Human prion diseases can be classified as sporadic, hereditary or acquired. The cause of sporadic Creutzfeldt-Jakob disease (CJD) is unknown, hereditary cases are associated with mutations of the prion protein gene (PRNP) and acquired forms are caused by the transmission of infection from human to human or, as a zoonosis, from cattle to human. Although acquired forms of human prion disease are rare, the transmission of a fatal and untreatable neurological disorder has had major implications for public health and public policy.

**Iatrogenic CJD**

Since the first evidence of iatrogenic transmission of CJD in 1974, via a corneal transplant, other mechanisms of iatrogenic transmission have been identified including neurosurgical instruments, depth electrodes, human pituitary hormones and human dura mater grafts. All these transmissions have involved cross-contamination with material in, or adjacent to, the brain where the expected levels of infectivity would be highest (Table 1). The route of inoculation has been parenteral, either by surgery or by intramuscular injection.

**Table 1** Total cases of iatrogenic CJD world-wide

<table>
<thead>
<tr>
<th>Mode</th>
<th>Cases (n)</th>
<th>Mean incubation period (years)</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosurgery</td>
<td>4</td>
<td>1.6</td>
<td>Visual/cerebellar/dementia</td>
</tr>
<tr>
<td>Depth electrodes</td>
<td>2</td>
<td>1.5</td>
<td>Dementia</td>
</tr>
<tr>
<td>Corneal transplant</td>
<td>3</td>
<td>15.5*</td>
<td>Dementia</td>
</tr>
<tr>
<td>Dura mater</td>
<td>136</td>
<td>6*</td>
<td>Visual/cerebellar/dementia</td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>162</td>
<td>12*</td>
<td>Cerebellar</td>
</tr>
<tr>
<td>Human gonadotrophin</td>
<td>5</td>
<td>13</td>
<td>Cerebellar</td>
</tr>
</tbody>
</table>

*Range 1.5–30 years.

*Estimated on incomplete data.

Data courtesy of Dr P Brown.
Corneal grafts and depth electrodes

Iatrogenic transmission of CJD was first suggested in 1974; CJD developed 18 months after transplantation of a cadaveric corneal graft, which had been obtained from a donor who had died of pathologically confirmed CJD. A second case was described in 1997 in which both donor and recipient died from pathologically confirmed CJD, although the delay between corneal transplant and the development of CJD was 30 years. These cases provide strong circumstantial evidence of transmission of CJD through cadaveric corneal grafts.

Two cases were reported in 1977 in which CJD developed 2 years after stereotactic EEG recordings. The instruments had previously been used in a patient with rapidly progressive dementia and myoclonus, who was later confirmed as having died of CJD. The electrodes had been disinfected with ethanol and formaldehyde vapour. The possibility that CJD had been transmitted via the electrodes was subsequently supported by transmission of CJD to a chimpanzee 18 months after intradural implantation of the suspect electrodes.

Neurosurgical transmission

The original publication by Nevin and co-workers suggested that CJD was transmitted via contaminated neurosurgical instruments in the 1950s. A small number of patients with CJD underwent invasive procedures, including brain biopsy, and concurrent in-patients underwent neurosurgery for other conditions (e.g. removal of meningioma or cortical undercut). The re-admission of three of these cases 18–24 months later to the same hospitals with CJD provides strong circumstantial evidence of transmission through contaminated neurosurgical instruments. A similar case has been described in France, but there have subsequently been no further published cases implicating neurosurgical instruments. The clinical features in these cases were very similar to sporadic CJD.

Dura mater grafts

The transmission of CJD from patient to patient by cadaveric dura mater grafts was first recognised in 1987 and there have now been at least 136 cases world-wide, including 88 cases identified in Japan. Almost all of these cases have involved the insertion of Lyodura grafts produced by B. Braun Melsungen AG and processed before May 1987. Exceptions to the use of Lyodura grafts include one case in which the source was unknown, one case in which locally produced dura was...
implanted and one case associated with Tutoplast dura. The risk of transmission of CJD through dura mater grafts had been thought to be low because only a small number of recipients would receive contaminated material from any individual infected donor. The large number of Lyodura-associated cases of CJD suggests that there may have been cross-contamination during the production process.

