

Transmissible Spongiform Encephalopathies

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Importance

Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases caused by prions. Although these infections usually remain asymptomatic for years, the disease is always progressive and fatal once the clinical signs develop. TSEs affecting animals include scrapie (tremblante de mouton, rida), bovine spongiform encephalopathy (BSE, “mad cow disease”), feline spongiform encephalopathy (FSE), transmissible mink encephalopathy (TME, mink scrapie) and chronic wasting disease (CWD). Although some prion diseases usually occur in one or a few closely related species, other prions can cross species barriers. BSE has a particularly wide host range. Cattle are the most important hosts for this disease, but some other ruminants, cats, lemurs and humans can also be affected; in cats, the disease is known as feline spongiform encephalopathy, and in humans, it is called variant Creutzfeldt-Jakob disease (vCJD). Recent evidence suggests TME might also be caused by a variant of the BSE agent. The discovery that BSE can cross species barriers and is zoonotic has raised concerns about all TSEs. Prion diseases in livestock can also result in trade sanctions. For these reasons, many countries are conducting control or eradication programs for these diseases. The U.S. has eradication and flock certification programs for scrapie, a certification program for chronic wasting disease in captive cervids, and a surveillance program for BSE.

Etiology

Transmissible spongiform encephalopathies are caused by unconventional disease agents. These agents are resistant to the treatments that ordinarily destroy bacteria, spores, viruses and fungi. They are generally thought to be prions, although a minority opinion suggests that TSEs may be caused by virinos or retroviruses. Prions are infectious proteins that appear to replicate by converting a normal cellular protein into copies of the prion. The cellular protein, which is called PrP_c, is found on the surface of neurons. Pathogenic isoforms of PrP_c are designated PrP^{Sc}, PrP^{BSE} or PrP^{TSE} are other names for this protein. Prions that cause different diseases (e.g. BSE or scrapie) are considered to be different strains of PrP^{Sc}. Additional strain variations and atypical prions have been found for some agents, particularly scrapie and BSE. Atypical scrapie prions include the Nor98 agent, a strain that can occur in sheep that are genetically resistant to classical scrapie. Known BSE agents include the ‘classical’ BSE prion and at least two atypical BSE prions. One atypical prion has higher molecular mass fragments than classical BSE and is called ‘H-type’; the other has a lower molecular mass and is called ‘L-type’ or bovine amyloidotic spongiform encephalopathy (BASE). Atypical BSE prions may represent additional strains of BSE or spontaneously occurring prions. There may also be more than one variant of the CWD prion.

FSE is caused by the BSE prion; however, one TSE in a housecat, reported in 1998, was caused by a prion that was distinct from BSE. The authors suggested that this may have been a new type of FSE. No other infections with this prion have been reported in cats. The origin of the TME agent, which causes a rare TSE in mink, is still unknown. Although this disease might be caused by certain strains of the scrapie prion or another agent, current evidence suggests it is most likely to be caused by a BSE prion, possibly L-type BSE.

A disease formerly called “spongiform encephalopathy of exotic ruminants” is now known to be BSE occurring in ruminants other than cattle.

Species Affected

Scrapie

Scrapie affects sheep, goats and moufflon. The Nor98 form of scrapie has been reported in both sheep and goats. Rats, mice, hamsters, monkeys and a variety of other laboratory and wild animals can be infected experimentally by intracerebral inoculation or other parenteral routes.



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Bovine spongiform encephalopathy

BSE occurs mainly in cattle. However, the host range of this zoonotic prion is unusually broad compared to most prions. BSE has been reported from exotic ruminants in zoos, including nyala, kudu, gemsbok, oryx, eland and bison. Field cases have been documented in two goats, and experimental infections have been reported in both sheep and goats. Two lemurs at a French zoo were apparently infected in contaminated feed. In addition, the BSE agent has been experimentally transmitted to mink, mice, marmosets and cynomolgus monkeys. Pigs could be infected by the intracranial, intravenous and intraperitoneal routes, but short-term feeding trials did not cause disease. BSE prions also cause FSE in cats and variant Creutzfeldt-Jakob disease in humans.

Feline spongiform encephalopathy

FSE has been found in domesticated cats (housecats) and captive wild cats including cheetahs, pumas, ocelots, tigers, lions and Asian golden cats.

Transmissible mink encephalopathy

TME has been reported only in ranches; however, experimental infections can be established in other species. Raccoons are readily infected by oral as well as parenteral inoculation. Other species including striped skunks, ferrets, American sable (pine martens), beech martens, cattle, sheep, goats, hamsters and nonhuman primates (rhesus macaque, stump-tailed macaque, squirrel monkey) can be infected by intracerebral inoculation. Cattle, sheep, goats, hamsters, raccoons, striped skunks and squirrel monkeys are relatively easy to infect by this route, but the long incubation period in ferrets suggests that a species barrier exists. Nontransgenic mice are not susceptible to TME.

Chronic wasting disease

Chronic wasting disease affects cervids including mule deer, black-tailed deer, white-tailed deer and Rocky Mountain elk. Recently, infections have been described in both wild and experimentally infected moose. Other cervids such as red deer and reindeer/caribou may also be susceptible; the normal PrP^c proteins found in these animals are very similar to the proteins found in affected species. There is currently no evidence that CWD prions infect domesticated animals other than captive cervids. Many non-cervid species including cattle, sheep, goats, ferrets, mink, raccoons and squirrel monkeys have been infected, but only by direct intracerebral inoculation. Attempts to infect cattle by feeding prions have failed. CWD prions do not replicate readily in most laboratory rodents, although hamsters are susceptible to intracerebral inoculation to a limited degree.

Geographic Distribution

Scrapie

Scrapie can be found worldwide. This disease has been reported in Europe (including the United Kingdom), the Middle East, Japan, Canada, the United States, Kenya, South Africa, Colombia and parts of Asia. The scrapie status of many countries is not known because they have no surveillance for this disease. Australia and New Zealand have remained free of scrapie; although outbreaks occurred in these two countries, the disease was eradicated by slaughtering the imported sheep and their flockmates soon after they were released into the country.

The Nor98 form of scrapie was first reported from Norway in 1998. Since 2002, Nor98 and other atypical scrapie agents have been detected in a number of European countries. Nor98 was diagnosed for the first time in U.S. sheep in March 2007.

Bovine spongiform encephalopathy

Cases of BSE have been reported in indigenous cattle in most European countries, Canada, the U.S., Israel and Japan. This disease was seen in imported cattle in the Falkland Islands and Oman. Some countries including Iceland, Australia and New Zealand appear to be free of BSE; however, the presence or absence of this disease can only be determined in countries that have adequate surveillance programs.

Atypical BSE prions have recently been reported in Europe, the U.S. and Japan.

Feline spongiform encephalopathy

FSE has been found in countries where BSE occurs and in animals imported from these countries. Most cases have been seen in the United Kingdom. In addition, a few infected housecats have been found in Norway, Switzerland, Northern Ireland and Liechtenstein, and infected zoo cats have been reported from Australia, Ireland, France and Germany. Most of the cases in zoo animals occurred in cats that had lived in the U.K., but one cheetah had been born in France, and another is thought to have been infected in the Netherlands.

FSE has not been documented in the U.S., where only three cases of BSE have been reported in cattle as of 2008.

Transmissible mink encephalopathy

Several outbreaks of TME were reported in the United States between 1947 and 1985; no cases have been documented in the U.S. since that time. Many of the incidents occurred in Wisconsin, but ranches in Minnesota and Idaho were also affected during some years. TME has also been seen in ranch-raised mink in Canada, Finland, Germany and the former U.S.S.R.

Chronic wasting disease

Chronic wasting disease is endemic in the U.S. and Canada. This disease was originally reported only from a limited area encompassing northeastern Colorado,

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southwestern Nebraska, and southeastern Wyoming; however, recent surveillance suggests it is currently more widespread. CWD has been identified in at least 14 U.S. states and two Canadian provinces. As of 2008, this disease has been found in wild deer and elk populations extending from the original focus in Colorado and Wyoming east to New York and West Virginia, as well as in distinct foci in Utah and New Mexico. This infection has also been reported in captive cervid herds in a number of U.S. states. In some wild populations, CWD occurs in focal areas separated by long distances, and may be associated with transmission from captive herds, imported animals or game farms. In others, it seems to have been spread by the natural movement of wild cervids.

Chronic wasting disease was reported in imported deer and elk in Korea in 2001 and in the offspring of imported elk in 2004; no infections were reported in indigenous cervids. Limited surveillance in Europe has not revealed any evidence of this disease to date. Whether CWD has been imported to other countries is unknown.

Transmission

All TSEs are acquired primarily by ingestion. Prions occur mainly in the central nervous system (CNS), but some agents may also be found in lymphoid tissues or other organs. Animals become infected with the BSE or FSE agent when they eat contaminated tissues from infected animals. Scrapie and CWD can be spread horizontally between animals and/or acquired from the environment. Animals carry prions for life, and can transmit the agent even if they remain asymptomatic. Cooking or rendering an infected tissue does not make it safe to eat.

BSE was first reported in the 1980s, when it caused an explosive epidemic among U.K. cattle. The origins of this disease are unknown, but this epidemic occurred when prions were amplified by recycling tissues from infected cattle into ruminant feed supplements. Young animals may be particularly susceptible to infection; some studies suggest that most cattle become infected with BSE during the first six months of life. The risks of transmission from various bovine tissues are still incompletely understood; however, the highest prion concentrations occur in the brain, spinal cord, retina and ileum. In cattle, BSE prions can accumulate in the brain as early as 24 months after infection. Small quantities of the BSE agent have also been found in the dorsal root ganglia, trigeminal ganglion, thoracic ganglia, peripheral nerves, adrenal glands, tonsils and bone marrow, particularly in the late stages of disease. BSE has not been found in muscle; however, meat could become contaminated with CNS tissues during slaughter or processing. Epidemiological evidence and transmission studies suggest that BSE is not transmitted in milk, semen or embryos. There is little or no evidence that BSE is transmitted horizontally between cattle, but the offspring of infected animals have an increased risk of developing

this disease. The BSE prion appears to be transmitted to cats when they ingest contaminated bovine tissues. Horizontal transmission has not been reported between cats. FSE prions have been detected in the CNS and retina, and to some extent in the peripheral nerves, some lymphoid organs, kidney and adrenal gland.

