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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

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INTRODUCTION. The transmissible spongiform encephalopathies (TSEs) comprise an unusual group of neurologic diseases of humans and animals. They are apparently caused by proteinaceous agents called *prions* that are devoid of nucleic acids (Prusiner 1982). Although debate continues (Chesebro 1998; Farquhar et al. 1998), there is now a great deal of evidence supporting the hypothesis that TSEs are caused by abnormal, protease-resistant forms (PrP^{res}) of cellular proteins (PrP^{c}) coded for and normally synthesized in central nervous system (CNS) and lymphoid tissues (Prusiner 1991). It is thought that these abnormal proteins arise through posttranslational modifications in tertiary structure of PrP^{c}, resulting in decreased α-helical content and increased amounts of β-sheet (Prusiner 1997). In humans, PrP^{res} may arise sporadically through somatic mutations or spontaneous conversion of PrP^{c} to PrP^{res}, as a result of germline mutations in the PrP gene resulting in familial disease; or they may be acquired by infection (Prusiner 1997). In animals, TSEs are infectious; spontaneous and familial forms have not been identified, though they may occur.

On entering a susceptible host by some natural or experimental process, PrP^{res} promotes production of species-specific PrP^{res} from PrP^{c} in lymphoid and CNS tissues. The finding that PrP^{res} catalyzes production of PrP^{res} from PrP^{c} in vitro added weight to the hypothesis that this is its mode of action in vivo (Kocisko et al. 1994; Raymond et al. 1997).

Thus, although the TSEs behave like infectious diseases, the agents appear to have no inherent genetic identity, and if this is so, the disease is more correctly perceived and classified as a special type of toxicity. Prions have remarkable resistance to environmental conditions and a range of treatments that typically kill or inactivate conventional infectious agents (Millison et al. 1976; Taylor et al. 1995).

Prior to 1980, naturally occurring TSEs had been reported in four species: scrapie in domestic sheep *Ovis aries* and goats *Capra hircus* (Dickinson 1976); transmissible mink encephalopathy (TME) in mink *Mustela vison* (Hartsough and Burger 1965); and kuru, Creutzfeldt-Jakob disease (CJD), and Gerstmann-Sträussler-Scheinker syndrome of humans (Prusiner and Hadlow 1979; Collinge and Palmer 1997). More recently, chronic wasting disease (CWD) was reported in deer *Odocoileus* spp. and Rocky Mountain elk *Cervus elaphus nelsoni* in the United States (Williams and Young 1980, 1982). Bovine spongiform encephalopathy (BSE) was diagnosed in cattle *Bos taurus* (Wells et al. 1987), in domestic cats *Felis catus* (Pearson et al. 1992), and in wild mammals in or from Great Britain (Jeffrey and Wells 1988; Kirkwood and Cunningham 1994a) or in France (Bons et al. 1996, 1999). Bovine spongiform encephalopathy was associated with a variant of CJD (vCJD) in a few humans beginning in 1996 (Will et al. 1996).

A disease indistinguishable from scrapie occurred in mouflon *Ovis musimon* in the United Kingdom (Wood et al. 1992). In addition, several suspect cases of TSE were reported in albino tigers *Panthera tigris* (Kelly et al. 1980) and ostriches *Struthio camelus* (Schoon et al. 1991), but these were not confirmed and probably were not prion diseases.

Recent studies draw somewhat conflicting conclusions about the pathogenesis of the TSEs. In part, this may be due to variation in the different agents, different doses and routes of exposure, and different animal models used to study these diseases; natural hosts are seldom employed in these studies.

Substantial evidence exists for genetic variation in susceptibility to some prion diseases among and within species. For example, there are differences in susceptibility to scrapie among breeds of sheep (Hunter et al. 1992; O'Rourke et al. 1997b) and differences in incubation period associated with genotype in mice (Bruce et al. 1994). Genetic variation in susceptibility to sporadic and iatrogenic prion disease in humans is recognized (Collinge and Palmer 1994). In contrast, there is no evidence for variation in susceptibility to BSE among cattle (Wilesmith 1994).

