Creutzfeldt-Jakob Disease (CJD) is a rare brain disorder that causes a rapidly fatal dementing illness. This disease was first described by Creutzfeldt and Jakob in the early 1920s.

CJD belongs to a group of diseases called Transmissible Spongiform Encephalopathies. This group of diseases include: classical CJD, scrapie of the sheep, mink transmissible encephalopathy, deer/elk chronic wasting disease, bovine spongiform encephalopathy (BSE), and feline spongiform encephalopathy.

**Etiology**

The agents responsible for these diseases all show some “unconventional” characteristics that separates them from the viruses.

- The infected tissues contain an infectious agent that can be transmitted to other animals with varying degrees of success and long incubation periods. Ninety percent of CJD infected tissue will cause a similar disease in monkeys after a long incubation.

- The infectious agents are filterable and replicate like viruses. There stops the analogy with viruses.

- The unusual pattern of resistance to disinfectants suggest that these agents do not have a nucleic acid genome for their reproduction.

- There is no evidence of immune (cellular or humoral) or inflammatory response. There is no cytopathic effect and no formation of viral-like particles.

The most recent hypothesis is that of an “infectious protein”. In the brains of diseased animals, there is an accumulation of filamentous proteins. This protein can infect other animals. It loses its infectious properties after proteolytic treatment. Thus the term Prion was introduced, standing for proteinaceous infectious particle. This protein, abbreviated PrP is the replicative molecule (and not a nucleic acid, as in viruses).

All prion diseases have the following characteristics:

- No immune (cellular or humoral) or inflammatory response
- No cytopathic effect and no formation of viral-like particles
- All infections cause subacute spongiform encephalopathies:
  - Vacuolar changes in CNS cells
  - Spongiform degeneration
  - Loss of neurons
  - Amyloid plaques, when present, are diagnostic
  - Accumulation of filamentous proteins in brains

Revised 3/8/2013
Epidemiology

Classical CJD or sporadic CJD: The disease occurs in sporadic cases worldwide at a very low rate of one case per million per year. It has been reported from some 50 countries in the world. The cause of the sporadic cases is unknown. Attempts to link these cases with disease in animals were not successful. In areas where scrapie was prevalent, there was no higher incidence of CJD. Until recently, there was no evidence that these cases were linked to animal infectious agents. The current hypothesis is that sporadic prion disease results from the spontaneous conversion of PrPc (the normal prion protein) into PrPsc (the abnormal prion protein).

Most affected patients are 40 to 75 years old. Cases in those as young as 16 years and as old as 85 years have been reported.

Familial cases or Gerstmann Sträussler Scheinker (GSS disease): CJD rarely occurs in small familial clusters. In the 1980s there were 73 families known worldwide with more than one case of CJD (for a total of 286 cases). The most recent hypothesis is that many familial diseases may arise from a mutation of the PrP protein. Most cases of GSS are familial and are linked with a specific mutation resulting in a modified PrP which then causes the disease. The disease occurs with an autosomal-dominant pattern of inheritance. Familial CJD accounts for about 10% of cases. Twelve point mutations and several insertions associated with familial CJD have already been identified in the gene encoding PrP (designated the PRNP gene in humans). The two best-known foci of familial CJD are in rural Slovakia and among Libyan Jews living in Israel.

CJD is not transmitted by contact, droplet, or exposure to blood and body fluids of sick patients. The incidence is NO higher among individuals with the greatest exposure to human blood and blood products, namely those with hemophilia, sickle cell anemia and thalassemia or health care workers.

CJD can be transmitted from person-to-person through direct contact of brain tissue from the sick person to the brain tissue of the recipient. Such contact has been observed through:
- Graft of dura mater
- Use of improperly sterilized neurosurgical instruments
- Human growth or gonadotropic hormone therapy

Infectivity of tissue

To date, all known cases of iatrogenic CJD have resulted from exposure to infectious brain, dura mater, pituitary, or eye tissue. This is likely due to the high levels of abnormal prions in the CNS. However, from the results of tissue infectivity studies in experimental animals and epidemiological studies in humans, it has been well established that the infectious agent may be present in many body tissues (Table), but that prions are present in lower numbers than in the brain; therefore, transmission is less likely. Consistent experimental transmission of infectivity has been possible with homogenates of brain, spinal cord and eye tissue.