Outbreaks of TME occur when mink ingest prions from contaminated tissues in their feed. Horizontal transmission by cannibalism or other means has not been ruled out, but seems to be rare. In at least one outbreak, kits sharing a cage with their dam did not become infected. TME prions have been reported in the mesenteric lymph node, spleen, thymus, kidney, liver, intestine and salivary gland of experimentally infected mink that had prions in the CNS. TME is not known to be transmitted vertically, and mink born during one outbreak had no signs of disease the following year.

Scrapie, in contrast, spreads between animals by contact. Most sheep become infected with scrapie prions from their dam. In genetically susceptible, infected ewes, scrapie prions may be found in the reproductive tract, including the placenta, during pregnancy. Vertical transmission might be possible *in utero*, but current evidence suggests that most animals become infected by licking or ingesting fetal membranes and fluids soon after birth. In confined lambing areas, the disease can also spread to the offspring of uninfected sheep. Uninfected adult ewes may be infected from this source, although they are more resistant. Transmission can also occur by direct contact between sheep. The scrapie agent has been detected in the nervous system, salivary glands, tonsils, lymph nodes, nictitating membrane, spleen, distal ileum, proximal colon and muscles. Contaminated fomites such as knives could theoretically spread scrapie prions, and some animals were infected by a contaminated vaccine. Transmission of scrapie has not been studied extensively in goats; however, most infected goats have a history of contact with sheep, and are probably infected by contact with the placenta or nasal secretions.

Chronic wasting disease is also spread horizontally. Horizontal transmission in cervids is linked to the presence of CWD prions in lymphoid tissues such as the tonsils. Elk, which have relatively small amounts of prions in these tissues, transmit CWD less efficiently than deer. In deer, CWD prions are known to occur in saliva and blood; they can be transmitted experimentally between animals by oral inoculation of saliva, as well as by blood transfusion. Whether CWD prions can be shed in milk, urine or feces is unknown. Prions have also been detected in the skeletal muscles of deer, and in heart muscle from white-tailed deer and elk. The occurrence of prions in blood suggests that no tissues from infected cervids should be considered prion-free. Vertical transmission of CWD may be possible, but it has not been documented, and does not seem to be a major route of spread.

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Some prions can persist for several years in the environment; CWD and possibly scrapie may be acquired from this source. Cases of CWD have been reported after exposure to infected carcasses left to decompose in pastures approximately two years earlier. Infectivity was also reported on pastures more than two years after deer with CWD were removed. The importance of environmental contamination is controversial for scrapie. A recent report suggests that the scrapie agent persisted in a sheep barn in Iceland for 16 years. This prion has also been isolated from an experimentally contaminated soil sample after three years. Environmental sources are unlikely for TME; this disease does not seem to recur during subsequent years on the same farm. Acquisition of BSE or FSE from the environment has not been reported.

Zoonotic transmission

In humans, variant Creutzfeldt-Jakob disease usually results from the ingestion of BSE prions, but iatrogenic routes of transmission are also possible. Probable human-to-human spread has been reported in several patients who received blood transfusions from asymptotically infected individuals. Other iatrogenic routes may be possible, including transmission in transplants or by contaminated equipment during surgeries. Person-to-person transmission does not occur during casual contact.

Incubation Period

All transmissible spongiform encephalopathies have incubation periods of months or years. The incubation period is 2 to 8 years for BSE in cattle and 2 to 5 years for scrapie in sheep. The incubation period for FSE in cheetahs is estimated to be 4.5 to 8 years. The incubation period in housecats has not been determined; however, all housecats with FSE have been at least two years old, and most were between the ages of four and nine years. The minimum incubation period for CWD is approximately 16 months, and the average incubation period is probably 2 to 4 years. The incubation period for TME in ranched mink is 6 to 12 months.

Clinical Signs

Transmissible spongiform encephalopathies are usually insidious in onset and tend to progress slowly. In most of these diseases, the clinical signs primarily involve the nervous system; however, in CWD, wasting is also a prominent sign. Once an animal becomes symptomatic, these diseases are relentlessly progressive and fatal.

Scrapie

The signs of scrapie are variable in sheep, and can be influenced by the strain of the prion and the animal's genotype and/or breed. The first signs are usually behavioral: affected sheep tend to stand apart from the flock and may either trail or lead when the flock is driven. As the disease progresses, animals usually become hyperexcitable and have a high-stepping or unusual hopping gait and/or a fixed stare, with the head held high.

Other clinical signs may include ataxia, incoordination, blindness, trembling or convulsions when being handled. Intense pruritus is common and may lead to rubbing, scraping or chewing. Scratching of the dorsum or pressure over the base of the tail may cause a characteristic nibbling response due to pruritus. Loss of condition is common in the early stages, and significant weight loss or emaciation may be seen late. The fleece may be dry and brittle. Drinking behavior and urination can also change, with affected animals drinking small quantities of water often. Most animals die 2 to 6 weeks after the onset of symptoms, but deaths may occur up to six months later.

In sheep with the Nor98 variant, incoordination and ataxia appear to be major symptoms. Pruritus seems to be minimal or uncommon, although it has been seen in some animals. Loss of body condition, anxiety, tremors, abnormal menace responses and/or a subdued mental status have been reported in some cases, but not others. Some cases of atypical scrapie have been found by routine surveillance in apparently healthy flocks at slaughter.

Variable clinical signs have been reported in goats with scrapie. In one case, the only symptoms were listlessness, weight loss and premature cessation of lactation. The signs may also resemble scrapie in sheep, with behavioral changes such as irritability and loss of inquisitiveness, as well as hyperesthesia, incoordination, posture abnormalities, unusual alertness, restlessness, tremors, teeth grinding, salivation, impaired vision or regurgitation of rumen contents. Some goats have been reported to stamp and hold their heads down as if they are bothered by nonexistent flies. In late stages, animals may appear drowsy and have difficulty rising. Pruritus is less common in goats than in sheep; if it occurs, it is typically less intense and often localized over the tailhead or withers. As in sheep, the disease is progressive, with prostration and death 1-6 months after the onset of the first signs.

Bovine spongiform encephalopathy

The signs of BSE are usually insidious, and may include gait abnormalities (particularly hindlimb ataxia), hyperresponsiveness to stimuli, tremors, and behavioral changes such as aggression, nervousness or apprehension, changes in temperament and even frenzy. The combination of behavioral changes, hyperreactivity to stimuli and gait abnormalities is highly suggestive of BSE, but some animals exhibit only one category of neurological signs. Pacing, a modified gait in which the legs move in lateral pairs, occurred in 25% of the cattle with BSE in one study, and may be suggestive of this disease. Intense pruritus is not usually seen, but some animals may lick or rub persistently. Nonspecific signs include loss of condition, weight loss, teeth grinding (possibly due to visceral pain or neurological disease) and decreased milk production. Decreased rumination, bradycardia and altered heart rhythms have also been reported. The clinical signs usually worsen gradually over a few weeks to six months, but rare cases can develop

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acutely and progress rapidly. Rapid, acute-onset neurological disease seems to be particularly common in exotic ruminants in zoos. The final stages are characterized by recumbency, coma and death.

Little is known about the features of atypical BSE in cattle. Although neurological disease has been reported, very few cases have had the classical combination of behavioral disturbances, sensory signs and gait abnormalities. Some atypical strains have been found in asymptomatic cattle during routine surveillance.

Various neurological signs have been reported in experimentally infected sheep. In one study, Cheviot sheep mainly developed ataxia with minimal pruritus, and died in a few days to a week. In indigenous French breeds, the clinical signs included ataxia and intense pruritus with loss of fleece. These animals deteriorated slowly and died in approximately three months. The only known BSE cases in naturally infected goats were discovered during routine surveillance at slaughter.

Feline spongiform encephalopathy

In housecats with FSE, the first signs are usually behavioral changes such as uncharacteristic aggression, or unusual timidity and hiding. Gait abnormalities and ataxia are also characteristic; these defects initially affect the hindlegs. Affected cats often display poor judgment of distance. Some cats develop a rapid, crouching, hypermetric gait. Hyperesthesia is common, particularly when cats are stimulated by sound or touch. Some cats may have an abnormal head tilt, develop tremors, stare vacantly or circle. Excessive salivation, decreased grooming, polyphagia, polydipsia and dilated pupils have also been reported. In the late stages of the disease, somnolence is common and convulsions may occur. Similar clinical signs have been reported in zoo cats. Death occurs after 3 to 8 weeks in housecats, and 8 to 10 weeks in cheetahs.

Transmissible mink encephalopathy

The early clinical signs of TME can be subtle, and may include difficulty eating and swallowing, and changes in normal grooming behavior. Affected mink often soil the nest or scatter feces in the cage. Later, animals may become hyperexcitable and bite compulsively. Affected mink often carry their tails arched over their backs like squirrels. Incoordination, circling, clenching of the jaw, and self-mutilation (particularly of the tail) may also be seen. When death is imminent, mink tend to become somnolent and unresponsive; convulsions can occur but are not common. Once the clinical signs appear, TME is always progressive and fatal. Death usually occurs within 2 to 8 weeks.

In one experiment, mink inoculated orally with the classical BSE agent developed a fatal neurological disease that resembled TME; however, the animals tended to become unusually docile rather than aggressive.

Raccoons that are experimentally inoculated with TME prions develop neurologic signs including lethargy,

abnormal responses to external stimuli, altered behavior and incoordination.

Chronic wasting disease

Some deer with subclinical or early clinical CWD may die suddenly after handling; however, cervids typically have progressive weight loss, lassitude and behavioral changes that progress over several weeks to months, with many animals becoming severely emaciated before they die. Ataxia, head tremors, teeth grinding, repetitive walking of the enclosure's perimeter, hyperexcitability when handled, or other neurologic signs may be seen; neurologic signs and behavioral changes are sometimes subtle, particularly in elk. In some animals, difficulty swallowing may lead to excessive salivation. Esophageal dilation and regurgitation, as well as aspiration pneumonia, have also been reported. Affected animals may carry their head low and have a fixed gaze, particularly in the late stages of disease; this can alternate with more normal alertness. Other late signs include polydipsia/ polyuria and syncope. Pruritus has not been reported in cervids; however, the coat may be rough and dry, with patchy retention of the winter coat in summer. Most affected animals die within a few months, although a few may live for up to a year or more. Occasionally, the disease can last only a few days, particularly in elk. Whether moose become ill is unknown.