Studies of the pathogenesis of scrapie after intragastric inoculation of mice suggested neural spread of the agent from the gastrointestinal tract to thoracic spinal cord via the sympathetic nervous system (Kimberlin and Walker 1989). In hamsters orally infected with scrapie, the route to the CNS was hypothesized to be the vagus nerve to the parasympathetic vagal nucleus (dorsal motor nucleus of the vagus) in the medulla oblongata, the initial site of detection of PrP^{res} in the CNS (Beekes et al. 1998). Evidence of infectivity in cattle orally infected with large doses of BSE agent was found first in the CNS in thoracic and lumbar spinal cord (Wells et al. 1998). Neuroinvasion in scrapie-infected mice was linked to B lymphocytes (Klein et al. 1997). There is no known immune response to TSE

agents in affected hosts; however, the lymphoreticular system plays a role in pathogenesis of disease in rodent models.

Histopathologic changes in animals and humans with TSEs are qualitatively similar and confined to the CNS. Lesions include vacuolation of neuronal perikarya and neurites, neuronal degeneration and loss, gliosis (mainly astrocytic), and accumulation of PrP^{res} (Wells and McGill 1992; McGill and Wells 1993). The pathogenetic mechanisms of neurodegeneration are not understood but are under study (Sakaguchi et al. 1996; Tobler et al. 1996; Jeffrey et al. 1997; Williams et al. 1997; Hegde et al. 1998). Scrapie-associated fibrils (SAFs), which are fibrillar aggregates of PrP^{res}, may be revealed by electron-microscopic examination of detergent extracts of brain from affected animals (Merz et al. 1984; Hope et al. 1988; Wells and McGill 1992).

With the importance of BSE and scrapie in domestic livestock, and the heightened concern about the relationship of these diseases and human health, more attention will certainly be focused on the TSEs in the future.

CHRONIC WASTING DISEASE

History and Distribution. Chronic wasting disease (CWD) was first recognized in 1967 as a clinical syndrome of unknown etiology among captive mule deer *Odocoileus hemionus* at wildlife research facilities in Colorado (Williams and Young 1992). The disease was diagnosed in 1978 as a spongiform encephalopathy by histopathologic examination of CNS from affected animals. Shortly afterward CWD was recognized among captive deer in Wyoming (Williams and Young 1980). Diagnosis of CWD in Rocky Mountain elk from these same facilities quickly followed (Williams and Young 1982). Deer and elk in a few zoological gardens in the United States and Canada were identified with CWD in subsequent years (Williams and Young 1992). Apparently it did not persist in these locations. Chronic wasting disease has recently become a concern to the game farm industry following its diagnosis in elk in Saskatchewan, Canada, and in South Dakota, Nebraska, Montana, Colorado, and Oklahoma.

In 1981, CWD was recognized in a free-ranging elk in Colorado (Spraker et al. 1997). Subsequently, it was found in free-ranging elk in Wyoming, and in free-ranging mule deer [1985 (M.W. Miller unpublished)] and white-tailed deer *Odocoileus virginianus* [1990 (E.S. Williams unpublished)] in both states. The known distribution of CWD currently includes captive and free-ranging cervids in southeast Wyoming and north-central and northeast Colorado (Miller et al. 2000) and several game farms in the United States and Canada.

Host Range. Only three species of Cervidae are known to be naturally susceptible to CWD: mule deer, white-tailed deer, and Rocky Mountain elk. Subspecies of these cervids probably are also naturally susceptible. Pronghorn *Antilocapra americanus,* Rocky Mountain bighorn sheep *Ovis canadensis,* mouflon, mountain goats *Oreamnos americana,* moose *Alces alces,* and a blackbuck *Antilope cervicapra* have been in contact with CWD-affected deer and elk or resided in premises where CWD had occurred but have not developed the disease. Domestic livestock are not known to be naturally susceptible to CWD, and a few cattle, sheep, and goats have resided in research facilities with CWD for prolonged periods without developing the disease.

Many species are experimentally susceptible to CWD by intracerebral inoculation, an unnatural but commonly used route for the study of prion disease. Mink, domestic ferret *Mustela putorius furo,* squirrel monkey *Saimiri sciureus,* mule deer, domestic goat (Williams and Young 1992), and laboratory mice (Bruce et al. 1997) are susceptible to CWD by this route on primary passage.

Etiology. The origin of CWD is not known. Spontaneous development of PrP^{res} might have occurred in deer, with subsequent transmission to other deer and elk. An alternate explanation is that CWD is actually scrapie occurring in cervids. Chronic wasting disease could also have originated by infection with an as-yet-unrecognized prion.

