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THE PUBLIC HEALTH IMPACT OF PRION DISEASES[1]

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■ **Abstract** Several prion disease–related human health risks from an exogenous source can be identified in the United States, including the iatrogenic transmission of Creutzfeldt-Jakob disease (CJD), the possible occurrence of variant CJD (vCJD), and potential zoonotic transmission of chronic wasting disease (CWD). Although cross-species transmission of prion diseases seems to be limited by an apparent "species barrier," the occurrence of bovine spongiform encephalopathy (BSE) and its transmission to humans indicate that animal prion diseases can pose a significant public health risk. Recent reports of secondary person-to-person spread of vCJD via blood products and detection of vCJD transmission in a patient heterozygous at codon 129 further illustrate the potential public health impacts of BSE.

INTRODUCTION

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of animal and human brain diseases that are uniformly fatal and often characterized by a long incubation period and a multifocal neuropathologic picture of neuronal loss, spongiform changes, and astrogliosis (3). Investigators believe the etiologic agents of TSEs are abnormal conformers of a host-encoded cellular protein known as the prion protein. Prion diseases do not characteristically elicit an immune response by the host, and the mechanism of brain damage is poorly understood. However, progressive neuronal accumulation of the disease-associated prions may damage neurons directly, and diminished availability of the normal prion protein may interfere with the presumed neuroprotective effect of the normal prion protein, contributing to the underlying neurodegenerative process.

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Prion diseases attracted much attention and public concern after an outbreak of bovine spongiform encephalopathy (BSE) occurred among cattle in many European countries and scientific evidence indicated the foodborne transmission of BSE to humans (67, 74). Variant Creutzfeldt-Jakob disease (vCJD), the new form of human disease resulting from BSE transmission, is distinguished from the classic form of CJD by the much younger median age of affected patients, its clinical and neuropathologic features, and the biochemical properties of the protease-resistant prion protein (5, 7, 25, 72). The classic form of CJD was first reported in the 1920s, decades before the first BSE cases were identified in the mid-1980s (3). About 10%–15% of CJD cases occur as a familial disease associated with pathogenic mutations of the prion protein gene, and about 85% of classic CJD cases occur as a sporadic disease with no recognizable pattern of transmission. The stable, almost predictable, occurrence of the disease in many areas of the world, primarily in the elderly, led to the speculation that sporadic CJD may occur from de novo spontaneous generation of the self-replicating prions, presumably facilitated by somatic random mutations. Beginning in the 1970s, iatrogenic person-to-person transmission of the CJD agent was reported in a small percentage of CJD patients (12). This iatrogenic spread involved the use of contaminated corneal and dura mater grafts, neurosurgical equipment, and cadaver-derived human growth hormone. At present, the number of iatrogenic CJD cases is on the decline as a result of public health preventive measures implemented as the various modes of transmission were identified.

In addition to BSE and iatrogenically transmitted CJD, another prion disease of potential public health concern in the United States is chronic wasting disease (CWD) of deer and elk. CWD in free-ranging cervids has been endemic in a tricorner area of Colorado, Nebraska, and Wyoming, and new foci of infection have been detected in others parts of the United States and the Canadian province of Saskatchewan (6).

ETIOLOGIC AGENT OF PRION DISEASES

Most of the earliest studies done to identify the agents of TSEs focused on describing the causative agent of scrapie, a prion disease of sheep known to have been occurring in Europe for centuries. Lack of suitable laboratory models or cell culture systems had limited the efforts to characterize the scrapie agent; however, the successful transmission of scrapie to mice in 1961 greatly facilitated the identification and characterization of the scrapie agent (63). Several theories had been proposed to describe its characteristics. Owing to the transmissibility of the agent, retention of its infectivity after filtration, and the long incubation period before disease onset, scrapie was thought to be caused by a slow virus. The possibility that the agent could be a viroid was considered also. However, no viral particles or disease-specific nucleic acids were identified in association with scrapie infection (1, 62). Resistance of the scrapie agent to radiation, nucleases, and standard

sterilization and disinfection agents and its inactivation by procedures that modify proteins led to the suggestion that the scrapie agent is not a virus but, instead, might be composed primarily of a protein (1). In 1966, Alper et al. suggested the possibility that the scrapie agent could replicate in the absence of nucleic acids. Pattison & Jones also investigated this possibility and suggested that the scrapie agent might be a basic protein or associated with such a protein, thus igniting a controversy among many of their contemporaries (62). In 1967, Griffith carefully outlined the potential pathways by which such a protein agent could support its own replication (38).

