Lingering Doubts about Creutzfeldt-Jakob disease: Mode of transmission

Running Title: Creutzfeldt-Jakob disease

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Abstract
Based on clinical and pathological observation Creutzfeldt-Jakob disease (CJD) been classified into three groups: (1) Familial; (2) Iatrogenic; (3) Sporadic: Shortly after the appearance of bovine spongiform encephalopathy (BSE), CJD a disease normally seen in older patients was identified in young patients with non-classical presentation. It now appears that patients all age groups have died of BSE infection. The distinguishing features between classical CJD and "new variant" (vCJD) include: a) Initial presentation with dementia; b) Confluent spongiform changes are very unusual in the cerebellum; c) PrP plaques are rarely observed.

For vCJD: a) Initially, difficulty with balancing and ataxia; b) Confluent spongiform changes are seen in the cerebellum; c) A large number of PrP plaques are seen.
The recipient of blood, human pituitary-derived growth hormone (hGH), and those infected with the BSE revealed extensive vacuolation of the cerebellum with numerous PrP positive plaques. However, in the brains of the blood recipient and hGH, PrP plaques were much smaller in size and have a similar distribution but is different from those infected with the BSE strain of the agent. These similarities and differences in size and distribution of PrP plaques demonstrate, the route of infection. Many of the brains of CJD cases infected through tissue grafts, electrodes and operations, have not been examined for PrP because immunostaining technique was not available in the past. To confirm human-to-human transmission it is important that these patients' brains should be re-examined for size and distribution of PrP plaques. The pattern and distribution of PrP plaques should be used as a guide to determine the strain and the route of infection.
Increasing number of CJD cases in the young population has further increased the risk from human to human transmission through tissue grafts, operations and blood and blood products. It is obvious that symptom-free phase in humans and animals cannot be regarded as infection-free. There is an urgent need to screen all animals going into human food chain. And also human blood and organ donors for CJD. There is an urgent need to clean all the surgical and dental instruments from all patients before they are reused by a pre-soak method.
There are two clinically distinct strains of scrapie in sheep: Type I, "itchy" and Type II, the ataxic "trembly" type. The clinical signs of Type II scrapie in sheep, ataxia is similar to those seen in BSE, vCJD and kuru. Evidence suggests that Type II is the cause of BSE, vCJD and Kuru. There is clear evidence of BSE maternal transmission. When cattle or mink are injected with the Type I strain, only a few will become ill exhibiting different clinical symptoms to those seen in BSE. When cattle, cat or mink are fed with Type I infected sheep brains, so far none developed clinical disease. By contrast feeding or injection with the BSE strain, 100% of calves, cats and mink develop the clinical disease. For eradication of BSE and to reduce the risk of infection to humans, the development of a vaccine against BSE is suggested. Such possibility should be fully explored.
Introduction

All human and animal transmissible spongiform encephalopathies (TSEs) of the central nervous system (CNS) identified by common findings the vacuole distribution in the brain. TSEs have a common infectious agent with over 20 different strains strain of the agent some with unique properties.

Creutzfeldt-Jakob disease
Creutzfeldt-Jakob disease (CJD) is a fatal neurological disease of man, attributed to a slow virus infection, with an incubation period extending into many years. Typically, CJD presents as a progressive mental deterioration similar to those seen in cases of Alzheimer's disease (AD). It is important to stress in older patients, the two diseases cannot always be distinguished while the patient is alive. Compared with Alzheimer's disease, CJD follows a more rapid course over a period of four to seven months and is almost invariably accompanied by a variety of neurological abnormalities, especially visual, cerebellar, and extrapyramidal deficits. The term CJD used by many authors has covered a wide spectrum of clinical symptomatology and neuropathology features, which are known to vary from case to case as discussed by myself in detail.