Characteristics of the agent causing CWD are poorly understood, but the agent is presumed to be a prion. Based on mouse strain typing, it appears to differ from the BSE agent (Bruce et al. 1997), many strains of scrapie, and the TME agent (M.E. Bruce personal communication). The marked similarity of CNS lesions and epidemiology strongly suggests CWD agent is the same in captive and free-ranging deer and elk.

Transmission and Epidemiology. The mode of transmission of CWD is unknown. There is no evidence that CWD is a food-borne disease associated with rendered ruminant meat and bonemeal as was the case in BSE (Wilesmith et al. 1988). Occurrence of the disease among captive deer and elk, many of which were acquired as neonates, fawns, or adults, provides strong evidence of lateral transmission (Williams and Young 1992; Miller et al. 1998; Miller et al. 2000). Maternal transmission may also occur; however, this has not been definitively determined. It is likely transmission occurred from mule deer to elk.

The scrapie agent is found in many lymphoid tissues, including those of the digestive tract (Hadlow et al. 1980, 1982), suggesting the agent may be shed through the alimentary tract. Lymphoid tissues of affected deer and elk contain PrP^{res}; thus, alimentary tract shedding may also occur in CWD. The TSE agents are extremely resistant in the environment (Brown and Gajdusek 1991); pasture contamination has been suspected of being the source of scrapie agent in some outbreaks of sheep scrapie (Greig 1940; Pálsson 1979). Concentration of deer and elk in captivity or by artificial feeding may increase the likelihood of transmission between individuals.

The youngest animal diagnosed with natural CWD was 17 months of age, suggesting this as an approximate minimum incubation period; however, without knowledge of when the animal was infected, it is impossible to accurately determine the incubation period. Maximum incubation periods are not known. Most cases of CWD among deer and elk residing in facilities with a long history of CWD are in 3–7-year-old animals. The age of onset of clinical signs is variable in animals brought into facilities as adults or among animals in herds newly recognized to have CWD. For example, one elk in a presumed newly infected herd was more than 15 years old. It is not known when during the course of infection an animal may be infectious.

In one study, more than 90% of mule deer residing on a premises for more than 2 years died or were euthanized due to CWD (Williams and Young 1980). Chronic wasting disease was the primary cause of adult mortality [5 (71%) of 7 and 4 (23%) of 23] in two captive elk herds (Miller et al. 1998).

Relatively little is known about the epidemiology of CWD in free-ranging cervids. In addition to necropsy and examination of brains from animals showing clinical signs suggestive of CWD to determine its distribution (targeted surveillance), brains from deer and elk harvested by hunters in the CWD-endemic area have been used to estimate prevalence. Within endemic areas, prevalence of preclinical CWD, based on histopathology and/or immunohistochemistry for PrP^{res}, is estimated at less than 1%–8% (Miller et al. 2000). Chronic wasting disease has not been found in cervids outside the endemic areas.

Preliminary modeling suggested lateral transmission is necessary to maintain CWD at the prevalence observed in surveillance programs. Maternal transmission may occur, but in the model this route of transmission alone was not adequate to maintain the disease at observed levels (Miller et al. 2000).

Clinical Signs. The most striking clinical features of CWD in deer and elk are loss of body condition and changes in behavior. Clinical signs of CWD may be more subtle and prolonged in elk than in mule deer. Affected animals may increase or decrease their interaction with handlers or other members of the herd. They may show repetitive behaviors, such as walking set patterns in their pens or pastures, show periods of somnolence or depression from which they are easily roused, and may carry their head and ears lowered. Affected animals continue to eat, but they consume reduced amounts of feed, leading to gradual loss of body condition. As the disease progresses, many affected animals display polydipsia and polyuria; increased salivation with resultant slobbering or drooling; and incoordination, particularly posterior ataxia, fine head tremors, and wide-based stance. Esophageal dilatation, hyperexcitability, and syncope are rarely seen. Death is inevitable.

In captive herds newly experiencing CWD, sporadic cases of prime-aged animals losing condition, being unresponsive to symptomatic treatment, and death from pneumonia are common. Aspiration pneumonia, presumably from difficulty swallowing and hypersalivation, may lead to misdiagnosis of the condition if the brain is not examined.

