when it was first identified and the possibility of transmission to humans was first theorized, very little was known about the disease. In the past 17 years, there has been an immense research effort and consequently, a great deal is now known about BSE, its epidemiology, and the risk of transmission to humans. This issue of *Large Animal Veterinary Rounds* gives a summary of our present knowledge of the disease.

What is BSE?

BSE was first definitively diagnosed in 1986. The first recorded clinical case started to show signs in April 1985 on a small dairy farm in southeast England. The index case was initially noticed as walking in an abnormal manner with an arched back and mild ataxia, which led the farmer and his local veterinarian to suspect pyelonephritis. After an extensive diagnostic "work up" and multiple failed therapies, the cow was euthanized and submitted to one of the governmental Veterinary Investigation Centers for a full postmortem. As part of the examination, the brain was examined microscopically and revealed the characteristic "spongiform" changes similar to those seen in ovine "scrapie." Further examination of tissues under electron microscopy identified the characteristic scrapie-associated fibrils (SAF). This discovery prompted a search for similar cases. Within a short while, 4 cases were identified with historical references to a further 12 cases. This initial discovery was published as little more than a curiosity.¹ The first clinical case report followed shortly thereafter, describing the clinical signs and the lack of any definitive diagnostic tests.²

To date there have been approximately 180,000 cases of BSE diagnosed in the United Kingdom. The peak in the number of cases occurred in 1993 and the number of cases has now fallen dramatically (Figure 1). Twenty-two countries have also been affected, mainly with sporadic cases. The Republic of Ireland has seen more cases than any other country, with the exception of the UK, with 1238 confirmed cases.

BSE is one of a number of naturally occurring transmissible spongiform encephalopathies (TSE). Scrapie is the oldest one known; it affects sheep and occasionally goats. Chronic wasting disease (CWD) is seen in white-tailed deer and elk. Transmissible mink encephalopathy (TME) affects mink. Four distinct spongiform encephalopathies have been identified in humans. These are:

- Kuru, a disease specific to the Fore tribe of Papua, New Guinea. The transmission of the disease, in this case, was associated with a tribal custom of handling the brains of recently deceased relatives. The disease has now died out.
- Creutzfeldt-Jakob disease (CJD), a spontaneous, sporadically occurring disease affecting approximately 1 in 1 million people. The disease has also been transmitted iatrogenically during some medical procedures.



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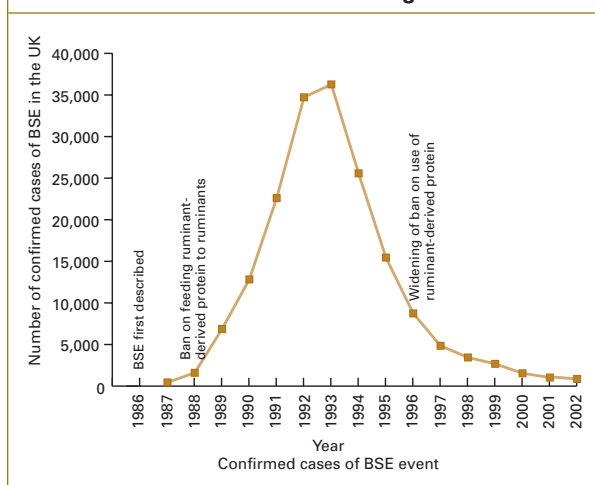
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Figure 1: Time distribution of confirmed cases of BSE in the United Kingdom



- Gerstmann-Sträussler-Scheinker syndrome (GSS) and Fatal Familial Insomnia (FFI) are rare genetic disorders with a familial transmission pattern.

All of these diseases have a number of similar characteristics, including a prolonged incubation period (measured in years), spongiform changes seen in the brain on histopathology, the presence of fibrils within the tissues of the brain, and an apparent infectious agent that appears to be smaller and more resistant to inactivation than a virus.

The prion theory of disease

This theory was first proposed by Prusiner in 1982 to explain some of the peculiarities of the infectious agent for scrapie in sheep.³ The term “prion” was taken from proteinaceous infectious particle. The scrapie agent was considered unconventional for a number of reasons.

