Summary: Reports on this topic were sent to the OIE from 14 Member Countries: Albania, Belgium, Cyprus, Denmark, Finland, Germany, Israel, Latvia, Lithuania, Norway, Slovakia, Spain, Switzerland and the United Kingdom (UK).

Many countries carry out surveillance and monitoring for transmissible spongiform encephalopathies (TSEs): these include bovine spongiform encephalopathy (BSE), Creutzfeldt-Jakob disease (CJD), feline spongiform encephalopathy (FSE), scrapie and transmissible mink encephalopathy (TME). Measures to prevent BSE have been introduced in many countries.

The BSE epidemic in Switzerland is nearing its peak and the UK epidemic is declining rapidly. Recent data indicate an average risk of maternal transmission of BSE to calves of about 1%. There may also be a small risk of horizontal transmission to unrelated calves born up to 3 days after a subsequently affected cow has calved. However, transmission of BSE other than by contaminated feeds will not be sufficient to sustain an endemic infection in cattle. Prevention of food-borne infection is expected to eradicate BSE.

Twelve cases of a new variant of CJD (vCJD) have been described in the UK. These cases may be associated with exposure to BSE before measures were taken to protect public health. However, there is no direct evidence of a link, and uncertainty about the epidemiology of sporadic CJD makes it difficult to formulate and investigate other possible causes of vCJD.

Feed borne exposure to BSE may have caused cases of scrapie in sheep. It is conceivable that the BSE agent, or a mutant strain of scrapie, may spread naturally in sheep and eventually pose a risk to man.

Some countries, notably Cyprus and Norway, are attempting to control scrapie. The discovery of polymorphisms in the PrP gene that are associated with susceptibility will facilitate research into the epidemiology of scrapie. It may be possible to eradicate the disease by reducing the spread of infection and by breeding sheep that are resistant to the disease. However, research is needed into the possibility of genetically resistant carriers of infection.

Some rendering processes have been shown to reduce BSE infectivity by 80-fold. This may not be enough to guarantee the disinfection of bovine waste material containing central nervous system tissue where most of the BSE agent becomes concentrated.

Current methods for detecting modified PrP protein are not sensitive enough to demonstrate the absence of infection.

1. SUMMARY OF REPORTS

1.1. Albania

- Creutzfeldt-Jakob disease (CJD) has never been identified.

- Bovine spongiform encephalopathy (BSE) has not been found by continuous surveillance according to the OIE International Animal Health Code Chapter 3.2.13. Animal protein has never been used in cattle feeds. No cattle have been imported from the United Kingdom (UK) for almost 20 years. Deboned meat from UK cattle was imported during the period 1991-1994 and then banned.

1.2. Belgium
• Bovine spongiform encephalopathy has been notifiable since September 1990. The surveillance for BSE is linked to that for rabies. From 1990 to 1994, this formed part of a collaboration involving four other Member Countries with endemic rabies. All cattle showing a nervous disorder are slaughtered and tested for rabies and the negative cases are then tested for BSE. The surveillance network now includes all ruminants, cats and dogs. Brain tissue is examined according to methods recommended by the European Union (EU): by histology, immunocytochemistry and for the presence of scrapie-associated fibrils. Between 31 May 1990 and 17 July 1996, 1,165 ruminant brains were examined from 494 cattle, 201 sheep and 20 wild ruminants. All were negative. The risks of BSE are considered to be very low because of the small population of sheep (127,000) compared to that of cattle (about three million), the infrequency of scrapie cases (the last five were in 1992), and the fact that animal protein is not fed to livestock.

1.3. Cyprus

• Creutzfeldt-Jakob disease was confirmed in a 59-year-old woman who died in 1995. The neuropathological findings did not show this to be a case of "new variant" of CJD.

• Scrapie was identified in 1985. A comprehensive control policy has been in operation since 1987. Scrapie is a notifiable disease. All flocks of sheep and goats are inspected twice a year. Suspect cases are destroyed except for the brain which is removed for histological examination. Owners are compensated. All animals in the flocks of origin are identified by ear tags and movements are prohibited except for the destruction of suspect cases and the slaughter of other animals. Confirmation of scrapie results in an epidemiological investigation and the slaughter of parents and progeny of confirmed cases. Premises with suspected or confirmed cases are disinfected weekly with sodium hydroxide. The whole flock is slaughtered when a high incidence of scrapie has occurred. Depopulated farms are left without animals for three years and disinfection is continued. Scrapie has been confirmed in 99 flocks. In 36 of these, all animals were slaughtered. A detailed register is kept of all suspected and positive flocks.