The clinical course of CWD varies from a few days to a year, with most animals surviving a few weeks to 3–4 months. Although a protracted clinical disease is typical, occasionally acute death may occur in white-tailed deer (M.W. Miller unpublished). Caretakers familiar with individual animals often recognize subtle changes in behavior well before those not familiar with the particular animal detect abnormalities or serious weight loss occurs. Also, those who have seen clinically affected animals are more astute at detecting early behavioral changes than naive observers.

The clinical course of CWD in free-ranging deer and elk is probably shorter than in captivity. Wild cervids must forage, find water, and are susceptible to predation, all factors affecting longevity of sick animals in the wild.

Pathogenesis. The pathogenesis of CWD is not specifically known, though considerable research is currently under way to better understand the dynamics of the disease in deer and elk. Based on similarities in clinical course, neuropathology, and distribution of PrP^{res}, pathogenesis of CWD is likely similar to scrapie (Hadlow et al. 1980, 1982) The CWD agent probably enters the animal by ingestion, perhaps from environmental contamination or direct interaction with animals shedding the agent. In mule deer fawns experimentally infected with CWD, PrP^{res} was detected in retropharyngeal and ileocecal lymph nodes, tonsil, and Peyer's patches by 42 days after inoculation (Sigurdson et al. 1999).

The parasympathetic vagal nucleus in the medulla oblongata is the site of the most severe and consistent lesions in deer (Williams and Young 1993) and is the site of PrP^{res} accumulation, prior to development of spongiform changes (E.S. Williams unpublished; T.R. Spraker personal communication). Distribution of lesions in the brain (Williams and Young 1993) may explain clinical signs. Emaciation may be associated with hypothalamic damage, and polydipsia may reflect damage to the paraventricular and supraoptic nuclei and subsequent diabetes insipidus (Williams and Young 1992).

Pathology. Alterations in clinical chemistry and hematology may occur in CWD-affected animals, but the alterations are not diagnostic. In captive deer, low urine specific gravity (1.002–1.010) reflects polydipsia and possibly inability to concentrate urine (Williams and Young 1980). In free-ranging animals, urine specific gravity may not be as low because they may not have ready access to water and may be dehydrated at death. Other nonspecific changes in clinical pathology reflect emaciation or intercurrent diseases.

The gross lesions of CWD are nonspecific. Carcasses may be in poor nutritional state or emaciated, but may be in fair condition if the animal died of aspi-

ration pneumonia or after only a short clinical course. Aspiration pneumonia with or without fibrinous pleuritis may be present in some animals. Rumen contents contain excessive water in those animals displaying polydipsia; sometimes the contents appear frothy. Sand and gravel are often abundant in the forestomachs.

Microscopic lesions of CWD have been described in mule deer and elk (Williams and Young 1993; Hadlow 1996). The lesions are qualitatively typical of TSEs. Distribution of lesions is similar in deer and elk, with some minor differences in degree. In all cases of clinical CWD, lesions are in the parasympathetic vagal nucleus in the dorsal portion of the medulla oblongata at the obex, in hypothalamus and thalamus, and in olfactory tracts and cortex. Other regions of the brain, in particular, thalamus and cerebellum, show typical spongiform changes with varying degrees of severity. Lesions are usually mild in the cerebral cortex, hippocampus, and basal ganglia.

Plaques composed of PrP^{res} can be appreciated on routine hematoxylin-eosin staining in most clinically affected white-tailed deer and in a few mule deer but are not obvious in elk (Bahmanyar et al. 1985; Williams and Young 1992). In white-tailed deer, plaques are often surrounded by vacuoles in the neuropil, which allows them to be easily visualized. The plaques stain strongly on immunohistochemistry for PrP^{res} by using a variety of polyclonal and monoclonal antibodies (Guiroy et al. 1991a,b; Williams and Young 1992; Liberski et al. 1993; O'Rourke et al. 1998b). Patterns of immunostaining in CWD include granularity and amorphous clumps on neuronal membranes, perivascular aggregates, and large, apparently extracellular accumulations of PrP^{res}.

Scrapie-associated fibrils are found in brains and spleen of deer and elk with CWD (Williams and Young 1992; Spraker et al. 1997). The ultrastructural lesions of CWD are typical of lesions found in the other TSEs (Guiroy et al. 1993, 1994; Liberski et al. 1993).