For dura mater-associated cases of CJD in Japan, the mean latency period from receipt of the graft to the onset of CJD was 8.2 years (range, 1.3–16.1 years) and for the 114 reported cases world-wide by the millennium, the interval from the implantation of the graft to the development of clinical disease ranged from 1.5–18 years with a mean of about 6 years. The risk of developing CJD after exposure to a dura mater graft is difficult to estimate because of limited information on the number of recipients. The major risk, however, appears to be in those individuals who received grafts between 1981 and 1987 (Fig. 1) and in Japan the minimum risk has been estimated at approximately one case of CJD per 3000 Lyodura graft recipients.

The majority of patients with dura mater-related CJD present with symptoms and signs consistent with sporadic CJD, but in some cases the presentation is less typical. A cerebellar syndrome has been described occasionally, but this does not necessarily correlate with the anatomical site of the original graft.

![Fig. 1](https://academic.oup.com/bmb/article-abstract/66/1/255/284826)

**Fig. 1** Dura mater cases world-wide shown by year of operation and year of onset of symptoms for CJD. Mean incubation period from operation to onset of symptoms was 6.8 years (range, 1–16 years).
**Human pituitary hormones**

The treatment of short stature in children with human pituitary-derived growth hormone (hGH) was initiated in the late 1950s, and about 30,000 children had been treated with hGH world-wide by 1985. Small numbers of women were treated for infertility with human pituitary gonadotrophin over a similar period. In 1985, the occurrence of CJD in two hGH recipients in the US\textsuperscript{10,11} and one case in the UK\textsuperscript{12} provided strong circumstantial evidence of transmission of CJD via hGH, not least because the young age of the patients contrasted with that usually observed in CJD. Since then, CJD has developed in over 160 hGH recipients in a number of countries including the US, UK, France, New Zealand, and The Netherlands (Table 2). The overall proportion of CJD cases in the recipient population is about 1 in 100, but this proportion varies between countries, with the highest rate in France. The contrasting inter-country incidence may relate to differences in the methods of sourcing of pituitary glands or variations in hormone production. hGH was withdrawn in most countries in 1985 and human pituitary gonadotrophin has also been withdrawn in many countries following the occurrence of CJD in four recipients in Australia\textsuperscript{13}.

hGH production required the pooling of many thousands of glands and it is presumed that contamination of the hormone preparation occurred when pituitary glands derived from patients who died from or were incubating CJD were included in the production process. The circumstantial evidence suggesting a causal link between hGH and CJD has been supported by transmission studies in which a squirrel monkey developed prion disease following inoculation with 1 of 76 potentially contaminated lots of hGH\textsuperscript{14}. The incubation period in hGH-related CJD is impossible to estimate precisely because the timing of infection is not known. However, the estimated mean incubation period is 12 years with a range of 4.5 to over 25 years, based on the latency from the mid-point of treatment to the onset of clinical illness.

The clinical features of human pituitary hormone-related CJD are distinct from sporadic CJD. In the great majority of cases, the initial presentation

| Table 2 Number of deaths from hGH-related CJD by country |
|---------------------------------|-----|
| **Country** | **Deaths (n)** |
| France | 89 |
| UK | 41 |
| USA | 23 |
| New Zealand | 5 |
| The Netherlands | 1 |
| Brazil | 1 |
| Australia | 1 |
| Qatar | 1 |

Data courtesy of Dr P Brown.
involves a progressive cerebellar syndrome, and other features including dementia develop late, if at all. It is possible that the route of inoculation of the infectious agent may be an important determinant to clinical expression of disease. In kuru, presumed to be due to a peripheral route of infection, cerebellar signs predominate in the early stages as in human pituitary hormone recipients, whereas in iatrogenic CJD, due to central inoculation, the clinical features are similar to sCJD.

Variant CJD

In the late 1980s, the possibility that bovine spongiform encephalopathy (BSE) might be transmissible to the human population was considered by many scientists and official bodies in the UK (and elsewhere) to be unlikely. However, it was recognised that there was a potential for prion strains to change their pathogenicity after cross-species transmission and it was recommended that CJD should be studied nationally in order to identify any change in the characteristics of this condition following the appearance of BSE in UK cattle. In 1995 and early 1996, a small number of cases of CJD with a remarkably early age at death were identified in the UK. By March 1996, 10 cases had been identified with an average at death of 29 years and with an unusual clinical and pathological phenotype for CJD, including extensive deposition in the brain of florid plaques. An article entitled A new variant of Creutzfeldt-Jakob disease in the UK was published in April 1996 and suggested that these cases might be causally linked to the epidemic of BSE in UK cattle.

