

Zoonosis Update

Transmissible spongiform encephalopathies

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Transmissible spongiform encephalopathies affect humans and other animals. Clinically, the diseases involve severe, progressive neurodegeneration with an invariably fatal outcome. The TSEs are linked by the unusual nature of their causative agent, which is believed to be a transmissible protein devoid of nucleic acid. This protein, known as a prion (a pseudoabbreviation for proteinaceous infectious particle), is a hallmark feature and purported pathogen of human and other animal TSEs.¹ For many years, the natural transmission of TSEs appeared to be almost exclusively relegated to their respective phylogenetic and species lineages; however, the association in the mid-1990s between a TSE of cattle (BSE) and a human TSE (vCJD) brought TSEs into the realm of zoonotic diseases. Recent spread of another animal TSE (CWD) among cervids in North America has raised concerns about the potential for this disease to be transmitted to humans.

General Characteristics of TSEs

The causative agents of TSEs are believed to be abnormal isoforms of a cellular protein. This cellular protein, known as the PrP^C, is a membrane glycoprotein found in various tissues throughout the body, but present in particularly high concentrations in lymphoreticular and nervous tissues.¹ The exact function of the PrP^C remains unclear, although mice in which the PrP^C gene is suppressed and the protein product is not expressed appear phenotypically unaffected.¹⁻³ Several potential functional roles for the PrP^C have been hypothesized.¹ Conversion of this protein from its normal tertiary structure, which is rich in α helices, into an abnormal structural form, which has a much greater proportion of β -pleated sheet configuration, changes the physicochemical properties of the protein, resulting in an abnormal form (PrP^{TSE}). This abnormal protein has increased resistance to the effects of formaldehyde, ethanol, proteases, nucleases, and radiation, which are treatment measures that would commonly inactivate other transmissible agents.¹ The abnormal proteins form amyloid fibril aggregates and induce neuron destruction through mechanisms that remain unclear. The resultant neuropathologic lesions of the TSEs typically include large vacuoles in the brain parenchyma; histologically, affected tissue has a spongiform appearance—hence the term spongiform encephalopathy.

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ABBREVIATIONS

BASE	Bovine amyloidotic spongiform encephalopathy
BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt-Jakob disease
CWD	Chronic wasting disease
MBM	Meat-and-bone meal
PrP ^C	Cellular prion protein
PrP ^{TSE}	Abnormal transmissible spongiform encephalopathy-related prion protein
TSE	Transmissible spongiform encephalopathy
vCJD	Variant Creutzfeldt-Jakob disease

The conversion of PrP^C to the abnormal PrP^{TSE} may occur spontaneously; the mechanism for this change is unknown. In some affected humans, TSEs have a genetic component in that point mutations in the host PrP^C gene result in less stable, more readily transformable PrP^C. In other instances, it is hypothesized that the appearance of the abnormal form of the protein may be facilitated by a spontaneous, somatic mutation or by introduction of the abnormal protein from an exogenous source. The subsequent interaction between the abnormal protein and other normal proteins may involve the initial formation of an intermediate heterodimer, which converts the normal form of the protein into one with an abnormal tertiary structure. This process may become self-perpetuating and result in ongoing conversions of the normal protein to the pathogenic form that overwhelms potential self-correcting cellular mechanisms.⁴ Thus, TSEs are considered both hereditary and transmissible.

Because of many unknown factors, the underlying mechanism responsible for the infectivity of TSE-causing agent remains a matter of debate. The protein-only hypothesis suggests that the pathogenic prion does not require nucleic acid to replicate and convert the normal PrP^C to the abnormal form and result in development of TSE. An alternate hypothesis suggests that a yet undiscovered intermediate factor or factors, involving nucleic acid, are responsible for the development of TSEs and the protein conversion process.⁵ Although less accepted in the scientific community, other factors (including viral and bacterial pathogens) have been suggested to play a role in the genesis and propagation of the pathogenic protein.⁶⁻¹⁰