Transmission occurs in less than half of the attempts with preparation of lung, liver, kidney, spleen, lymph node, and CSF. Transmission to primates has never been documented with any body fluid other than CSF. Prions have been isolated from the blood of infected guinea pigs, mice, and patients with CJD. There are no known cases of CJD attributable to the reuse of devices contaminated with blood or to the transfusion of blood products. Therefore, although transmission of CJD from human blood to laboratory animals by means of intracerebral inoculation have been reported, attempts to transmit CJD from CJD-infected patients to primates by means of whole blood or serum have failed.

Table: Tissues as sources of prions and risk of transmission through fomites
- **High risk:** Brain (including dura mater), spinal cord, and eye (e.g., corneas)
- **Low risk:** CSF, liver, lymph node, kidney, lung, and spleen
• **No risk:** Peripheral nerve, intestine, bone marrow, whole blood, leukocytes, serum, thyroid gland, adrenal gland, heart, skeletal muscle, adipose tissue, gingiva, prostate, testis, placenta, tears, nasal mucus, saliva, sputum, urine, feces, semen, vaginal secretions, and milk

Surgical instruments that came in contact with "no risk" tissues can be sterilized the usual way.

The **incubation period** for iatrogenic CJD is long, ranging from two to 30 years.

**Clinical Description**

Dementia (memory loss, mood changes, judgement errors) is always present and is often the first manifestation of the disease. Patients lose interest, become apathetic or irritable, experience sleep disorders, intellectual decline and disorientation. They may also have tremors, disturbances of gait, stance and loss of motor control.

As the disease progresses, the patient may experience hallucinations, delusional ideas and confusion. In some patients the cerebellar and visual abnormalities (even cortical blindness) predominate. At the end, patients are mute, stuporous, spastic and rigid. The disease rapidly progresses to death within six months. Less than 10% have an illness that lasts up to three years.

CJD may be mistaken for Alzheimers with myoclonus, multi-infract dementia, alcoholic or nutritional deficiency syndromes or brain tumors. However, the presence of cerebellar involvement, typical EEG changes and rapid deterioration over a few months, secures the diagnosis.

**Laboratory Tests**

Most laboratory tests are of little value in the diagnosis of CJD. Examination of the CSF may reveal a mild elevation in the protein, but otherwise, the CSF is normal.

**Detection of the 14-3-3 proteins:** The 14-3-3 proteins are a family of conserved regulatory molecules expressed in all eukaryotic cells. A striking feature of the 14-3-3 proteins is their ability to bind a multitude of functionally diverse signaling proteins, including kinases, phosphatases and transmembrane receptors.

Detection of 14-3-3 proteins has been described in the CSF of patients with CJD by using a modified western blot (WB) technique. The analysis of 14-3-3 protein in cerebrospinal fluid (CSF) was shown to be highly sensitive and specific for the diagnosis of CJD. The positive predictive value is 95% and the negative predictive value is 92%. CSF analysis for 14-3-3 protein should thus be performed in any case suspect for CJD.

False positive results have been reported in conditions producing acute neuronal destruction such as herpes simplex encephalitis, hypoxic brain damage, atypical encephalitis, intracerebral metastases of a bronchial carcinoma, metabolic encephalopathy, progressive dementia of unknown cause, ischaemic stroke, vascular dementia, HIV associated dementia and paraneoplastic syndromes.

Confirmation is made on the typical histologic pattern of spongiform encephalopathy. Microscopic examination of brain specimens from people with all types of CJD reveals a spongiform change accompanied by neuronal loss and gliosis. The diagnosis of CJD is facilitated by the immunohistochemical demonstration of PrP-res in the brain parenchyma. In addition, amyloid plaques composed of PrP-res may be found in specimens, depending on the TSE (transmissible spongiform encephalopathies). In new variant CJD (nvCJD), "florid" plaques (flower-like amyloid plaques surrounded by halos of vacuoles) have been consistently present. Biopsy specimens of the pharyngeal tonsil that show a marked accumulation of PrP-res, have also been valuable in the diagnosis of nvCJD.
**Surveillance**

CJD is not a reportable condition at this date. However, cases suspected of being of iatrogenic origin, cases suspected of being new variant, or cases that underwent brain surgery should be reported because of their public health importance.