The important clinical diagnostic symptoms of CJD are: myoclonic jerks, mental deterioration, and Electroencephalograph (EEG) pattern of slow tracing. EEG is a technique for recording the electrical activity of the brain through the intact skull. In about 50% of CJD cases EEG specific pattern changes are important diagnostic indicators. However, in 25% of sporadic, and in almost all the new variant of CJD cases, the EEG pattern changes appear only in the advanced stage of the illness, when patients are no longer able to stand or walk. Other abnormal EEG discharges have been consistently observed in only two groups: subacute spongiform encephalopathy (SSPE) and in herpes encephalopathy. In many CJD cases death occurs within 3 to 6 months, but cases have been recorded with deaths resulting after 10 years. When one or more of these features is absent, particularly in cases with a long clinical duration of illness, the diagnosis of CJD becomes
Three Groups of CJD Cases

Epidemiological studies of the worldwide occurrence of CJD have revealed the existence of three groups: (1) Familial: these cases occur within the same. (2) Iatrogenic: these constitute a small percentage and are caused by accidental inoculation (through contaminated instruments) and some through the effect of contaminated human growth hormone (hGH). (3) Sporadic: Sporadic CJD, which forms the majority of cases, is rare, but found worldwide. Whatever the initial symptoms of the clinical disease and pathological findings may be, a transmissible infecting agent is common to them all, as is the case with all other SEs.

The Familial form of CJD

The proportion of patients with familial CJD represent approximately 5 to 15% of the total CJD cases. The major distinguishing features of familial disease are the earlier age at onset and the longer duration of illness. The problem with familial cases comes when one finds cases within a family where the relationship is by marriage. In general, the patients with familial CJD do not differ appreciably in their clinical and neuropathological features from sporadic CJD. There is no evidence that mothers are more frequently affected than fathers. Genealogical evidence shows skipped generations where there is no CJD case, single-generation occurrence, matrimony and twin occurrence and evidence of preponderance in maternal or paternal line relations. All these have made understanding difficult.

Iatrogenic CJD: Infection caused by the process of accidental inoculation: It continues to appear in new and unforeseen circumstances. Originally ascribed to contaminated instruments and grafts. The disease more recently turned up in a group of patients given growth hormone treatment. It is known that CJD is rapidly transmissible by a direct inoculation of infectious material from human to human, with incubation periods from two to five years. The differences in the incubation period for disease observed in these cases may be attributable, in part, to the route of inoculation, the dose of infectious material and the source of infection.

Since 1985, more than 65 cases of CJD have been described among recipients of pituitary-derived hGH. These cases have been reported in the USA, UK, and France. The clinical presentation in the hGH recipients of CJD cases starts with cerebellar function deterioration with
severe ataxia, especially of the legs, while mental deterioration is a late manifestation. These symptoms seen in hGH recipients were also typical of kuru cases. The EEG was consistent with a diffuse encephalopathy, although periodic discharges were absent. It is interesting to note that the clinical presentation of these hGH patients also resembles that of the "new strain" of CJD cases described in this paper.

Transmission of CJD from Human Tissue Graft

A 55-year-old man died following a case history of two months of incoordination, memory deficiency, involuntary movements and myoclonic. CJD was confirmed by histopathological examination of the brain. Soon after his death, a corneal transplant was performed from this donor to a 55-year-old woman. Approximately 18 months later she developed lethargy, nausea and ataxia. During the next eight months, neurological deterioration progressed and walking and swallowing difficulties developed. She died eight months from the onset of the disease, and CJD was confirmed after the neuropathological examination of the brain. In France between 1992 and 1994, four patients died. They all had received dura matter graft between four and seven years before the onset of CJD.

Two patients, a young man of 17 and a woman of 23, underwent surgical excision for intractable epilepsy. Both developed CJD 2.5 years and 2.25 years after stereotactic electroencephalographic exploration using silver electrodes. In both cases, two out of nine of the electrodes used had been previously implanted in the brain of a 69 year-old woman who had suffered from CJD. The electrodes used had been sterilised with 70% alcohol and formaldehyde for inactivation of the CJD virus.