In 1992, an attempt was made to determine the prevalence of scrapie in the Paphos district by random survey of brains collected in abattoirs. No positive cases were found but, for reasons of cost, the number of brains examined was statistically small. An investigation of the PrP genotype as a risk factor in the epidemiology of scrapie is about to start. Research is recommended on whether or not maternal transmission occurs in goats. There is a need for criteria by which regions and countries can be certified as scrapie-free. It is suggested that the OIE International Animal Health Code Commission prepare a Chapter on scrapie.

• Bovine spongiform encephalopathy was made notifiable in 1990. No cases have been found. Animal tissues have never been incorporated into feeds for ruminants. The feeding to ruminants of concentrates derived from ruminant material was prohibited in 1990, and from all mammalian material in 1994. The island is considered to be free of BSE. All clinically suspect cases of BSE will be investigated using the laboratory methods recommended by the Scientific Veterinary Committee of the EU. It is proposed that the OIE International Animal Health Code Commission insert a new Article into Chapter 3.2.13 that specifies the heat treatments which can inactivate the BSE agent.

1.4. Denmark

• Scrapie has never been reported.

• Bovine spongiform encephalopathy is a notifiable disease. In 1992, a case was diagnosed in a five-year-old animal that was imported from the UK in June 1988. The affected herd was destroyed, the premises cleaned and disinfected, and pastures were ploughed. A suspect case was observed in another herd in an animal imported from the UK in 1989. This case was not confirmed. However, the decision was made to destroy all cattle imported from the UK at the end of their productive life. Altogether, 220 imported cattle have been identified, ear tagged and their movement restricted. No live cattle have been imported from the UK since March 1990, including calves under six months of age. Meat-and-bone-meal has not been imported from the UK for many years. The feeding of ruminant protein to ruminants has been banned since June 1990. Denmark is considered to be free of BSE by the criteria in Chapter 3.2.13 of the OIE International Animal Health Code.

1.5. Finland

• Chronic wasting disease of deer has never been recorded.
• Scrapie is a notifiable disease. It has never been recorded. The number of adult sheep is approximately 55,000. Each year, 10-20 sheep with suspicious neurological signs are examined histologically for scrapie. All have been negative. Listeriosis has been the most frequent diagnosis. Between July 1995 and May 1996, 387 slaughtered sheep over three years of age were also examined histologically for scrapie, again with negative results.

• Bovine spongiform encephalopathy is a notifiable disease. There are approximately 400,000 cows. About 60 cattle with suspicious neurological signs have been examined histologically for BSE since 1986. All were negative. In the 1980s, 89 live cattle were imported from the UK, the last one in 1988. Eighteen are still alive and under surveillance. They will not be slaughtered for human or animal food. Meat-and-bone-meal is mainly imported from Denmark, the Netherlands and Sweden. None has been imported from the UK since 1980. In 1990 the use of imported animal protein in feedstuffs for ruminants was banned. The use of any mammalian protein in ruminant feeds was banned in 1995.

• Feline spongiform encephalopathy (FSE) has not been recorded, even though 20-30 cats with a history of neurological disease are examined histologically each year.

• Transmissible mink encephalopathy (TME) occurred on one mink farm in 1966. The cause of the outbreak was not established and there have been no outbreaks since.

1.6. Germany

• Scrapie is a notifiable disease. Confirmation of scrapie results in the slaughter and incineration of the whole flock. Four cases have been identified since 1945: in 1990, 1991, 1995 and June 1996. The first three outbreaks occurred in flocks into which imported sheep had been introduced. The cause of the fourth case is unknown.

• Bovine spongiform encephalopathy was identified in 1994 in four cattle that had been imported from the UK. There have been no cases since. In accordance with Article 3.2.13.3 of the OIE International Animal Health Code, the cattle population is considered to be free of BSE.

• Transmissible spongiform encephalopathies have not been found in any other animal species.

1.7. Israel

• Bovine spongiform encephalopathy has never been recorded in the cattle population that is currently 355,000. Since 1982, veterinary surveillance of dairy cattle has been encouraged by compulsory insurance of animals older than six months against total condemnation in slaughterhouses. The number of compensations is 1,000-1,500 a year. There is also a livestock insurance and veterinary services scheme which provides for one-two visits a week to more than 90% of dairy farms. Between 1991 and 1995, 520 brains from cattle older than two years that were reported to have signs of central nervous system or neuromotor disease were examined histologically for BSE. All were negative. BSE was made notifiable in April 1992.