Post Mortem Lesions [Click to view images](#)

There are no pathognomonic gross lesions for TSEs, although non-specific lesions may be seen. Wasting of the carcass is very common in cervids with CWD. This disease can also result in a rough, dry coat, patchy retention of the winter coat in summer, megaesophagus and aspiration bronchopneumonia. The rumen contents are often watery, and may be frothy or contain increased amounts of sand and gravel. Abomasal or omasal ulcers can be found in some cervids. The urine is often dilute in animals that had access to water, but some wild cervids are dehydrated. Some carcasses may be in good condition, particularly in the early stages of the disease. Weight loss, loss of condition, or emaciation can also be seen in other TSEs.

The typical histopathologic lesions are confined to the CNS. TSE lesions are usually but not always bilaterally symmetrical. Neuronal vacuolation and non-inflammatory spongiform changes in the gray matter are pathognomonic. Astrocytosis can be seen in the CNS of animals with scrapie, CWD or TME, but not BSE. Amyloid plaques occur in scrapie, but are not found in TME or FSE. Although such plaques are not typical of classical BSE, they can be detected in animals with atypical L-form BSE. In cervids, the presence of amyloid plaques varies with the species: these lesions are fairly common in deer, but immunohistochemical staining is necessary to demonstrate the presence of amyloid in elk.

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Morbidity and Mortality

TSEs are diseases of adult animals. BSE is seen most often in 4 to 5-year-old cattle, particularly dairy animals. Most cases of CWD in captive cervids occur between the ages of two and seven years. Scrapie is rare in sheep less than a year old, and CWD has not been reported in cervids less than 16 months of age.

The animal's genotype influences the onset and severity of some TSEs. This is particularly well-known in sheep, where susceptibility or resistance to the classical form of scrapie is associated with polymorphisms in the PrP gene at codons 136, 154 and 171. Sheep with the ARR/ARR genotype at these locations are highly or completely resistant to classical scrapie, while sheep with the VRQ/VRQ genotypes are most susceptible. The remaining genotypes are intermediate in susceptibility. Sheep with resistant genotypes develop clinical disease after longer incubation periods, or not at all. The genotype also influences transmission in sheep. A genetically resistant fetus suppresses the appearance of prions in the placenta of an infected, scrapie-susceptible ewe. Ewes with resistant genotypes do not produce scrapie-positive placentas, regardless of the genotype of the fetus. Atypical scrapie is also influenced by the genotype; however, it can occur in sheep resistant to classical scrapie. Genotype may affect scrapie susceptibility in goats, but its influence is poorly understood. Genetics may also have some influence on susceptibility and/or the length of the incubation period in CWD, but no cervid genotype seems to be completely resistant to this disease.

The case fatality rate for all TSEs is 100%; the disease is always fatal in an individual animal once the clinical signs appear. The flock or herd mortality rate for the contagious TSEs (scrapie and CWD) varies. Typically, the annual mortality rate for scrapie in an affected flock is 3 to 5%; however, up to 20% of the animals in severely affected flocks may die each year. In newly infected herds of farmed cervids, the prevalence of CWD can be less than 1%. However, once this disease has become established, 50% of the herd or more often becomes infected, and in some cases, the incidence may be as high as 100%. Generally only one cervid in a herd shows signs of CWD at any time. The herd mortality rates for other TSEs, which are transmitted by prions in the feed, vary with exposure. In countries with severe BSE epidemics, multiple cattle are often affected in a herd. During the height of the epidemic in the U.K., the annual incidence of BSE in affected herds was approximately 2-3%. In mildly affected countries, this disease can be sporadic, with only single cases detected in a herd. TME is the rarest of the TSEs, and has only been seen in ranched mink. In the U.S., outbreaks of this disease (affecting one to several ranches) were reported in 1947, 1961, 1963 and 1985. Up to 60-90% of the mink on a ranch may die; in one outbreak, the mortality rate in adult mink was 100%.

How frequently a TSE occurs in the population varies with the country, species and disease. The prevalence of scrapie is low in U.S. sheep: in 2002-2003, slaughter surveillance estimated the overall prevalence as 0.20% in mature sheep, with most cases occurring in black-faced sheep. Scrapie is rare in goats; only sporadic cases have been reported worldwide. The prevalence of CWD in wild deer and elk varies. In some states, this disease is absent or occurs in less than 0.1% of wild deer; in others, it can be much higher, with local "hot spots" as high as 30%. CWD is less common in wild elk than deer, and the prevalence in this species is usually less than 1%. The incidence in moose is unknown; however, moose tend to be solitary, which reduces the risk of transmission, and CWD is probably rare. More than 97% of cases found during the surveillance of wild deer and elk are subclinical.

BSE epidemics have been reported in several European countries. The first outbreak occurred in the U.K., where more than 180,000 cases have been confirmed since the 1980s. The U.K. epidemic peaked in 1992, with nearly 1,000 new cases confirmed each week. As a result of control measures (particularly feed bans), the incidence declined to approximately 5-10 new cases per week in 2004. The peak of the epidemic curve occurred later in countries where feed bans were established more recently. Only three cases of BSE have been reported in the U.S. One case occurred in an animal imported from Canada. Two others were reported in indigenous cattle; one was caused by the H-form of atypical BSE. Little is currently known about the incidence of atypical BSE in cattle. The number of FSE cases in cats has paralleled BSE outbreaks in cattle, and has declined as BSE has been controlled. As of October 2008, nearly a hundred cases of FSE have been diagnosed in housecats worldwide, the majority in the UK. Twenty-two cases of FSE have been confirmed in zoo cats, with the most recent case in 2007.

Diagnosis

Clinical

TSEs should be suspected in animals that develop slowly progressive, fatal neurologic diseases. A combination of behavioral changes, hyperreactivity to stimuli and gait abnormalities is highly suggestive of BSE in cattle; however, this classical combination does not occur in all animals. Behavioral changes and ataxia are the most common symptoms in cats with FSE. Pruritus strengthens the diagnosis of scrapie in sheep and goats, but the absence of pruritus does not rule it out. BSE may also be a possibility in sheep and goats with neurologic signs. Chronic wasting disease should be suspected in cervids over the age of 16 months that have weight loss or chronic wasting, unusual behavior, neurologic signs, excessive salivation, polyuria/polydipsia, signs of aspiration pneumonia and/or unusual retention of the winter coat.

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Differential diagnosis

Other neurologic diseases caused by bacterial, viral or parasitic infections, as well as nutritional diseases, toxicities, neoplasia and trauma must be ruled out. The specific differentials vary with the species.

Laboratory tests

TSEs are usually diagnosed by detecting prions in the CNS and/or other tissues. Accumulations of prions can be found in unfixed tissues by immunoblotting (Western blotting), and in fixed tissues by immunohistochemistry. Several rapid diagnostic tests based on enzyme-linked immunosorbent assays (ELISAs) or automated immunoblotting are available for BSE, scrapie and CWD. Rapid tests allow large numbers of samples to be screened, and are often used in surveillance and slaughter testing. Positive samples in rapid tests are confirmed with more specific assays such as immunohistochemistry or immunoblotting. BSE or scrapie may also be diagnosed by finding prion fibrils called scrapie-associated fibrils (SAF) with electron microscopy in brain extracts; however, this test has low sensitivity. Some diagnostic tests may not detect atypical BSE or scrapie prions.

Histological examination of the brain is also helpful in diagnosis, but some animals in the early stages have few or no spongiform changes. Animal inoculation may be used to detect prions in special circumstances, but this technique is lengthy and labor intensive, and it is rarely used. Serology is not useful for diagnosis, as antibodies are not made against prions.

Samples to collect

Before collecting or sending any samples from animals with a suspected foreign animal disease, the proper authorities should be contacted. Samples should only be sent under secure conditions and to authorized laboratories to prevent the spread of the disease. A fatal human encephalopathy has been linked to BSE; samples should be collected and handled with all appropriate precautions. There is currently no indication that other TSEs are zoonotic; however, caution should still be used with all prion-contaminated tissues.

TSEs are usually diagnosed after the animal's death. During necropsy, a standard neuropathologic approach should be followed to rule out other causes of disease. Brain samples should be taken as soon as possible after death; both unfixed (fresh) and formalin-fixed tissues should be collected. In some animals, the entire head may be sent. Where a disease is endemic, surveillance is sometimes conducted using hindbrain samples taken via the foramen magnum.

Extraneural tissues are also collected in some species. In sheep, samples from the spleen and a variety of lymph nodes should be sent to the laboratory unpreserved. In deer, prions can usually be found in the tonsils and retropharyngeal lymph nodes before they accumulate in

the brain and before clinical signs appear. Both lymphoid tissue and brain (obex) samples should be tested in elk. Approximately 10-15% of elk that have prions in the brain do not have prions in the lymphoid tissues; this occurs in less than 1% of deer. In experimentally infected mink, prions have been found in the salivary gland, intestine, mesenteric lymph node, spleen, thymus, kidney and liver, but only after prions were detected in the brain. Fresh tissues should be kept cold and sent to the laboratory as soon as possible on wet ice or gel packs. Fixed samples should not be frozen.

Live animal tests are available only for scrapie and chronic wasting disease. In classical scrapie, prions can sometimes be found in peripheral lymphoid tissues before they appear in the brain, but this is not consistent. The third eyelid test is used to diagnose scrapie in some countries, including the U.S. This test detects prions in the nictitating membrane by immunohistochemistry. Similar tests are done using tonsil biopsies in some countries. The detection of prions in the placenta may be helpful for disease surveillance in some sheep flocks. Chronic wasting disease can be diagnosed in live animals, particularly deer, with tonsil biopsies. Lymphoid biopsies are less useful in elk, which have only small amounts of prions in these tissues. Antemortem tests do not detect prions in all infected animals. The need for anesthesia and invasive procedures also limits the usefulness of these tests.

Techniques to detect prions are relatively insensitive compared to assays for other types of pathogens; for example, BSE prions cannot usually be detected in the brain until 3 to 6 months before the onset of disease.