The clinical features of prion disease in humans and other animals are characterized by long incubation periods (generally intervals of years) and progressive neurologic dysfunction that invariably results in death (generally within a year after onset). Among the various

human prion diseases, sporadic CJD is by far the most common. However, it is quite rare; there is approximately 1 case/1,000,000 humans/y in many countries.¹¹ Other forms of TSEs in humans include vCJD, familial CJD, iatrogenic CJD, fatal familial insomnia, sporadic familial insomnia, and Gerstmann-Straussler-Scheinker syndrome.¹¹ Kuru is likely now eradicated as a result of the cessation of ritual endocannibalism among natives of New Guinea since the 1950s. Transmissible spongiform encephalopathies in animals include scrapie, BSE, CWD, and some other uncommon TSEs in mammals (ie, transmissible mink encephalopathy, TSE of captive ruminants [onyx, kudu, and bison], and feline spongiform encephalopathy [domestic cats, tigers, cheetahs, and pumas]).^{12,13}

An important concept with respect to TSEs as zoonotic illnesses is that of the species barrier.^{14,15} The TSE agents that cause disease in certain animal species appear, in many instances, to have great difficulty or an inability to cause disease in other species, even those that are closely related. It appears that the relative susceptibility of a species to TSE infectivity may be influenced by a few base pair differences encoded by the species' prion protein gene, which confer resistance or, conversely, susceptibility to TSE agent transmission.¹⁶ Although all factors that contribute to the susceptibility of a particular species to TSE disease are not elucidated, susceptibility appears to be attributable to a complex interaction between the particular species' prion protein primary amino acid sequence, the type and distribution of polysaccharides on the associated prion glycoprotein, the protein's tertiary structure, and likely other host factors.¹⁶ Species barriers against TSE agents can often be breached to varying degrees in laboratory settings. However, the causal association of BSE with vCJD clearly indicates that the bovid-human species barrier may be abrogated under natural conditions; thus, any TSE may be considered a potential human zoonotic pathogen depending on the available routes of introduction and the likelihood that, via such routes, a particular TSE agent might successfully breach the species barrier between the natural host and humans.

Scrapie

Scrapie is a TSE of sheep and goats. It has long been recognized as a clinical disease; in the United Kingdom, the disease in sheep was described in the early 1700s.¹⁷ Scrapie occupies a distinctive position in the overall history of prion diseases because its experimental transmission between sheep in the 1930s demonstrated for the first time the transmissible nature of the causative agent.^{17,18}

Scrapie appears to be endemic throughout the world with the probable exception of Australia and New Zealand, where the disease was first detected in the 1950s.^{17,19} Subsequently, massive slaughtering campaigns appear to have been successful in eliminating scrapie from both of those countries. In other countries, estimates of the prevalence of scrapie are mainly based on slaughter surveillance data and vary considerably. The prevalence in various countries has been estimated at 0.1% to 0.3%.²⁰⁻²² In the United States, scrapie is more prevalent among black-faced sheep breeds (Suffolk and

Hampshire breeds); however, white-faced breeds are also susceptible to the illness.²⁰ In Great Britain and the European Union, scrapie affects many different breeds.

Clinically, scrapie is characterized by a slow, gradual progression of neurologic and dermatologic abnormalities. Onset of clinical signs may occur several months to years after exposure. Early clinical features include generalized wasting and loss of body mass, tremors, and behavioral changes. Pruritus may develop, and infected sheep frequently rub themselves against objects and compulsively chew at their coat (wherein lies the genesis of the term scrapie). Clinical signs then gradually progress, with development of ataxia, recumbency, and occasionally blindness.²³ Death generally follows severe weakness, usually within 2 to 4 weeks. The transmission of the scrapie prion agent is believed to occur through licking of newborns, the placenta, or other birthing materials from infected dams. Research data have indicated that the scrapie agent can be transmitted through blood and blood products, although large volumes of blood are needed for this type of transmission.²⁴