• Over the years, a series of increasingly rigorous measures have been taken to protect two populations: high-producing dairy cattle which are maintained in a very centralised and intensive husbandry system; and a community of Libyan Jews with a mutation of the PrP gene that is associated with an annual incidence of CJD of more than 100 per million.

Live cattle from the UK have been banned since May 1988 and, since January 1995, no imports from other countries have been allowed from farms where BSE has been diagnosed. Imports from the UK of animal meal of ruminant origin were banned in December 1988. A total ban on the importation from all countries of ruminant-derived meat and bone meal for use in food animals has been in force since July 1990. Currently, consignments of imported meat-and-bone meal are routinely tested to confirm the species of origin. There have been restrictions on imports of pet food from the UK since August 1989. Imports from the UK and Ireland of bovine brain, spinal cord, tonsils, thymus, spleen and the intestinal tract were prohibited in December 1990. Importation of these tissues from other countries has been restricted since February 1991 and, since July 1996, are generally not permitted. Imports of bovine meat are permitted from countries that comply with the OIE International Animal Health Code, Chapter 3.2.13 but a limitation on the age of source animals is being contemplated.

1.8. Latvia

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• Transmissible spongiform encephalopathies has never been identified in animals.

1.9. Lithuania

• Bovine spongiform encephalopathy has not occurred in any cattle imported from the UK in the last 20 years. Imports of livestock from countries where BSE was registered during the last five years are prohibited.

1.10. Norway

• Scrapie has been diagnosed in 33 flocks in four counties (in the south and west) since 1981. No cases have been found in two counties since 1985 but scrapie continues to occur in the other two counties: eight flocks affected in 1995 and 17 flocks in 1996. All affected flocks are destroyed and strict measures are taken to disinfect the premises. Movements of live sheep from affected counties have been prohibited for several years. Since October 1995, contacts between affected flocks have been restricted. A programme to eradicate scrapie was introduced in May 1996. About 600 flocks are known to have had contact with affected flocks during the last 10 years. Their owners are given financial incentives to slaughter the whole flock and restock from unaffected parts of the country. The industry has decided that meat from sheep and lambs from these contact flocks will not be marketed.

1.11. Slovakia

• Creutzfeldt-Jakob disease has occurred sporadically in some regions where sheep are reared. There have been no clinical cases associated with BSE.

• Bovine spongiform encephalopathy has not been recorded. No material of animal origin has been fed to ruminants in the past. Since August 1994, the use of bone meal, meat-and-bone-meal, and tallow in feeds for ruminants has been prohibited. Imports of the following from UK were banned in January 1993: live cattle, beef and beef products, meat- and-bone-meal from the carcases of sheep and cattle. Since April 1996, there has been a total ban on the importation of live cattle and sheep, and of certain products from them, including semen, embryos, meat-and-bone- meal and other feedstuffs. Also banned is the transit of live cattle and sheep from France, Ireland, Portugal, Switzerland and the UK.

1.12. Spain

• Transmissible spongiform encephalopathies have never been officially reported in any animal species.

1.13. Switzerland

• Scrapie was first reported in 1982. Another case occurred in 1991, three in 1993 and one in 1995. The sheep population is about 400,000.

• Bovine spongiform encephalopathy was first diagnosed on 2 November 1990. Disease control measures were introduced on 1 December 1990. These included a ban on the feeding of animal protein to ruminants, notification of suspect cases and histological examination of brains, registration of all cattle on affected farms, incineration of carcases of affected cattle, destruction of semen, eggs and embryos obtained from them, and tattooing of the left ear of progeny with the letters "BSE".

For consumer protection, the December 1990 control measures also require that milk from suspect cases is not sold. The following tissues have to be removed from all slaughtered cattle and rendered appropriately: obvious nervous and lymphatic tissue, and the specified bovine offals (SBOs: brain, spinal cord, thymus, spleen and intestines of cattle older than 6 months). Tonsils were already being removed for other reasons. Since May 1996, the skull (including brain and eyes) and spinal cord have to be incinerated, and the origin of all bovine meat and meat products must be declared.