The National Prion Disease Pathology Surveillance Center (NPDPSC) was established in 1997 by the Centers for Disease Control and Prevention (CDC) in collaboration with the American Association of Neuropathologists and recognized by Congress as the organization responsible for human prion surveillance in the United States. The Office of Public Health (OPH) collaborates with the NPDPSC to strengthen surveillance for prion diseases or transmissible spongiform encephalopathies. The plan is to implement an effective process of reporting timely suspected cases of CJD and other prion diseases.

It is critically important for OPH, that as many cases of suspected prion disease as possible are accurately diagnosed through examination of tissue obtained at autopsy, as tissue examination is the only definitive way to identify variant CJD and the various forms of prion disease.

The NPDPSC performs
- Histopathology, immunohistochemistry
- Western blot
- Prion gene analysis in autopsy and biopsy tissues to establish not only the diagnosis but also the type of prion disease.
- Cerebrospinal fluid (CSF) is also examined for the presence of the CJD protein marker 14-3-3.

All tests are free of charge and the results are reported to the health care provider. Data from individual cases are available upon request. Remaining brain tissues are stored and made available to other laboratories for research.

The NPDPSC currently tests approximately 60% of cases with prion disease (assuming the commonly accepted incidence of approximately one case per million of the general population per year) while other major prion surveillance centers perform tissue examination in 70%-80% of the cases (see attachment for cases referred and diagnosed).

To increase detection of suspected prion diseases in Louisiana, report all suspected cases of prion disease to the state of Louisiana Department of Health (DOH) Infectious Disease Section 504-568-8313 and to NPDPSC (216-368-0587) as soon as the diagnosis is suspected. The Surveillance Center is fully compliant with HIPAA regulations.

Information about the NPDPSC, specimen collection and shipping instructions can be obtained by visiting its website at [www.cjdsurveillance.com](http://www.cjdsurveillance.com) or by calling 216-368-0587.

All correspondence and shipments should be addressed to:
National Prion Disease Pathology Surveillance Center
Division of Neuropathology, Room 418
Case Western Reserve University
2085 Adelbert Road
Cleveland, Ohio 44106-4907
Telephone: 216-368-0587
Email: cjdsurv@case.edu

**Case Definition**

A case of CJD is defined as a dementing illness based on clinical symptoms.
Investigation

The purpose of investigation is to identify cases; to determine if the case is sporadic, inherited, or iatrogenic; and to monitor the trends and incidence of CJD in Louisiana.

- Upon receipt of a report of CJD, contact the physician and/or hospital (and possibly the coroner) to confirm the diagnosis.
- Question for other cases in the family.
- Obtain history of long term residence in a country endemic for Bovine Spongiform Encephalopathy (BSE), in particular Great Britain, history of dura mater graft or any brain tissue transplant, human gonadotropic or growth hormone administration, history of brain surgery.
- Contact the health care provider to monitor the course of the disease.
- Suggest the physician discuss the issue of autopsy with the patient’s family when appropriate. In the NPDSC’s experience, the great majority of the families give consent for autopsy. NPDSC can help make arrangements for the autopsy by identifying institutions willing to perform the procedure and, when necessary, by covering the expenses.
- Collect clinical information regardless of whether the autopsy was performed or not. Although it is essential that tissue be examined in as many cases as possible, if an autopsy cannot be performed, the case will be classified as possible or probable prion disease based on clinical data.
- Encourage physicians to clearly indicate the diagnosis of CJD on the patient’s death certificate when the clinical diagnosis applies because CJD is also monitored from mortality data.
- Advise patients’ families about supporting organizations. The CJD Foundation operates a national toll-free line to assist families and professionals (800) 659-1991.

Hospital precaution and isolation: Standard precautions. No isolation is necessary.

There are concerns about the possibility of nvCJD being transmitted via infected surgical instruments. This had always been a theoretical risk, but the conclusive evidence of tonsil infection in the living, confirmed it.

In the United States there is a growing consensus that ultraconservative processing regimens are not necessary. Two major factors significantly affect the sterilization strategy for CJD contaminated instruments and devices.

One is the type of tissue to which the instrument has been exposed and the other is the cleanability of the device.