Diagnosis. Clinical signs of CWD are not specific, and currently diagnosis is based on examination of the brain for spongiform lesions and/or accumulation of PrP^{res}. The parasympathetic vagal nucleus in the dorsal portion of the medulla oblongata at the obex is the most important site to be examined for diagnosis of CWD (Williams and Young 1993) and should be submitted for histopathologic examination on every animal suspected of having CWD. The whole head or whole brain can be submitted to the diagnostic laboratory to ensure that the correct portion of the brain is examined. Supplemental tests include negative-stain electron microscopy for SAF or Western blotting for detection of PrP^{res} in brain (Williams and Young 1992; Spraker et al. 1997).

Demonstration of PrP^{res} in lymph nodes, tonsil, and conjunctival lymphoid tissues is useful in antemortem diagnosis of sheep scrapie (Ikegami et al. 1991; Schreuder et al. 1996, 1998; O'Rourke et al. 1998a). These techniques are currently being tested in deer and elk to determine their sensitivity and specificity.

Differential Diagnoses. Differential diagnoses of CWD in deer and elk include a wide variety of diseases that cause CNS disease and emaciation. Animals with brain abscesses, traumatic injuries, encephalitis, meningitis, peritonitis, pneumonia, arthritis, starvation, nutritional deficiencies, and dental attrition have been submitted to laboratories as CWD suspects. Aspiration pneumonia is often seen as a terminal event in deer and elk with CWD and, when it is recognized in a prime-aged cervid, CWD should be considered.

Immunity. There is no known immune response to the CWD agent. In sheep and mice, PrP genotype plays a major role in development of scrapie. There is marked homology between mule deer, white-tailed deer, and elk PrP gene sequences (Cérvenakova et al. 1997; K. O'Rourke personal communication). Polymorphism was detected in mule deer (codon 138, serine or asparagine) (Cérvenakova et al. 1997; O'Rourke et al. 1997a), white-tailed deer (K. O'Rourke personal communication), and elk [codon 132 (129), methionine or leucine] (Cérvenakova et al. 1997; Schatzl et al. 1997; O'Rourke et al. 1998b). It is not yet known whether particular PrP genotypes confer resistance or increase susceptibility to CWD; however, codon 132 methionine homozygotes were overrepresented in free-ranging and captive CWD-affected elk when compared to unaffected elk (O'Rourke et al. 1999).

Control and Treatment. There is no known treatment for animals affected with CWD, and it is considered 100% fatal once clinical signs develop. If an affected animal develops pneumonia, treatment with antibiotics might prolong the course of illness but will not alter the fatal outcome.

Control of CWD is problematic. In the face of long incubation periods, subtle early clinical signs, absence of reliable antemortem diagnostic tests, extremely resistant infectious agent, possible environmental contamination, and lack of understanding of transmission, designing methods for control or eradication of CWD is extremely difficult. Management currently involves quarantine or depopulation of CWD-affected herds. Two attempts to eradicate CWD from captive cervid facilities failed, though the cause of the failure was not determined; residual environmental contamination following facility cleanup was possible (Williams and Young 1992).

Management of CWD in free-ranging animals is even more problematic. Long-term active surveillance to determine distribution and prevalence of CWD has been instituted to assist in evaluating changes over time and effect of management intervention. Translocation and artificially feeding cervids in the endemic areas has been banned in an attempt to limit range expansion and to decrease transmission of CWD. Localized population reduction in areas of high CWD prevalence is being considered.

Public Health Concerns. No cases of human disease have been associated with CWD. There is a long history

of human exposure to scrapie through handling and eating sheep tissues, including brain, yet there is no evidence that this presents a risk to human health. However, in the absence of complete information and in consideration of the similarities of animal and human TSEs, hunters harvesting deer and elk in the endemic areas or meat processors and taxidermists handling cervid carcasses should take some commonsense measures to avoid exposure to the agent and to other zoonotic pathogens. Sick animals should not be harvested for consumption; hunters, game-meat processors, and taxidermists should wear latex or rubber gloves when dressing a deer or elk from these areas; and the brain, spinal cord, lymph nodes, spleen, tonsils, and eyes should be discarded and not consumed, because these organs probably contain the greatest amount of CWD agent. Since TSE agents have never been demonstrated in skeletal muscle, boning game meat is an effective way to reduce the potential for exposure.

Management Implications. The presence of CWD in captive and free-ranging cervids is a serious management problem. Captive populations are quarantined, which limits usefulness and value of the animals for research or commerce. Indemnity for depopulated cervids currently is not available. Guidelines for management of captive herds with CWD are being developed by federal, state, and provincial animal health officials.

