1.1 The Disease

Transmissible spongiform encephalopathies (TSEs) are a group of slowly progressive, neurodegenerative disorders affecting humans and animals. They are characterized by a long incubation period, a novel infectious agent, and are invariably fatal. Known TSEs include:

- Creutzfeldt-Jakob disease (CJD), Kuru, Gerstmann-Straussler-Scheinker (GSS), and fatal familial insomnia (FFI) in humans;
- Scrapie in sheep and goats;
- Transmissible mink encephalopathy (TME) in mink;
- Chronic wasting disease (CWD) of deer and elk; and
- Bovine spongiform encephalopathy (BSE) in cattle.

In addition, there are examples of TSEs that are thought to occur as the result of exposure to BSE infected bovine material, such as feline spongiform encephalopathy (FSE) and variant Creutzfeldt-Jakob disease (vCJD).

Etiology

1. Although considerable research has been undertaken since BSE was first described in the United Kingdom (UK) in 1985–1986, the precise nature of the causative agent remains controversial, as it does with all the TSE-associated diseases.

   While a number of theories describe the etiology, the protein only or **prion theory** has emerged to dominate the literature. The prion theory takes advantage of the fact that a modified form of a normal, host encoded, membrane associated, prion protein is the only disease specific macromolecule consistently isolated in BSE-affected animals. The prion theory assigns infectivity to a structurally modified form of the prion protein (PrP) which in turn promotes the conversion of other prion molecules to the same, abnormal form. The accumulation of these abnormal isoforms (PrPsc) within the affected cell cytoplasm, interferes with normal cell function, contributes to the characteristic spongiform changes, and eventually results in cell death.

   The PrPsc is extremely resistant to heat, ultraviolet and ionizing radiation, and a large range of chemical disinfectants. It is insoluble in detergent and has a predominately beta sheet structure making it relatively protease resistant—a characteristic that has been exploited in the development of rapid post-mortem diagnostic tests for the disease.

   Until recently, bioassays demonstrated that, unlike scrapie, BSE was caused by a single strain or isoform. More recent findings are suggestive of the possible existence of more than one strain.

Susceptible Species

2. Cattle, sheep, goats, pigs, mice, mink, and marmosets have all been successfully infected with BSE (injected IC) under experimental conditions. Oral transmission to sheep, goats, and mink has also been achieved. Pigs and chickens have shown no evidence of disease after oral exposure despite an extended incubation period.

   The Office International des Epizooties (OIE) lists the species susceptible to BSE as all members of the family *Bovidae* including cattle, bison and water buffalo.

World Distribution

3. BSE was first described in the UK almost two decades ago. By July 2005, BSE has been reported in native-born cattle in twenty-four countries with a geographic distribution that included Europe, the Middle East, North America, and Asia.

Epidemiology

4. Where genotype is known to influence the incubation period of some TSE diseases in some other species, to date it has not been demonstrated to influence the pathogenesis of BSE in cattle. Likewise, there is no breed or sex predilection.

Incubation Period

The incubation period observed in cattle infected with BSE is variable, ranging from 2–8 years, with the majority of affected animals being identified between 4–5 years of age. The youngest bovine diagnosed with BSE was a 20-month-old aclinical case (Italy). Exposure to infectivity at an early age is thought to result in a shorter incubation period. Exposure to a larger doses of infectivity is also thought to shorten the incubation period.

Modes of Transmission

***Meat and Bone Meal (MBM)*:** Significant research has accumulated to demonstrate that the inclusion of contaminated MBM in prepared feeds is the primary transmission vehicle.

According to the current scientific knowledge, BSE infectivity has been demonstrated in the following tissues, to varying degrees, which if fed to susceptible species could result in the transmission of the infective agent:

Scientific Steering Committee Estimate of Cattle Infectivity Dose (ID)50		
Tissue	**Cattle infectivity dose (ID)50 per BSE case**	**Percentage of total infective load per bovine**
Brain	5000	64.1%
Spinal cord	2000	25.6%
Trigeminal ganglia	200	2.6%
Dorsal Root ganglia	300	3.8%
Ileum	260	3.3%
Eyes	3	0.04%
Tonsils	1	0.01%

The following listed materials have been determined by the OIE not to be a source of BSE infectivity:

- gelatin and collagen prepared exclusively from hides and skins;
- milk and milk products;
- semen and *in vivo* derived embryos as detailed in *3.3 Premises Control Actions (2)* and *3.3 Premises Control Actions (5)*;
- protein-free tallow (maximum level of insoluble impurities of 0.15% in weight) and derivatives made from this tallow;
- dicalcium phosphate (with no trace of protein or fat);
- hides and skins.