- If the item is exposed to high-risk tissue that contains a high prion burden and cannot be cleaned effectively, the instrument should be processed using one of the extended or specialized sterilization methods (decontaminated initially by autoclaving at 132 °C-134 °C for 18 minutes in a pre-vacuum sterilizer, or 12ºC for one hour in a gravity displacement sterilizer, or soaked in 1 N NaOH for one hour before terminal cleaning, wrapping and sterilization by conventional means), or discarded.
- When a potentially contaminated device is able to be cleaned and the prion/tissue load decreased or removed physically, the probability of infection transmission is significantly reduced, even if the tissue in question is a high risk tissue. Appropriate cleaning and reprocessing procedures should be carried out, however, in accordance with standard principles of disinfection and sterilization.
- If the item is not exposed to high-risk tissue or can be cleaned effectively then conventional processing and sterilization and disinfection protocols can be used.
- Among the most frequently asked questions are those regarding appropriate reprocessing protocols for flexible endoscopes after use on a patient with CJD. The current guidelines for cleaning and disinfection of these instruments need not be changed.
Environmental (Housekeeping) Surfaces: Environmental surfaces would not be expected to be associated with transmission of CJD to health care workers or patients. Floors, walls, counter tops, or other housekeeping surfaces in medical wards, autopsy rooms and laboratories that are contaminated with high-risk tissues should be cleaned with a suitable detergent in the conventional fashion. A 1:10 dilution of chlorine bleach can be used to spot decontaminate visible residues of tissue before cleaning.

**NEW VARIANT CREUTZFELD JACOB DISEASE (nvCJD)**

**History of nvCJD**

In 1985, the first cases of Bovine Spongiform Encephalopathy (BSE or Mad Cow Disease) were described in Great Britain. Based mainly on epidemiologic evidence, it appears that this represents a massive (170,000 cases since 1990) common-source epidemic. Shortly after the recognition of BSE, epidemiologic studies indicated that the source of infection was the meat and bone meal used in concentrated cattle feed. Changes in the rendering procedures of offal combined with a mutation seemed to have triggered this enzootic.

Since this disease could be transmitted to other animals, there was some concern for transmission to humans through consumption of infected animal tissue. The death in May, 1995 of the first adolescent ever to be diagnosed with CJD in the United Kingdom was followed in October, 1995 by the death of a second adolescent; by January 1996, three other young (29 years of age) persons became ill. Atypical pathologic results were beginning to be defined in these patients. On March 8, 1996, eight more cases of what came to be known as new variant CJD or variant CJD (vCJD) were reported. Since then the annual number of human cases reported in Great Britain ranged from ten to 30 per year.

**NvCJD is a variant of BSE**

- The analysis of the PrP fragments after protease digestion (position of the three fragments) and the relatively high concentrations of the di-glycosylated form indicated that nvCJD was distinct from the previously recognized forms of CJD and that similarities existed between the cases of vCJD and BSE. Thus, nvCJD is now regarded as human BSE.
- So far there is only a working hypothesis that transmission is likely the result from inclusion in the human food chain of tissues that contain the highest concentration of the transmissible agent. The major differences in human exposure to these tissues would have occurred before sick animals were banned from the human food chain in 1988 and again in 1989 when the specified bovine offals of otherwise healthy animals were removed from the human food chain.

**Epidemiology**

The cases were distinguished by the relatively young age at which the symptoms started. That age range is now 16 years to 52 years.

Infectivity is present throughout the body tissues in nvCJD patients. Infectivity is absent in the body tissues in all other forms of CJD and neurological disorders in patients. Infectivity throughout the body has serious consequences for iatrogenic cases.

This suggests that new variant CJD is uniquely different from all other forms of CJD, strengthening the supposition that it has a different cause. The presence of infectivity in non-nervous tissue for nvCJD suggests a similar effect for BSE and amplifies the likelihood of foodborne passage. The presence in non-nervous tissue can be used as a differential diagnosis of nvCJD vs. other CJD.

**Blood:** Significant concentrations of PrP-Sc in lymphoreticular tissues of variant CJD patients, but not in classical CJD patients, together with evidence for a key role for mature B lymphocytes in prion
pathogenesis, emphasized concerns that blood and blood products derived from patients incubating variant CJD may represent a greater risk than with material from classical CJD.

**Clinical picture**

The early symptoms are often psychiatric. It may be six or seven months before any neurologic signs appear.