There is now convincing evidence that vCJD is indeed a new disease. No case with a similar neuropathological appearance has been identified despite review of archival material, including a systematic study in Europe. Additional evidence comes from laboratory studies, which have demonstrated that the isotype of prion protein (PrP) deposited in the brain in vCJD is similar to experimentally transmitted BSE and that florid plaques are present in the brains of macaque monkeys inoculated with BSE. Laboratory transmission studies in wild-type human transgenic and bovine transgenic mice demonstrate that the transmission characteristics of vCJD, including incubation period and distribution of neuropathological changes, are very similar in BSE and vCJD but distinct from sCJD. The evidence of a causal link between BSE and vCJD is now compelling.

Clinical features of vCJD

vCJD and sCJD have a different age distribution. Figure 2 indicates that the age at death from CJD in the UK has a bimodal distribution, which
is distinct from previous experience in the UK or from any other country that has carried out systematic surveillance for CJD. It is of note that there is an overlap between vCJD and sCJD in the age of death, but that even in the UK there is a higher incidence of sCJD in the age group 40–44 years at death.

The duration of illness is more prolonged in vCJD in comparison to sCJD, with a median duration of illness in vCJD of 13 months in comparison to 4 months in sCJD. Although there is an overlap of clinical characteristics, the vCJD cases as a group are clinically relatively distinct from sCJD and are also remarkably homogeneous in comparison to the disparate clinical presentations in sCJD. In vCJD, the early clinical course is dominated by psychiatric symptoms, although a minority have neurological symptoms from the onset, usually in the form of persistent pain or memory impairment. After about 6 months, there are frank neurological signs, including ataxia, cognitive impairment and involuntary movements, which may be dystonic, choreiform or myoclonic. There is progressive neurological deterioration and patients become mute, incontinent and bed-bound. Death is often due to intercurrent infection.

**Epidemiology**

Up to May 2003, 135 cases of vCJD had been identified in the UK. Analyses of the numbers of deaths from vCJD by year (Fig. 3) had
shown an increasing trend with time, but recent data raise the possibility that the epidemic has peaked\(^{19}\). Mathematical models estimating the total future number of cases have indicated a wide range of future scenarios. Early calculation estimated that there might be thousands or more cases of vCJD in the UK and, although more recent models provide more conservative estimates\(^{20}\), there remains uncertainty about the likely size of the total vCJD epidemic. All these calculations necessarily depend on a range of unknown assumptions including critical determinants such as the mean incubation period of BSE in humans or the infectious dose of BSE for humans.

The favoured hypothesis is that transmission of BSE to the human population was through dietary exposure, likely to high-titre (CNS) bovine tissues, probably in the 1980s\(^{21}\). The evidence supporting this hypothesis is currently weak, but there is no reasonable alternative hypothesis and there are major methodological difficulties in establishing an increased risk for vCJD through past composition of commonly consumed food products.

Risk factors for vCJD included a young age, methionine homozygosity at codon 129 of the prion protein gene (\(PRNP\)) and residence in the UK. The reason for the young age distribution of cases is not known, but
could relate to an increased age-related exposure to BSE through consumption of particular foodstuffs or an increased susceptibility to infection in the young because of yet to be identified biological factors. All tested cases of vCJD in the UK to date (114 cases) are methionine homozygotes at codon 129 of PRNP compared to about 39% of the general Caucasian population. The genotype at this locus also influences the likelihood of developing sCJD and iatrogenic CJD (Table 3). In vCJD, methionine homozygosity may be a true susceptibility factor but there is also the possibility, by analogy with other forms of human prion disease, that variations at this locus may influence incubation period. Cases of human BSE infection with a valine homozygous or heterozygous codon 129 genotype may yet occur and could have a different phenotype from vCJD.