***Horizontal and Vertical Transmission*:** BSE is not considered to be a contagious disease; however, other potential modes of transmission need to be considered.

- Horizontal transmission:
  The current body of scientific evidence concludes that horizontal transmission does not occur.

- Vertical transmission—from sire:
  Epidemiological studies have demonstrated that semen used for commercial artificial insemination and prepared in accordance with internationally recognized protocols is not associated with a risk of BSE transmission.

- Maternal transmission:

Experiments have concluded that in vivo derived bovine embryos collected in accordance with internationally recognized protocols are not associated with a risk of BSE transmission.

Although there is no direct evidence of BSE transmission from cow to calf, it is assumed that maternal transmission can occur. It is estimated that calves born to infected cows during the last one-sixth of the incubation period may become infected (less than 10% of the time). If maternal transmission occurs, it would be at a rate insufficient to initiate or to propagate the disease.

Vectors: There is no indication that insect or arthropod vectors are implicated in the transmission of BSE.

Fomites and Iatrogenic Transmission: In general, fomites associated with normal agricultural husbandry are not considered risks in BSE transmission. Nevertheless, iatrogenic transmission of TSE within the sheep and human populations has been well documented and supports the possibility of its occurrence in the cattle population. Veterinary instruments and procedures, which could result in the transmission of nervous or lymphoid tissue, should be considered in terms of their potential to transmit infection.

Pathogenesis

5. Although considerable research has been undertaken since BSE was first described in the UK, the precise nature of the causative agent remains controversial, as in all TSE diseases. The prion protein is a normal membrane associated protein that is located most prominently in the central nervous system. It is a major component in the development of the TSE associated diseases. Modified forms of this protein are associated with infectivity and are a significant finding in the neuropathology of BSE. The function of the unmodified prion protein has not been determined with certainty.

   The prion hypothesis assigns infectivity to a structurally modified form of the prion protein which in turn promotes the conversion of other prion protein molecules to the same, abnormal form. The process involved in this conformational change is poorly described. The accumulation of these abnormal isoforms of the prion protein interferes with the normal function and appearance of the infected nerve cell. One of the major criticisms of the prion protein hypothesis is that in the absence of any nucleic acids, the strain variations observed in other TSE diseases are not explained. It is suspected that strain differences could be the result of mutations in the PrP gene resulting in tertiary conformational changes of the prion protein.

Ingested modified prion may be absorbed across the gut wall at Peyer's patches. This would be consistent with the observation that there appears to be an age related susceptibility to the infectious agent. Young cattle are estimated to be as much as ten times more susceptible than adults. A number of researchers have calculated that susceptibility peaks at some point between 0.5 and 1.5 years of age and then steadily declines in the following years to a level approximating 10% of the peak value. BSE infectivity has not been detected in the blood of infected cattle, leading some investigators to speculate that neuroinvasion can occur directly via peripheral nerves or the lymphoreticular system, and then via the peripheral nerves. The debate continues around whether the spleen is a source of BSE infectivity. If there is infectivity in the blood or spleen it may occur at a level below the current detection limits.

Distribution of Infectivity

Long term experiments using calves orally challenged with brain material derived from confirmed cases of BSE have concluded. The results indicate that beginning as early as six months post infection up until 18 months post infection only the distal ileum has any significant amount of infectivity. This is consistent with the location of the Peyer's patches in the wall of the distal ileum.

In excess of 18 months post infection, infectivity was detected in the following tissues: small intestine (distal ileum), brain, spinal cord, dorsal and trigeminal root ganglia. One study concluded bone marrow was slightly infectious when the animal was clinically affected; however, this finding has not been replicated. Despite numerous attempts, this experiment failed to find any consistent changes associated with the brains of affected animals more than three months before the onset of clinical signs.

Infectious Dose

Experimental evidence confirms that as little as .001 gram of infected brain material, administered orally to susceptible cattle, will result in the development of clinical BSE.