Implications for free-ranging populations of deer and elk are significant. Deer and elk are not translocated from CWD-endemic areas, surveillance programs are expensive for wildlife management agencies, and the impact of the disease on the population dynamics of deer and elk is not currently known. Preliminary modeling suggests that CWD could detrimentally affect populations in endemic areas (M.W. Miller unpublished). Public and agency concerns and perceptions about human health risks associated with all the TSEs may ultimately influence management of herds of free-ranging cervids in the endemic areas.

BOVINE SPONGIFORM ENCEPHALOPATHY IN NONDOMESTIC SPECIES

Distribution and Host Range. Cases of TSE, now recognized as caused by the BSE agent, were diagnosed in ten species of Bovidae and Felidae (Table 17.1) at or from zoological collections in the British Isles (Kirkwood and Cunningham 1994a). Cases occurred in cheetah *Acinonyx jubatus* exported to Australia (Peet and Curran 1992) and France (Baron et al. 1997). A possible case of TSE associated with BSE agent was reported in a rhesus macaque *Macaca mulatta* (Bons et al. 1996); however, this diagnosis has been questioned (Baker et al. 1996). Recently, spongiform encephalopathy associated with oral exposure to the BSE agent was confirmed in captive brown lemurs *Eulemur fluvus* and

TABLE 17.1—Wild mammals reported with naturally occurring transmissible spongiform encephalopathies

Scientific name	Common Name	Disease[a]	References
Bovidae			
Taurotragus oryx	Eland[b]	BSE	Fleetwood and Furley 1990; Kirkwood and Cunningham 1994a
Tragelaphus strepsiceros	Greater kudu[b]	BSE	Kirkwood et al. 1990; Kirkwood and and Cunningham 1994a
Tragelaphus angasii	Nyala[b]	BSE	Jeffrey and Wells 1988
Oryx dammah	Scimitar-horned oryx[b]	BSE	Kirkwood and Cunningham 1994a
Oryx gazella	Gemsbok[b]	BSE	Jeffrey and Wells 1988
Oryx leucoryx	Arabian oryx[b]	BSE	Kirkwood et al. 1990
Bison bison	Bison	BSE	R. Bradley, personal communication
Ovis musimon	Mouflon[b]	Scrapie	Wood et al. 1992
Cervidae			
Odocoileus hemionus	Mule deer[b,c]	CWD	Williams and Young 1980
Odocoileus virginianus	White-tailed deer[b,c]	CWD	Spraker et al. 1997
Cervus elaphus nelsoni	Rocky Mountain elk[b,c]	CWD	Williams and Young 1982
Felidae			
Felis concolor	Cougar[b]	BSE	Willoughby et al. 1992
Felis pardalis	Ocelot[b]	BSE	Kirkwood and Cunningham 1994b
Panthera tigris	Tiger[b]	BSE	Kirkwood and Cunningham 1999
Acinonyx jubatus	Cheetah[b]	BSE	Peet and Curran 1992; Kirkwood and Cunningham 1994b; Kirkwood et al. 1995; Baron et al. 1997
Mustelidae			
Mustela vison	Mink[b]	TME	Hartsough and Burger 1965; Hadlow and Karstad 1968; Hartung et al. 1970

[a]BSE, bovine spongiform encephalopathy; CWD, chronic wasting disease; TME, transmissible mink encepalopathy.
[b]Captive animals.
[c]Free-ranging animals.

a mongoose lemur *Eulemur mongoz* in France (Bons et al. 1999).

Transmission and Epidemiology. The epidemiology of BSE in zoo animals in Great Britain is similar to that of BSE in cattle. The epidemic in cattle arose through the practice of including ruminant-derived protein in cattle feeds (Wilesmith et al. 1988, 1991). It was thought that changes in rendering procedures used in preparing this material resulted in failure to inactivate the agent, which was hypothesized to be a strain of scrapie from sheep. The first clinical cases were diagnosed in cattle in 1986. Subsequent analysis of the epidemic in cattle revealed there must have been widespread exposure to the agent via proprietary feeds starting during the winter of 1980–81 (Wilesmith et al. 1988, 1991).