Residence in the UK is a relative, but not a necessary, risk factor for the development of vCJD. The numbers of cases of vCJD by country are listed in Table 4. Attribution of vCJD by country is defined as the country of normal residence at the time of disease onset. All the cases of vCJD in the UK, together with the Canadian, Irish and US cases, were potentially exposed to BSE in the UK after examination of life-time residential history. The French cases and the Italian case had not been resident in the UK and must have been exposed to indigenous cases of BSE or export from the UK of infected cattle, cattle feed or food products in the 1980s.

vCJD is a new disease, caused by infection with a novel strain of prion in humans. Although there is no evidence to date suggesting that sCJD is transmitted from case to case via general surgical instruments or blood products, this may not apply to vCJD. The peripheral pathogenesis of vCJD is different from other forms of human prion disease, with

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**Table 3** Percentage of codon 129 PrP genotypes in CJD and in the normal population

<table>
<thead>
<tr>
<th></th>
<th>Met/Met</th>
<th>Met/Val</th>
<th>Val/Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal population</td>
<td>39%</td>
<td>50%</td>
<td>11%</td>
</tr>
<tr>
<td>Sporadic CJD</td>
<td>68%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>hGH-related CJD</td>
<td>48%</td>
<td>20%</td>
<td>32%</td>
</tr>
<tr>
<td>vCJD</td>
<td>100%</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 4** Cases of vCJD world-wide (May 2003)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>135</td>
</tr>
<tr>
<td>France</td>
<td>6</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>1</td>
</tr>
<tr>
<td>Italy</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
</tr>
</tbody>
</table>
immunostaining for prion protein in lymphoreticular tissues\textsuperscript{22} and, presumably, higher levels of peripheral infectivity. It is possible that there may be a risk of transmitting vCJD through contaminated surgical instruments or through labile or fractionated blood products donated by individuals who later develop vCJD. There is currently no evidence of transmission of vCJD through these routes, but this does not preclude such a possibility because the incubation period could be long and the period of current observation is short. A range of measures to minimise the risk of secondary transmission of vCJD have been taken in the UK and other countries.

Kuru

Kuru is geographically restricted to the Okapa area of the highlands of Papua New Guinea\textsuperscript{23}. Over 2700 cases of kuru have been documented since 1957 in a total population within the kuru region of 36,000 people. The identification of ritual cannibalism as the mechanism of disease transmission followed years of meticulous research by Dr Carleton Gajdusek and colleagues\textsuperscript{24}. Laboratory transmission studies in primates proved that kuru was caused by a transmissible agent, despite the absence of evidence of infection histologically or serologically. This seminal discovery led to the successful laboratory transmission of CJD and initiated research into the epidemiology and pathogenesis of human prion disease.

Kuru affected predominantly women and children of either sex in the early years of the epidemic; however, as time has passed, the incidence of the disease has declined and the proportion of affected adult males and females has become more similar. No children born after 1959 have been affected and there is no evidence of vertical transmission of infectivity in kuru, despite the breast-feeding of infants by many hundreds of clinically affected mothers\textsuperscript{25}. The possibility of transmission through endocannibalism was raised by anthropological enquiry, and the decline in the epidemic following the cessation of endocannibalism in the late 1950s is consistent with this mechanism of transmission. Women and children consumed diseased relatives as a mark of respect, leading to a familial aggregation of cases. Virtually all tissues were eaten, including brain and viscera. The excess of cases in females and children is consistent with the available descriptions of the rituals, since they, and not the men, ate the internal organs, in particular the brain. The incubation period ranges from 4.5 years to at least 40 years and cases are still occurring, albeit at a very low rate. The mean incubation period has been estimated to be about 12 years.

Clinically, cases of kuru presented with a pure cerebellar syndrome\textsuperscript{26}. In contrast to sCJD, other neurological signs (e.g. upper motor neuron
signs and myoclonus) did not occur. In the later stages, communication was often difficult because of severe dysarthria but, in the majority of patients, dementia was absent. The total illness duration in adults ranged from 6–36 months.

The scientific study of kuru has been crucial to current understanding of prion diseases. From a clinical perspective, there is a remarkable consistency in the clinical picture in kuru, following exposure to an exogenous infectious agent, and the epidemiological pattern of kuru has demonstrated that human diseases can be transmitted through a peripheral route, either orally or, perhaps, transdermally.

Conclusions

Measures introduced to minimise the risk of transmission of prion diseases must take into account a number of unusual features of these diseases: (i) prolonged incubation periods extending to years or longer; (ii) the absence of a practicable test for the presence of infection during the incubation period; and (iii) the remarkable resistance of prions to disinfection. Despite the accumulation of relevant scientific information, many types of acquired prion disease were not anticipated and there is a need for vigilance regarding novel mechanisms of prion transmission.

References

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11 Gibbs CJJ, Joy A, Reid Heffner DO et al. Clinical and pathological features and laboratory


