

Creutzfeldt-Jakob Disease and other Prion Diseases



Creutzfeldt-Jakob Disease
Foundation, Inc.

CJD HelpLine 1.800.659.1991

CJD Foundation National Toll Free HelpLine 1-800-659-1991

The Creutzfeldt-Jakob Disease (CJD) Foundation, a nonprofit 501(c)(3) has established a NATIONAL TOLL FREE HelpLine. The number is **1-800-659-1991**. The HelpLine is answered 9-5 Monday thru Friday. At all other times messages can be left and they will be returned promptly.

PATIENTS, FAMILY MEMBERS, MEDICAL PROFESSIONALS, HEALTHCARE WORKERS, FUNERAL DIRECTORS, EMBALMERS AND OTHERS ARE ENCOURAGED TO PHONE WITH:

- *Questions about a suspected or confirmed CJD diagnosis*
- *General questions concerning CJD*
- *Concerns about hospice care*
- *Questions concerning patient care*
- *Questions concerning family support*
- *Specific questions about physicians or researchers*
- *Questions about surveillance*
- *Concerns about funeral arrangements and/or autopsy*
- *Information to share*
- *Donations to The CJD Foundation to support the HelpLine and the work of the Foundation.*

The Foundation can also be contacted through our web site, www.cjdfoundation.org.

CJD and Other Prion Diseases

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Introduction

Prion diseases are a group of rare, invariably fatal brain disorders which occur both in humans and certain animals. They first came to public attention in the mid 1980s in the form of the BSE epidemic. BSE (bovine spongiform encephalopathy) is a prion disease of cattle. It is now believed that BSE might have arisen spontaneously in British cattle sometime in the early 1970s. Tissue from infected animals may have contaminated cattle feed, leading to the silent spread of the BSE epidemic. There is also a theory that BSE came from feed contaminated with scrapie, the long established sheep prion disease. Inevitably, concern over whether BSE could pass to humans mounted.

In humans the best known of the prion diseases is Creutzfeldt-Jakob Disease (CJD), which reportedly affects around one person per million per year. In the United States this translates to 280-300 new cases per year. It is well known that CJD is very difficult to diagnose leading to speculation that the one case per million report may be incorrect. Most of the cases are classical or sporadic CJD (sCJD), occurring for no, as yet, known reason. The sporadic form accounts for approximately 85% of the cases, the familial form approximately 15%. The third type of CJD is acquired by infection, there are at least two types:

- 1). iatrogenic - acquired by infection - see page 3
- 2). exposure to BSE contaminated meat, variant CJD (vCJD), or KURU

In December, 2003 the first case of Bovine Spongiform Encephalopathy (BSE) was discovered in Washington State, USA. This cow was imported to the U.S. from Canada. Although technically this cow was "Canadian," the concern over a case of BSE discovered in North America points out the need for more serious attention to be paid to cattle testing. A second case of BSE was announced in June of 2005. The cow, born in the U.S., was slaughtered in November 2004, tested and found inconclusive. In June the tissue was retested and found to be positive.

The main indications which can lead to a possible diagnosis of CJD are rapid dementia and a range of neurological symptoms including unsteady gait and sudden jerky movements. The brains of people and animals with prion disease show characteristic damage known as spongiform changes. When seen under a microscope the brain tissue looks spongy because it is punctuated by many tiny holes where cells have been lost. For this reason these diseases are known as spongiform encephalopathy's although the term prion disease is preferred.

Most prion diseases are transmissible in the laboratory although the infectious agent is not a conventional bacterium or virus. Instead, the infectivity is associated with an abnormal protein or prion. Because prions are so unusual and prion diseases are unique in that they can be both inherited and transmitted, the area has attracted enormous scientific and medical interest. This provides a ray of hope that all this attention may, one day, lead to a cure. *

Human Prion Diseases

FORM	CAUSE	DISTINGUISHING FEATURES
<p>Sporadic Includes 5 subtypes with distinct clinical & pathological features</p>	Unknown	Affects mainly people over age of 50. Ataxia, dementia spongiform change, rarely plaques. Short course.
<p>Inherited prion diseases Familial CJD Gerstmann-Straussler-Scheinker Syndrome (GSS) Fatal Familial Insomnia (FFI)</p>	Inherited mutation in PrP gene	Often younger onset than sporadic CJD. Symptom pattern depends on type of mutation, but sometimes like sporadic. Course of illness is usually longer.
<p>Acquired by Infection iatrogenic*</p>	Contamination through brain surgery, corneal transplant, dura mater graft, human growth hormone	The age at onset depends on the age at exposure and on the incubation time. Clinical and pathological features often indistinguishable from sporadic CJD.
Variant CJD	Exposure to BSE	Young onset and longer duration than classical CJD. Psychiatric signs at presentation. Distinctive “daisy” plaques.

*Iatrogenic CJD younger onset. Ataxia rather than dementia. Growth hormone cases show plaques.

More about prions...

Prions are different from bacteria and viruses

The discovery that prion diseases were transmissible led researchers to the natural conclusions that the infective agent had to be a bacterium or a virus. When, however, infectious tissue remained infectious after treatment with both heat (which destroys most bacteria) and ultraviolet light (which should inactivate viruses) the conclusion was that some other kind of infectious agent was responsible.

In 1982, neurologist Stanley Prusiner of the University of California provided the first direct evidence that the infectious agent was a protein. (This is where the word 'prion' comes from - proteinaceous infectious particle.) The idea, originally put forward by the British investigators Griffith and Patterson, was highly unusual and even heretical at first-although it has slowly gained acceptance over the years.