The cases in zoo animals are thought to have been caused by the BSE agent for three reasons: their temporal and geographic coincidence with the BSE epidemic in cattle; affected zoo animals were either known, or suspected, to have been exposed to contaminated feeds; and the pathology and incubation period of the disease in various strains of mice inoculated with brain homogenates from an affected nyala *Tragelaphus angasii* and a greater kudu *Tragelaphus strepsiceros* were nearly identical to those occurring when mice were inoculated with BSE from cattle (Jeffrey et al. 1992; Bruce et al. 1994). The ungulates were exposed to feeds containing ruminant-derived protein, and the carnivores were exposed to tissues, probably including CNS, from cattle incubating BSE that were considered unfit for human consumption (Kirkwood and Cunningham 1994a,b).

The question of whether BSE is laterally or maternally transmissible in cattle has received vigorous investigation. At present, there is some indication that it is transmissible vertically or by other routes at a low rate (Donnelly et al. 1997a; Wilesmith et al. 1997). The occurrence of cases in greater kudu that were born after the July 1988 ban on inclusion of ruminant-derived protein in ruminant feeds [Her Majesty's Stationery Office (HMSO) 1988] and that were not thought to have been exposed via the diet raised the possibility that lateral transmission might have occurred in this species (Kirkwood et al. 1992, 1994; Cunningham et al. 1993; Kirkwood and Cunningham 1994a). However, the pattern of the epidemic in cattle has since revealed that some degree of feed contamination was present for a considerable period after the July 1988 ban, and the possibility that the kudu were exposed to these feeds cannot be excluded. Because of this, and the fact that no further cases have occurred in this species since 1992, which exceeds the apparent average incubation period of 31 months, it is possible that all the kudu cases could, as in cattle, have been due to ingestion of contaminated feeds.

It seems reasonable that the cases in eland *Taurotragus oryx* (Fleetwood and Furley 1990) and scimitar-horned oryx *Oryx dammah*, born, like some of the kudu, quite long after the July 1988 feed ban, were due to exposure to contaminated feeds. Measures to ensure the exclusion of ruminant-derived protein from feeds were subsequently tightened in the United Kingdom, and there has been a marked decline in the number of cases among cattle, indicating the efficacy of these measures (Donnelly et al. 1997b). Decline in the number of new cases in zoo ungulates during recent years supports this and, although no firm conclusions can be drawn at this stage, provides no evidence for natural transmission between antelope.

Because dates of infection of affected zoo animals were not known, incubation periods of the disease could not be determined precisely. However, data on age at death suggest that incubation periods vary between species, and they are clearly longer in Felidae (62–84 months) than in Bovidae (28–48 months).

Clinical Signs. Clinical signs in zoo animals have been reviewed by Kirkwood and Cunningham (1994a), and a detailed description of clinical signs in one greater kudu has been published (Kirkwood et al. 1994). These include various signs of CNS dysfunction, including ataxia, abnormal head and ear posture, fine muscle tremors, myoclonus, dullness, behavioral changes, excessive lip and tongue movements, and weight loss. In most cases, the disease progressed over weeks, and there was gradual progression of severity but, in some cases, the disease appeared to have a rapid onset and a course of only a few days.

Pathogenesis. The specific pathogenesis of BSE in zoo animals has not been studied. The route of spread of the agent after oral exposure to central nervous and other tissues remains unclear. Although infectivity has been detected in several tissues other than CNS in sheep with scrapie and cattle with BSE, lesions have been observed only in the CNS.

Pathology. The comparative pathology of BSE and the recent cases of spongiform encephalopathy in greater kudu and domestic cats have been reviewed (Wells et al. 1993). In cheetah, spongiform changes involved the entire brain axis, and vacuolation of the neuropil was the most prominent feature (Kirkwood et al. 1995). All the zoo animals that were examined for SAF were positive (Kirkwood and Cunningham 1994a).

Diagnosis. Clinical signs are not specific, but the disease may be strongly suspected in animals that show progressive behavioral changes or ataxia, postural abnormalities, and abnormal muscle movements; the suspect animals reside in or were imported from the United Kingdom or other European countries with endemic BSE; and where there is potential exposure to BSE-contaminated feeds. The disease cannot be confirmed during life, and diagnosis depends on detection of characteristic histopathologic changes and other analyses of CNS material collected at postmortem examination. In addition to detection of SAF, these

analyses include immunostaining and immunoblotting techniques for PrP^{res} (Scott et al. 1990). Further confirmation and, possibly, some information about strain type can be obtained by inoculating brain homogenates into panels of various genotypes of mice and studying the incubation periods and lesion profiles (Jeffrey et al. 1992; Bruce et al. 1994, 1997).