The BSE epidemic increased exponentially until 1994. By 15 May 1996, 214 cases had occurred throughout the country, all in dairy cattle. There is no evidence of differences in breed susceptibility. BSE has occurred in 206 herds of which 200 had only one case. The dairy cattle population is about 800,000 and the average herd size is 19. About 85% of affected animals are four to six years of age. The youngest cow was 2.6 years and the oldest was 10.2 years. The average age when cases are killed is 5.2 years, but this has started to increase as the feed ban reduces the number of younger cases. This observation and a dramatic reduction in the annual rate of increase of cases suggests that the epidemic may reach a peak in 1995, and then decline.
However, 10 cases of BSE were born after the feed ban, between December 1990 and December 1991. There are no indications of either maternal transmission or the illegal use of meat and bone meal in cattle feeds. Nevertheless, implementation of the feed ban is being strictly controlled by laboratory analysis of random samples of concentrated ruminant feeds. Between 1991 and 1994, 3 of 544 samples tested (less than 0.6 %) contained traces of meat-and-bone-meal.

Analysis of the BSE risk factors indicates that the epidemic was not related to the occurrence of scrapie in Switzerland, nor to changes in the conditions of rendering animal wastes to produce meat-and-bone-meal. Until 1993, rendering was carried out at 120-133°C for 20-30 minutes at a pressure of 3 bar. Since then, the conditions used are 133°C for 20 minutes at 3 bar. Significant recycling of BSE infection in the cattle population is unlikely. The evidence suggests that BSE was a direct consequence of imported meat-and-bone-meal, much of which came from Belgium, France and Germany. Some of this imported meat-and-bone-meal probably originated from the UK. Until November 1990, concentrated feeds contained about 2.6 % meat-and-bone-meal.

In June 1990, imports were banned from the UK of rendered animal protein, live cattle and meat. Rendered animal protein from other countries was also banned unless produced under conditions equivalent to those used in Switzerland. Since May 1996, an additional requirement is that bovine heads and spinal cords must not have been used to produce any imported animal protein.

1.14. United Kingdom

- Creutzfeldt-Jakob disease has been monitored nationally since 1990. The number of cases has increased over the period 1990-1994. This is probably due to improved ascertainment of cases, particularly in patients over 75 years old. The annual mortality is less than 1 per million. A few cases are iatrogenic and some are familial, the latter being associated with specific mutations of the human PrP gene. The majority of cases are sporadic with no significant spatial clustering.

Studies of dietary histories have indicated statistical associations of sporadic CJD with the consumption of various meat products, including veal and venison. So far, none of these associations has been consistent in successive years and there is evidence that they could be the result of recall bias when dietary histories were obtained from relatives.

Analysis of occupational histories has revealed an excess of CJD cases in farmers who have had animals with BSE in their herds. However, no biologically plausible link with BSE has been identified. Several other countries where few or no cases of BSE have been reported have incidences of CJD in the general population (1) and in farmers (9) which are similar to those found in the UK.

Ten cases of a new variant CJD (vCJD) were reported in April 1996 (52). They are not associated with any known mutations of the PrP gene. Cases of vCJD differ from sporadic cases in presentation of psychiatric symptoms at a comparatively young age, with none of the typical electroencephalogram features, and the clinical duration is longer. These cases have a characteristic neuropathological profile, of which the most striking feature is the deposition of PrP amyloid plaques in specific regions of the brain. Five cases had a clinical onset in 1994. Given the long incubation period of the natural TSE, it is possible that vCJD cases were the result of exposure to BSE before the end of 1989 when the use of the specified bovine offals (SBOs) in human food was banned. Since April, two more cases have been confirmed in the UK.

- Scrapie was made a notifiable disease on 1 January 1993. The disease was confirmed on 116 premises in 1995.

- Bovine spongiform encephalopathy continues to decline as a result of the ban on the use of ruminant-derived protein in ruminant feeds (July 1988) and the requirement to exclude SBOs from animal feeds (September 1990). Less than 200 suspect cases are reported each week compared to over 1,000 per week at the peak of the epidemic in early 1993. About 75 % of suspect cases are subsequently confirmed. The expected shift in the age profile of cases continues with fewer cases in the younger animals.

By the end of May 1996, about 27,000 cases (of a total of 160,540) had been confirmed in animals born after the 1988 feed ban. Many of these cases were the result of contaminated ruminant protein that was already in the food chain. However, cases have occurred in cattle born in 1990 (3,581), 1991 (1,320), 1992 (119) and in 1993 (1). The results of a case-control study (21) imply leakage of some BSE infected material into animal feeds.
Several changes in legislation have been made to improve the efficiency of the control measures. These include a requirement to stain SBOs with a special dye (April 1995); tighter controls of record keeping (August 1995); the use of dedicated lines for rendering plants processing SBOs (August 1995); disposal of the whole skull (containing the brain and eyes) as an SBO (August 1995); disposal of the whole vertebral column (containing the spinal cord) in premises other than slaughterhouses (August 1995); and a prohibition on the use of the bovine vertebral column in the manufacture of mechanically recovered meat (December 1995). A complete ban on the feeding of any mammalian meat-and- bone-meal to farm animals, including horses and farmed fish, was introduced in April 1996 to prevent accidental feed-borne infection of cattle with feeds for monogastric animals. Also in April 1996, it became illegal for mammalian meat-and- bone-meal to be used as fertilizer on agricultural land.