Abnormal prions are infectious proteins

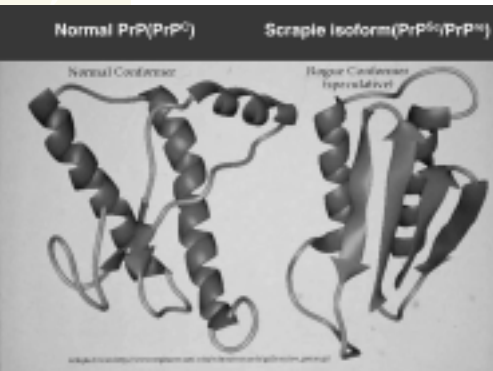
Proteins are essential to life. They are molecules made up of thousands of smaller chemical units called amino acids, joined together like beads on a necklace. Once formed in a living cell, a protein molecule folds in a curl. Protein molecules are fairly flexible and can adopt a number of subtly different shapes: in this simple chemical fact may lie the heart of the whole prion enigma.

The prion protein, PrP, can exist in two forms: normal and abnormal. For convenience, these are written PrP^C and PrP^{Sc}. The normal form exists in the human brain and in other parts of the body. It is also found in many other mammals and even in birds. However, its function is unknown. Genetic modification can produce laboratory

mice which do not have PrP^C and these seem to be quite healthy, suggesting that it is not essential to life.

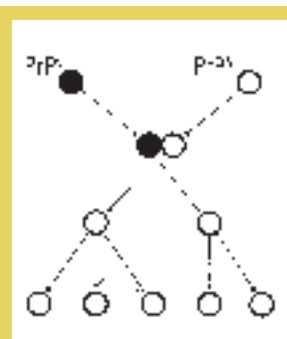
The strange behavior of abnormal prions

The abnormal form of prion protein has unusual properties. First, unlike the normal form, it is not broken down by enzymes. It also forms tiny fibers called scrapie associated fibrils (SAFs) in the test tube. It has been found that tissue that forms a lot of SAFs is often the most infectious. Finally, the SAFs often clump together to form a chemical structure called amyloid. In some cases of CJD and other prion diseases amyloid deposits, known as plaques, are also found in the brain under the microscope during microscopic examination of the brain obtained at autopsy. Plaques are also found in other non-prion diseases such as Alzheimer's disease and in aging brains (although the plaques in these cases are not made of prion protein).



*A computer model of the structure of a prion molecule. Such models give useful insights into the pathology of CJD, and may point to potential treatments**

* Photo courtesy of Fred E. Cohen, MD, Dept. of Cellular & Molecular Pharmacology University of California, San Francisco (UCSF)



Conversion of a PrP^C molecule to PrP^{Sc}, leading to a cascade of PrP^{Sc}, and eventually brain damage

Ways in which abnormal prions are transmitted

Dr. Stanley Prusiner's idea is that a single molecule of PrP^{Sc} can convert molecules of PrP^C into the abnormal form. These newly converted molecules can in turn, "corrupt" more normal molecules leading to a cascade effect which would eventually cause brain damage.

It may be that once in a while (very rarely) a molecule of PrP^{Sc} spontaneously converts into the abnormal form, setting the scene for sporadic CJD and that would explain the relatively low incidence of CJD, one case per million per year.

In familial CJD, it is known that there are mutations in the PrP gene which are inherited from one parent. These may produce forms of the PrP molecule which are more likely to be converted into the abnormal form. Finally, in CJD acquired by transmission (iatrogenic and variant) PrP^{Sc} molecules enter the body from an infected source, and set about corrupting the normal PrP of their "host".

Information helpful in understanding an autopsy report

The PrP gene, as other genes, may have variations. Some of these variations such as the mutations mentioned above, can cause an inherited prion disease. Others do not cause disease and are called polymorphisms. This issue is further complicated by the fact that the PrP gene, as other genes, consists of halves called alleles, one from each parent. To some extent, the two alleles function independently and each encodes for a PrP molecule. Because of the presence of mutations and polymorphisms, the two alleles may be different. For example, mutations causing familial prion diseases are generally inherited only from one parent, hence they are located only in one of the two alleles.

In this case the patient is heterozygous for the mutation. An important polymorphism of the PrP gene is located at codon 129.* Codon 129 of the PrP gene may encode either for the amino acid methionine (M) or the amino acid valine (V). Because each allele may have either M or V, people may have M in each of the two alleles, i.e. they are M/M or homozygous M, V/V or homozygous V, or M/V or heterozygous. The presence of M or V does not cause disease by itself, but if an individual develops CJD, the disease is likely to be different according to whether the CJD patient is M/M, V/V or M/V. Therefore, the polymorphism at codon 129 is a modifier of the disease in sporadic CJD. Another modifier is the type of the PrP^{Sc} present in the brain tissue of cases of sporadic CJD. Commonly, two types, type 1 and 2, of PrP^{Sc} are distinguished. The combination of the polymorphism at codon 129 and the PrP^{Sc} identify fairly accurately the subtype of sporadic CJD. For example, sporadic CJD M/M 1 (sporadic CJD in a homozygous M patient with PrP^{Sc} type 1) corresponds to typical sporadic CJD. (1)

* The codon is the coding unit of the gene and directs the synthesis of an individual amino acid; it is generally identified with a number such as 129 that refers to the position of the amino acid it encodes in the protein, i.e. the 129th amino acid of PrP.

(1) Pierluigi Gambetti, MD, Director,
National Prion Disease Pathology Surveillance Center

Sporadic CJD

Sporadic means “occurring here and there” and that no major risk factors have been discovered.

Sporadic CJD is subdivided into five subtypes, some of which have different ages at onset, duration and clinical presentation. The typical subtype, which accounts for over 50% of all prion diseases, generally presents at 60-65 years. The incidence of sporadic CJD in the U.S is around 1 case per million per population, that is, around 250-300 new cases every year.

The incidence of sporadic CJD does not seem to be significantly higher in countries where BSE and scrapie are common than it is in countries free of these diseases. Therefore, based on the present evidence, a link between animal prion diseases and sporadic CJD seems unlikely.