A 28-year-old woman developed CJD 19 months after a neurological operation, which involved the grafting of commercially available dura mater. An additional case was reported in a 25-year-old man in New Zealand, who rapidly developed progressive dementia 31 months after neurosurgery for head injuries sustained during a fall. Dura mater tears were repaired with commercially prepared imported cadaveric human dura mater graft. CJD was confirmed after the neuropathological examination of the brain. The patient had no family history of degenerative neurological disease nor had he received hGH treatment. Several further cases raised suspicion, and gave conclusive proof of accidental transmission
from person to person. Another 28 year old female underwent the resection of her right ear and a dural graft was placed in the right temporal area. The woman while pregnant complained of nausea, vomiting and over the following four weeks developed unsteady gait and slurred speech. Mental status deterioration was present and the patient was unable to walk. Repeated EEG over a period of time showed marked slowing with sharp periodic waves typical of CJD. The patient died and the disease was confirmed from biopsy.

The potential consequences of such an event were recognised, and a project to assess some members of the Medical Research Council (MRC) considered the risk in 1970s in the UK, to examine the risk that some hGH batches might be contaminated with the CJD agent. A study was commissioned by the MRC. The group working on the slow virus research, based at the Edinburgh Neuropathogenesis Unit, undertook to monitor the efficacy of the method followed for the preparation of hGH. There are a number of drawbacks and problems with this kind of experiment. A limited amount of the total material is inoculated, possibly once or twice in these experiments and the level of the virus may remain undetectable. This does not imply necessarily the complete absence of virus. Further, because of the slow nature of the virus activity, the disease is undetected since the animals are killed or die before the clinical symptoms appear. In some instances, tissue from the first set of animals, who have reached the end of their life span, is passaged into fresh groups of animals. In such experiments, it is always a problem when to terminate the experiment and how to interpret negative results as is very obvious from the CJD cases associated with hGH.

**CJD and Blood Transfusion**

Persistent viraemia (presence of virus in blood) and preferential replication of the virus in low-density lymphocytes have been demonstrated by two different groups in 1980s. Tateishi (1985) and Klein et al (1993) independently transmitted the disease from blood samples of a patient (and mice) infected with CJD. They also inoculated mice with 20 µl of 10% crude suspension made in normal saline of the brain, cornea, and untreated cerebrospinal fluid (CSF) and urine from this patient. Animals infected by above sources of material showed clinical signs and common pathological changes; the incubation period
varied, the brain, 789 ± 112 days; cornea, 1037 days; blood, 1080 ± 69 days; urine 880 ± 55 days while animals inoculated with CSF only remained healthy. Mouse-to-mouse transmission through blood inoculation has been successful after a mean incubation period of 365 days.

**Blood Transfusion: Incidence**
Esmonde et al (1993) in one epidemiological study in the UK of 202 definite and probable cases identified 21 CJD patients who had received a blood transfusion, and 29 who had donated blood. With a definite history of blood transfusion and comparison with controls, they found no significant difference. The mean interval from blood transfusion to the onset of the clinical symptoms of CJD was reported to be 174 months, median 114, ±18, range 2 to 588. The clinical features recorded in the blood transfusion CJD recipients were similar to those observed in the sporadic cases, and therefore, Esmonde et al suggested that blood transfusion is not a major risk factor for CJD. However, he concluded that epidemiological evidence does not exclude the possibility that isolated cases of CJD are caused by the transmission of the causative agent through transfused blood. Further, every precaution should be taken to ensure that blood and blood products are not obtained from individuals having CJD, or from high risk members of CJD families, or people who have been treated with hGH. More efficient methods must be developed to detect pathogens. As viraemia has been proved in guinea pigs, mice and CJD patients, blood for transfusion and blood products for medical use must be fully tested.