Immunity. There is no known immune response to TSE agents. Patchiness of the distribution of cases among taxa in zoo animals suggested variation in susceptibility to the BSE agent among species (Kirkwood and Cunningham 1994a; Kirkwood et al. 1995). However, this remains to be confirmed.

Treatment and Control. No treatment is available to halt, reverse, or delay the development of these diseases. Control of BSE in zoo animals has been discussed (Cunningham 1991; Kirkwood and Cunningham 1992, 1994a). Measures to prevent inclusion of rendered products in feeds (HMSO 1988) for zoo ruminants should effectively control the disease unless vertical or horizontal transmission occurs.

Since September 1990, there has been a statutory ban in the United Kingdom on feeding specified offal (brain, spinal cord, spleen, thymus, tonsils, and intestines) from cattle older than 6 months to any animals (HMSO 1990). This legislation did not preclude feeding tissues from zoo ungulates, but Kirkwood and Cunningham (1994a) considered it advisable not to feed to animals the offals of any species that could have been exposed to BSE. Furthermore, in the absence of information about tissue distribution of the agent in zoo animals, they considered that it would be prudent to avoid using any tissues of zoo animals in BSE-endemic countries as food for others.

Public Health Concerns. There is no known human health risk from zoo ungulates or felids with BSE, because these animals are not part of the human food chain. Contact with clinically affected animals is not considered a health risk, but appropriate protective measures should be taken during postmortem examinations.

Management Concerns. Management implications depend on whether BSE is naturally transmissible among zoo animals. If it is, then introduction of an incubating animal into a population of captive or free-living wild animals is likely to have serious consequences (Cunningham 1991; Kirkwood and Cunningham 1994a). The disease may therefore severely compromise movements between zoological collections for breeding management or for reintroduction to the wild. Animals that could have been exposed to the BSE agent, their offspring, or contacts should not be moved into populations that have not been exposed, unless the damage that this would cause to a conservation breeding program outweighs the risk of introduction of a TSE (Kirkwood and Cunningham 1994a). However, even if there is no risk of spread to conspecifics during life, tissues from affected or carrier animals could present a risk if eaten by other animals. For this reason, it has been recommended that no animal that could have been exposed to the BSE or other TSE agent should be used in reintroduction programs (Cunningham 1991; Kirkwood and Cunningham 1994a).

TRANSMISSIBLE MINK ENCEPHALOPATHY.

Transmissible mink encephalopathy is a rare TSE of ranched mink (Marsh and Hanson 1979); it has never been diagnosed in free-ranging mink. Only a few outbreaks have occurred in North America and Europe (Marsh 1976). The disease is thought to be associated with inadvertently incorporating sheep with scrapie into mink feed (Marsh and Hanson 1979); however, several TME outbreaks were associated with feeding cattle and not sheep (Marsh et al. 1991). This has led to the hypothesis that an unidentified spongiform encephalopathy may be circulating in cattle in the United States (Marsh et al. 1991; Robinson 1996). Neither BSE nor any other bovine TSE has been identified in the United States.

Transmissible mink encephalopathy causes 60%–100% morbidity within a population and 100% mortality of affected mink during outbreaks (Robinson 1996). Animals show behavioral changes and become aggressive, ataxic, and carry their tail over their backs, until they become somnolent, moribund, and die. The disease is not transmissible among affected animals except occasionally by bite wounds or cannibalism (Marsh and Hanson 1979). The microscopic lesions are qualitatively typical of the TSEs, but the lesions tend to be more severe in the rostral portions of the brain in comparison to the distribution of lesions in ruminants (Eckroade et al. 1979). Transmissible mink encephalopathy has been experimentally transmitted by intracerebral inoculation to cattle (Robinson et al. 1995) and to sheep, goats, and a variety of laboratory species, including primates (Marsh 1976; Hadlow et al. 1987). Striped skunks *Mephitis mephitis* and raccoons *Procyon lotor* were also experimentally susceptible to TME (Eckroade et al. 1973). Transmissible mink encephalopathy may be considered of greatest importance as a model of the TSEs, primarily through the carefully crafted studies of Marsh, Hadlow, and colleagues, rather than as a significant disease of domestic animals or humans. It is of potential management concern to those raising mink but is of no known concern to free-ranging species.

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