Figure 1

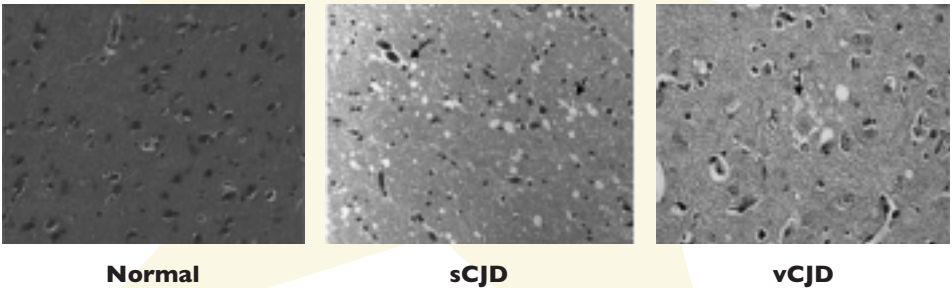


Figure 1. Microphotographs comparing normal brain tissue, brain from a subject with sporadic CJD-MMI (sCJD), and from variant CJD (vCJD). Note the fine spongiform degeneration that is evenly distributed in sCJD (some of the vacuoles are identified by arrows) and mostly clustered around a plaque in vCJD (arrowheads). The plaques surrounded by vacuoles are commonly referred to as “florid” or “daisy” plaques and are the hallmark of vCJD.

Figure 2

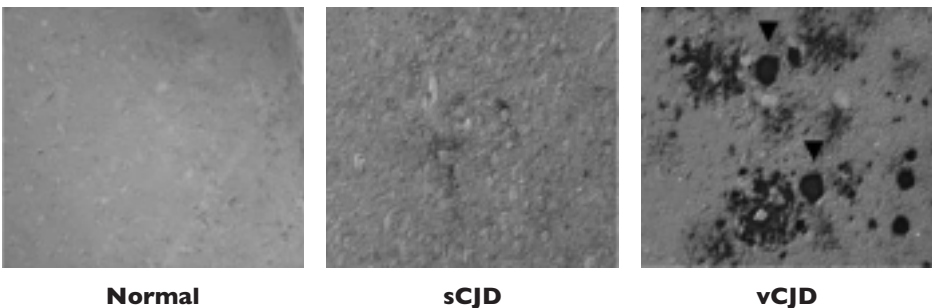


Figure 2. Immunohistochemical staining of the prion protein (PrP) in the same brain tissues. With the procedures used, there is no PrP staining in the normal brain. In contrast of sCJD-MMI shows a fine “synaptic” staining (brown color) indicating a fairly even distribution of scrapie PrP. In vCJD the staining is unevenly distributed and forms areas of intense staining, especially in the plaques (arrowheads).

What are the symptoms of Sporadic CJD?

Sporadic CJD usually comes “out of the blue” although the patterns of symptoms may vary from person to person.

- In the “typical” subtype of sporadic CJD (sCJD M/M 1), early symptoms are often like those of depression, mood swings, memory lapses, social withdrawal and lack of interest. However, rapid progression to dementia and obvious neurological symptoms distinguish CJD from depression.
- Within weeks, the patient may become unsteady on his/her feet, lacking in coordination and markedly clumsy. This pattern of symptoms is known clinically as cerebellar ataxia, because it is caused by damage to the cerebellum the part of the brain which controls movement. In some people, these are the first symptoms.
- Later symptoms may include blurred vision, hallucinations, blindness, rigidity in the limbs, sudden jerky movements and incontinence.
- Speech may become more difficult or slurred. Swallowing may become difficult.
- Eventually, the patient loses the ability to move or speak and will require full time nursing care. In this state, clinically known as akinetic mutism, the patient may appear to be following what is going on around them, but in fact they are not aware of their surroundings at this stage.

Virtually all patients die within a few months of onset of symptoms, some within a few weeks. Other subtypes can linger for several years.

In some subtypes, the first clinical signs may affect movements often resulting in unsteady gait rather than dementia.

Familial CJD

Familial means “occurring in families”. Some families have a mutated gene which makes the development of abnormal prion protein more likely.

Approximately 5-10% of all cases of CJD account for Familial CJD. In the Familial form of CJD there is a mutation in the PrP gene that seems to make the conversion into the abnormal form more likely. More than two dozen different mutations in the gene that encodes the “prion” protein are known. The translated portion of the gene has 253 codons, and mutations occur in many different regions, but the majority are found between codons 175 and 220, which in the encoded protein are composed of alpha helical domains.

All of the mutations are inherited in an autosomal dominant pattern. Therefore, if one parent carries the mutation, there is a 50-50 chance for each child to inherit the mutation and the presence of a mutation in only one allele is sufficient to cause the disease. If a family consisted of 100 children, half of them would carry the mutation and half of them would not, but in the more realistic situation of families with smaller numbers of children, the proportion that inherits the mutation may not reflect these statistical odds: one, two or three of four children may be found to be mutation-positive.

Since CJD does not usually strike until later in life, people carrying the gene may not realize that they may have passed it on to their children, although they may well be aware of a problem with neurological disease within the family. However, since CJD was recognized only relatively recently as a disease in its own right, some family members in years past may have been wrongly diagnosed. Their condition might have been thought to be psychiatric illness, Parkinson’s disease, or some other neurological disease such as Alzheimer’s disease or Huntington’s chorea.

People with a relative who has or had CJD can be genetically tested for the CJD mutation. Genetic testing can be easily accomplished from a small sample of blood, but the choice of learning the result is a very individual matter, and should never be made without the involvement of a knowledgeable genetic counselor and serious thought about its consequences. For example, it might be supposed that knowing a negative test result would be cause for great relief and happiness, but it may also be cause for intense guilt: how is it that I escaped and my sister did not? (2)

Prevention and Therapy

Familial disease could in principle be eradicated in a single generation by the use of prenatal genetic testing of the fetus and therapeutic abortion, but this extremely sensitive issue is a matter of individual choice based on ethical and religious considerations and will certainly never be accepted by all families with inherited disease. Another therapeutic approach would probably meet with much less resistance is genetic engineering to neutralize the gene that encodes the “prion” protein, which we know to be essential to the development of disease. However, the technical difficulties of genetic engineering have so far impeded this strategy in all inherited human diseases, including CJD. When these difficulties are solved, Familial CJD may be the first kind of CJD to be successfully treated. (2)