Diversity of the genotypes at specific codons within the sheep prion gene appears to influence susceptibility or, conversely, resistance to scrapie transmission. Specifically, variations in the amino acids at codons 136, 154, and 171 in the sheep prion protein gene appear to be strongly associated with susceptibility to scrapie.²⁵ Sheep prion diseases are essentially classified as classic scrapie and more recently described variant forms or atypical scrapie, primarily related to the Nor98 strain of scrapie.^{26,27} Classic scrapie usually develops in sheep 2 to 5 years of age and is primarily associated with polymorphisms at codon 171, as well as at codon 136, of the sheep prion protein gene. It is characterized by the typical neurologic features and clinical signs of scrapie and by the classic spongiform neuropathologic changes and prion deposition within various tissues of the lymphoreticular system and other regions. However, the characteristic neuropathologic features may be absent; thus, immunohistochemical detection of the prion agent is the gold standard for diagnosis. Atypical scrapie associated with the Nor98 strain was originally detected by surveillance testing of Norwegian sheep and affects primarily older animals with a distinctive genotype.²⁸ The Nor98 scrapie strain is most often detected during routine screening of culled animals. Atypical scrapie differs from classic scrapie in that the characteristic pruritus and neurologic findings are frequently absent or ill-defined, typical spongiform neuropathologic changes are generally absent, and the agent does not appear to exist outside of the CNS. Atypical scrapie does not appear to be as highly transmissible as classic scrapie.²⁸

Classic scrapie may be suspected on the basis of clinical signs and diagnosed on the basis of characteristic histopathologic changes within the CNS or results of immunodiagnostic testing of brain or lymphoid tissues for the scrapie agent. In live sheep, lymphoid tissue is often obtained via biopsy of the third eyelid or rectum.²⁹ The scrapie agent may be detectable in several tissues and body fluids, including spleen, tonsils, rectum, tongue, retinas, CSF, and blood, prior to the appearance both of clinical signs and deposition of PrP^{TSE} in nervous tissue, thereby possibly allowing for preclin-

ical screening of herds.²³ Scrapie eradication is generally predicated upon mandatory premise and individual identification of all breeding animals, slaughter surveillance of adult culled breeding stocks, traceback and testing of flocks of origin, further traceback of breeding animals sold from the source flocks, and depopulation of genetically susceptible animals in those flocks.

Despite the presence of the scrapie agent in domestic sheep flocks and the undoubted exposure of humans to the agent for centuries, there has been no epidemiologic or scientific evidence of scrapie transmission to humans.²³ However, transmission to other primates, rodents, and other species has been achieved experimentally.^{30,31}

BSE and vCJD

Bovine spongiform encephalopathy (colloquially known as mad cow disease) is a TSE of cattle. Initially, from 1985 through 1986, an outbreak of unusual deaths among cattle in disparate parts of the United Kingdom was identified; the illness preceding death was characterized by an insidious onset of incoordination, generalized wasting and loss of body mass, and unusual aggression toward other cattle and humans.^{32,33} The clinical features and neuropathologic changes among affected cattle were consistent with a TSE.

In 1987, the UK Ministry of Agriculture officially reported that the novel disease in cattle appeared to be a new form of TSE, the clinical and histopathologic features of which were similar to those associated with scrapie. The BSE epizootic among cattle in the UK subsequently developed, peaking at > 37,000 confirmed cases/y in 1992.³⁴ How BSE actually emerged as a clinical entity remains unclear. The leading hypotheses include a spontaneous or stochastic conversion of the normal cattle PrP^C to the abnormal form or cross-species transmission of scrapie via cattle feed contaminated with the scrapie agent. It is widely believed, however, that the perpetuation and spread of BSE among cattle was attributable to the practice of feeding MBM, presumably products derived in part from neural or lymphoreticular tissues contaminated with the BSE agent. This hypothesis is supported by the higher incidence of BSE among dairy rather than beef cattle, because the former are more frequently fed MBM.³³

Shortly after the recognition of BSE in the United Kingdom, important BSE control measures were instituted including a ban on the use of ruminant-derived protein sources for ruminant feed (introduced in July 1988) and a ban against use of bovine brains, spinal cords, and other specified offals in feeds for nonruminant animals and poultry (introduced in September 1990).³⁵ In addition, in November 1989, another specified-offals ban was instituted that forbade inclusion of materials with the highest risk of infectivity in the human food supply.