- It was resistant to inactivation by formalin; this was demonstrated when large numbers of sheep developed scrapie after being vaccinated against louping ill using a formalin inactivated vaccine derived from the brain of louping ill-infected sheep that were also carrying scrapie.
- The scrapie agent did not cause any detectable immune response.
- The incubation period (measured in years) was longer than any known viral disease.
- The agent was associated with the membrane fraction of homogenized brain tissue and was extremely small.

There is now a great deal of evidence to suggest that a prion is nothing more than protein. The size of the infectious agent is thought to be less than 50 kDa. This means that if it were formed from DNA or RNA it could contain no more than 12 base pairs of nucleic acid. Furthermore, the agent is resistant to ultraviolet light and the action of nuclease enzymes, essentially ruling out nucleic acid content.

Identification of the protein associated with the disease led to the discovery that it was in fact a normal cellular pro-

tein, chromosomally coded for in mammalian species. The prion protein (PrP) is a 253 amino acid protein that can undergo extensive post-translational modification by glycosylation. The natural form of the protein designated PrP^c, is a membrane-associated protein with a tertiary structure consisting of 40% α -helix with almost no β -pleated sheet. In contrast, the abnormal disease associated form of the protein (PrP^{BSE}) has the identical primary structure, but a tertiary structure that is 50% β -pleated sheet and only 20% α -helix. The only difference between the two forms of the protein appears to be in the way they are folded. The PrP^{BSE} is an extremely stable protein that is resistant to proteases; therefore, it accumulates in the cells where it aggregates to form fibrils. All humans with the familial form of spongiform encephalopathy have been found to carry genetic defects in the coding for PrP.

In BSE, it is hypothesized that the abnormal PrP^{BSE} is able to catalyze the conversion of PrP^c to PrP^{BSE} thereby spreading disease. This theory may go some way to explain why infection in one species typically has difficulty crossing the “species barrier” and infecting a different species since the amino acid sequence of the infectious PrP and the endogenous PrP^c are not the same.

While the prion theory does explain a number of the unusual properties of the BSE agent and related diseases, it does not explain all the unanswered questions. In particular, it does not address the fact that there appear to be different “strains” of prion disease. Furthermore, these strains retain their characteristics even after passage through another species. These strains may be identified by looking at the pattern of disease produced following infection in specific strains of inbred mice. A more rapid method of strain identification may be achieved through Western blot analysis to distinguish between the different glycoforms of PrP.

The mechanism by which PrP is able to migrate from the gut to the central nervous system (CNS) is not known, but it is thought to gain access to the peripheral nerves and then ascend to the CNS (see reference for a detailed review of the theory of prion disease).⁴

Clinical signs

In the absence of any *antemortem* test, the suspicion that a cow is suffering from BSE is dependant on the recognition of clinical signs. The onset of the disease is insidious with a gradual progression over a period of months. It is also important to recognize that the vast majority (>97%) of cases of BSE have occurred in dairy cows. Dairy cows are used to being handled and are accustomed to a daily routine. Furthermore, they are often individually recognized by the producer and consequently, very subtle changes in behavior may be recognized. Based on the author’s experiences in the UK, the earliest signs may be as simple as entering the parlor in a different order than is customary; in addition, cows typically start kicking during milking.

As the signs progress over subsequent weeks, the clinical signs are best characterized as apprehension and nervousness, progressing to hyperesthesia, weight loss, and progressive ataxia, especially affecting the hindlimbs. It is important to recognize that not all cows show all the clinical signs. The key points are the apprehension and the progressive nature of the signs. Other common signs include a fine tremor and a persistent nervous licking of the muzzle.⁵

Diagnosis

Although there has been significant international effort to develop some form of blood test for BSE, a test has still not been developed. Diagnosis is dependent on histological examination of the brain, in particular the obex region of the brainstem. This portion of the brain typically survives slaughter with a captive bolt gun, but suspect cases must be euthanized by injection with a barbiturate or a similar drug, in order to prevent damage to the CNS. The histopathological changes of the spongiform encephalopathies are characteristic, revealing bilateral symmetric intracytoplasmic vacuolation of the neurons. The diagnosis may be confirmed by immunohistochemistry with staining for the prion protein fibrils.