Diagnostic Aids

- A good history and physical examination are sufficient to make a correct diagnosis fairly early in the course of the illness in nearly all patients with the typical features of CJD, and at least raise a suspicion in most patients with an atypical illness.
- Electroencephalography (EEG): a periodic sharp wave pattern occurs in about 80% of the cases with the typical subtype, but is not common in the other subtypes, in its most characteristic form electrocardiogram-like regularity is seen in very few other diseases. A less definite, but still suggestive periodic pattern, is called 'burst wave suppression', in which short periods of comparative electrical silence are broken by a quick succession of sharp waves.
- Special analysis of the spinal fluid for the presence of a protein designated as "14-3-3" that is released from damaged or dying nerve cells, and is detectable in over 90% of patients with typical CJD. As with the EEG, it is not entirely specific, and can be detected in some patients with other disorders such as viral encephalitis, the acute oxygen deficiency often associated with strokes, and Alzheimer's disease. Apart from Alzheimer's disease, these disorders can usually be easily distinguished from CJD by the clinical history and routine spinal fluid examination.
- Magnetic resonance imaging (MRI), has only recently been appreciated as a useful radiological aid to the diagnosis of CJD. In about 80% of the cases, an increased signal can be seen to 'light up' the basal ganglia on one or both sides of the brain. Because radiologists are usually searching for asymmetrical radiological changes, the significance of these often bilateral bright spots was overlooked for many years. They may also be seen in cases of Wilson's disease and in carbon monoxide poisoning, disorders that are readily distinguished clinically from CJD.

None of these tests are sensitive enough to identify every case of CJD, and none is entirely specific for the diagnosis; however if two or all three of them are positive, the diagnosis is virtually certain to be CJD. Unfortunately, the chances are low that all tests may be positive in atypical subtypes. Because of the availability of this battery of laboratory tests, brain biopsy is no longer needed or advised in the diagnostic evaluation of suspected cases of CJD. However, brain biopsy may be in order when a treatable disease such as encephalitis must be ruled out.

What are the symptoms of Familial CJD?

The symptoms of the familial form of CJD vary, depending on the type of mutation involved. There may even be great variation in the symptoms within affected members of the same family. Often Familial CJD strikes at an earlier age than the sporadic form: the average age of onset is 52, compared to 65.

Symptoms may include but are not limited to:

- Initially depression, bizarre or uncharacteristic behavior, and memory lapses
- Fatigue and visual disturbances
- Within weeks, unsteadiness (gait ataxia) and lack of coordination (cerebellar ataxia)
- Difficulties with speech and/or swallowing
- Sudden jerky movements (myoclonus), rigid limbs, maybe blindness and incontinence

Iatrogenic CJD

Iatrogenic means “caused by medical treatment”, but more generally this form of CJD is transmitted by direct contact with infected tissue from someone with the disease.

The first indication that human prion diseases might be transmissible through infected tissue came with the discovery of a strange disease called kuru among the Fore People of Papua New Guinea in the 1950s. Kuru mainly affected women and children, and was similar to CJD except that ataxia was the predominant symptom and dementia was rare. The brains of these patients showed severe damage to the cerebellum, the part of the brain which controls movement, along with the spongiform change to characteristics of prion disease. A further feature was the appearance of deposits called plaques within the brain tissue; this distinguished kuru from CJD, where plaques only occur in a minority of cases.

Kuru was eventually linked to the funeral practices of the Fore people in which it was common for the women and children to eat the body of their dead relatives, including the brain, and cannibalistic practices involving vital organs. Since the victims of kuru continued to be given these funeral rites, the disease perpetuated itself.

The incubation time for kuru is between three and 40 years. When the Fore people stopped these funeral rites and the country was taken over by Australia the number of new cases went down dramatically, but there is still the occasional case occurring in an older person in whom the disease has had a very long incubation period. Kuru has been of great importance in helping us to understand the human prion diseases, and in particular the risks of their being transmitted from person to person. Brain tissue from a person with CJD contains prions and if this tissue enters into the normal PrP in the body of an uninfected person, this infected tissue can change it into the abnormal form and, thereby transmit the disease.

Some medical procedures carry a risk of transmitting CJD. For instance, a few people have contracted CJD from brain surgeries done with instruments which were previously used on a CJD patient. In these cases the infection was delivered intracerebrally, that is, directly into the brain. The prion agent survives the normal disinfection procedures which would destroy bacteria and viruses but this was not known at the time. Now, instruments which have been used on the brain of someone with suspected CJD are destroyed.

Intracerebral transmission of CJD has also occurred with corneal transplants and grafts of dura mater, the rough membrane which covers the brain and is used in various kinds of surgery. The incubation time for intracerebral iatrogenic CJD is 19-46 months.

CJD has also been transmitted by treatment with human growth hormone. This is known as peripheral transmission, because the route to the brain of the infective agent is through the body, not directly into the brain. Human growth hormone, which is used to treat children with short stature, used to be prepared from human pituitary glands, its natural source. Typically 2,000 glands would be pooled to make one batch of growth hormone which, in turn, would be split into many hundreds of doses and distributed. Therefore, the inclusion of just one gland from someone with CJD had the potential to infect many people.

The incubation time for peripheral iatrogenic CJD is longer than for the intracerebral form, and is more like kuru (itself a peripherally transmitted disease) possibly around 15 years. Therefore, there could be more growth hormone-related cases to come. In the USA since 1977, growth hormone is made synthetically rather than being extracted from the pituitary gland so there is no current risk from this source.

What are the symptoms of iatrogenic CJD?

Where transmission is intracerebral, the symptoms are like sporadic CJD. However, peripherally acquired CJD is more like kuru with symptoms of ataxia predominating and dementia being a rare feature.

Variant CJD

Variant CJD is so-called because it differs in some ways from other forms of CJD (especially that it occurs in young people). vCJD has only been identified since 1994.