Farms and feedmills are subject to frequent inspection and random sampling. During February to May 1996, 2,341 samples were collected and tested for the presence of mammalian protein in animal feeds. Fourteen positive samples (less than 0.8%) have been investigated. Currently, about 6,000 samples are tested each year, but this is being increased to 24,000 a year. Unannounced inspections of slaughterhouses between the summer of 1995 and the end of April 1996 revealed 24 instances of pieces of spinal cord being left attached to carcases. About 2 million cattle were slaughtered during this period. There have been no such instances subsequently.

However, these improved controls will not prevent disease from developing in cattle that are already infected. Inevitably, further cases will be confirmed. The characteristically low incidence of BSE within affected herds makes it very difficult to reduce, substantially, the number of future cases by selective culling of cattle in birth cohorts most at risk of BSE. Nevertheless, this strategy is being considered.

Following the discovery of vCJD, additional measures were introduced in March 1996 to safeguard public health. The SBO ban was extended to include whole heads of all cattle over 6 months except for the tongue, provided it can be removed without being contaminated. A temporary prohibition was put on the sale for human consumption of all meat from cattle over 30 months of age.

• Feline spongiform encephalopathies cases are falling from an average of one case per month in 1990-1994 to a total of eight cases in 1995. One case has been reported in 1996.

• Transmissible spongiform encephalopathies cases in exotic species in zoos now total 28: Ankole cow (two); cheetah (four, including two exported cases); eland (six); gemsbok (one); kudu (six); nyala (one); ocelot (two); oryx (two); puma (three); tiger (one). The second case in an ocelot and the case in a tiger were diagnosed in 1996.

2. EPIDEMIOLOGY

2.1. Creutzfeldt Jacob disease

Creutzfeldt-Jakob disease occurs world-wide. Apart from iatrogenic cases which are rare, the epidemiology of the disease is not well understood.

About 10-15% of all CJD cases are familial, including Gerstmann-Straussler-Scheinker disease (GSS) and fatal familial insomnia (FFI). These cases are associated with one or more of a number of specific mutations of the human PrP gene (16, 17, 23). In contrast, no known mutations of the PrP gene are associated with the majority of CJD cases which occur sporadically (36).

Current opinion favours a genetic cause of all forms of familial CJD. Supporting evidence comes from the spontaneous development of spongiform encephalopathy in mice that express a PrP transgene with a mutation equivalent to that associated with GSS (24). The additional claim that these mice spontaneously produce a TSE agent is controversial. It has been suggested that sporadic CJD could be the result of somatic mutations of the PrP gene or a spontaneous conversion of normal PrP protein to pathogenic forms (38) but there is no evidence for either mechanism.

An alternative hypothesis arises from the fact that experimental transmissibility is a common feature of familial CJD, GSS, FFI and sporadic CJD (4, 35, 40). This implies an infectious etiology for all of these diseases. The patterns of occurrence of CJD do not correlate with the world distribution of sheep, scrapie or the consumption of sheep products (3, 50), although this conclusion has been challenged (12). Nor is there evidence that clearly implicates any other zoonotic source of infection, including cattle (51). The simplest alternative
hypothesis is that the primary cause of all forms of CJD is a high-incidence, endemic infection of man with a non-neuroinvasive or non-pathogenic strain of agent that is harmless in people carrying the normal PrP gene (27, 28). Germline mutations of this gene might allow the common infection to be pathogenic, leading to the occurrence of disease with a familial pattern. Mutations in the agent, followed by positive selection of the mutant in the central nervous system, could produce sporadic cases of CJD at a frequency that lected the mutation rate of the agent (27, 28). However, this hypothesis is difficult to test without a sensitive, non-biological method for detecting CJD infection in man.

Although the recent cases of vCJD (52) may be related to exposure to BSE infection before the introduction of the SBO ban (November 1989), there is no direct evidence of a link. It may be significant that one case of vCJD has been reported in France (6) where the BSE-associated risks were very much lower than in the UK. However, the uncertainties about the cause of sporadic CJD make it difficult to formulate and investigate alternative hypotheses for the cause of vCJD.