Although the protein-only hypothesis was considered almost heretical, Griffith downplayed the fear that the existence of a protein agent would cause the whole theoretical structure of molecular biology to come tumbling down. His proposal that scrapie could arise spontaneously from a host gene was later challenged by the fact that scrapie spread among sheep within a herd, indicating the infectious nature of the disease. However, his spontaneous host gene theory persisted as an explanation for the occurrence of most sporadic CJD cases and familial human prion diseases. Subsequent studies by Prusiner et al. (65) demonstrated a hydrophobic protein to be an essential component of the scrapie agent, but no specific polypeptide was identified. To underscore the requirement of a protein for scrapie infectivity, Prusiner (63) introduced the term prion in 1982 to describe the proteinaceous infectious particle. In the same year, Prusiner et al. (64) and Bolton et al. (10) reported the major success of the purification of scrapie prion and the demonstration of its relatively high resistance to proteinase K treatment.

Soon after the discovery of prions, their similarity with a normal cellular protein, which is a structural component of cell membranes, was identified (59). This cellular protein was given the name prion protein. In humans, the prion protein is encoded by genes located on the short arm of chromosome 20. Although the exact function of this protein is unknown, a protein found in such abundance in mammals, particularly in neurons, could have multiple functional roles. Several putative functions of the prion protein have been proposed, including supporting neuronal synaptic activity, binding copper, and interacting with other cell-surface proteins to provide neuroprotective functions (50). Prions are primarily distinguished from the cellular prion protein by their three-dimensional structure. The cellular prion protein is predominantly composed of the α-helix structure and is almost devoid of β-sheet, whereas about 43% of scrapie prions are composed of β-sheet (60). Other distinguishing characteristics of prions include their resistance to inactivation by proteolytic enzymes, conventional disinfectants, and standard sterilization methods (63). Prions are abnormal conformers of the cellular prion protein, the presence of which appears to be a prerequisite for the replication and propagation of prions (14). Although the exact mechanism of prion replication remains unclear, the agent is believed to promote the conversion of the cellular prion protein into the abnormal conformer by an autocatalytic or other unidentified process (66, 68).

Prions causing TSEs in different species and in some instances different disease phenotypes in the same species can be distinguished by several laboratory

methods, indicating the existence of different prion strains (13, 61). In the absence of disease-specific genetic material, it is unclear how strain differences are encoded by different prions. The three-dimensional structure of prions has been suggested as a site where strain differences reside (68).

IATROGENIC CREUTZFELDT-JAKOB DISEASE

The iatrogenic transmission of CJD was first reported by Duffy et al. in 1974 (33) in a 55-year-old patient who developed autopsy-confirmed CJD 18 months after receipt of a corneal graft. Autopsy confirmed that the donor of the corneal graft also died as a result of CJD. Since then, one patient each with a probable and a possible risk of CJD transmission via corneal graft has been reported from Germany and Japan, respectively (40, 48). The German patient died at 46 years of age, 30 years after receipt of the corneal graft. The CJD transmission in this patient was considered probable primarily because her CJD illness, although, typical for the disease, it was not confirmed by neuropathologic testing. The donor of the cornea, however, died as a result of autopsy-confirmed CJD. In the Japanese case, the recipient died of confirmed CJD, but no information was available on the donor of the corneal graft.

Three additional cases of CJD (two from the United States and one from Japan) in corneal graft recipients have been reported but not published. All three cases occurred independently of each other, and investigations indicated no evidence of CJD in the cornea donors. Because of the large number of corneal transplantations carried out each year, particularly among the elderly, it is expected that sporadic CJD, not causally linked with the corneal grafts, will occur among this population.

Creutzfeldt-Jakob Disease Associated with Neurosurgical Equipment

In 1977, two unusually young patients aged 17 and 23 years were reported to have acquired CJD 16–20 months after having a stereotactic electroencephalographic (EEG) procedure in which depth electrodes were used that had been implanted 2–3 months earlier on a patient who subsequently died of autopsy-confirmed CJD (8). The heat-sensitive EEG electrodes were cleaned with benzene and disinfected with 70% ethanol and formaldehyde vapor between uses. Contamination of the EEG electrodes was demonstrated >2 years after their original use by experimentally implanting the electrodes into a brain of a chimpanzee who became ill 18 months after implantation (36).

Worldwide, four CJD patients causally linked with exposure to contaminated neurosurgical instruments have been identified (72, 75). Three of these cases occurred in the 1950s in the United Kingdom, and the patients' CJD illnesses were confirmed by neuropathology testing of autopsy brain tissues. Their neurosurgical procedures were performed within one month of craniotomy procedures in

other patients who subsequently died of CJD. The fourth patient was reported in 1980 from France. The absence of recent CJD cases associated with a neurosurgical procedure was believed to be due to advances in standard hospital instrument sterilization procedures. Although these advances well may have prevented CJD transmission via contaminated neurosurgical instruments, several laboratory studies indicated that current standard sterilization procedures may not completely inactivate the CJD agent (26). Recent investigations of possible CJD transmissions via neurosurgical procedures in two U.S. patients illustrate the difficulty in identifying and linking each patient with exposure to potentially contaminated instruments used on a possible index CJD patient many years earlier. In both case-patients, closure of the hospitals and unavailability of medical records precluded an accurate assessment of the CJD risk associated with their past neurosurgical procedures.