The duration of the illness is relatively long, averaging approximately 14 months as opposed to the four to five months in classic CJD.

**Laboratory**

Pathologic results show florid plaques and extensive cerebellar involvement with multiple PrP deposits. As with BSE and FSE, the neuropathologic appearances are the mainstay of laboratory confirmation.

**Hospital precaution and isolation:** Standard precautions. No isolation is necessary.
Other Prion Diseases

**Scrapie**

Scrapie is an encephalopathy of sheep and less often of goats. It was first described in 1738 and was known in Europe (Britain, France, Germany and Iceland). Its incidence ranges from 5% to 50% in infected flocks. The overall picture is that of an endemic infection that fluctuates over many years. The main mode of transmission is *in utero* from ewe to newborn lamb. Epidemiologically minded shepherds had noticed that animals ingesting feed contaminated by fetal membranes caught the disease, therefore establishing its infectious nature. Experimentally, the infectious agent is transmitted by ingestion of tissues (mainly brain) or parenteral administration of filtrates of tissues from infected animals.

The disease occurs rarely before the age of two years.

The pathogenesis has been best studied with the scrapie agent. The intestinal tract and abdominal lymph nodes are infected first; infection appears in the brain a year or more later. Gastrointestinal tract involvement implies that, in nature, the scrapie agent probably infects sheep by the oral route. In experimental mouse and goat models of scrapie, after subcutaneous inoculation, the pathogenic agent also first appears in the lymphatic tissues and spleen before it can be detected in the nervous system. The route of entry of the pathogen, the infectivity of blood and of other tissues at different stages of infection and the distribution of the agent in infected animal species, all pose central questions for estimating the risk to humans from potential exposures to various TSE agents.

The animal first develops an intense itching (compulsive rubbing of hind limbs). Central nervous system symptoms consist of weakness and incoordination of the hind quarters, tremors and spastic movements later accompanied by paralysis and epileptiform convulsions. The animal loses weight and dies within six months.

Several other problems can cause clinical signs similar to scrapie in sheep, including: diseases of ovine progressive pneumonia, listeriosis and rabies; the presence of external parasites; pregnancy toxemia; toxins.

As natural scrapie occurs only in sheep of specific PrP genotypes, one proposed aetiology was that scrapie is simply a genetic disease. However, Cheviot and Suffolk sheep of scrapie-susceptible genotypes are found in Australia and New Zealand, both generally accepted to be scrapie-free countries. A study of more common Australia and New Zealand sheep breeds (Merinos and Poll Dorsets) was carried out in order to obtain more generally applicable estimates of Australia and New Zealand sheep PrP genotype frequencies. It was confirmed that animals of highly susceptible PrP genotypes are found in Australia and New Zealand. Interestingly, the Poll Dorset sheep, although born in New Zealand, were brought to the United Kingdom (UK) as young adult animals and subsequently remained free of clinical scrapie despite 21% of the sheep having scrapie-susceptible genotypes. These results have implications for the genetic control of occurrence of the equivalent human diseases.

**The survey of sheep scrapie strains in UK since 1986.**

To date, nine UK isolates of scrapie contemporary with the outbreak of BSE have been strain-typed. None has proved to be BSE-like and all seven that have been transmitted to mice, have strain typing characteristics within the range expected of classical scrapie.

**Scrapie in the U.S.**

The first case of scrapie in the United States was diagnosed in 1947 in a Michigan flock. The Michigan flock owner had imported sheep of British origin through Canada for several years.
In 1999, there were 29 confirmed cases of scrapie reported in the United States. Over 900 flocks in the U.S. have been diagnosed with the disease since it was introduced in 1947, the majority occurring in the eastern portion of the country. Scrapie has been diagnosed in flocks in 45 of the 50 states. In the U.S., scrapie has primarily been reported in the Suffolk breed. It has also been diagnosed in Cheviots, Corriedales, Dorsets, Hampshires, Finn sheep, Merinos, Shropshires, Montadales, Southdowns, Rambouillets and a number of crossbreeds.

Control includes developing a flock plan with the flock owner including the destruction of the affected animal. Rams are not known to transmit the disease. Infected females have a high probability for transmission. Owners of infected or source flocks must either conduct a post-exposure monitoring and management plan for five years after the last scrapie-positive or high-risk animal is removed, or participate in the National Voluntary Scrapie Flock Certification Program (VSFCP), complete monitored category and remain in compliance with the standards for exposed flocks for five years after the last scrapie-positive or high-risk animal is removed. The VSFCP is administered by the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA), and cooperating state animal health authorities.