Recommended actions if a transmissible spongiform encephalopathy is suspected

Notification of authorities

Most TSEs are reportable diseases in the U.S. BSE, FSE and TME must be reported immediately. Scrapie is also reportable. The U.S. has a scrapie eradication program, with the goal of disease eradication by 2010, as well as a flock certification program. Chronic wasting disease is a reportable disease in many states. All deaths must be reported in farmed cervid herds participating in the U.S. herd certification program, and samples must be submitted from these animals by a CWD-certified veterinarian or other authorized individual.

Federal: Area Veterinarians in Charge (AVIC):

http://www.aphis.usda.gov/animal_health/area_offices/

State Veterinarians:

<http://www.aphis.usda.gov/vs/sregs/official.html>

Control

There is no vaccine or treatment for any transmissible spongiform encephalopathy. BSE, FSE and TME can be prevented by not feeding tissues that may contain prions

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to susceptible species. Complete avoidance is necessary, as cooking or rendering cannot completely inactivate these agents. Banning ruminant (or mammalian) tissues from ruminant feed has significantly reduced the number of new cases of BSE and controlled epidemics in cattle. Surveillance and tracing of BSE-infected animals also reduces the incidence of disease. Countries may place trade bans on the importation of live animals and certain ruminant proteins from BSE-affected nations.

Diseases that can be spread horizontally, such as scrapie and CWD, require additional methods of control. The risk of introducing these diseases can be reduced by maintaining a closed herd/ flock or minimizing outside purchases of stock. If replacement animals must be added, they should be from herds that are known to be uninfected. Animals in scrapie- or CWD-certified herds are tested periodically for the disease. If it is found, the herd is quarantined, and a herd plan is developed. In some cases, the herd is depopulated. Genotyping is often used to reduce the incidence of the classical form of scrapie. Genetically susceptible sheep are removed from infected flocks, and genetically resistant breeding stock are selected. In particular, the use of resistant rams can decrease or eliminate the shedding of prions from genetically susceptible, infected ewes when they give birth. In addition, the fetal membranes and placenta should be removed immediately after sheep have lambed, and the bedding should be changed between parturitions.

Controlling CWD in wild cervids is very difficult. Some states have culled their herds to reduce the population density and decrease the spread of disease. Culling programs might be able to eradicate CWD from a limited area if it was introduced recently. Infected captive cervids should be kept from contact with wild cervids. Many states and provinces have restrictions on the transportation of tissues from hunter-killed cervids in CWD-endemic areas.

Decontamination of prion-contaminated tissues, surfaces and environments is difficult. These agents are highly resistant to most disinfectants (including formalin), heat, ultraviolet radiation and ionizing radiation, particularly when they are protected in organic material or preserved with aldehyde fixatives, or when the prion titer is high. Prions can bind tightly to some surfaces, including stainless steel and plastic, without losing infectivity. Prions bound to metal seem to be highly resistant to decontamination. Few effective decontamination techniques have been published. A 1-2 N sodium hydroxide solution, or a sodium hypochlorite solution containing 2% available chlorine, has traditionally been recommended for equipment and surfaces. Surfaces should be treated for more than 1 hour at 20°C (68°F). Overnight disinfection is recommended for equipment. Cleaning before disinfection removes organic material that may protect prions. Recently, milder treatments including a phenolic disinfectant, an alkaline cleaner (KOH with detergents), and an enzymatic cleaner

combined with vaporized hydrogen peroxide have been shown to inactivate scrapie prions. The alkaline cleaner and phenolic disinfectant were also demonstrated to be effective against BSE prions. These disinfectants may be useful for items that cannot withstand harsher decontamination procedures. Physical inactivation of prions can be carried out by porous load autoclaving at 134-138°C (273-280°F) for 18 minutes at 30 lb/in². Autoclaving items in water is more effective than autoclaving without immersion. Dry heat is less effective; hamster-adapted scrapie prions can survive dry heat at temperatures as high as 360°C (680°F) for an hour. A combination of chemical and physical decontamination can be more effective than either procedure alone; chemical disinfection should be carried out first, then the items should be rinsed and autoclaved. Anecdotal evidence suggests that decontamination of contaminated facilities is very difficult. Even the harshest combination of chemical and physical disinfection is not guaranteed to destroy all prions.

Because prions may be able to survive in the environment for years and are difficult to disinfect, precautions should be taken to avoid contamination of surfaces and equipment during necropsies. Disposable plastic-coated paper sheets can be used to protect tables and other surfaces. Disposable instruments and work clothing can also be used.

Prevention of zoonotic prions in food

Precautions must be taken to prevent zoonotic and potentially zoonotic prions from entering the food supply for humans. Tissues that have a high risk of transmitting BSE have been banned from human food in many countries. Slaughter and processing techniques that have a high risk of contaminating muscle tissues with CNS are also prohibited. Surveillance can help prevent infected animals from being used in food. Some nations conduct active surveillance of cattle at slaughter (using rapid tests) to detect cases of BSE; positive carcasses are destroyed. Other countries with a low incidence of disease, including the U.S., test only a percentage of cattle at slaughter. In the U.S., surveillance is targeted particularly at high-risk cattle such as nonambulatory animals and those with neurological disease.

Precautions should also be taken with CWD, although no human infections have been reported. The CWD prion occurs in meat and blood, and infected carcasses should never be eaten. Hunters should consider having carcasses tested for CWD; information on this program is available from most state wildlife agencies. Gloves should be worn when field-dressing a cervid carcass. Boning-out the meat and minimizing the handling of the brain, spinal cord and lymphoid tissues associated with the gastrointestinal tract (e.g. tonsils) from cervids may reduce the risk of exposure, but will not necessarily remove all prions.

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Public Health

BSE is the only prion disease known to be zoonotic; people who have eaten BSE prions may develop variant Creutzfeldt-Jakob disease. The prevalence of this disease is unknown. Most cases have been seen in people who lived in the U.K. during the peak of the BSE epidemic. As of October 2008, 167 cases of probable or confirmed vCJD, including 164 deaths from this disease, have been reported in the U.K. The incidence peaked in 2000, when 28 cases were diagnosed, and gradually fell to five cases per year in 2005 and 2006. As of June 2008, an additional 23 cases had been reported from France, as well as four from Ireland, three each from the United States and Spain, and two from the Netherlands and Portugal. Canada, Italy, Japan and Saudi Arabia have each reported one case. To date, all cases of vCJD in the U.S. seem to have been acquired in other countries. The number of people who are infected but asymptomatic is unknown.

The symptoms of vCJD are broadly similar to the sporadic (genetic) form of Creutzfeldt-Jakob disease, but usually appear in younger patients. The median age of onset is 26 years for vCJD (range 12–74 years), and 65 years (range 15–94 years) for sporadic CJD. In vCJD, the first signs are usually psychiatric symptoms such as anxiety, depression, insomnia and social withdrawal, and/or persistent painful sensory symptoms. In most patients, frank neurological signs such as gait disturbances, ataxia, incoordination, memory loss, slurring of speech and tremor appear a few months later; however, neurological signs coincide with or precede psychiatric symptoms in a minority of patients. Cognitive function gradually deteriorates. Chorea, dystonia, myoclonus, visual disturbances and dementia typically develop late in the course of disease. Most patients die in six months to two years. Only supportive treatment is available.

Prevention is based on the avoidance of high-risk tissues from cattle, particularly the CNS and ileum. Whether tissues with lower levels of prions are also infectious is unknown, but no tissues from known cases of BSE should be eaten. Person-to-person transmission can be reduced by the use of disposable surgical instruments in high-risk surgeries and other procedures. Transmission in blood cannot be completely prevented with current techniques; however, many countries do not allow people who have spent time in the U.K. and/or other European countries to be blood donors. Other measures, such as universal leucodepletion of blood, have also been taken in some countries. In animal studies, blood cells carried a higher risk of transmission than plasma.

Although laboratory or abattoir-related cases have not been reported, veterinarians and laboratory workers should always take precautions when conducting necropsies on BSE-suspects or handling tissues; BSL-3 is the recommended level of protection. Standard precautions include the use of protective clothing and the avoidance of penetrating injuries, contamination of abraded skin, and ingestion. A negative pressure laminar

flow hood should be used for tissue manipulations whenever possible. Because prions may be able to survive in the environment for years and are difficult to disinfect, precautions should be taken to avoid contamination of surfaces and equipment. No vaccine is available.

There is no evidence that any prion other than BSE can be transmitted to humans; however, because FSE is caused by BSE prions, and TME might be related to a variant of BSE, caution should be used when performing necropsies or working with tissues (particularly the CNS) from animals infected with these diseases. Spongiform encephalopathies were reported simultaneously in a cat and its owner in 1998; however, the man was found to have the sporadic form of Creutzfeldt-Jakob disease, rather than vCJD, and the disease in the cat differed clinically from FSE. The prions isolated from both man and cat appeared to be similar, but differed from the BSE prion. It is not known whether these prions might have been transmitted between the man and the cat, whether both contracted the disease from a common source, or if the incident was due to chance. No other infections with this prion have been reported in cats.

Whether people are susceptible to CWD is not known. As of 2008, surveillance, investigation of suspicious cases of neurologic disease in humans and epidemiological studies have found no evidence that this disease is zoonotic. Molecular compatibility studies suggest that there is a significant species barrier and the CWD prion is not well adapted to infect humans. Nevertheless, the possibility that CWD could be zoonotic cannot be ruled out at this time. Meat, lymphoid tissues and CNS could contain this agent. Because prions can also occur in the blood and saliva of deer, no tissues from CWD infected cervids should be considered safe to eat.

It is very unlikely that scrapie is zoonotic: this disease has been known since early in the 18th century, and no human case has ever been reported.