**JD and EB**
Two sisters, aged 51 and 59, both developed the clinical symptoms about six years apart. They lived together for 42 years but were separated for the last 10 years. The family related their clinical symptoms to BSE cows on their farm. JD died first in 1989. She woke up one morning with her shoulder hurting. Within days, she developed a weakness in her legs and found it difficult to walk and was treated with anti-depressants. Her neurologist initially suggested Huntington's Chorea. In the hospital, after an EEG test, CJD was confirmed. No post-mortem was carried out.

In September 1996 the second sister, EB, after an illness of over 18 months, also died at the age
of 59 suffering with CJD. She developed a slight tremor in hands, which appeared similar to early symptoms of Parkinson's disease, which gradually progressed to staggering and loss of balance. Unlike her sister, who was a blood donor, EB was a recipient of blood, and had received fairly large volumes of blood over a four-year period. The author tried to trace EB’s blood donors. Out of five, only three were traceable, and these were fit and healthy. A comparative histopathological examination of the brain revealed extensive vacuolation of the cerebellum and numerous PrP positive plaques. The PrP plaques were much smaller in size compared to the patients infected with the BSE strain of the agent, but were similar in size and distribution in the cerebellum to those observed in human growth hormone cases. This identical clustering distribution of PrP plaques in the brain of patient EB strongly suggests that this case was infected through blood transfusion.

3) Sporadic: Sporadic CJD, which forms the majority of cases, is rare but found worldwide. The annual incidence of classic CJD has been estimated to be one per million of the human population. However, published data did not support the claim of one per million. The annual incidence among ethnic groups in some countries may reach more than one per million, while in the general population in the USA it ranges from 0.26 to 0.4, France, 0.32, and England 0.09. Since BSE appeared, the incidence of all CJD cases in the UK has increased year by year it is now, nearly 2 per million.

An Ataxic form of Subacute CJD

Foley et al (1955) reported three cases of subacute progressive Encephalopathy occurring in middle aged patients under the heading “The Ataxic-Cerebellar Form of CJD”. Later Brownwell et al (1965), described an additional four cases of the ataxic-cerebellar form of CJD. The outstanding clinical features, in order of their appearance reported, are rapidly progressive ataxia of cerebellar, with imperfect articulation of speech due to disturbances of muscular control (dysarthria); involuntary rhythmic jerking movements, dementia, progressing to coma and, finally, a state of generalised muscular rigidity in which the involuntary movements tended to disappear. In the final stage speech was totally lost. The duration of the disease in these cases was about 13 months with a mean of seven months.

New Strain CJD Cases

A new variant of CJD has been identified in the UK and it is unique in that it affects young people. The clinical course of the disease in the new strain is distinct from that usually
seen in sporadic CJD. These symptoms are the same as those seen in the ataxic-cerebellar form of CJD and those seen in growth hormone treated patients. Symptoms include behavioural and mood changes along with depression becoming more marked with a swaying and weaving gait. The patient tending to trip and stumble. Balancing and walking become difficult and the patients feel as if they are going to fall and need support. Memory impairment becomes apparent with the progression of disease. None of these cases had the typical EEG patterns traditionally associated with CJD. During the last stage, EEG results showed some slow amplitude activity. A similar pattern is observed in growth hormone treated patients. Symptoms were so different from typical CJD cases as to cause these patients to be referred to a psychiatrist. Initial diagnosis in all these cases was made by demonstrating nemavirus and SAF in their brains or in urine samples. Based on conventional and accepted diagnostic criteria for CJD, none of these cases would be even classified as “probable” cases of CJD on clinical grounds.

**Routine Diagnosis and Confirmation of CJD Cases**

The diagnosis of CJD often presents problems, because of the time taken to process tissues for histological examination. Confirming the condition by transmission of the disease into animals because of its long incubation periods extends the required time even further. The difficulties faced in reaching the correct diagnosis may partially explain the low incidence of the disease and the current known cases perhaps represent only the tip of the iceberg. It is conceivable that large segments of the population are infected without any, or with only trivial or subclinical signs, or the true nature of the disease maybe concealed by some other co-existing disease.