Neurosurgical instruments used on patients suspected of having CJD should be decontaminated by using procedures recommended for reprocessing such instruments (26). Various hospital infection control professionals have consulted the Centers for Disease Control and Prevention (CDC) after CJD was confirmed in patients who underwent neurosurgical procedures with instruments that were subsequently used on other patients before being reprocessed with the appropriate CJD decontamination methods. These episodes have created several ethical and legal dilemmas, including whether potentially exposed patients should or should not be informed about any possible risk. In a minority of these instances, hospital personnel made a decision to inform the patients exposed to neurosurgical instruments that were not cleaned using the recommended CJD decontamination methods. The decision-making process may be further complicated if the contaminated instruments are mixed with other instruments during reprocessing, making identification of potentially exposed patients almost impossible. The circumstances surrounding such episodes vary and are best handled by a local hospital review board consisting of pertinent physicians, ethicists, hospital administrators, infection control professionals, and possibly others. Greater emphasis should be placed on identifying ways of preventing such episodes from occurring again. One recommended method of prevention is to consider as potentially "CJD contaminated" any neurosurgical instruments used on patients who undergo a craniotomy procedure for a condition not clearly diagnosed before the procedure (26). Those instruments could either be reprocessed using the methods recommended for CJD-contaminated instruments or quarantined until the diagnosis is clarified.

A local hospital review board may wish to consider the following factors while deliberating on the possible notification of potentially exposed patients: (*a*) whether autoclaving or heat was used to reprocess the instruments in question (standard autoclaving procedures seem to be superior to conventional chemical disinfection); (*b*) reprocessing potentially CJD-contaminated instruments numerous times using standard autoclaving methods may completely eliminate infectivity; (*c*) whether potentially contaminated instruments were kept moist throughout the neurosurgical procedure (drying of tissues on surgical instruments may interfere with complete inactivation of the CJD agent); (*d*) the ability to identify potentially contaminated

neurosugical instruments and to link them to potentially exposed patients; (*e*) the potential negative impact of informing patients about possible exposure to a fatal, untreatable brain disease; (*f*) no practical CJD-specific test is currently available to screen live patients for prion infection; and (*g*) no prophylactic treatment is currently available to mitigate the risk of CJD.

Human Growth Hormone–Associated Creutzfeldt-Jakob Disease

In 1985, three U.S. patients aged 20–34 years were reported to have developed CJD after receipt of pituitary-derived human growth hormone (hGH) through the National Hormone and Pituitary Program (NHPP) (17, 37, 46). The patients received the hormone between 1963 and 1980 for growth failure secondary to hGH deficiency, and their identification led to the discontinuation of hGH use in the NHPP. A follow-up study was initiated of 6272 of the estimated total of 7700 patients who had received hGH as part of the NHPP (56). As of April 2004, 26 of the total estimated NHPP patients, including 21 of the originally identified study cohort, developed CJD. All 26 patients began their hormone treatment before a size exclusion chromatography purifying step was introduced in the extraction process in 1977 (56). The median incubation period of the U.S. hGH-associated CJD cases was estimated at 20.5 years (range, 10–30).

Worldwide, ~165 hGH-associated CJD patients were reported, including ~89 in France, 41 in the United Kingdom, and 5 in New Zealand (56, 72, 73). The cases in New Zealand and Brazil are linked to the U.S. outbreak because the patients received hGH imported from the United States. In the United States, through 2003, approximately 1 in 100 hGH recipients who began treatment before 1977 developed CJD. The risk of hGH-associated CJD varies by country primarily because of differences in the pituitary donor selection criteria and methods employed in hormone extraction and purification. The proportion of recipients developing CJD in the United Kingdom is ~2 times higher and in France is >5 times higher than that in the pre-1977 recipients in the United States (12, 72). The lower median incubation period for cases in France (10 years) and the United Kingdom (16 years) suggests that the hGH used in these countries may have contained a higher infectious dose of the CJD agent. Between 1963 and 1985, at least 140 infected pituitary glands may have been processed in the United States and randomly distributed among many hGH lots (34). The hGH-associated CJD outbreak may not completely resolve for many more years because of the relatively young age at which most recipients were treated and the long incubation period associated with TSE exposure.