Internet Resources

Canadian Food Inspection Agency (CFIA). BSE
<http://www.inspection.gc.ca/english/anima/heasan/disemala/bseesb/bseesbindexe.shtml>

CFIA. Chronic Wasting Disease of Deer and Elk (including information on the herd certification program)
<http://www.inspection.gc.ca/english/anima/heasan/disemala/cwdmdc/cwdmdce.shtml>

Centers for Disease Control and Prevention (CDC). Prion Diseases.
<http://www.cdc.gov/ncidod/dvrd/prions/index.htm>

Chronic Wasting Disease Alliance
<http://www.cwd-info.org/>

European Commission. BSE / Scrapie
http://ec.europa.eu/food/food/biosafety/bse/index_en.htm

Manual for the Recognition of Exotic Diseases of Livestock
<http://www.spc.int/rahs/>

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- The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>
- The National Creutzfeldt-Jakob Disease Surveillance Unit,
United Kingdom.
<http://www.cjd.ed.ac.uk/index.htm>
- United Kingdom. Department for Environment Food and
Rural Affairs (DEFRA). Bovine Spongiform
Encephalopathy
<http://www.defra.gov.uk/animalh/bse/index.html>
- DEFRA. Other TSEs
<http://www.defra.gov.uk/animalh/bse/othertses/index.html>
- United States Department of Agriculture (USDA),
Animal and Plant Health Inspection Service (APHIS).
<http://www.aphis.usda.gov/>
- USDA APHIS. Bovine Spongiform Encephalopathy
http://www.aphis.usda.gov/newsroom/hot_issues/bse/index.shtml
- USDA APHIS. Chronic Wasting Disease (including
information on the CWD Certified and Monitored
Herd Programs).
http://www.aphis.usda.gov/animal_health/animal_diseases/cwd/
- USDA APHIS. Scrapie Program
http://www.aphis.usda.gov/animal_health/animal_diseases/scrapie/
- USDA APHIS. Transmissible Mink Encephalopathy.
http://www.aphis.usda.gov/lpa/pubs/fsheet_faq_notice/fs_a.html
- USDA Foreign Agricultural Service. Bovine Spongiform
Encephalopathy
<http://www.fas.usda.gov/DLP/BSE/bse.html>
- United States Food and Drug Administration. Bovine
Spongiform Encephalopathy
<http://www.fda.gov/oc/opacom/hottopics/bse.html>
- U.S. Geological Survey. Chronic Wasting Disease
http://www.nwhc.usgs.gov/disease_information/chronic_wasting_disease/index.jsp
- World Health Organization. Bovine Spongiform
Encephalopathy
<http://www.who.int/mediacentre/factsheets/fs113/en/>
- World Organization for Animal Health (OIE)
<http://www.oie.int>
- OIE Manual of Diagnostic Tests and Vaccines for
Terrestrial Animals
http://www.oie.int/eng/normes/mmanual/a_summry.htm
- OIE Terrestrial Animal Health Code
http://www.oie.int/eng/normes/mcode/A_summry.htm
- Alverson J, O'Rourke KI, Baszler TV. PrPSc accumulation
in fetal cotyledons of scrapie-resistant lambs is
influenced by fetus location in the uterus. *J Gen Virol.*
2006;87:1035-41.
- Anderson CA, Bosque P, Filley CM, Arciniegas DB,
Kleinschmidt-Demasters BK, Pape WJ, Tyler KL.
Colorado surveillance program for chronic wasting
disease transmission to humans: lessons from 2 highly
suspectious but negative cases. *Arch Neurol.*
2007;64:439-41.
- Andreoletti O, Lacroux C, Chabert A, MonnerEAU L,
Tabouret G, Lantier F, Berthon P, Eychenne F, Lafond-
Benestad S, Elsen JM, Schelcher F. PrP(Sc) accumulation
in placentas of ewes exposed to natural scrapie: influence
of foetal PrP genotype and effect on ewe-to-lamb
transmission. *J Gen Virol.* 2002;83:2607-16.
- Andreoletti O, Morel N, Lacroux C, Rouillon V, Barc C,
Tabouret G, Sarradin P, Berthon P, Bernardet P, Mathey
J, LugaN S, Costes P, Corbière F, Espinosa JC, Torres
JM, Grassi J, Schelcher F, Lantier F. Bovine spongiform
encephalopathy agent in spleen from an ARR/ARR
orally exposed sheep. *J Gen Virol.* 2006;87:1043-1046.
- Andreoletti O, Simon S, Lacroux C, Morel N, Tabouret G,
Chabert A, LugaN S, Corbiere F, Ferre P, Foucras G,
Laude H, Eychenne F, Grassi J, Schelcher F. PrPSc
accumulation in myocytes from sheep incubating natural
scrapie. *Nat Med.* 2004;10:591-3.
- Animal Health Australia. The National Animal Health
Information System (NAHIS). Bovine spongiform
encephalopathy [online]. Available at:
http://www.brs.gov.au/usr-bin/aphb/ahsq?dislist=alpha.*
Accessed 7 Nov 2001.
- Animal Health Australia. The National Animal Health
Information System (NAHIS). Scrapie [online].
Available at: http://www.aahc.com.au/nahis/disease/dislist.asp.* Accessed 7 Nov
2001.
- Angers RC, Browning SR, Seward TS, Sigurdson CJ, Miller
MW, Hoover EA, Telling GC. Prions in skeletal muscles
of deer with chronic wasting disease. *Science.*
2006;311:1117.
- Arnold ME, Wilesmith JW. Estimation of the age-dependent
risk of infection to BSE of dairy cattle in Great Britain.
Prev Vet Med. 2004;66:35-47.
- Arsac JN, Andreoletti O, Billeude JM, Lacroux C, Benestad
SL, Baron T. Similar biochemical signatures and prion
protein genotypes in atypical scrapie and Nor98 cases,
France and Norway. *Emerg Infect Dis.* 2007;13:58-65.
- Baeten LA, Powers BE, Jewell JE, Spraker TR, Miller MW.
A natural case of chronic wasting disease in a free-
ranging moose (*Alces alces shirasi*). *J Wildl Dis.*
2007;43:309-14.
- Balter M. Intriguing clues to a scrapie-mad cow link.
Science. 2001;292:827-829.

References

- Aguzzi A, Heikenwalder M, Miele G. Progress and
problems in the biology, diagnostics, and therapeutics of
prion diseases. *J Clin Invest.* 2004;114:153-160.

Transmissible Spongiform Encephalopathies

- Barlow RM. Transmissible mink encephalopathy: pathogenesis and nature of the aetiological agent. *J Clin Pathol Suppl (R Coll Pathol)*. 1972;6:102-9.
- Baron T, Belli P, Madec JY, Moutou F, Vitaud C, Savey M. Spongiform encephalopathy in an imported cheetah in France. *Vet Rec*. 1997;141:270-271.
- Baron T, Bencsik A, Biacabe AG, Morignat E, Bessen RA. Phenotypic similarity of transmissible mink encephalopathy in cattle and L-type bovine spongiform encephalopathy in a mouse model. *Emerg Infect Dis*. 2007;13:1887-94.
- Baron T, Biacabe AG, Arsac JN, Benestad S, Groschup MH. Atypical transmissible spongiform encephalopathies (TSEs) in ruminants. *Vaccine*. 2007;25:5625-5630.
- Bartz JC, Kincaid AE, Bessen RA. Rapid prion neuroinvasion following tongue infection. *J Virol*. 2003;77:583-91.
- Bartz JC, McKenzie DI, Bessen RA, Marsh RF, Aiken JM. Transmissible mink encephalopathy species barrier effect between ferret and mink: PrP gene and protein analysis. *J Gen Virol*. 1994;75:2947-53.
- Beekes M, McBride PA. The spread of prions through the body in naturally acquired transmissible spongiform encephalopathies. *FEBS J*. 2007;274:588-605.
- Belay ED, Maddox RA, Williams ES, Miller MW, Gambetti P, Schonberger LB. Chronic wasting disease and potential transmission to humans. *Emerg Infect Dis*. 2004;10:977-84.
- Bellworthy SJ, Dexter G, Stack M, Chaplin M, Hawkins SA, Simmons MM, Jeffrey M, Martin S, Gonzalez L, Hill P. Natural transmission of BSE between sheep within an experimental flock. *Vet Rec*. 2005;157:206.
- Benestad SL, Sarradin P, Thu B, Schonheit J, Tranulis MA, Bratberg B. Cases of scrapie with unusual features in Norway and designation of a new type, Nor98. *Vet Rec*. 2003;153:202-8.
- Béringue V, Andréoletti O, Le Dur A, Essalmani R, Vilotte JL, Lacroux C, Reine F, Herzog L, Biacabé AG, Baron T, Caramelli M, Casalone C, Laude H. A bovine prion acquires an epidemic bovine spongiform encephalopathy strain-like phenotype on interspecies transmission. *J Neurosci*. 2007;27:6965-6971.
- Bessen RA, Marsh RF. Biochemical and physical properties of the prion protein from two strains of the transmissible mink encephalopathy agent. *J Virol*. 1992;66:2096-101.
- Bradshaw JM, Pearson GR, Gruffydd-Jones TJ. A retrospective study of 286 cases of neurological disorders of the cat. *J Comp Pathol*. 2004;131:112-20.
- Braun U, Gerspach C, Ryhner T, Hauri S. Pacing as a clinical sign in cattle with bovine spongiform encephalopathy. *Vet Rec*. 2004;155:420-422.
- Brown P, Abee CR. Working with transmissible spongiform encephalopathy agents. *ILAR J*. 2005;46:44-52.
- Brown P, Gajdusek DC. Survival of scrapie virus after 3 years' interment. *Lancet*. 1991;337:269-70.
- Brown P, McShane LM, Zanusso G, Detwile L. On the question of sporadic or atypical bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. *Emerg Infect Dis*. 2006;12:1816-1821.
- Buschmann A, Biacabe AG, Ziegler U, Bencsik A, Madec JY, Erhardt G, Luhken G, Baron T, Groschup MH. Atypical scrapie cases in Germany and France are identified by discrepant reaction patterns in BSE rapid tests. *J Virol Methods*. 2004;117:27-36.
- Buschmann A, Luhken G, Schultz J, Erhardt G, Groschup MH. Neuronal accumulation of abnormal prion protein in sheep carrying a scrapie-resistant genotype (PrPARR/ARR). *J Gen Virol*. 2004;85:2727-33.
- Carmona P, Monzon M, Monleon E, Badiola JJ, Monreal J. *In vivo* detection of scrapie cases from blood by infrared spectroscopy. *J Gen Virol*. 2005;86:3425-31.
- Centers for Disease Control and Prevention (CDC). Chronic wasting disease [online]. CDC; 2007 Jan. Available at: <http://www.cdc.gov/ncidod/dvrd/cwd/>. Accessed 19 Sept. 2008.
- Centers for Disease Control and Prevention [CDC]. Fact sheet: Variant Creutzfeldt-Jakob disease [online]. CDC; 2007 Jan. Available at: http://www.cdc.gov/ncidod/dvrd/vcjd/factsheet_nvcjd.htm. Accessed 20 Aug 2007.
- Chang B, Cheng X, Yin S, Pan T, Zhang H, Wong P, Kang SC, Xiao F, Yan H, Li C, Wolfe LL, Miller MW, Wisniewski T, Greene MI, Sy MS. Test for detection of disease-associated prion aggregate in the blood of infected but asymptomatic animals. *Clin Vaccine Immunol*. 2007;14:36-43.
- Chronic Wasting Disease Alliance. Carcass transportation regulations in the United States and Canada [online]. Available at: <http://www.cwd-info.org/index.php/fuseaction/policy.main>. Accessed 19 Sept 2008.
- Cunningham AA, Kirkwood JK, Dawson M, Spencer YI, Green RB, Wells GA. Bovine spongiform encephalopathy infectivity in greater kudu (*Tragelaphus strepsiceros*). *Emerg Infect Dis*. 2004;10:1044-1049.
- Doherr MG. Brief review on the epidemiology of transmissible spongiform encephalopathies (TSE). *Vaccine*. 2007;25:5619-5624.
- Eckroade RJ: 1972. Neuropathology and experimental transmission to other species of transmissible mink encephalopathy. PhD Thesis, University of Wisconsin, Madison, WI.
- Eckroade RJ, Zu Rhein GM, Hanson RP: Transmissible mink encephalopathy in carnivores: clinical, light and electron microscopic studies in raccoons, skunks and ferrets. *J Wildl Dis* 9:229-240, 1973.
- Eckroade RJ, Zu Rhein GM, Marsh RF, Hanson RP. Transmissible mink encephalopathy: experimental transmission to the squirrel monkey. *Science*. 1970;169:1088-90.