In the atypical cases, the clinical symptoms and neuropathological features were markedly different from those seen in typical sporadic CJD. The unusual features included the absence of the EEG changes seen in "classical" CJD. Based on conventional and accepted diagnostic criteria for CJD, none of these cases would have been considered as even "probable" cases of CJD on clinical grounds. Initially, they had been identified as CJD cases because their brains were examined by touch "impression" and negative staining technique, which demonstrated the presence of tubulofilamentous particles and SAF in
their brains, and which confirmed the diagnosis. This technique helped to identify and confirm the diagnosis. In sporadic CJD cases, confluent spongiform changes in the cerebellum are very rare.

Plaques

Based on immunohistochemical staining process, two types of plaques have been identified in CJD brain tissue.

(i) amyloid β-protein positive (APP) plaques - termed amyloid plaques - are a "hallmark" of AD. A small number of amyloid plaques have been observed in about 15% of CJD cases.

(ii) Protease-resistant protein (PrP 27-30 kDa) positive plaques derived from PrP33-35 kDa precursor protein (PrP^C). It is important to point out that PrP positive plaques have not been observed in AD or any other none-SE neurological disorder.

Those infected with the BSE strain of the agent, the most consistent striking neuropathological feature was the staining of PrP plaques varying in size from 2-35m. Immunohistochemical staining showed that pericellular PrP plaques were extensively distributed throughout the cerebrum and cerebellum, with smaller numbers in the basal ganglia, thalamus and hippocampus.

The size and pattern distribution of PrP plaques differences were very obvious in the cerebellum of recipients of pituitary-derived hGH CJD cases when compared to young sporadic CJD patients infected with the BSE agent. The exception was one patient, EB, who had received blood. The PrP plaques were much smaller in size, as seen in hGH cases. This identical size and distribution of PrP plaques in brains of hGH treated and blood recipient cases suggests that the blood transfusion case was infected through infected blood.

Urine test

An ion-capture technique was used to demonstrate amyloid precursor protein, or its segments, in clinically diagnosed cases of AD. This involves concentration of APP from urine samples, and the concentrate was subjected to Western blotting. Using APP antibody 369, it was possible to demonstrate one, two or all three APP segments from urine of AD cases, but not from healthy individuals, and this may provide a significant contribution for diagnostic work in relation to CJD and nvCJD. Similarly, this technique could be applied using PrP antibody to demonstrate protease-resistant protein/SAF in BSE and CJD by Western blotting, or a concentrated sample can be used to prepare grids for electron
microscopic examination.

**Nemavirus Particles in Creutzfeldt-Jakob Disease Brains**

Examination of CJD brains by cutting thin sections revealed tubulofilamentous particles termed Nemavirus particles (NVP), similar to those seen in natural scrapie of sheep and experimental scrapie in mice, rats and hamsters, and are described in detail in a separate section. These are seen in all transmissible SEs including BSE. The number and distribution of NVP may vary from one case to another, and even, in the same case, from one area of the brain to another. Further, it has been demonstrated that scrapie-associated fibrils (SAF) form the core of these particles and that, as with scrapie, the Nemavirus in the outer coat contains a single-stranded DNA protected by an unknown protein layer.

**Development of Touch Impression Technique**

To simplify the examination of experimentally infected animal tissues by EM, a simple impression technique has been developed to demonstrate NVP/SAF (Narang et al, 1987; 1988) and this method was validated by experiments, using a variety of known human and animal viruses. This method was applied to experimental scrapie CJD brains. NVP have been identified in all scrapie and CJD cases so far examined. The method was also applied to tissue samples taken from hamsters at various stages of the incubational period of the disease and from uninfected tissues, without the researcher knowing which samples were from normal and which were from infected animals. The status of all tissues under test was correctly identified, on the basis of the presence or absence of NVP. Furthermore, the samples taken 20 days post-inoculation, which is a quarter of the way through the incubation period, gave consistently positive results by the touch method. However, histological examination of these brains revealed no spongiform changes. It would seem reasonable to conclude from this that the technique could be applied for routine sample screening of suspected animals for diagnostic purposes.