The early feed bans resulted in a dramatic decline in the BSE epizootic. However, cattle born following institution of the feed bans continued to develop BSE, presumably because of difficulties in fully implementing the bans and preventing cross-contamination of ruminant feed with MBM intended for nonruminants such as pigs and chickens.^{36,37} Thus, in 1996, a total ban

on feeding any mammalian MBM to any farm animal or use of MBM as fertilizer was implemented in the United Kingdom; feeds that contained MBM were recalled. From 1988 to 1996, veterinary public health measures such as the implementation and stricter enforcement of the increasingly restrictive feed bans enabled the successful control of BSE in the United Kingdom.

More recently, similar to scrapie, at least 2 atypical forms of BSE have been recognized: the L- and H-type BSEs.³⁸ Each may be classified on the basis of their different PrP^{TSE} profiles determined via western blot analysis. The L-type BSE is a form of BASE; via western blot analysis, it is characterized by a slightly lower molecular mass of unglycosylated PrP^{TSE}, compared with that of classic BSE.³⁹ Bovine amyloidotic spongiform encephalopathy was first identified in 2 cows in Italy during a period of active pathologic surveillance. Brain deposition of this pathologic isoform correlates with the formation of congophilic amyloid plaques; in cattle, deposition occurs in supratentorial locations with relatively little involvement of the brainstem, a distribution that is distinct from that of BSE. Results of an experimental study⁴⁰ have highlighted the possible similarity of BASE with a subtype of human sporadic CJD, leading to the hypothesis that as yet unrecognized strains of BSE may result in human disease. This hypothesis needs to be interpreted with caution because a link between BASE, or other newly identified PrP^{TSE} strains, and human illness has not been determined.

Via western blot analysis, the H-type BSE is characterized by a slightly higher molecular mass of unglycosylated PrP^{TSE}, compared with that of classic BSE. The H-type BSE, similar to the L-type, has been detected during active surveillance of healthy slaughtered animals or ill or dead cattle. Most animals with either type of atypical BSE have no specific clinical signs of BSE and are essentially clinically indistinguishable from each other. Approximately 85% of the atypical BSE cases involve cattle > 10 years old; cattle with classic BSE are typically much younger.

By the end of 2001, feed bans prohibiting inclusion of tissues from cattle at highest risk of BSE infection in animal feeds were enacted across the entire European Union and in other countries concerned about this new potentially zoonotic disease. Such bans were needed because, although the number of BSE cases was declining in the United Kingdom after 1992, cases of BSE were being identified in many countries, including European countries, Israel, Japan, Canada, and the United States (Table 1). By October 2007, BSE was identified in native-born cattle in 25 countries. In the United States, 3 cases of BSE were reported by August 2007; these included 2 indigenous animals that had atypical BSE and 1 animal imported from Canada that had classic BSE.⁴¹⁻⁴³ The classic BSE cases detected outside of the United Kingdom are largely thought to be attributable to consumption of exported contaminated MBM prior to the feed ban or as a result of exportation of BSE-infected cattle. Development of atypical BSE in cattle outside of the United Kingdom may likewise be a consequence of contaminated feed consumption, but the possibility, which is still under investigation, that they represent forms of sporadic or spontaneous disease has

Table 1—Year of first detection and approximate number of cases of BSE among native-born cattle by country (based on data collected through September 2007).³⁴

Country	Year first detected	Approximate number of cases
United Kingdom	1987	184,533
Ireland	1989	1,593
Portugal	1990	1,021
Switzerland	1990	464
France	1991	984
Belgium	1997	133
Luxembourg	1997	3
The Netherlands	1997	82
Liechtenstein	1998	2
Denmark	2000	14
Germany	2000	409
Spain	2000	681
Austria	2001	5
Czech Republic	2001	26
Finland	2001	1
Greece	2001	1
Italy	2001	135
Japan	2001	33
Slovakia	2001	23
Slovenia	2001	7
Israel	2002	1
Poland	2002	55
Canada	2003	11
United States	2005	2
Sweden	2006	1

been raised because atypical BSE characteristically develops in much older animals.³⁸ As surveillance efforts and capacity differ greatly among various countries, it is possible that the distribution and prevalence of BSE worldwide is underestimated.