Diagnosis

6. BSE is diagnosed through the detection of the abnormal prion protein in brain. The brainstem including the obex is required for testing. Tissues are to be submitted fresh. There are a number of tests available to establish a preliminary diagnosis of BSE (Western blot, ELISA). In Canada, the official confirmatory diagnostic tool is the examination of specific areas of the brain by histopathology and/or scrapie-associated fibrils (SAF) immunoblot to detect characteristic changes and by immunohistochemistry to detect the presence of protease resistant prion protein.

Clinical Signs

BSE is an afebrile neurodegenerative disease of adult cattle. The initial signs of BSE are non specific and largely behavioural. Consequently, the early clinical diagnosis is only possible after repeated observation and knowledge of normal behaviour. The most important differential diagnostic aspects observed in the UK are the insidious onset and chronic progression of clinical signs.

The clinical signs can be grouped into three categories, with the predominant findings in each arranged in order of decreasing frequency.

- Disturbance of behaviour
  - – Apprehension, fearfulness
  - – Aggressiveness
  - – Tremors: trembling and muscle twitching
- Disturbances of locomotion
  - – Abnormal posture
  - – Lack of co-ordination, primarily in the hind limbs
  - – Recumbency in later stages
- Disturbance of sensitivity
  - – Easily startled by minor disturbances such as noise or movement of people or animals
  - – Hypersensitivity to light, touch and noise
- In addition there is often loss of body weight, condition and reduced milk production, despite continued appetite.

The duration of the clinical disease can range from less than two weeks to as long as one year. The majority of cases will require euthanasia within two months of onset.

Pathology

There are no characteristic gross pathological changes associated with BSE. Histopathology reveals bilaterally symmetrical spongiform degeneration affecting the nerve cells of the brain stem nuclei. The degree of spongiform degeneration is variable, whereas the extent of reactive gliosis correlates with the degree of neuronal loss.

Mortality/Morbidity

The disease is invariably fatal. There is no treatment, or vaccine available.

Differential Diagnosis

The differential diagnosis of BSE should include the bovine neurological diseases caused by viral agents, bacteria, and other infectious, toxic or metabolic disturbances that affect the central nervous system. Accordingly, the following disorders are most likely to clinically resemble BSE:

– rabies
– listeriosis - bacterial encephalitis
– nervous ketosis
– hypomagnesemia (grass tetany)
– hypocalcemia
– thromboembolic meningoencephalitis
– spinal cord or brain abscess or neoplasia
– traumatic injury
– lead poisoning or other toxicity
– polioencephalomalacia

Resistance and Immunity

7. In cattle infected with BSE there is no immune response, passive or acquired, to the presence of the BSE agent.

Vaccination

8. There are no vaccines available.

Public Health

9. While BSE is a cattle disease, the human disease called variant Creutzfeldt-Jacob Disease (vCJD) has been associated with the consumption of products derived from BSE-infected cattle. Specified risk material (SRM) are tissues that, in BSE-infected cattle, contain the agent that may transmit the disease. In diseased animals, the infective agent is concentrated in certain tissues such as the brain and spinal cord. Cattle tissue identified as SRM is not generally consumed as food; however, during processing, SRM could be unintentionally included in meat products destined for human consumption.

The Government of Canada has amended the *Food and Drug Regulations* and the *Health of Animals Regulations* to prevent SRM from entering the human food supply. The regulations establish a definition for SRM and prohibit the sale or import for sale of food products containing SRM under the *Food and Drug Regulations* from countries that are not BSE-free. Amendments to the *Health of Animals Regulations* require the removal of SRM from carcasses and prohibit the use and export of SRM in food for human consumption.

SRM is currently defined as the skull, brain, trigeminal ganglia (nerves attached to the brain), eyes, tonsils, spinal cord and dorsal root ganglia (nerves attached to the spinal cord) of cattle aged 30 months or older, and the distal ileum (portion of the small intestine) of cattle of all ages. Regulatory amendments have been initiated to move tonsils to the list of tissues to be removed from cattle of all ages.

The removal of SRM is internationally recognized as the most effective public health measure in preventing the transmission of BSE. Canada does not support the routine testing of healthy slaughter cattle as it is not as an efficient or cost effective measure to protect human health as the removal of SRM.

Because of BSE's zoonotic potential, safety precautions to prevent exposure to the BSE agent should be taken by laboratory and field staff involved in the sampling of potentially infectious tissue (brain) from BSE suspect or equivalent risk animals as detailed in 6.2 *Appendix 2—Sanitary Precautions/Disinfectants.*