Transmission

The first epidemiological study of BSE cases in the United Kingdom by Dr. J. Wilesmith et al in 1987, implicated the use of cattle feedstuffs that utilized ruminant-derived proteins.⁶ The use of meat and bone meal as a supplemental protein was very widespread in the UK dairy industry and created an extended common source epidemic. The use of meat and bone meal in rations explained the geographic distribution and breed distribution of BSE cases. During their lifetime, dairy cows were far more likely to have received meat and bone meal than beef cattle and as a result, BSE predominately affected dairy cattle. The ban on feeding ruminant-derived protein to ruminants, implemented in July 1988, began to show significant effects on the age-specific incidence of BSE by 1992. This 4-year lag period is due primarily to the long incubation period of BSE. Subsequently, several studies demonstrated the ability of the prion to survive the rendering process and remain infective.^{7,8}

Despite the implementation of the feeding ban, cases continued to arise in cattle born after the ban. Although some of these cases were undoubtedly due to carry-over of feed supplies and poor compliance by feed mills, research began to intensify on other aspects of transmission. Direct transmission can occur with chronic wasting disease and scrapie, but it has not been shown to occur with BSE. Horizontal transmission experiments through close contact or through pasture contamination have not been successful. Experimental studies have also shown that BSE is not transmitted through milk or via fetal membranes or placenta. However, a cohort study by Wilesmith et al demonstrated

the potential for limited maternal transmission.⁹ Subsequent studies suggested that up to 10% of BSE cases that occurred early in the epidemic were the result of maternal transmission.

Tissue infectivity

Meat and bone meal tends to make up a relatively small proportion of the diet of a dairy cow or calf. Typically, meat and bone meal comprise only 2% to 4% of the diet. It is also evident that brain and spinal cord make up a relatively small proportion of the ingredients in meat and bone meal. Therefore, it is not surprising that only relatively small amounts of infected tissue are necessary to cause BSE infection. BSE was demonstrated to pass to sheep and goats via the oral route with as little as 0.5 grams of brain material; furthermore, a large study demonstrated that as little as 1 gram of BSE-infected brain, if given orally, would cause disease in calves. Experimental studies on the pathogenesis of BSE have revealed that brain, spinal cord, and ileum are the tissues that can be infective.¹⁰

The origins of BSE

The origins of BSE have been debated since the disease was first identified in 1986. One thing that is certain, based on epidemiological modeling, is that the case seen in 1986 did not represent the first case of BSE. It is generally accepted that the first case probably occurred in the late 1970s and passed through cattle at least twice prior to the disease's identification.

It is important to recognize that the original hypothesis, that the disease represented the spread of scrapie from sheep, influenced much of the research performed since 1986. This hypothesis was based largely on circumstantial evidence. There were the apparent similarities between the pathology of the 2 diseases. Furthermore, the UK had a large sheep population as well as a large cattle population, a situation that is found almost nowhere else in the world. In such an environment, rendered meat and bone meal derived from cull sheep was being fed back to dairy cattle. Studies have since indicated that scrapie is not caused by an individual strain of prion. A number of different strains have been identified, but none of the strains identified to date have shown any relationship to BSE.

“Review of the origin of BSE” was a report published by a review committee established by the British government in 2001. The report concludes that 3 possible sources of the disease exist:

- BSE represents an abnormal strain of scrapie that entered the bovine food chain and was subsequently cycled through cattle several times prior to 1986.
- BSE was originally a form of spongiform encephalopathy in an exotic ruminant in one of the zoological parks in the UK. Such animals did enter the rendering process prior to 1990 and the infectious agent would then have been cycled as described above.

- We know that CJD occurs spontaneously in the human population at the rate of approximately 1 case per million. It is possible that BSE may have occurred spontaneously in a cow that was then rendered.

Unfortunately, it is doubtful if the exact source of the disease will ever be fully defined.

Can BSE be transmitted to other species?