In May 1990, enhanced surveillance for CJD was instituted in the United Kingdom to identify possible changes in the pattern of CJD that might indicate an association with the ongoing BSE epizootic. Nevertheless, the UK Ministry of Health provided initial reassurance that BSE posed no threat to human health. Sporadic CJD is the prototypical human TSE and is characterized by rapidly progressive dementia in association with several other typical findings, including movement disorders, myoclonus, and dystonia; a characteristic electroencephalographic pattern; and rapid progression to akinetic mutism and death. The median interval between diagnosis of the disease and death is < 6 months.¹¹ Creutzfeldt-Jakob disease typically develops in older individuals (median age of onset, 68 years).⁴⁴

During the period of heightened CJD surveillance, the UK National CJD Surveillance Unit identified several cases of CJD that had highly atypical features, including an unusually young age at onset and death (median age at death, 28 years), a more protracted course of illness, and neuropathologic changes characterized by multiple amyloid (so-called florid) plaques surrounded by vacuoles; strain properties of this CJD agent were similar to that of the BSE agent. The disease was termed new vCJD, which was later changed to vCJD.^{45,46}

Soon after this variant form of CJD was recognized, it was suggested to be directly linked to the BSE outbreak. This observation was later strengthened by epidemiologic and laboratory evidence.⁴⁵ It was pro-

posed that an oral route of transmission, presumably by ingestion of beef products contaminated with tissues containing high concentrations of the BSE agent, was responsible for the transmission to humans. No specific food product has been definitively established as the cause of vCJD; however, frequent consumption of beef and beef products likely to contain mechanically recovered meat, head meat, or both (including burgers and meat pies) was associated with increased risk for development of vCJD.^{47–49} Interpretation of these findings should be tempered by the fact that recall bias in food consumption studies cannot be excluded; an unexpected association of frequent chicken consumption with vCJD was considered to be a specious finding.

The epidemic of vCJD has continued. Most reported cases involve persons residing in the UK (Figure 1). However, as of November 2007, affected individuals have been identified in 11 countries. Three cases of vCJD have been identified in the United States; these persons were suspected of acquiring vCJD while residing in the United Kingdom (n = 2) or Saudi Arabia (1). Current epidemiologic data indicate that the number of vCJD cases in the United Kingdom, assessed by year of disease onset, is decreasing; the apparent peak of the epidemic occurred in 1999. However, several recent developments have suggested that this favorable outlook needs to be viewed with caution. In a prevalence study⁵¹ of lymphoreticular prion protein deposition among patients undergoing appendectomy or tonsillectomy in the United Kingdom in 2004, PrP^{TSE} was detected in 3 appendix specimens among 12,674 tissue specimens examined; from this, it was estimated that approximately 3,800 people in the United Kingdom were likely infected with the vCJD agent. In addition, blood transfusion-associated transmissions of the vCJD agent in 4 humans have recently been reported,^{52,53} raising the possibility that person-to-person transmission of vCJD might potentially delay control of the vCJD outbreak. Finally, genetic analyses of a blood transfusion recipient infected with the vCJD agent but who did not develop neurologic disease and of 2 of the appendix specimens identified in the lymphoreticular prevalence study revealed the presence of at least 1 valine amino acid at the polymorphic codon 129 of the human PrP^C gene. More than 50% of the population in the United Kingdom has such a polymorphism. However, on the basis of data collected up to November 2007, all individuals with clinical vCJD who were tested were homozygous for methionine at codon 129; the finding of the pathologic phenotype in methionine-valine heterozygotes and valine homozygotes suggests that a wider population than initially suspected is susceptible to infection and possibly to development of clinical signs of vCJD if exposed to the agent.⁴⁵ The long incubation period associated with prion diseases, the possible transmission of vCJD by blood transfusion, and the identification of vCJD infections in persons with at least 1 valine present at codon 129 of the human PrP^C gene lend uncertainty to predictions regarding the vCJD epidemic.