Transmissible Spongiform Encephalopathies

- Editorial team. Fourth case of transfusion-associated vCJD infection in the United Kingdom. *Euro Surveill.* 2007;12:E070118.4.
- Eghiaian F, Grosclaude J, Lesceu S, Debey P, Doublet B, Tréguer E, Rezaei H, Knossow M. Insight into the PrP^C → PrP^{Sc} conversion from the structures of antibody-bound ovine prion scrapie-susceptibility variants *Proc Natl Acad Sci U S A.* 2004;101:10254-10259.
- Eloit M, Adjou K, Couplier M, Fontaine JJ, Hamel R, Lilin T, Messiaen S, Andreoletti O, Baron T, Bencsik A, Biacabe AG, Beringue V, Laude H, Le Dur A, Vilotte JL, Comoy E, Deslys JP, Grassi J, Simon S, Lantier F, Sarradin P. BSE agent signatures in a goat. *Vet Rec.* 2005;156:523-524.
- Espinosa JC, Andréoletti O, Castilla J, Herva ME, Morales M, Alamillo E, San-Segundo FD, Lacroux C, Luga S, Salguero FJ, Langeveld J, Torres JM. Sheep-passaged bovine spongiform encephalopathy agent exhibits altered pathobiological properties in bovine-PrP transgenic mice. *Virology.* 2007;81:835-843.
- Espinosa JC, Morales M, Castilla J, Rogers M, Torres JM. Progression of prion infectivity in asymptomatic cattle after oral bovine spongiform encephalopathy challenge. *J Gen Virol.* 2007;88:1379-1383.
- European Food Safety Authority [EFSA]. EFSA opinion on the likelihood of BSE infectivity in specified risk material. EFSA; 2007 Jul. Available at: http://www.efsa.europa.eu/en/press_room/press_release/pr_srm_back_calculation.html. Accessed 25 Aug 2007.
- European Food Safety Authority [EFSA] Scientific Expert Group. Scientific report of the European Food Safety Authority on the evaluation of rapid post mortem TSE tests intended for small ruminants. EFSA; 2005 May. 17 p. Question no. EFSA-Q-2003-084. Available at: http://www.efsa.eu.int/science/tse_assessments/bse_tse/983/biohaz_sr31_smallruminantstests_en1.pdf. Accessed 4 Apr. 2007.
- Everest SJ, Thorne L, Barnicle DA, Edwards JC, Elliott H, Jackman R, Hope J. Atypical prion protein in sheep brain collected during the British scrapie-surveillance programme. *J Gen Virol.* 2006;87:471-7.
- Everest SJ, Thorne LT, Hawthorn JA, Jenkins R, Hammersley C, Ramsay AM, Hawkins SA, Venables L, Flynn L, Sayers R, Kilpatrick J, Sach A, Hope J, Jackman R. No abnormal prion protein detected in the milk of cattle infected with the bovine spongiform encephalopathy agent. *J Gen Virol.* 2006;87:2433-2441.
- Fischer JR, Nettles VF (College of Veterinary Medicine, The University of Georgia). National chronic wasting disease surveillance in free-ranging cervids: accomplishments and needs [online]. In: USAHA 2002 Proceedings; 2002 Oct 20-23; St. Louis, MO. Available at: <http://www.usaha.org/speeches/speech02/s02cwndss.html>. * Accessed 2 Dec 2003.
- Fichet G, Comoy E, Dehen C, Challier L, Antloga K, Deslys JP, McDonnell G. Investigations of a prion infectivity assay to evaluate methods of decontamination. *J Microbiol Methods.* 2007;70:511-8.
- Fichet G, Comoy E, Duval C, Antloga K, Dehen C, Charbonnier A, McDonnell G, Brown P, Lasmézas CI, Deslys JP. Novel methods for disinfection of prion-contaminated medical devices. *Lancet.* 2004;364:521-526.
- Foster J, McKenzie C, Parnham D, Drummond D, Chong A, Goldman W, Hunter N. Lateral transmission of natural scrapie to scrapie-free New Zealand sheep placed in an endemically infected UK flock. *Vet Rec.* 2006;159:633-4.
- Gavier-Widen D, Noremark M, Benestad S, Simmons M, Renstrom L, Bratberg B, Elvander M, af Segerstad CH. Recognition of the Nor98 variant of scrapie in the Swedish sheep population. *J Vet Diagn Invest.* 2004;16:562-7.
- Gavier-Widén D, Stack MJ, Baron T, Balachandran A, Simmons M. Diagnosis of transmissible spongiform encephalopathies in animals: a review. *J Vet Diagn Invest.* 2005;17:509-27.
- Georgsson G, Sigurdarson S, Brown P. Infectious agent of sheep scrapie may persist in the environment for at least 16 years. *J Gen Virol.* 2006;87:3737-40.
- Giovannini A, Savini L, Conte A, Fiore GL. Comparison of BSE prevalence estimates from EU countries for the period July to December 2001 to the OIE and EU GBR classifications. *J Vet Med B Infect Dis Vet Public Health.* 2005;52:262-271.
- Goldmann W. PrP genetics in ruminant transmissible spongiform encephalopathies. *Vet Res.* 2008;39:30.
- Goldmann W, Hunter N, Smith G, Foster J, Hope J. PrP genotype and agent effects in scrapie: change in allelic interaction with different isolates of agent in sheep, a natural host of scrapie. *J Gen Virol.* 1994;75:989-995.
- Gombojav A, Ishiguro N, Horiuchi M, Shinagawa M. Unique amino acid polymorphisms of PrP genes in Mongolian sheep breeds. *J Vet Med Sci.* 2004;66:1293-5.
- González L, Chianini F, Martin S, Sisó S, Gibbard L, Reid HW, Jeffrey M. Comparative titration of experimental ovine BSE infectivity in sheep and mice. *J Gen Virol.* 2007;88:714-717.
- Gould DH, Voss JL, Miller MW, Bachand AM, Cummings BA, Frank AA. Survey of cattle in northeast Colorado for evidence of chronic wasting disease: geographical and high-risk targeted sample. *J Vet Diagn Invest.* 2003;15:274-7.
- Greenwood P. Federal disease control--scrapie. *Can Vet J.* 2002;43:625-9.
- Hadlow WJ, Karstad L. Transmissible encephalopathy of mink in Ontario. *Can Vet J.* 1968;9:193-6.