Studies have been conducted looking for cross species transmission of BSE.¹¹ BSE may infect mice, calves, sheep, goats, and mink when the infectious agent is given by injection. Sheep can also be infected following an oral challenge of infected material. A number of studies have been performed investigating the possibility of infecting pigs and poultry. The rationale is that these 2 species typically consume large amounts of meat and bone meal as part of their diet. Pigs can become infected with BSE, but only after repeated injections with contaminated material. BSE has not been shown to infect poultry.

Since BSE was recognized in 1986, a number of sporadic spongiform encephalopathies have been identified in the UK. Analysis of infected material from these cases has confirmed that the infectious agent is indistinguishable from BSE. Such species include domestic cats (87 confirmed cases), exotic cats in zoos (9 cases), and exotic ruminants (ankole cattle 2, American bison 1, kudu 6, eland 6, oryx 2, nyala 1, and gemsbok 1). The ingestion of contaminated meat and bone meal is thought to link all these cases.

What are the zoonotic risks?

Without a doubt, one of the most asked questions regarding BSE during the early years of the epidemic in the UK was whether the disease could be transmitted to humans. The British government took the opinion that since it was assumed that BSE came from scrapie and that scrapie was not transmissible to humans, BSE did not represent a human health risk. It was also assumed that the “species barrier” would be sufficient to prevent the spread of BSE from cows to humans. This assumption was challenged in 1995 when a new variant of CJD was recognized in the UK.¹² Termed vCJD, the new form of the disease was distinguished from classical CJD based upon the age of the sufferers, the pattern of the pathology within the CNS, and the clinical findings. Classical CJD typically affects people >40-years-old, while those infected with vCJD are typically in their 20s. The pattern of pathology observed in the brain of patients with vCJD also differed from that seen with CJD, resulting in subtle changes in the disease manifestation. Definitive evidence became available in 1997, when 2 independent

research groups typed the infectious agent in vCJD as indistinguishable from BSE.^{13,14} To date, there have been 131 confirmed cases of vCJD in the UK and 8 other cases worldwide (most of the cases identified outside the UK occurred in individuals who had been residents in the UK during the 1980s).

Given the long incubation period characteristic of diseases such as CJD, it seems likely that individuals suffering from vCJD were likely exposed to BSE by consuming material from animals infected with BSE prior to the widespread recognition of the disease in 1988. Further evidence in support of this theory is demonstrated by the fact that the number of cases of vCJD now appears to be declining.

It should be noted that while such deaths are obviously tragic, the number of cases of vCJD is extremely low when you consider that the majority of the population of the UK (approximately 60 million) was exposed to potentially infected material.

The British experience of BSE

When examining the response of the British Government to BSE, it is easy to be critical with the benefit of hindsight. It is important to remember that the disease was unheard of before 1986 and consequently, nothing was known about the disease. In addition, the magnitude of the problem was not fully realized until 1988 and the risk to human health was not proven until the late 1990s. Finally, it should be recognized that the disease was already very widespread and had been cycled through the national cattle herd several times before the first case was diagnosed.

The first action of the British government was a study commissioned in early 1987 to investigate 200 cases of BSE. The results, published in late 1987, implicated meat and bone meal as the source of the infection. In early 1988, the Southwood Working Party began to further investigate BSE and a feed ban to prevent ingestion of ruminant-derived protein by ruminants was introduced. BSE was also made a notifiable disease to ensure that all suspected cases were reported and such cattle were destroyed with compensation. The Southwood Committee reported in early 1989 and a second committee, the Tyrrell Committee on Research, was formed in order to coordinate research into BSE. A plan was formulated to ensure that high-risk tissues from cattle could not enter either the human or the animal food chains. These tissues, including brain, spinal cord, spleen, thymus, and intestine, were designated specified bovine offals (SBOs) and had to be removed and destroyed. Meanwhile, the export of British cattle older than 6 months was banned by the European Union. In the same year, the

importance of the ability to trace cattle was recognized and it was recommended that producers improve record keeping. A law was introduced to this effect later in the year.

By 1993, there had been 100,000 confirmed cases of BSE in the UK, but little progress in control had been made beyond the introduction of the original feeding bans. In 1994, the European Union adopted a similar feed ban prohibiting the use of ruminant protein in ruminant feed.