In 1995, two cases of CJD were found among teenagers in the UK. This was extremely unusual and alarming because only four cases of CJD (one in Britain) had ever been reported in this age group. By 1996, the number had increased to ten, and it was evident that a new type of prion disease, called variant (vCJD), had arrived in Britain. The occurrence of an epidemic of prion disease, BSE, among UK cattle from 1986 was thought to be no coincidence. vCJD was soon linked to exposure to BSE prior to the ban on specified offal (brain and spinal cord) from cattle in the human food supply which was applied in 1989.

The total number of deaths from vCJD detected in the UK since 1995 currently stands at 141 (May, 2004). More recently a small number of cases have been detected in Mainland Europe, namely France (6), Ireland, Italy, Hong-Kong*, Canada*, USA* (1 each).

vCJD differs from sporadic CJD in several respects. All the cases reported to date, except one, have been young with average age at onset of symptoms being 28. The course of the illness is longer than in sporadic CJD, being typically around a year. The symptoms, at least at the outset, are usually more of a psychiatric than neurological type. Finally, although the brains of people with vCJD when examined post mortem did show the characteristic spongiform change giving a spongy appearance under the microscope there were also other changes (described below).

One case each is known to have occurred in the US and Canada. However, in both cases, evidence indicates that the disease had been acquired in the UK.

Scrapie PrP (PrP^{Sc}) is known to exist in different forms called strains, such as PrP^{Sc} type 1 and 2 mentioned above. In 1996 it was shown that all the vCJD cases were affected by the same strain of PrP. This strain had never been seen before in humans and, moreover, it bore a marked similarity to the strain of PrP seen in BSE. Later, laboratory mice were injected with vCJD prions and developed symptoms like BSE, but unlike those of sporadic CJD. Furthermore, the pattern of the disease resembles that of kuru. All this is strong evidence that vCJD is caused by exposure to BSE.

But how might these young people have been exposed to BSE? Spinal cord from infected animals may have ended up in mechanically recovered meat, used in the manufacture of sausages, hot dogs and hamburgers. Both the vCJD cases, and controls without the disease, had consumed these products prior to 1989 and so had a substantial proportion of the rest of the population. There was no other obvious link between diet and exposure to BSE, nor to occupation, nor to surgery.

It is not yet known for sure what the likely route of transmission in vCJD is. It may be that young people consume more of whatever foodstuffs carried the most infectivity, or it may be that young people are just more susceptible to transmission of CJD via BSE. BSE contaminated foodstuffs were also fed to sheep, pigs and poultry, so exposure through their consumption cannot be ruled out.

It is not known how many other people will develop vCJD without knowing the route of exposure. However, if it is like kuru, which has an incubation time of up to 40 years (time from exposure to onset of symptoms), there could be many more cases of vCJD in the future.

On May 21, 2004 a report was released by the U.K. indicating that scientists who examined 12,674 stored appendix and tonsil samples identified three positive for prion proteins. Applying these findings to the U.K. population (60 million) experts estimate about 3,800 people would test positive for prion proteins.

Scientists suspect these findings might indicate people can carry the disease without developing symptoms. They would still be able to spread the disease to others via contaminated surgical instruments, blood transfusions or organ donations.

** Disease acquired in U.K.*

What are the symptoms of vCJD?

The symptoms of vCJD are quite different from those of classical CJD. Often, the patient will be referred first to a psychiatrist, rather than a neurologist, which may lead to a delay in diagnosis. After several weeks or months, more clear cut neurological symptoms may set in, including:

- Unsteadiness in walking and sudden jerky movements
- Anxiety, depression, withdrawal and behavioral changes
- Progressive dementia (loss of mental function, marked by symptoms such as memory loss)
- Persistent pain and odd sensations in the face and limbs

Eventually, the patient may lose the ability to move or speak and will need 24 hour nursing care. Death occurs approximately a year after the onset of symptoms.

Please see page 6 for two sets of microphotographs that show comparisons of normal, sporadic and variant CJD.

Investigation and diagnosis of CJD

General Practitioners should be aware of CJD although most of them will never see a case. A prompt referral to a neurologist should follow reporting of any suspicious pattern of symptoms. A number of investigations should be carried out including:

- **Magnetic Resonance Imaging (MRI)** This type of scan produces an image of the brain. In CJD, the scan looks normal except in some cases a certain amount of brain shrinkage (atrophy) may be revealed. MRI is important for ruling out other conditions, such as a brain tumor. The MRI may also show relatively specific changes which aid diagnosis, particularly in vCJD. The diffusion weighted MRI has proven to be a valuable diagnostic tool.
- **Computerized Tomography (CT)** scans of the brain are useful in excluding other conditions but do not show the specific changes useful in diagnosis.
- **Electroencephalogram (EEG)** An electroencephalogram, which measures the electrical activity of the brain, is currently one of the most useful aids in diagnosing CJD as it may show changes which are characteristic of the disease. However, these changes have not been seen in any of the cases of vCJD.
- **Brain biopsy** Taking a sample of tissue from the brain may be useful in helping reach a diagnosis. This involves taking a sample of brain tissue usually from the frontal lobe, and involves a neurosurgical procedure (brain operation). If the tissue shows spongiform change, then the diagnosis would be positive. However, the lack of spongiform change does not necessarily mean the person does not have CJD. It could be that the disease has not affected the part of the brain sampled. Furthermore, the National Prion Disease Pathology Surveillance Center does specific stains and biochemical analysis that allow for ruling out or establishing the diagnosis of CJD in virtually all the cases. Brain biopsy is not done routinely. It poses possible risks to the patient and the medical team performing the surgery.
- **Tonsil biopsy** Recently it has been shown that infectivity can be seen in tonsil tissue in some cases of vCJD. A tonsil biopsy may therefore be useful in diagnosis, although the idea remains controversial. Recent research also found infectivity in the appendix (which had been previously removed) of a man who went on to develop vCJD. (see *page 15*)
- **Lumbar puncture (Spinal Tap)** In a lumbar puncture, a sample of the cerebrospinal fluid (CSF) which surrounds the brain and spinal cord is taken by inserting a hollow needle into the lower part of the spinal column. The presence of three 'marker' proteins in the CSF called 14-3-3, S100 and NSE may be helpful in diagnosis. Examination of CSF is also done to exclude inflammation or infection of the brain as a cause of the symptoms.