Cases of scrapie have also been reported in goats raised in contact with sheep. There is no scientific evidence scrapie of sheep and goats can be transmitted to humans.

**Transmissible Mink Encephalopathy**

In 1942, the first outbreak of Transmissible Mink Encephalopathy, a scrapie-like disease, was reported in two mink breeding farms in Wisconsin. Epidemiologic data suggest that the infection was introduced by dietary supplement of ovine origin. Transmission occurs probably through the wounds inflicted by their mates and cannibalism. Vertical transmission (mother to offspring) does not occur in minks. Experimentally minks can be infected by inoculation of sheep scrapie brain material.

**Deer/Elk chronic wasting disease (CWD)**

CWD was first identified by biologists in the 1960s as a disease syndrome of captive deer. CWD is in the family of transmissible spongiform encephalopathies. CWD is a disease that attacks deer and some elk, but at this point, has never been linked to humans. It was detected in herds on the Wyoming/Colorado border in 1981, but it could have been in the herds before that. Herds of deer and elk below Cheyenne on the Wyoming/Colorado border have CWD and the disease has been detected in private elk herds around the USA. More recently, CWD has been diagnosed in privately-owned elk on game farms in Nebraska, Oklahoma, South Dakota and Canada. In areas with the highest outbreak of the disease, only 5% of the deer population and only 1% of the elk are known to have CWD.

There are no tests that can detect the disease in live animals. Only after brain tissue has been examined are biologists certain an animal has the disease. Infected deer and elk transmit the disease through animal-to-animal contact and/or contamination of feed or water sources with saliva, urine and/or feces. Transmission by feces was recently shown to be an important mode of transmission. Infected animals spread the prion through their feces long before they become ill. Each deer excretes about two pounds of fecal pellets a day. As wild herds move around, or captive herds are trucked between states, more soil becomes infected. In captive herds, up to 90% of animals develop the disease. CWD is more likely to occur in areas where deer or elk are crowded or where they congregate at man-made feed and water stations. In wild herds, one third of animals can be infected.

Prions tend to bind to clay in soil and to persist indefinitely. When deer graze on infected dirt, prions that are tightly bound to clay will persist for long periods in their intestinal regions. Outside the laboratory, nothing can inactivate prions bound to soil. They are also impervious to radiation. There is no chance chronic wasting disease will be eradicated.
The animal begins to show clinical signs, like twitching, staggering, circling, not eating or rubbing off hair. Other symptoms include excessive salivation, increased thirst and urination, stumbling, trembling and depression, always followed by death.

Because of the death of a Utah hunter, Doug McEwen, in March, 1999 from what is believed to have been Creutzfeldt-Jakob disease, officials from the USDA, Food and Drug Administration (FDA) and the CDC, along with state agencies, look more closely at tests from a year's hunt. Officials tried to establish some link between the disease and McEwen and a similar case that was diagnosed in Nebraska. McEwen had been a longtime hunter and frequently consumed wild game, but never hunted in the Wyoming/Colorado area, which had herds of deer and elk suffering from CWD. Officials hoped to take at least half of the target samples from areas where McEwen hunted.

### Mad Cow Disease /Bovine Spongiform Encephalopathy (BSE)

In 1985, the first cases of **Bovine Spongiform Encephalopathy (BSE or Mad Cow Disease)** were described in Great Britain. Based mainly on epidemiologic evidence, it appears that this represents a massive (170,000 cases since 1990) common-source epidemic. A variety of clinical signs have been observed, but the three cardinal features of the disease are nervousness, heightened reactivity to external stimuli, and difficult movement, particularly of the hind limbs. Spongiform change is evident in the brain and neuropathological tests remain the mainstay of a BSE diagnosis. The animal wastes away and dies within six months. The disease was transmitted experimentally to mice and cattle by use of brain homogenates from cattle with clinical BSE; thus BSE has all the features that define classical TSEs.