Transmissible Spongiform Encephalopathies

- Hadlow WJ, Race RE, Kennedy RC. Experimental infection of sheep and goats with transmissible mink encephalopathy virus. *Can J Vet Res.* 1987;51:135-44.
- Happ GM, Huson HJ, Beckmen KB, Kennedy LJ. Prion protein genes in caribou from Alaska. *J Wildl Dis.* 2007;43:224-8.
- Hamir AN, Miller JM, O'Rourke KI, Bartz JC, Stack MJ, Chaplin MJ. Transmission of transmissible mink encephalopathy to raccoons (*Procyon lotor*) by intracerebral inoculation. *J Vet Diagn Invest.* 2004;16:57-63.
- Heim D, Mumford E. The future of BSE from the global perspective. *Meat Sci.* 2005;70:555-562.
- Henry C, Knight R. Clinical features of variant Creutzfeldt-Jakob disease. *Rev Med Virol.* 2002;12:143-150.
- Hill AF, Collinge J. Subclinical prion infection in humans and animals. *Br Med Bull.* 2003;66:161-70.
- Hilton DA. Pathogenesis and prevalence of variant Creutzfeldt-Jakob disease. *J Pathol.* 2006;208:134-141.
- Hoffmann C, Ziegler U, Buschmann A, Weber A, Kupfer L, Oelschlegel A, Hammerschmidt B, Groschup MH. Prions spread via the autonomic nervous system from the gut to the central nervous system in cattle incubating bovine spongiform encephalopathy. *J Gen Virol.* 2007;88:1048-1055.
- Horby P. Variant Creutzfeldt-Jakob disease: an unfolding epidemic of misfolded proteins. *J Paediatr Child Health.* 2002;38:539-542.
- Hunter N. Scrapie and experimental BSE in sheep. *Br Med Bull.* 2003;66:171-183.
- Irani DN. Johns Hopkins Department of Neurology. Resource on prion diseases [online]. Bovine spongiform encephalopathy. Available at: <http://www.jhu-prion.org/animal/ani-bse-hist.shtml>. * Accessed 7 Nov 2001.
- Irani DN. Johns Hopkins Department of Neurology. Resource on prion diseases [online]. Feline spongiform encephalopathy. Available at: <http://www.jhu-prion.org/animal/anifse-hist.shtml>. * Accessed 7 Nov 2001.
- Irani DN. Scrapie [online]. Johns Hopkins Department of Neurology. Resource on prion diseases. Available at: <http://www.jhu-prion.org/animal/ani-scrapie2-hist.shtml>. * Accessed 7 Nov 2001.
- Irani DN. Johns Hopkins Department of Neurology. Resource on prion diseases [online]. Transmissible mink encephalopathy. Available at: <http://www.jhu-prion.org/animal/anitme-hist.shtml>. * Accessed 7 Nov 2001.
- Jacques CN, Jenks JA, Jenny AL, Griffin SL. Prevalence of chronic wasting disease and bovine tuberculosis in free-ranging deer and elk in South Dakota. *J Wildl Dis.* 2003;39:29-34.
- Jewell JE, Brown J, Kreeger T, Williams ES. Prion protein in cardiac muscle of elk (*Cervus elaphus nelsoni*) and white-tailed deer (*Odocoileus virginianus*) infected with chronic wasting disease. *J Gen Virol.* 2006;87:3443-50.
- Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2006. Bovine spongiform encephalopathy. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/100200.htm>. Accessed 16 Aug 2007.
- Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2006. Chronic wasting disease. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/100300.htm>. Accessed 18 Sept 2008.
- Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2006. Scrapie. Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/102400.htm>.
- Kahn CM, Line S, editors. The Merck veterinary manual [online]. Whitehouse Station, NJ: Merck and Co; 2006. Transmissible mink encephalopathy (Mink scrapie). Available at: <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/170903.htm>. Accessed 11 Oct 2008.
- Kariv-Inbal Z, Ben-Hur T, Grigoriadis NC, Engelstein R, Gabizon R. Urine from scrapie-infected hamsters comprises low levels of prion infectivity. *Neurodegener Dis.* 2006;3:123-8
- Kelly DF, Wells GA, Haritani M, Higgins RJ, Jeffrey M. Neuropathological findings in cats with clinically suspect but histologically unconfirmed feline spongiform encephalopathy. *Vet Rec.* 2005;156:472-477.
- Kim TY, Shon HJ, Joo YS, Mun UK, Kang KS, Lee YS. Additional cases of chronic wasting disease in imported deer in Korea. *J Vet Med Sci.* 2005;67:753-9.
- Kong Q, Huang S, Zou W, Vanegas D, Wang M, Wu D, Yuan J, Zheng M, Bai H, Deng H, Chen K, Jenny AL, O'Rourke K, Belay ED, Schonberger LB, Petersen RB, Sy MS, Chen SG, Gambetti P. Chronic wasting disease of elk: transmissibility to humans examined by transgenic mouse models. *J Neurosci.* 2005;25:7944-9.
- Konold T, Bone G, Ryder S, Hawkins SA, Courtin F, Berthelin-Baker C. Clinical findings in 78 suspected cases of bovine spongiform encephalopathy in Great Britain. *Vet Rec.* 2004;155:659-666.
- Konold T, Davis A, Bone G, Bracegirdle J, Everitt S, Chaplin M, Saunders GC, Cawthraw S, Simmons MM. Clinical findings in two cases of atypical scrapie in sheep: a case report. *BMC Vet Res.* 2007;13:3:2.
- Kreeger TJ, Montgomery DL, Jewell JE, Schultz W, Williams ES. Oral transmission of chronic wasting disease in captive Shira's moose. *J Wildl Dis.* 2006;42:640-5.
- Kubler E, Oesch B, Raeber AJ. Diagnosis of prion diseases. *Br Med Bull.* 2003;66:267-279.
- Lacroux C, Corbiere F, Tabouret G, Lukan S, Costes P, Mathey J, Delmas JM, Weisbecker JL, Foucras G, Cassard H, Elsen JM, Schelcher F, Andreoletti O. Dynamics and genetics of PrPSc placental accumulation in sheep. *J Gen Virol.* 2007;88:1056-61.

Transmissible Spongiform Encephalopathies

- Lasmézas CI, Comoy E, Hawkins S, Herzog C, Mouthon F, Konold T, Auvré F, Correia E, Lescoutra-Etcheagaray N, Salès N, Wells G, Brown P, Deslys JP. Risk of oral infection with bovine spongiform encephalopathy agent in primates. *Lancet*. 2005;365:781-783.
- Le Dur A, Beringue V, Andreoletti O, Reine F, Lai TL, Baron T, Bratberg B, Vilotte JL, Sarradin P, Benestad SL, Laude H. A newly identified type of scrapie agent can naturally infect sheep with resistant PrP genotypes. *Proc Natl Acad Sci U S A*. 2005;102:16031-6.
- Lezmi S, Bencsik A, Monks E, Petit T, Baron T. First case of feline spongiform encephalopathy in a captive cheetah born in France: PrP(sc) analysis in various tissues revealed unexpected targeting of kidney and adrenal gland. *Histochem Cell Biol*. 2003;119:415-22.
- Lord Phillips, chair. The BSE inquiry: The report. A report to the Minister of Agriculture, Fisheries and Food, the Secretary of State for Health and the Secretaries of State for Scotland, Wales and Northern Ireland. Report no. HC 887-1. London: Her Majesty's Stationery Office; 2000. Available at: <http://www.bseinquiry.gov.uk/report/>. Accessed 2006 Jan.
- Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products. *Br J Haematol*. 2006;132:13-24.
- Luhken G, Buschmann A, Brandt H, Eiden M, Groschup MH, Erhardt G. Epidemiological and genetical differences between classical and atypical scrapie cases. *Vet Res*. 2007;38:65-80.
- Marsh RF. Animal model of human disease: Kuru, Creutzfeldt-Jakob disease (slow virus infections). Animal model: transmissible mink encephalopathy, scrapie-like disease of mink. *Am J Pathol*. 1972;69:209-12.
- Marsh RF, Kincaid AE, Bessen RA, Bartz JC. Interspecies transmission of chronic wasting disease prions to squirrel monkeys (*Saimiri sciureus*). *J Virol*. 2005;79:13794-6.
- Masujin K, Matthews D, Wells GA, Mohri S, Yokoyama T. Prions in the peripheral nerves of bovine spongiform encephalopathy-affected cattle. *J Gen Virol*. 2007;88:1850-1858.
- Mathiason CK, Powers JG, Dahmes SJ, Osborn DA, Miller KV, Warren RJ, Mason GL, Hays SA, Hayes-Klug J, Seelig DM, Wild MA, Wolfe LL, Spraker TR, Miller MW, Sigurdson CJ, Telling GC, Hoover EA. Infectious prions in the saliva and blood of deer with chronic wasting disease. *Science*. 2006;314:133-6.
- McKenzie D, Bartz JC, Marsh RF. Transmissible mink encephalopathy. *Semin. Virol*. 1996;7:201-206.
- Miller MW, Wild MA. Epidemiology of chronic wasting disease in captive white-tailed and mule deer. *J Wildl Dis*. 2004;40:320-7.
- Miller MW, Williams ES, Hobbs NT, Wolfe LL. Environmental sources of prion transmission in mule deer. *Emerg Infect Dis*. 2004;10:1003-6.
- Moum T, Olsaker I, Hopp P, Moldal T, Valheim M, Moum T, Benestad SL. Polymorphisms at codons 141 and 154 in the ovine prion protein gene are associated with scrapie Nor98 cases. *J Gen Virol*. 2005;86:231-235.
- Novakofski J, Brewer MS, Mateus-Pinilla N, Killefer J, McCusker RH. Prion biology relevant to bovine spongiform encephalopathy. *J Anim Sci*. 2005;83:1455-1476.
- Onnasch H, Gunn HM, Bradshaw BJ, Benestad SL, Bassett HF. Two Irish cases of scrapie resembling Nor98. *Vet Rec*. 2004;155:636-7.
- Orge L, Galo A, Machado C, Lima C, Ochoa C, Silva J, Ramos M, Simas JP. Identification of putative atypical scrapie in sheep in Portugal. *J Gen Virol*. 2004;85:3487-3491.
- Pattison J. The emergence of bovine spongiform encephalopathy and related diseases. *Emerg Infect Dis*. 1998;4:390-4.
- Promed Mail. BSE, sheep - UK: experimental transmission. Aug 19, 2005. Archive Number 20050819.2432. Available at <http://www.promedmail.org>. Accessed 2 Apr 2007.
- Promed Mail. Chronic wasting disease, elk - South Korea (Kyungsang). Nov 25, 2004. Archive Number 20041125.3155. Available at <http://www.promedmail.org>. Accessed 30 Sept 2008.
- Promed Mail. Feline spongiform encephalopathy, cat – Switzerland. Aug 24, 2003. Archive Number 20030824.2132. Available at <http://www.promedmail.org>. Accessed 19 Sept 2007.
- Promed Mail. Feline spongiform encephalopathy, cheetah – Germany. Sept 13, 2007. Archive Number 20070913.3038. Available at <http://www.promedmail.org>. Accessed 19 Sept 2007.
- Promed Mail. Scrapie, atypical, sheep - USA (WY): 1st report. Mar 18, 2007. Archive Number 20070318.0949. Available at <http://www.promedmail.org>. Accessed 2 Apr 2007.
- Race BL, Meade-White KD, Ward A, Jewell J, Miller MW, Williams ES, Chesebro B, Race RE. Levels of abnormal prion protein in deer and elk with chronic wasting disease. *Emerg Infect Dis*. 2007;13:824-30.
- Raymond GJ, Raymond LD, Meade-White KD, Hughson AG, Favara C, Gardner D, Williams ES, Miller MW, Race RE, Caughey B. Transmission and adaptation of chronic wasting disease to hamsters and transgenic mice: evidence for strains. *J Virol*. 2007;81:4305-14.
- Richt JA, Kunkle RA, Alt D, Nicholson EM, Hamir AN, Czub S, Kluge J, Davis AJ, Hall SM. Identification and characterization of two bovine spongiform encephalopathy cases diagnosed in the United States. *J Vet Diagn Invest*. 2007;19:142-54.
- Robinson MM, Hadlow WJ, Huff TP, Wells GA, Dawson M, Marsh RF, Gorham JR. Experimental infection of mink with bovine spongiform encephalopathy. *J Gen Virol*. 1994;75:2151-5.