- **Blood tests** Blood and other biochemical tests are usually normal in CJD.

Currently, the only way to diagnose CJD with certainty is by examination of the brain after death. There are four basic examinations that are carried out to establish or exclude the diagnosis of prion disease: 1) Histological; 2) PrP immunohistochemical examinations (both carried out on fixed tissue examined under the microscope); 3) Western blot; 4) Gene analysis.

1) Histological examination. The brain of someone with CJD nearly always shows signs of spongiform change; the brain tissue has the appearance of a sponge when seen under the microscope. Spongiform change results from a mixture of tiny bubbles within neurons and bigger holes distributed throughout the brain tissue. It affects mainly the grey rather than white matter of the brain. It may be found in the cerebral cortex, basal ganglia, thalamus and cerebellum. Increased number of astrocytes, the cells in the brain which support and supply nutrients to neurons, are often seen in CJD. Often neurons are decreased in number. Plaque deposits of prion protein are seen in only 10 per cent of cases of sporadic CJD. However, plaques are seen in some cases of familial CJD and in all cases of iatrogenic CJD caused by growth hormone treatment. In vCJD, where the brain pathology is very characteristic, a particular type of plaque known as a florid plaque is typical of the disease. The florid plaque are surrounded by an area of spongiform change.

2) PrP immunohistochemistry (IHC) is a technique that allows for the identification of abnormal PrP in the brain tissue under the microscope using antibodies. The presence and distribution of the abnormal PrP is established and correlated to that of the tissue lesions examined in I.

3) While the above techniques are carried out on fixed tissue, Western Blot requires the unfixed (frozen) tissue. When WB PrP^{Sc} is separated from other brain proteins and visualized with specific antibodies to PrP. This technique can detect much smaller amounts of PrP^{Sc} than IHC and can establish whether the affected tissue contains PrP^{Sc} type 1 or type 2. However, it cannot establish the distribution of PrP^{Sc}. Therefore, the two techniques are complementary.

4) Since, as stated before, the gene of the PrP can modify the subtype of CJD, it is very important to determine the PrP genotype in every patient with any prion disease. Genetic analysis could be carried out on unfixed tissue, commonly brain, or blood.

The difficulties involved in diagnosing CJD may have prevented the identification of the disease in some cases. Since the disease progresses rapidly, the patient may die before a diagnosis can be made. Furthermore, some physicians may not even consider the possibility of a CJD diagnosis because the disease is deemed to be rare and the clinical symptoms of CJD can often be attributed to other ailments. Consequently, CJD may be

mistaken for a variety of psychological illnesses and other neurological disorders like Alzheimer's Disease, Pick's Disease, Huntington's Disease, cerebral hematomas and vascular irregularities. The extent to which such misdiagnosis may have occurred is presently unknown.

Is there any treatment or cure for CJD?

At the present time, there is no confirmed effective treatment to arrest or cure CJD. The disease is inevitably fatal. The only treatments available for CJD patients focus on easing their symptoms and discomfort. Such measures may include drugs for controlling pain and myoclonus, catheters to collect urine, intravenous fluids, feedings through tubes and frequent repositioning of the patient to avoid bedsores.

Researchers have been experimenting with drugs like quinacrine, pentosan polysulphate, chlorpronazine, and flupertine as potential therapies for CJD. Scientists are also examining the use of certain antibodies for the prevention and treatment of prion diseases. The development of a vaccine is likewise being studied.

Is research currently being conducted on CJD?

Yes, government agencies and public and private institutions around the world are engaged in researching all aspects of CJD for the ultimate purpose of finding the means for preventing, treating and curing this disease. The crisis in Great Britain involving BSE and vCJD has generated a great deal of research.

Among the many areas being studied are the unique nature of the infectious agent and how it destroys the brain. Scientists are also trying to ascertain which factors affect infectivity, susceptibility to disease and the onset of symptoms. Many researchers are trying to develop new, reliable diagnostic tests that can detect the disease before symptoms of the disease occur. Such pre-clinical tests in people can be useful not only for the development of therapies before significant damage occurs, but also to ensure the safety from transmissible agents to blood, blood products, organs and surgical instruments. In December, 2003 the U.K. reported its first case of suspected transmission of vCJD by blood transfusion, the donor gave blood 3.5 years prior to becoming symptomatic. The recipient was 69 years old, he died of vCJD 6.5 years after transfusion*. As of January 2006 two more transfusion transmission cases have been reported, one in the U.K. and one in Ireland. Pre-clinical detection of these agents in animals (transmissible spongiform encephalopathies, TSE's) can be used to safeguard the food chain from TSE's.

Relatives of CJD patients who wish to assist research should have the patient's treating physician contact the National Prion Disease Pathology Surveillance Center. In order to confirm a CJD diagnosis, monitor the incidence of CJD in the U.S. and conduct research, the Surveillance Center has requested brain tissue samples, as well as blood, cerebrospinal fluid and urine.

* Dr. Robert Will, Consultant Neurologist, CJD Surveillance Unit, Edinburgh, Scotland

Animal prion disease

Prion diseases have been found in several animals. Scrapie, a prion disease in sheep, has been known since the 18th century and is found at a low level in many parts of the world. The name comes from a Scottish word and refers to the peculiar tendency of sheep with scrapie to scrape their fleece against trees and bushes. Affected animals become unsteady and startle easily. There is no evidence that scrapie has ever jumped the species barrier to cause prion disease in humans.

It has long been the practice to add protein from the carcasses of ruminants (sheep and cows) to animal feed. In the UK tissue from an infected cow is believed to have contaminated the animal feed. Once the feed entered the bodies of other cows, they too contracted BSE and, in turn, this led to further cases when those carcasses were turned into feed. This 'cascade' effect led to the BSE epidemic. Prion diseases have also been found in ranchered mink (transmissible mink encephalopathy) TME and in mule deer and elk (chronic wasting disease) CWD. There have been a few cases in zoo animals and in domestic cats. However, there is no evidence of transmission to humans in any of these cases.