#### BSE epidemic in Great Britain

In Britain, cattle were given nutritional protein supplement (MBM for Meat and Bone Meal); viscera and trimmings of sheep and cattle were used. During rendering, carcasses from which all consumable parts had been removed were milled and then decomposed in large vats by boiling at atmospheric or higher pressures, producing an aqueous slurry of protein under a layer of fat (tallow). After the fat was removed, the slurry was desiccated into a meat and bone meal product that was packaged by the animal food industry and distributed to owners of livestock and other captive animals (e.g., zoo and laboratory animals, breeding species, pets). The process involved steam treatment followed by hydrocarbon solvent extraction to produce a protein rich and a fat-rich fraction. The protein rich fraction with only 1% fat was fed to cattle. The fat-rich fraction was sold as tallow. In 1970, the price of tallow fell and it was no longer profitable to extract the fat. Cattle were then fed a supplement with 14% fat. It seems that the high fat contents of the new supplement protected the infectious agents from steam inactivation. Starting in the 1970’s, cattle were fed a supplement which was contaminated with prions.

Even though **rendering procedures in other countries underwent changes similar** to those in the UK during the late 1970s, BSE has apparently emerged solely within the UK. The most plausible explanation is that the proportion of sheep in the mix of rendered animal carcasses and the proportion of scrapie infections in such sheep were probably higher in the UK than elsewhere. These proportions were apparently sufficient to bring very low levels of the etiologic agent in batches of rendered carcasses over the threshold of transmission in the UK, but not in other countries. An alternative explanation proposed in the recent Report of the BSE Inquiry is that a pathogenic mutation occurred in cattle in the 1970s. Either of these two hypotheses satisfies the need for an etiologic "seed" to survive the altered rendering process and escalate through recycling of an ever-larger number of infected carcasses. However, the bovine origin hypothesis assumes that a mutation occurred only in the UK and not in other countries where similar rendering processes would also have led to epidemic BSE if mutations were occurring. In humans, mutations have occurred all over the world, not just in the UK and there is no reason to suppose that humans differ in this respect from other mammalian species. It would therefore be peculiar if the UK had the misfortune to host the cattle world's only mutation.
Approximately two-thirds of the dairy herds in the United Kingdom have had at least one case of BSE compared with only one-sixth of the beef suckler herds. Furthermore, most of the affected suckler herds contained animals originating from dairy herds, which are fed differently.

The average age at which clinical BSE manifests itself is four to five years. Many animals in the national U.K. herd are slaughtered at significantly younger ages, and those infected with BSE would not have had a chance to develop the disease. Using methods developed for the retrospective analysis of the AIDS epidemic, Anderson and colleagues calculated that approximately one million animals in the U.K. herd must have been infected to have produced 170,000 clinical cases of BSE. These same workers predicted the number of cases of BSE that would occur in 1996 and in subsequent years. The calculations are based on a dominant feedborne source of infection; a small amount of cow-to-calf transmission was included because a long-term study, conducted by the U.K. Ministry of Agriculture, Fisheries and Food, indicated an increased incidence of BSE in calves born to mothers in the late stages of the incubation period of the disease. The results are compatible with a cow-to-calf transmission of approximately 10%, which in itself is not sufficient to perpetuate the BSE epidemic. The calculations predict a small number of cases and very few new infections by the beginning of the next decade. The predictions have been validated by the actual numbers in 1996 and 1997, which were 8,016 and 4,149, respectively.

Shortly after the recognition of BSE, epidemiologic studies indicated that the source of infection was the meat and bone meal used in concentrated cattle feed. Subsequently in July, 1988, ruminant protein in ruminant feed was banned. This ban immediately reduced the incidence of new infections, which began to be reflected in a diminution in the incidence of clinical cases five years later (the average incubation period) in 1993. Nevertheless, almost 36,000 cattle with BSE were born after the ruminant feed ban (a few as late as 1994), which indicates that the ban was not completely effective. Ruminant protein could be included in pig and poultry feed and cross-contamination of cattle feed in the production mills (and perhaps accidental exposure of cattle on the farm was possible) until the feeding of mammalian protein to all farm animal species in the United Kingdom was prohibited in 1996.

In 1989 the UK banned the use of brain and spinal cord - as well as tonsil, thymus, spleen and intestine - of cattle origin (known as Specified Bovine Offals or SBOs) in foods for human consumption. Cattle are continuously monitored for BSE in all affected countries; BSE is decreasing in the UK.