Infection with the BSE agent has been successfully established in calves via oral challenge and in sheep and goats via intracerebral and oral routes. Although a leading hypothesis about the source of the classic BSE

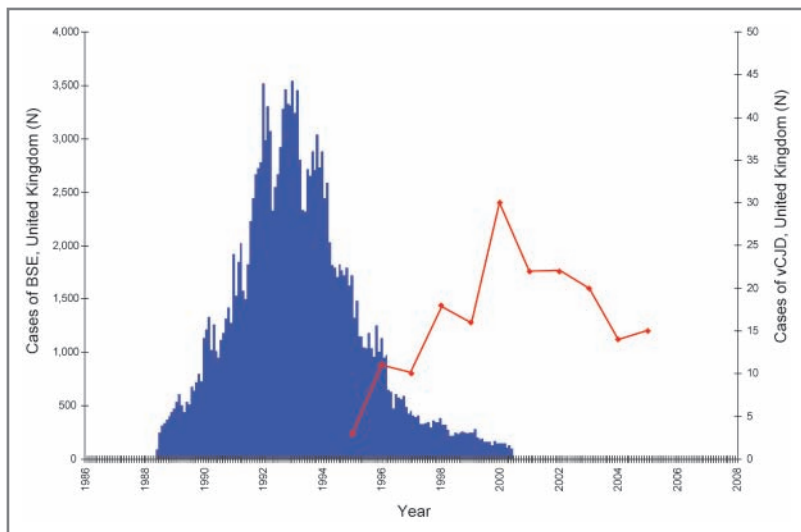


Figure 1—Numbers of reported cases of BSE in cattle by month (blue bars) and vCJD in humans by year of diagnosis (red diamonds) in the United Kingdom. Although not illustrated on the figure, relatively small annual numbers of BSE cases in the UK have been reported since 2001: 1,144 cases in 2002, 611 cases in 2003, 343 cases in 2004, 225 cases in 2005, 114 cases in 2006, and 49 cases in 2007 (through October).^{34,50}

agent is that it was derived from a strain of scrapie, the classic BSE agent has a greater capability of successful transmission between and among phylogenetically disparate species, indicating that BSE is associated with much lower species barriers than those associated with scrapie.¹⁶

Current efforts at eliminating BSE from cattle herds have essentially become an important human public health issue, and several serial steps have been enacted to protect animal feed and the human food supply from BSE contamination. The infectivity of various bovine tissues appears to be heterogeneous and changes with time in an infected animal. A focus of BSE elimination is to prevent the tissues with the highest risk of infectivity (so-called specified risk material) from getting into food for humans and feeds for other animals.³⁶ Thus, the current BSE-related feed and food bans in the United States and most other countries are directed toward specified risk materials, including the brain, skull, spinal cord, trigeminal and dorsal root ganglia, eyes, and vertebral column of cattle ≥ 30 months old and the tonsils and distal portion of the ileum of cattle of all ages. Additionally, various surveillance efforts are in place to detect BSE in at-risk cattle; these efforts center on testing of immobile or disabled cattle or those with clinical evidence of BSE. As experiences in the United Kingdom have revealed, effective BSE surveillance, strict feed bans, and aggressive removal of specified risk material from the human food chain can prevent development of BSE in cattle and vCJD in humans.

Although both the BSE and the vCJD outbreaks appear to be subsiding, it is quite possible that the full impact of the BSE epizootic on human health will not be fully realized for many years. Undoubtedly, many millions of people have been exposed to various amounts of BSE-contaminated products. Although it is reassuring that, to date, these exposures have resulted in only approximately 200 cases of vCJD, the

possibility that human illness will develop after extremely long incubation periods remains; the number of persons that have a subclinical or preclinical infection with the BSE-vCJD agent is unknown. The effects of various host factors (including age and phenotype at codon 129 of the human PrP^C gene) on susceptibility to BSE infection and the subsequent development of disease are undetermined. Furthermore, the risk of person-to-person transmission of the vCJD agent through contaminated surgical instruments, blood transfusions, and possibly donated organs may be greater than estimated presently.