Bovine Spongiform Encephalopathy (BSE) and Chronic Wasting Disease (CWD) in the US

Animal TSEs have been identified in the U.S. including transmissible mink encephalopathy (TME), scrapie and chronic wasting disease (CWD). The last case of TME in the United States was discovered in 1985. Scrapie, which affects sheep and goats is currently not considered to pose a threat to human health. CWD, which afflicts deer and elk, is being closely studied for any potential risk to human health.

CWD was first noticed in 1967 among deer in several Colorado research institutions. Subsequently, CWD has been discovered in wild deer and elk in Colorado, Wyoming, Nebraska and Wisconsin. Furthermore, the disease has been detected among captive elk in Colorado, Kansas, Nebraska, Montana, Oklahoma, South Dakota and Saskatchewan, Canada. It has also been detected in deer in New York, West Virginia, Illinois, Utah, New Mexico, Minnesota and Alberta, Canada. Surveillance programs are being conducted by individually affected states, as well as nationally by the Department of Agriculture.

At the present time there is no epidemiological evidence that CWD can infect humans, however; one study reported that abnormal CWD prion proteins in vitro can convert normal human proteins into abnormal forms, although inefficiently. Since the transmissibility of CWD to humans cannot be completely ruled out, experts caution people against consuming any part of a deer or elk showing evidence of CWD. Experts also warn against eating the brain, spinal cord, eyes, spleen, tonsils and lymph nodes of any harvested animal, as these tissues are known to harbor the CWD agent in infected animals. (3)

Frequently asked questions about CJD

1. Can you catch CJD from someone?

Prion diseases are not infectious in the usual way. For example, they are not spread by airborne droplets like colds and flu, or by body fluids or sexual contact like HIV. The overall evidence suggests that there is no increased risk of developing CJD from contact with a person suffering from the condition. No special precautions are required by anyone coming into contact with someone with CJD. However, it is sensible for anyone who might be exposed to the blood of a CJD patient (usually medical staff) to wear gloves.

2. How can we be sure that the clinical diagnosis of CJD is the correct one?

Each individual case of CJD can be assigned to one of three forms: sporadic, familial, and acquired. The diagnostic methods may vary depending on the type.

In sporadic CJD, the spinal fluid test has improved the diagnostic accuracy while the patient is alive, and it is now included as one of the diagnostic criteria along with the electroencephalogram (EEG). However, the only way, currently, of being sure of the diagnosis is by brain biopsy or autopsy.

In familial CJD, the diagnosis depends on development of particular neurological symptoms and the identification of a PrP gene mutation by genetic analysis.

In acquired CJD, iatrogenic is diagnosed on the basis of symptoms developing in someone with a relevant exposure. In vCJD, diagnosis is very difficult while the patient is alive. An MRI scan may prove to be useful; however, a definite diagnosis depends on examination of brain tissue or lymphoreticular tissue such as the tonsils.

3. Is the U.S. blood supply safe from CJD?

When it became evident in the mid 1990's that a significant proportion of plasma pools used in the production of therapeutic protein derivatives were 'contaminated' by donations from individuals who later died of sporadic Creutzfeldt-Jakob Disease (sCJD), regulatory agencies responded with guidance about quarantine and/or destruction of implicated product lots. These precautions were based upon laboratory evidence that low levels of infectivity were present in blood during both the incubation and clinical phases of disease in experimental rodent models; however, it was also appreciated that there was a serious discrepancy between the experimental data and epidemiological observations that, although anecdotal, failed to identify any instance of a human case of sCJD that could be traced to blood or blood products.

With the passage of time, systematically collected epidemiological data substantiated the absence of sCJD transmissions in blood

recipients, and began to weigh more heavily on the perception of risk to humans. Although it was finally decided that any such risk was negligible and plasma pools were no longer discarded upon knowledge of a contributing CJD donor, new evidence from the U.K. shows a transmission risk from vCJD cases (see page 18) (although deferrals designed to eliminate 'high risk' donor categories, such as growth hormone and dura mater recipients remained in force). (4)

4. Is there a risk in contracting CJD from organ transplant surgery?

The risk of contracting CJD from organ transplants is uncertain, but believed to be small. A woman later shown to have been suffering from CJD did provide material for three eye operations (cornea and sclera). Unfortunately, a transplant usually has to be done before a full post mortem, so this risk cannot be completely eliminated. However, it will usually be known if a potential donor is suspected of having CJD and would not be used. In the vast majority of cases, the benefit of having the transplant far outweighs the risk of contracting CJD from a donor who has no symptoms but could be in the incubation period for CJD. Note also that there is a risk of infection in any transplant.

5. I had to have a spinal tap. Am I at risk?

Lumbar puncture is now done using a single use kit which is destroyed after the test, so there is no risk of CJD transmission.

6. What about brain surgery?

Instruments used on the brain or nervous tissue of someone known to have or suspected of having CJD must be destroyed. Ideally single use disposable instruments should be used.

7. Is the person with CJD in pain?

Clinical experience of people in the later stages of CJD indicate that they lose awareness of their condition as the disease progresses. Obviously this saves them but not their families much mental suffering. In the early stages, however, patients with CJD can develop marked fear, which can be very distressing and is probably associated with visual hallucinations. They may feel discomfort, and some of the symptoms of the disease such as myoclonus, sudden jerking of the limbs are distressing to care givers. However, neurologists believe there is no pain associated with the disease itself. For example, there is no rise in pressure in the head which could cause headache or any other obvious cause of pain.