2.2. Scrapie

Scrapie occurs as an endemic infection of sheep, and possibly goats. Different strains of the scrapie agent are known to occur naturally. Infection is transmitted by a combination of maternal and horizontal routes but many of the details are not known (10, 22, 25). There is evidence for infection of pre-implantation embryos that were obtained from experimentally infected ewes (15), but the evidence from naturally infected ewes is unclear (14). Placenta can be a source of post-natal infection by the oral route (37) and transplacental infection may occur prenatally.

The control of scrapie is based on selective culling of affected female lines combined with husbandry measures to minimize the horizontal spread of infection at lambing. These control methods are difficult to apply in most commercial flocks and they are inadequate for eradicating widely endemic scrapie (25).

The major problem in the control of scrapie is the absence of a sensitive laboratory test for infection. The same problem impedes epidemiological research. This is because the spread of infection can only be deduced from the patterns of occurrence of the clinical disease. However, susceptibility to disease and incubation period depend on the strain of scrapie agent and the host genotype at the Sip/PrP gene locus (11). The result is that many infected sheep are sources of infection to others without developing the disease during their commercial lifespan.

An important discovery is that several polymorphisms in the nucleotide sequence of the coding region of PrP gene are linked to susceptibility to scrapie. However, the situation is complicated by the fact that at least three polymorphic sites are involved, at codons 136, 154 and 171 (2, 18, 33). In addition, the markers for susceptibility to scrapie vary according to the breed of sheep and the strain of agent (18). Nevertheless, the advent of genetic markers for susceptibility to scrapie in some breeds of sheep will allow a better understanding of the epidemiology of scrapie and lead to improved methods of control.

It may be possible to eradicate scrapie by combining methods to reduce the spread of infection with selective breeding using sires of Sip/PrP genotypes that have a low susceptibility to disease. However, studies of the way PrP gene controls the pathogenesis of scrapie in mice show that resistance to disease does not necessarily mean resistance to infection (8, 29). Therefore, the use of apparently resistant sires might create carriers that are persistently infected with some strains of scrapie and which could be sources of infection to other sheep, while remaining free of the disease (25). Further research is needed.

2.3 Bovine spongiform encephalopathy

All the evidence from the UK shows that BSE has occurred as an extended common source epidemic (48). The rapid decline in the number of cases, following the introduction of the feed ban in 1988, suggests that ruminant protein in the form of meat-and-bone-meal was the only significant vehicle of feed-borne infection. Throughout the epidemic, the average incidence of BSE within affected herds has been lower than 3% of adults (45). BSE is associated with a single strain of agent (5) and, in contrast to scrapie, variation in PrP or other host genes is not a major factor in the occurrence of disease. This means that all infected cattle are probably equally susceptible to disease and would develop clinical signs if they lived long enough (26). Therefore, the low incidence of BSE within affected herds is due to a limited exposure to infectivity in feed. The average exposure could have been as low as 14 oral Lethal Doses 50 units per tonne of concentrates (32).

This epidemiological pattern suggested that BSE may not be contagious. A case control study of cases born after the 1988 feed ban found a small risk of horizontal transmission of BSE to unrelated calves born up to three days
after a subsequently affected cow had calved (21). However, no increase in risk in the offspring of affected animals was detected within the sensitivity of the study (21). The interim results of a cohort study indicate a 10% risk of maternal transmission of BSE to calves born within four months of their dams developing BSE (49). Given that the mean incubation period of BSE is 60 months (46, 47), the average risk to all calves born to infected dams might be as low as 1%.

The cohort study does not indicate the mechanism of maternal transmission of BSE. However, the majority of calves were obtained from commercial dairy herds where they would have been fed colostrum, but not milk. In other studies, calves remain healthy 6.5 years after exposure, via the nose and mouth, to the placenta from BSE cases (34). The possibility of infection of the embryo is also under investigation (34).

Although these BSE transmission experiments are still in progress, present evidence makes it very unlikely that sources of infection other than feed will be epidemiologically significant in the long term. Control measures based on preventing food-borne infection of cattle will eventually lead to the eradication of BSE. In this respect, BSE is like TME and kuru, and unlike scrapie (26).