CWD

The emergence of BSE and its association with human illness has raised increasing concerns about another animal TSE. Chronic wasting disease is a TSE of deer, elk, and moose. It was first identified in the mid 1960s among cap-

tive mule deer in research facilities in northern Colorado⁵⁴; deer in these facilities were obtained from various sources, including from free-ranging wild populations and other research facilities. Initially, the disease was described as a distinct clinical syndrome of unknown etiology, which was characterized by progressive muscle wasting, progressive neurologic dysfunction, and ultimately death. In 1978, examination of the brains of affected deer revealed that it was a spongiform encephalopathy.^{55,56} In 1981, CWD was identified among free-ranging elk in Colorado, and within the next several years, it was detected among free-ranging herds in various areas of Colorado and Wyoming. Although it was initially thought that the affected animals were representative of the recent emergence of the disease in these areas, results of a modeling study⁵⁶ have suggested that CWD may have been present among these herds for more than 20 years prior to its initial identification.

Since its detection, CWD in free-ranging and farmed herds has been identified in an ever-expanding area, including states in the western, Midwestern, and eastern United States and 2 Canadian provinces (Figure 2). Movement of the disease through commercial trade of farmed cervids has been known since the mid-1990s; infected farmed herds have been identified in western states, Midwestern states, Saskatchewan, and Alberta. In 1997, a farmed elk from Saskatchewan that was exported to South Korea was identified as the first known internationally exported CWD-affected cervid.⁵⁷ Epidemiologic and laboratory data indicate that CWD may be transmitted directly via animal-to-animal contact and via environmental contamination with the CWD agent.^{58,59}

The clinical features of CWD are characterized by severe generalized wasting and loss of body mass, increased urination and drinking, excessive salivation, and movement disorders including trembling and ataxia. As with all TSEs, the illness is fatal, and death gener-

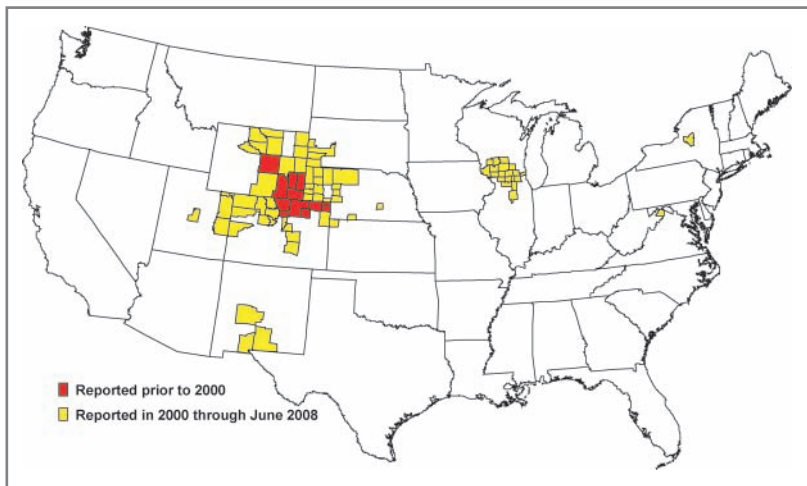


Figure 2—Geographic distribution of CWD in North America, through the end of December 2007. In the United States, cases of CWD in Colorado, Illinois, Kansas, Minnesota, Montana, Nebraska, New Mexico, New York, Oklahoma, South Dakota, Utah, West Virginia, Wisconsin, and Wyoming have been reported. In Canada, cases in Saskatchewan and Alberta have been reported.

ally occurs within 4 months of onset. The epidemiology of CWD is distinct from that of BSE. Data from captive mule deer indicate that lateral transmission of the agent occurs⁶⁰ and that the epidemiology of transmission is more similar to that of scrapie than that of BSE. Maternal transmission may occur but appears to be rare. One of the intriguing aspects of CWD epidemiology is the potential mechanism of agent shedding; findings of epidemiologic and laboratory studies^{58,61,62} suggest that environmental contamination with infected saliva and possibly feces is an important route for lateral transmission throughout a herd. The CWD agent likely persists in the soil and other environmental sources, making eradication of infection difficult.⁵⁸ Unlike the BSE agent, the CWD agent appears to spread efficiently and rapidly within a herd of animals. As with BSE, definitive diagnosis of CWD can be made histopathologically; spongiform changes are detectable in brain tissue at necropsy. However, immunohistochemical detection of the PrP^{TSE} agent in neural or lymphoid tissue has largely replaced histologic analysis, and various rapid ELISAs are being used.⁶²