Transmissible Spongiform Encephalopathies

- Robinson MM, Hadlow WJ, Knowles DP, Huff TP, Lacy PA, Marsh RF, Gorham JR. Experimental infection of cattle with the agents of transmissible mink encephalopathy and scrapie. *J Comp Pathol.* 1995;113:241-51.
- Ronzon F, Bencsik A, Lezmi S, Vulin J, Kodjo A, Baron T. BSE inoculation to prion diseases-resistant sheep reveals tricky silent carriers. *Biochem Biophys Res Commun.* 2006;350:872-877.
- Ryder S, Dexter G, Bellworthy S, Tongue S. Demonstration of lateral transmission of scrapie between sheep kept under natural conditions using lymphoid tissue biopsy. *Res Vet Sci.* 2004;76:211-7.
- Sabuncu E, Petit S, Le Dur A, Lan Lai T, Vilotte JL, Laude H, Vilette D. PrP polymorphisms tightly control sheep prion replication in cultured cells. *J Virol.* 2003;77:2696-700.
- Schuler KL, Jenks JA, DePerno CS, Wild MA, Swanson CC. Tonsillar biopsy test for chronic wasting disease: Two sampling approaches in mule deer and white-tailed deer. *J Wildl Dis.* 2005;41:820-4.
- Seeger H, Heikenwalder M, Zeller N, Kranich J, Schwarz P, Gaspert A, Seifert B, Miele G, Aguzzi A. Coincident scrapie infection and nephritis lead to urinary prion excretion. *Science.* 2005;310:324-6.
- Seidel B, Thomzig A, Buschmann A, Groschup MH, Peters R, Beekes M, Terytze K. Scrapie agent (Strain 263K) can transmit disease via the oral route after persistence in soil over years. *PLoS ONE.* 2007;2(5):e435.
- Shimada K, Hayashi HK, Ookubo Y, Iwamaru Y, Imamura M, Takata M, Schmerr MJ, Shinagawa M, Yokoyama T. Rapid PrP(Sc) detection in lymphoid tissue and application to scrapie surveillance of fallen stock in Japan: variable PrP(Sc) accumulation in palatal tonsil in natural scrapie. *Microbiol Immunol.* 2005;49:801-4.
- Sigurdson CJ, Aguzzi A. Chronic wasting disease. *Biochim Biophys Acta.* 2007;1772:610-8.
- Sigurdson CJ, Miller MW. Other animal prion diseases. *Br Med Bull.* 2003;66:199-212
- Smith M, Sherman D. Goat medicine. Pennsylvania: Lea and Febiger; 1994. Scrapie; p. 133-135.
- Smith PG, Bradley R. Bovine spongiform encephalopathy (BSE) and its epidemiology. *Br Med Bull.* 2003;66:185-198.
- Sohn HJ, Kim JH, Choi KS, Nah JJ, Joo YS, Jean YH, Ahn SW, Kim OK, Kim DY, Balachandran A. A case of chronic wasting disease in an elk imported to Korea from Canada. *J Vet Med Sci.* 2002;64:855-8.
- Spencer MD, Knight RS, Will RG. First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. *BMJ.* 2002;324:1479-82.
- Spraker TR, Gidlewski TL, Balachandran A, VerCauteren KC, Creekmore L, Munger RD. Detection of PrP(CWD) in postmortem rectal lymphoid tissues in Rocky Mountain elk (*Cervus elaphus nelsoni*) infected with chronic wasting disease. *J Vet Diagn Invest.* 2006;18:553-7.
- Stack M, Jeffrey M, Gubbins S, Grimmer S, González L, Martin S, Chaplin M, Webb P, Simmons M, Spencer Y, Bellerby P, Hope J, Wilesmith J, Matthews D. Monitoring for bovine spongiform encephalopathy in sheep in Great Britain, 1998-2004. *J Gen Virol.* 2006;87:2099-2107.
- Terry LA, Jenkins R, Thorne L, Everest SJ, Chaplin MJ, Davis LA, Stack MJ. First case of H-type bovine spongiform encephalopathy identified in Great Britain. *Vet Rec.* 2007;160:873-874.
- The National Creutzfeldt-Jakob Disease Surveillance Unit [CJD Unit], United Kingdom. CJD statistics [online]. CJD Unit, U.K.; 2007 Aug. Available at: <http://www.cjd.ed.ac.uk/figures.htm>. Accessed 16 Aug 2007.
- Touzeau S, Chase-Topping ME, Matthews L, Lajoux D, Eychenne F, Hunter N, Foster JD, Simm G, Elsen JM, Woolhouse ME. Modelling the spread of scrapie in a sheep flock: evidence for increased transmission during lambing seasons. *Arch Virol.* 2006;151:735-51.
- Tyshenko MG. Bovine spongiform encephalopathy and the safety of milk from Canadian dairy cattle. *Vet Rec.* 2007;160:215-218.
- United States Department of Agriculture Animal and Plant Health Inspection Service [USDA APHIS]. Bovine spongiform encephalopathy factsheet. USDA APHIS; 1999 Sept. Available at: <http://permanent.access.gpo.gov/lps3025/fsbse.html>. Accessed 16 Aug 2007.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service [USDA APHIS]. Bovine spongiform encephalopathy (BSE) [online]. Available at: <http://www.aphis.usda.gov/lpa/issues/bse/bse-overview.html>. * Accessed 29 Dec 2003.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service [USDA APHIS]. Bovine spongiform encephalopathy (BSE) response plan summary. USDA APHIS; 1998 Oct. Available at: <http://permanent.access.gpo.gov/lps3025/bsesum.pdf>. Accessed 215 Aug 2007.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service [USDA APHIS]. Bovine spongiform encephalopathy (BSE). Surveillance [online]. USDA APHIS; 2003 March. Available at: <http://www.aphis.usda.gov/lpa/issues/bse/bse-surveillance.html>. * Accessed 29 Dec 2003.

Transmissible Spongiform Encephalopathies

- U.S. Department of Agriculture, Animal and Plant Health Inspection Service [USDA APHIS]. Scrapie eradication. State-Federal-Industry uniform methods and rules. USDA APHIS; 2003 Oct. APHIS 91-55-066. Available at: http://www.aphis.usda.gov/animal_health/animal_diseases/scrapie/downloads/umr.pdf. Accessed 22 Mar 2007.
- U.S. Department of Agriculture. Animal and Plant Health Inspection Service [USDA APHIS]. Transmissible mink encephalopathy. USDA APHIS; 2002 Feb. Available at: http://www.aphis.usda.gov/lpa/pubs/fsheet_faq_notice/fs_ahtme.html. Accessed 5 Oct 2008.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service [USDA APHIS]. Transmissible spongiform encephalopathies [online]. USDA APHIS; 2000 July. Available at: <http://www.aphis.usda.gov/oa/pubs/ftse.html>. Accessed 7 Nov 2001.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service [USDA APHIS]. Centers for Epidemiology and Animal Health. Highlights of phase II: Scrapie: Ovine slaughter surveillance study 2002-2003 [online]. USDA APHIS; 2004 March. Available at: http://nahms.aphis.usda.gov/sheep/SOSS_highlights.pdf. Accessed 5 Apr 2007.
- U.S. Department of Health and Human Services [USDHHS]. Federal agencies take special precautions to keep “mad cow disease” out of the United States [online]. USDHHS; 2001 Aug. Available at: <http://www.cfsan.fda.gov/~lrd/hhsbse2.html>. Accessed 15 Aug 2007.
- Vaccari G, Di Bari MA, Morelli L, Nonno R, Chiappini B, Antonucci G, Marcon S, Esposito E, Fazzi P, Palazzini N, Troiano P, Petrella A, Di Guardo G, Agrimi U. Identification of an allelic variant of the goat PrP gene associated with resistance to scrapie. *J Gen Virol*. 2006;87:1395-402.
- Vascellari M, Nonno R, Mutinelli F, Bigolaro M, Di Bari MA, Melchioti E, Marcon S, D'Agostino C, Vaccari G, Conte M, De Grossi L, Rosone F, Giordani F, Agrimi U. PrPSc in salivary glands of scrapie-affected sheep. *J Virol*. 2007 81:4872-6.
- Williams ES. Chronic wasting disease. *Vet Pathol*. 2005;42:530-49.
- Williams ES, Miller MW. Transmissible spongiform encephalopathies in non-domestic animals: origin, transmission and risk factors. *Rev Sci Tech*. 2003;22:145-56.
- World Health Organization [WHO]. Bovine spongiform encephalopathy [online]. WHO; 2002 Nov. Available at: <http://www.who.int/mediacentre/factsheets/fs113/en/>. Accessed 16 Aug 2007.
- World Organization for Animal Health [OIE]. Animal diseases data [online]. OIE; 2002 Apr. Bovine spongiform encephalopathy. Available at: http://www.oie.int/eng/maladies/fiches/a_B115.htm. Accessed 17 Aug 2007.
- World Organization for Animal Health [OIE]. Manual of diagnostic tests and vaccines [online]. Paris: OIE; 2004. Bovine spongiform encephalopathy. Available at: http://www.oie.int/eng/normes/mmanual/A_00064.htm. Accessed 16 Aug 2007.
- World Organization for Animal Health [OIE]. Manual of diagnostic tests and vaccines [online]. Paris: OIE; 2004. Scrapie. Available at: http://www.oie.int/eng/normes/mmanual/A_00074.htm. Accessed 25 Mar 2007.
- Wyatt JM, Pearson GR, Gruffydd-Jones TJ. Feline spongiform encephalopathy. *Feline Pract*. 1993;21:7-9.
- Young S, Slocombe RF. Prion-associated spongiform encephalopathy in an imported Asiatic golden cat (*Catopuma temmincki*). *Aust Vet J*. 2003;81:295-296.
- Zanusso G, Casalone C, Acutis P, Bozzetta E, Farinazzo A, Gelati M, Fiorini M, Forloni G, Sy MS, Monaco S, Caramelli M. Molecular analysis of iatrogenic scrapie in Italy. *J Gen Virol*. 2003;84:1047-52.
- Zanusso G, Nardelli E, Rosati A, Fabrizi G, Ferrari S, Carteri A, De Simone F, Rizzuto N, Monaco S. Simultaneous occurrence of spongiform encephalopathy in a man and his cat in Italy. *Lancet*. 1998;352:1116-7.

*Link defunct as of 2008.