In 1994, European legislation was introduced to identify and trace the movement of all cattle. Throughout 1995, legislation was introduced to further ensure that no contaminated material could enter the food chain. In particular, the recovery of meat from the skull and spinal cord was discontinued.

In 1996, the first cases of vCJD were identified, leading to a great deal of public concern. This resulted in a number of new schemes to safeguard human health. These were:

- The prohibition in the UK of the sale of cattle for human consumption aged >30 months. This necessitated a form of cattle identification to ensure that the age of cattle could be verified.
- The prohibition on the export of all products of bovine origin from the UK.
- A further tightening of the rules on specified bovine offals.
- Meat and bone meal was also banned from being added to fertilizer.
- A detailed system of inspections and feed recalls was put in place to ensure that no meat and bone meal could enter ruminant rations.
- In 1997, a scheme was developed to trace animals considered to be at a high risk of exposure, either through contaminated feed or because they were offspring of known cases. These animals were destroyed.

Many of the controls regarding specific offal were also applied to sheep and goats. A more complete cattle identification and movement recording system was introduced with so called “cattle passports.” This was later developed into a computerized tracing system, the British Cattle Movement Service.

In 1997, a Europe-wide ban to ensure that “high risk” tissues from all ruminants could not enter any form of food chain was introduced. These tissues were classified Specified Risk Materials.

Since that time, there have been many legislative changes to try to reopen the British overseas cattle trade. The only significant change in policy has been the development of Europe-wide testing protocols for BSE surveillance in apparently unaffected animals. Animals aged >30-months can now enter the human food chain, but first must be tested as negative for BSE.

The feed ban introduced in 1990 is credited with causing the dramatic reduction in the number of cases seen since 1993. Many of the cases that have developed in animals born since 1992 have been traced back to either maternal transmission or to animals fed contaminated material on farms prior to the feed ban.

It is hard to draw many parallels between the situation facing Canada today and that facing the UK in the late 1980s. At that time, almost nothing was known about BSE and the epidemic was already very widespread. The situation in Canada remains the identification of a single animal that did not enter the human food chain. Furthermore, many of the lessons learned from the experience in the UK have already been acted upon by the Canadian Food Inspection Agency (CFIA) and others. The feeding of ruminant protein to ruminants, although never widespread in Canada, has been banned since 1996 and the national cattle identification program is in place. Further, the response of the CFIA to this case was very thorough and rapid. Consequently, this case does not indicate a significant risk to the health of the Canadian cattle herd or the general population.

Much of the epidemiological information regarding BSE in the UK was obtained from the British Government website: www.defra.gov.uk/animalh/bse (Accessed July 11, 2003), which is an extremely informative source of information on all aspects of BSE. Also: www.inspection.qc.ca

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Abstract of Interest

A cohort study to examine maternally-associated risk factors for bovine spongiform encephalopathy

WILESMITH JW, WELLS GA, RYAN JB, GAVIER-WIDEN D, SIMMONS MM. ADDLESTONE, SURREY.

This long-term cohort study, initiated in July 1989, was designed to examine maternally-associated risk factors for bovine spongiform encephalopathy (BSE), forming part of the epidemiological research programme to assess the risks of non-feedborne transmission of BSE. In this study, the incidence of BSE in offspring of cows which developed clinical signs of BSE is compared with that in offspring, born in the same calving season and herd, of cows which had reached at least six years of age and had not developed BSE. All offspring were allowed to live to seven years of age. The results indicate a statistically significant risk difference between the two cohorts of 9.7 per cent and a relative risk of 3.2 for offspring of cows which developed clinical BSE. However, there is some evidence that this enhanced risk for offspring of BSE cases declined the later the offspring was born, but was increased the later the offspring was born in relation to the stage of the incubation period of the dam. The results presented cannot distinguish between a genetic component and true maternal transmission or a combination of both risks, but they do not indicate either that the BSE epidemic will be unduly prolonged or that the future incidence of BSE in Great Britain will increase significantly.

Vet Rec 1997;141(10):239-43.

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