2.4. Other transmissible spongiform encephalopathies associated with bovine spongiform encephalopathy

Feline spongiform encephalopathies and cases of transmissible spongiform encephalopathies in exotic species in the UK seem to be associated with infection of the BSE agent (5). Most of the exotic ungulates were exposed to the same type of feed as cattle. The possibility that some cases in kudu may have been due to maternal transmission has been reinvestigated, and accidental feed contamination is a more likely explanation (34). The ruminant protein feed ban (July 1988) prevents infection by this route. The SBO bans of November 1989 (humans) and September 1990 (all animals) remove the most likely source of infection of the exotic felids, that is, spinal cord in raw meat. The vehicle of infection of domestic cats is unknown but they are now protected by the 1990 SBO ban and the number of cases reported each year is in decline.

3. PATHOGENESIS

3.1. Scrapie

The pathogenesis of scrapie has been studied intensively, in well characterised models of the disease in mice and hamsters (30), and also in sheep infected naturally (19).

Within a few weeks after injection by peripheral routes, multiplication of the agent takes place in the lymphoreticular system (LRS), for example, in spleen and lymph nodes. After intragastric infection, multiplication in Peyer's patch tissue of the alimentary tract is particularly important (31). Disease only develops if the agent enters, and then multiplies in, the central nervous system (CNS). In one model of scrapie, there is lifetime persistence of high titres of agent in the LRS but disease never develops because neuroinvasion occurs too late or not at all (8). It is this model which suggests how persistently infected carriers of scrapie could occur naturally in sheep. However, most of the scrapie strains studied are neuroinvasive. Much evidence points to a neuroinvasive pathway via the visceral autonomic nerves, particularly those of the sympathetic nervous system (30).

The characteristic range of incubation periods of each scrapie model depends on the strain of agent and host PrP genotype. Comparisons between models of widely different incubation periods reveal only very small differences in the times of onset of agent multiplication in the LRS. Even with some of the very long incubation period models, neuroinvasion is initiated within a few weeks of infection (30). The differences lie in the subsequent stages of multiplication and cell-to-cell spread of infection within the peripheral and central nervous systems, the overall speed of which correlates strikingly with incubation period. The onset of detectable multiplication of the agent in the brain is always about half-way through the incubation period (30).

Although less well studied, the pathogenesis of the other TSEs is probably similar to scrapie in most respects. However, studies of experimental TME in mink show that infectivity titres in the LRS are generally much lower than is found with scrapie (20). This difference in titres in tissues outside the CNS may be related to the fact that scrapie is a naturally infectious disease, whereas TME is not (20, 25). Like TME, the pathogenesis of BSE is also associated with low infectivity in the non-CNS tissues (see below).

3.2. Bovine spongiform encephalopathy
Information on the pathogenesis of BSE comes from two sources. First, the amount of infectivity in over 50 tissues from confirmed field cases of BSE has been measured by bioassays in mice. No infectivity was detected in any tissue except brain, spinal cord and the retina (34). This does not mean that the agent is absent outside the CNS because the sensitivity of bioassays of bovine BSE agent in mice will be reduced by the species barrier. It does suggest that, compared to titres in the CNS, titres in the LRS are proportionately lower with BSE than scrapie. In this respect, BSE resembles TME (26).

Secondly, the pathogenesis of BSE has been studied by measuring infectivity in tissues at different times after orally infecting cattle with very high doses of agent. Under these conditions, the incubation period of BSE was 35-37 months (43, 44). Infectivity data are available for pooled tissues from groups of three animals that were killed at 2, 6, 10, 14 and 18 months after infection. No infectivity was detected in any tissue (including the CNS) with the exception of ileum. Here, infectivity was not detected at two months, but thereafter it was present in progressively increasing titres (43, 44).

The finding of infectivity in the ileum is in contrast to the negative results when ileum was obtained from field cases of BSE. The difference is probably a consequence of the need to ensure that all the orally dosed cattle became infected. This was achieved using a dose of agent that was several orders of magnitude greater than the average exposure of cattle via contaminated feed. Such a large dose would have enabled a greater uptake of infection, and subsequent multiplication of agent, than occurs naturally. Studies of mice infected with scrapie by the intragastric route demonstrate the importance of Peyer's patches in the uptake and early multiplication of the agent (31). The same processes are likely to take place in cattle infected with BSE in the field, but without infectivity being detectable by bioassay in mice.

4. OTHER RESEARCH ASPECTS

4.1. Bovine spongiform encephalopathy in sheep

Scrapie developed in one out of six sheep that were orally dosed with a suspension containing 0.5 g. of BSE-affected brain. Strain-typing studies showed that the BSE agent was present in the brain of this sheep, and also in the spleen (13). The latter finding is in contrast to the failure to detect any infectivity in the spleen and other non-CNS tissues from BSE cases. This raises the possibility that sheep might be able to transmit the BSE agent, if present, by the same mechanisms that sustain natural endemic scrapie.