**Nature of the agent**

Recently, the BSE Inquiry reported evidence regarding the nature of the TSE agent and the supposed role of mutation. Already, it appears that the pronouncements of the BSE Inquiry have become conventional wisdom. Because of the overall importance of this matter, a number of
hypotheses on the nature of the agent have been proposed and discussed before (Narang, 1997, 2001). Depending upon which hypothesis an author favors, references are selected to support a chosen hypothesis and completely ignore references which do not fit a particular way of thinking. At times, hypotheses are being misquoted and stressed as facts. Since the public and the media have joined in the debate, the issue has become very complicated. Two major hypotheses, protein versus virus, along with mutation in the PrP gene hypothesis are discussed in detail.

Unlike many common viruses, the TSE agent infects a range of hosts and, has no species barrier effect. This property is not unique to the TSE agent. Foot and mouth and rabies viruses infect with equal potency across a wide range of animal species. The ability of the TSE agent to remain remarkably stable over a wide range of physical and chemical in particular, its resistance to nucleases, irradiation with ultraviolet light, hydrolysis, the degree of its physiochemical stability and that a remarkable amount of the infective dose can often survive to heat of 132°C for half an hour have been discussed before (Narang, 1996, 1997, 2001). Many of these properties such as the resistance to nucleases, to irradiation with ultraviolet light, or to hydrolysis, are not quite as unusual as previously thought. E coli and Clostridium botulinum after repeated irradiation developed resistance in a single strain. It is obvious that heat treatment does destroy infectivity (Narang, 1995). However, the majority of infectivity can be abolished by autoclaving, and almost all by 1N sodium hydroxide (over 55°C) and hypochlorite treatment (Narang, 1995).

When attempting to trace the origins of an apparently new disease, best first practice is to look for an agent that pre-existed in nature. In the past, two distinct clinical syndromes in sheep, both of which have been called scrapie. Type I is manifested by itchiness and loss of wool (the common type). Type II, is manifested by trembling and ataxia. When sheep are inoculated with brain tissue from cows with BSE, they develop trembling and ataxia (Type II scrapie). The major clinical signs, trembling and ataxia in BSE, Kuru, and many of the recent cases of CJD are identical. The BSE strain is the single most virulent strain and is capable of infecting a new host by oral route - animals such as cats, mink, cows and humans. It is obvious from the range of host species infected that the strain of the agent has an upper hand over clinical signs and incubation period, rather than the hosts’ genetic makeup. Prusiner and his colleagues considered that the individual prion, is the agent. Professor Roger Morris without evidence suggested to the BSE Inquiry (www.bse.org.uk) that a spontaneous mutation in a somatic cell of the prion protein gene in a single cow led to a sporadic case of BSE, while feeding of this animal to other animals was the cause of the eventual epidemic. Further, Dr Jim Hope suggested that a mutation in the PrP gene of the germ cell of sheep, and another in the
genome of the agent: not one but two mutations resulted in the generation of a novel scrapie strain. No evidence has been offered to support these theories.

Role of PrP: PrP33-35 kDa the precursor protein of PrP, is a normal cellular housekeeping protein and is not an essential component of the infectious agent has been discussed in detail in a previous review (Narang, 1997, 2001). Experimental transmission studies have revealed that the replication of the infectious agent starts only after inoculation or feeding of a new host species. None of the point mutations from the donor host are copied in the PrP gene. It is a well-established fact that the strain of the TSE agent “breeds true”, retaining its original properties during the passage from one animal species to another. These findings clearly demonstrate that prion is not the agent.

In a recent study involving transmission of the BSE agent to mice, it was found that, although all of the mice injected with homogenate from BSE-infected cattle brain exhibited neurological symptoms and neuronal death, about 55 percent of them had no vacuoles or detectable PrPSc. Next, when brains of PrPSc- mice were used to inoculate a second series of mice, most developed neurological signs but a few presented the PrPSc- pattern again. In the third pass, use of brains of PrPSc- mice from the second pass transmitted the classic form, and almost all of the PrPSc- negative pattern except in one, single mouse had disappeared. It is, therefore, clear that the BSE agent was replicating in the new host without benefit of PrPSc.