Currently, there is no compelling scientific evidence to support zoonotic transmission of CWD from cervids to humans. Several epidemiologic investigations^{54,63–66} of suspected cases of CJD among persons who hunted and consumed venison have been undertaken, but none of those investigations revealed evidence of CWD-associated human disease. Results of various laboratory studies⁶⁷ suggest that there is a strong species barrier between cervids and humans for transmission of the CWD agent. Conversion of the human PrP^C isoform to the abnormal isoform in the presence of the CWD PrP^{TSE} agent is inefficient; intracerebral inoculation of transgenic mice that were susceptible to human prion diseases with the CWD agent failed to induce prion disease.^{68–70}

However, the experience with BSE has provided a valuable public health lesson, and admittedly, information regarding transmission of CWD is incomplete.

As a result, public health officials promote precautionary measures. Active campaigns to raise awareness of CWD among hunters are in place in many areas in which cervid hunting is popular. In many CWD-endemic areas, hunters and taxidermists are urged to have their captured game tested for CWD prior to consumption of the meat, to avoid harvesting obviously ill animals, to discard tissues at highest risk of containing the CWD agent (including neurologic and lymphoreticular tissues), and to wear latex or rubber gloves when dressing killed animals. An additional public health concern has been the possibility that the CWD agent could be transmitted across the species barrier from cervids to cattle or sheep in adjacent grazing areas. Again, experimental evidence suggests that transmission of CWD to cattle is inefficient and is unlikely to occur in natural settings.^{71–74} Nonetheless, implementation of further surveillance and epidemiologic assessments remains prudent.

Other TSEs in Nonhuman Animals

Although of limited zoonotic relevance, several other TSEs in small mammals have been identified.^{12,75–77} Transmissible mink encephalopathy occurs as confined outbreaks in mink ranches, and the disease was first reported in Wisconsin in 1985. The underlying assumption has been that outbreaks occur because of consumption of feed contaminated with material from scrapie-affected sheep. However, the identification of atypical BSE in older US cattle, which may possibly represent cases of sporadic BSE, provides some support for a hypothesis that the BSE agent of cattle, not the scrapie agent of sheep, was the most likely source for at least 1 TME outbreak in Wisconsin.⁷⁸

During the BSE epizootic, spongiform encephalopathy was diagnosed in scores of domestic cats and in 14 captive exotic animal species in which such disease had not been previously identified. The affected species were in 2 phylogenetic families, the Bovidae and Felidae. Consumption of BSE-contaminated bovine carcasses and MBM is presumed to have been the source of the TSE infection in these animals.⁷⁹ Development of feline spongiform encephalopathy and other BSE-related spongiform encephalopathies in wild cats and various captive ungulates in zoos and preserves is likely to be rare and may be eliminated from those populations as feed control measures continue to reduce the transmission of the BSE agent among cattle.

Overview

Transmissible spongiform encephalopathies represent a fascinating facet of mammalian biology in that these diseases may be both infectious and inherited. Until recently, TSEs of both humans and other animals have been considered veterinary and medical curiosities, although it is evident that such diseases are dev-

astating to patients, families, and caregivers. However, the emergence of BSE and its etiologic link with vCJD have added a greater sense of public health importance to TSEs. Our knowledge and understanding of TSEs has increased in recent years, as evidenced by the exponential increases in research projects, data published in the scientific literature, funding, and scientific symposia devoted to the topic. However, a great deal of work has to be undertaken to fully understand and elucidate the epidemiology, pathophysiology, clinical features, and potential treatments for these diseases. Human and veterinary public health officials will need to remain vigilant for the continuing risk of the zoonotic transmission of animal TSEs for the foreseeable future.

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