The BSE epidemic in the UK probably originated from sheep scrapie (32, 48). However, the feed-borne recycling of infection in cattle rapidly led to the selection of a bovine-adapted BSE agent that is different from scrapie strains (5). Both sheep and cattle in the UK were exposed to BSE, via concentrated feed, prior to the ruminant protein feed ban (July 1988). Although the average contamination per tonne of feed was low (32), this resulted in over 160,000 cases of BSE because of the high rate of concentrate feeding to dairy cattle and the absence of a species barrier. In contrast, the risks of feed-borne infection of sheep with BSE would have been lower because UK sheep received much smaller amounts of concentrated feed and the effective exposure would also have been reduced by the extent of the species barrier.

Whether or not the BSE agent (or a new scrapie strain derived from it) could become endemic in sheep will be determined by three factors. First, the number of breeding ewes that were infected via feed, prior to 1988. Secondly, the extent to which the BSE agent was preferentially selected in sheep of different PrP genotype. Thirdly, the rate at which the new agent is transmitted naturally. Research is needed into whether the BSE agent is naturally transmitted between sheep because of the potential risks to man. However, the risks from scrapie could change at any time, in any affected country, if a mutant strain arose in sheep and became endemic.

4.2. Bioassays across the species barrier

Most bioassays of BSE infectivity have been carried out in mice because it is a cost-effective way of comparing the relative infectivity titres of a large number of tissues (34) and because incubation periods are shorter in mice than in cattle (5). Mice have also been used to compare the relative efficiencies of oral and parenteral routes of exposure to BSE (26).

However, the sensitivity of these bioassays will inevitably be reduced by the cattle-to-mouse species barrier. The consequence is that infectivity titres in the CNS will be underestimated, and potential differences in titre among some of the "BSE-negative" tissues will be obscured. The true difference in titre between tissues such as brain and muscle is likely to be several orders of magnitude greater than can be demonstrated by bioassays in mice. Bioassays of selected tissues in cattle are in progress in the UK.
The species barrier will also reduce the effect of any exposure of man to BSE in tissues from infected cattle. It has been shown that the expression of multiple copies of a human PrP transgene in mice that also expressed their own PrP gene, did not reduce the incubation period of injected BSE (7). Since the BSE agent seems to occur as a single strain, this finding implies that the cattle-to-man species barrier is greater than that between cattle and mice. How much greater the cattle-to-man species barrier might be is being investigated by studies involving the transmission of BSE to transgenic mice in which the mouse PrP gene has been deleted and replaced by the human PrP gene (7).

4.3. Inactivation studies

The BSE agent has properties similar to those of other TSE agents when exposed to heat, and to chemical disinfectants such as sodium hydroxide and hypochlorite (41). A large scale study has been carried out in which brains from BSE-affected cattle were mixed with waste animal material before being rendered using facsimiles of different commercial processes. No infectivity was detected in samples of tallow, nor in most samples of meat-and-bone-meal. However, the maximum demonstrable loss of infectivity was only 80-fold and some processes caused no loss of infectivity in meat-and-bone-meal (42).

An identical study is being carried out using brains from scrapie-affected sheep in which the titres of infectivity were higher. Again no infectivity was detected in samples of tallow. However, some scrapie infectivity survived in meat-and-bone-meal produced by all processes except those carried out under pressure at high temperatures. In these cases, the maximum demonstrable loss of infectivity was about 5,000-fold. These studies indicate that even the most effective rendering processes may not completely disinfect waste material containing high titres of scrapie or BSE.

4.4. Diagnosis

Despite much research, the detection of modified PrP protein in tissues outside the CNS provides the only laboratory test for early TSE infection. However, use of the test is limited to solid tissues, such as spleen and lymph nodes, obtained by biopsy or postmortem. Also, current methods for detecting modified PrP are not sufficiently sensitive to exclude the presence of infection. This is illustrated by a study of mice at different times after infection with mouse scrapie. The detection of modified PrP in spleen, by western blotting, was 100,000 to 10 million times less sensitive than bioassays (39).

This difference would be reduced by the use of high-affinity antibodies to PrP and efficient methods for measuring antibody binding. Further improvements would follow the development of antibodies which recognise epitopes that are unique to modified PrP. A major breakthrough could be anticipated if the genome of TSE agents was found to be a nucleic acid because polymerase chain reaction (PCR) technology could then be applied.

REFERENCES