**Infection in Other Animals in Great Britain**

A feline spongiform encephalopathy has been described in Britain in some 90 to 100 domestic cats. In 1990, a case of spongiform encephalopathy was diagnosed in domestic cats; 81 additional cases in cats have occurred with a wide geographic spread throughout the United Kingdom. The annual incidence at the height of the outbreak was probably 10 to 15 cases per million cats. The most likely source of the infection was commercially produced cat food. In 1989, the pet food industry removed the dangerous bovine tissues, the specified bovine offal, before a statutory ban in 1990. The number of cases of feline spongiform encephalopathy (FSE) diagnosed in the United Kingdom has been declining since 1994 (1994, 16 cases; 1995, 6 cases; 1997, 6 cases). It was found in only one cat, an adopted stray, that was apparently born after the ban on specified bovine offal in pet food.

Spongiform encephalopathy has not occurred in dogs; Careful watch was kept on the packs of hounds used for hunting in the United Kingdom because they are often fed carcasses unfit for human consumption.

BSE has also been transmitted to exotic ruminants in zoos in the United Kingdom. Between 1986 and 1992, cases have occurred in bison, nyala, gemsbok, two species of oryx, greater kudu and eland. These animals became infected by eating the same meat and bone meal-containing concentrated feed responsible for the disease in cattle.

BSE infection in species other than ruminants was always considered possible. The true incidence is probably many times higher than observed because diagnosis is patchy and the disease was not statutorily
notifiable until 1994. A TSE indistinguishable from BSE has also been found in puma, cheetah, ocelot, and a tiger in zoos in the United Kingdom between 1992 and 1995. These animals became infected as a result of being fed raw meat, which would have included bovine central nervous system, a practice which has now ceased.

**BSE in other European countries**

No other European country seems to have been affected to the extent of Britain, some foci of BSE exist, but they seem to be very limited compared to the British endemic. The European Union statistics show the following numbers from 1990 to 1996: 161,000 cases in Britain, 205 cases in Switzerland, 123 cases in Ireland, 31 in Portugal, 13 in France and 4 in Germany. In one group of countries - France, Portugal, Republic of Ireland and Switzerland - the disease occurred in native cattle; this was thought to be in part related to importation of cattle feed from the UK. In another group - Falkland Islands (Las Malvinas), Oman Sultanate, Germany, Canada, Italy and Denmark - cases were only identified in cattle imported from the UK.

**Diagnosis and screening**

The European Union approved (in 2000) a new test to detect PrP-res, the abnormal protease-resistant form of the prion protein that is the only known molecular marker for BSE and related prion disorders. This test appears to be as sensitive as the conventional mouse bioassay and because results are available within 24 hours, may be practical for systematic screening of animals.

Conventional mouse bioassay, while effective in identifying BSE-infected animals, is not commonly done and is not practical for large-scale systematic screening because results are not available until one to two years later.

**Kuru**

Kuru was recognized as a disease by western scientists in 1956. In the mountainous interior of Papua, New Guinea, Kuru affected some 2,000 people in a population of 35,000 living in adjacent valleys. Every year some 200 people died from Kuru. The disease is characterized by cerebellar ataxia (incoordination), shiver-like tremors leading to paralysis and death within three to nine months.

In the 1920’s, the practice of eating the brain of dead kinsmen started. Brain tissue of the dead were squeezed and packed into bamboo cylinders and steamed. Females who prepared the ritual experienced much higher rates of infections. In some tribes, there were no older women alive. Transmission seems to occur during the preparation or consumption of tissue. Steaming would not be able to inactivate the infectious heat-stable agent. Kuru was experimentally transmissible to apes and monkeys, but the oral route of transmission was difficult to prove. Some authors suggest that oral transmission may have played a lesser role than contamination of hands, inoculation to small cuts in skin and through the eyes during the preparation.

Between 1957 and 1962 this practice was totally abandoned and no new cases have occurred among children born since. From 2,000 cases and 200 deaths per year in the early 50’s, the number was down to 28 cases living and 22 deaths in 1980. None of the children born after 1957 from mothers already infected, have developed the disease.

Kuru showed that 1) a spongiform encephalopathy occurred in human, 2) that the disease was transmitted by an infectious agent and that 3) although the exact mechanism of transmission was not completely proven, preventive measures were able to stop disease transmission.