8. Is an autopsy necessary in CJD?

Post-mortem examination is not compulsory when CJD is suspected – the doctor will need the permission of the next of kin. It often helps the family to establish the definite cause of death. At present, this can be done with examination of brain tissue or, in the case of vCJD, also of tonsils obtained at biopsy or autopsy. Furthermore, autopsy examination to confirm the diagnosis of CJD helps

8. cont'd

protect public health and makes tissue available for research. The National Prion Disease Pathology Surveillance Center (NPDPS) under the auspices of the Centers for Disease Control and Prevention (CDC) examines tissues from as many cases as possible of suspected CJD in order to confirm or exclude the diagnosis of prion disease. The purpose of the NPDPS is to detect, in a timely manner, the presence of atypical cases in the US such as human cases of prion disease acquired from animals, i.e. BSE infected beef, deer and elk, and monitor the number and distribution of cases of prion disease in the US to detect other possible sources of infection such as the use of contaminated surgical instruments or tissue implants. Tissue examination from as many cases as possible is needed for the NPDPS to provide effective surveillance. The NPDPS provides assistance in coordinating autopsies and pays all costs. (5)

9. Is sporadic CJD increasing?

There is no consistent evidence that the number of cases of sporadic CJD is increasing except for an isolated report from Switzerland where a two fold increase has been recorded for the year 2001. No evidence of increase of the number of cases has been observed in the US. However, the NPDPS examines about 64% of the approximately 300 cases expected to occur in the US per year. Again, the number of cases examined by the NPDPS must be increased for the surveillance to be effective.

10. What is being done to protect us from CJD?

At present there is no way of protecting people from sporadic or familial CJD. Iatrogenic CJD is guarded against by destroying surgical instruments that have been used on people with CJD, and by not using their organs for transplant.

Glossary of clinical terms used in CJD

cerebellar ataxia: Shaky movements, unsteady gait and clumsiness caused by damage to the *cerebellum* a part of the brain which controls movement

myoclonus: Jerking movements of the limbs caused by sudden muscle spasms

akinetic mutism: A state of complete physical unresponsiveness caused by damage to the base of the brain

spongiform change: Brain damage characterized by a spongy appearance of brain tissue seen under a microscope

encephalopathy: Any disease in which the functioning of the brain is affected

(5) Pierluigi Gambetti, MD, Director,
National Prion Disease Pathology Surveillance Center

CJD figures

National Prion Disease Pathology Surveillance Center: Cases Examined

YEAR	REFERRALS	PRION DISEASE (TOTAL)	SPORADIC	FAMILIAL	IATROGENIC	vCJD
1997	104	60	54	6	0	0
1998	94	51	44	6	1	0
1999	114	74	65	9	0	0
2000	169	111	97	12	2	0
2001	247	154	138	16	0	0
2002	265 ¹	151	127 ¹	22	1	1 ²
2003	284 ³	191 ⁴	142	45	1	0
2004	360 ⁵	202 ⁶	167	21	0	0
2005	342 ⁷	176 ⁸	92	32	0	0
Total	1997	1170	926	169	5	1
¹ Includes 2 inconclusive		⁵ Includes 1 pending				
² Acquired in United Kingdom		⁶ Includes 8 type unknown, 3 type pending				
³ Includes 1 inconclusive		⁷ Includes 34 pending, 3 inconclusive				
⁴ Includes 3 type unknown		⁸ Includes 51 type pending, 2 type unknown				

What organizations can be contacted for further information on Creutzfeldt-Jakob Disease?

The Creutzfeldt-Jakob Disease Foundation, Inc

P.O. Box 5312 Akron, Ohio 44334
National CJD HelpLine 1.800.659.1991
Fax 330.668.2474

www.cjdfoundation.org
help@cjdfoundation.org

A non-profit organization promoting patient/family support, education, awareness, public policy awareness and research for all forms of CJD

National Prion Disease Pathology Surveillance Center

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Case Western Reserve University
2085 Adelbert Rd.
Cleveland, Ohio 44106
Phone: 216.368.0587
Fax: 216.368.2546
www.cjdsurveillance.com
email: cjdsurv@po.cwru.edu

CJD Insight, Information & Support Organized for Familial CJD

Deana Simpson, RN, Founder & Director
Phone: 586.786.6260
www.cjdinsight.org

Centers for Disease Control and Prevention (CDC)

1600 Clifton Road Atlanta, Georgia
Phone: 1.800.311.3456 or 404.639.3396
www.cdc.gov

CJD Voice

Moderator, Dorothy Kraemer
www.cjdvoice.org
Online discussion, support, and information site

National Organization for Rare Diseases (NORD)

P.O. Box 8923
New Fairfield, CT 06812-8923
Phone: 203.746.6518 or 1.800.NORD (6673)
Fax: 203.746.6481
www.rarediseases.org

Food and Drug Administration (FDA)

5600 Fishers Lane
Rockville, MD 20857
Phone: 301.443.1130
www.fda.gov

United States Department of Agriculture Food Safety and Inspection Services (FSIS)

Phone: 202.720.9113
Infoline: 1.800.535.4555
www.fsis.usda.gov
Information on food safety, meat and related products and meat inspection

United States Department of Agriculture Animal and Plant Health Inspection Service (APHIS)

Phone: 609.259.5825
301.734.7799
www.aphis.usda.gov
Information on animal health and BSE

CJD Support Network, U.K.

Gillian Turner, Moderator
Phone: 011 44 01630 673993
www.cjdsupport.net

The CJD Alliance, U.K.

www.cjdalliance.org.uk/
Contact: Graham Steel
Don Simms

CJD Support Group Network Foundation, Australia

<http://www.cjdsupport.org.au/>

About The CJD Foundation

- Provides support to families & caregivers through our toll free HelpLine and our web site
- Provides information to other concerned healthcare professionals, funeral directors and embalmers
- Promotes research and the dissemination of research findings
- Advocates for good quality care for those afflicted with CJD
- Actively promotes the development of a public policy response for CJD

For more information contact:

The CJD Foundation

P.O. Box 5312

Akron, Ohio 44334

or

843 N. Cleveland - Massillon Road, Suite 7A

Akron, Ohio 44333

330.665.5590

HelpLine 1.800.659.1991

Fax: 330.668.2474

www.cjdfoundation.org

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CJD & Prion Disease

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