Recently Balter (1999) analyzed the protein-only hypothesis suggested by Prusiner, that is, familial CJD is linked to a spontaneous mutation in the PrP gene (Prusiner, 1994). At the time, many researchers thought that the protein-only hypothesis had been validated when two of the mutant mice expressing high levels of the PrP appeared to have spontaneously developed neurological symptoms. Later, however, it became apparent that the pathology was different, and the brain tissues had no infectivity.

Recently Manson et al (1999) repeated Prusiner’s experiments with a new technique. Unlike the Prusiner study, the transgenic mice expressing high PrP levels did not spontaneously develop the disease during their life span of about 900 days. However, when these mice were inoculated with infected-brain extracts, they did develop the clinical disease after an average of about 280 days.

Furthermore, it is evident from Prusiner’s own studies that, despite human PrP being expressed
4- to 8-fold higher in levels by transgenic mice compared with normal human PrP\textsuperscript{C} levels, these mice with higher levels failed to develop PrP\textsuperscript{Sc} containing human or human-mice hybrid PrP\textsuperscript{Sc} (Telling, 1987). Following these experiments, Prusiner’s group, have concluded that another “X” protein, that is, a macromolecular chaperone other than PrP\textsuperscript{Sc}, is required in the posttranslational process as previously suggested by Narang (1992).

Sheep inoculated with BSE develop Type II scrapie exhibiting trembling. When cattle or mink are injected with the Type I strain, only a few will develop a clinical disease. By contrast, no clinical disease has so far been shown in cattle or mink by feeding them with Type I infected sheep brains. However, either by injecting or feeding with the BSE strain, 100% of calves and mink develop the clinical disease. Evidence suggests that Type II is the cause of BSE. Identical clinical signs of Type II trembling are found in kuru and many of the recent cases of Creutzfeldt-Jakob disease. The BSE agent has caused spongiform encephalopathies (SEs) in domestic cats, tigers and in some species of ruminants in zoos. The nature of the BSE agent remains unchanged when passaged through a range of species irrespective of their genetic make up demonstrating that variations in the host PrP gene is not a major factor in the susceptibility to the BSE agent. Since more than 85 zoo animals of many species have been diagnosed with SEs, from these studies it seems reasonable to conclude that the BSE agent can infect almost all mammalian species including humans. For eradication of BSE and to reduce the risk of infection to humans, the development of a vaccine against BSE is suggested. Such possibility should be fully explored.

For a number of years, the phenomenon of interference between the two strains of the agent has been known. Based on this phenomenon, I proposed that the Type I strain of scrapie acts as vaccine against BSE, Type II scrapie. Many people have eaten Type I strain unknown to them and, therefore, will have a natural protection. In summer 2000, at Birmingham, Dr. S. Prusiner stated that his colleague, Dr. Mike Scott, believes that sheep carry two strains of the agent: scrapie strain and the BSE strain. The agent has always been in sheep and probably always will be. Now Dr Stanley Prusiner has openly admitted the phenomena of interference between the two strains of the agent. He believes that the scrapie strain is somewhat dominant, preventing the BSE strain from infecting cattle and people when both are present. In other words, the scrapie strain acts as a vaccine against the BSE strain. The phenomena of interference will only be effective if the agent causing the disease is a virus. The final conclusion of these findings suggests that PrP itself is not the agent, therefore the infectious agent is something other than PrP\textsuperscript{Sc}. Therefore it must be a virus.
Further reading


Narang HK. Death on the menu. CJD Victims: Diagnosis and Care: Families Devastated by Mad Cow Disease Reveal their tragic stories. Newcastle Upon Tyne England: HH Publisher, 1997.