Dura Mater Graft-Associated Creutzfeldt-Jakob Disease

Transmission of CJD via dura mater grafts was first reported in 1987 in a 28-year-old woman from the United States who developed the disease 19 months after a

craniotomy procedure involving implantation of Lyodura, a brand of dura mater graft processed by B. Braun Melsungen AG of Germany (18, 69). In contrast to the processing procedures used by this German company, U.S. dura processors avoided commingling of dural grafts from different donors and kept records to facilitate identification and tracing of donors of each dural graft (19). The unusually young age of the 1987 U.S. case-patient, the previous association of CJD transmission with nervous tissue exposure, and the differences in processing of Lyodura compared with other dural grafts convinced public health investigators about the probable causal link of the patient's CJD illness with the Lyodura graft. In May 1987, because of this probable causal link, the Lyodura manufacturer revised its procedures for collecting and processing dura mater grafts to reduce the risk of CJD transmission. Commingling of dural grafts from different donors was discontinued and a sodium hydroxide treatment step was instituted to inactivate the CJD agent. Subsequent to widespread publication of this first case, many other Lyodura-associated CJD cases were reported worldwide, including in Germany, Italy, Japan, New Zealand, Spain, and the United Kingdom, and a second case was reported in the United States (20, 21, 47, 49, 53, 54, 57, 77).

By 2003, ~136 dura mater graft–associated CJD cases were reported worldwide (24, 72). Approximately 70% of these cases occurred in Japan, and over 90% of the cases were associated with receipt of Lyodura produced before May 1987. Japan has an unusually high number of the cases, presumably owing to the more frequent use of Lyodura in that country. On the basis of the outbreak in Japan, which appears to be ongoing, the estimated minimum risk of CJD among recipients of Lyodura within 17 years of implantation was 1 case per 1250 recipients (24). As of 2003, the median incubation period of 97 dura mater graft–associated CJD cases in Japan was about 122 months (range, 14 to 275).

In addition to the two Lyodura-associated CJD cases, two other dural graft–associated CJD cases have been reported in the United States. One of these cases was in a 39-year-old woman who had autopsy-confirmed CJD with illness onset in June 1998, 6 years after implantation of Tutoplast, a brand of dura mater graft produced by Pfrimmer-Viggo of Germany (39). The patient's young age, the time of dura implantation to CJD onset, and the report of unexplained neurologic disease in the dura mater donor indicated that the Tutoplast graft was the most likely source of CJD in the patient. This case represents the first clearly identified association of CJD with Tutoplast despite the use of >500,000 of these grafts worldwide since the early 1970s. The company's avoidance of commingling dural grafts from different donors likely played an important role in the absence of more reported CJD cases associated with Tutoplast. The fourth U.S. dural graft–associated CJD occurred in 1995 in a 72-year-old man (31). The investigation of this patient's illness indicated that the association with the dural graft used in this patient 54 months before his CJD onset may have been coincidental rather than causal.

After Japan announced the identification of 43 dural graft–associated CJD cases, Canada, Japan, and some European countries banned the use of human dura mater grafts in neurosurgical procedures (22). In the United States, the Food and Drug

Administration's (FDA) Transmissible Spongiform Encephalopathy Advisory Committee recommended that the decision to use dura mater grafts should be left to the treating neurosurgeon (24). However, the committee recognized the inherent risk of CJD transmission via dura mater grafts and encouraged the use of other alternatives whenever possible. It also recommended additional preventive measures to increase the safety margin of dural grafts processed in the United States. After the committee's recommendation, the number of dural grafts distributed for use in the United States declined to an estimated 900 grafts in 2002 from about 4500 grafts in 1997 (24).

BOVINE SPONGIFORM ENCEPHALOPATHY

United Kingdom

BSE was first recognized in the United Kingdom in 1986, where it caused a large outbreak among cattle (28, 67). The leading hypothesis for the origin of BSE is cross-species transmission of scrapie to cattle via the feeding of meat-and-bone meal that was contaminated by the inclusion of scrapie-infected sheep parts. Spontaneous occurrence of the disease in cattle, much like sporadic CJD in humans, has also been hypothesized. Although the origin of BSE remains controversial, it is widely accepted that the practice of using rendered BSE-infected carcasses for cattle feed had amplified the outbreak until a ruminant feed ban was instituted in 1988 (7, 28, 67). Because of concerns about cross-contamination of cattle feed with prohibited material intended for other species, a specified bovine offal ban (also known as specified risk material ban) was introduced in 1990 to remove the known infectious parts of cattle from all animal feed. A dramatic decline in the BSE outbreak was registered in response to these feed bans. Although the number of cattle confirmed with BSE in the United Kingdom as of 2003 is $>180{,}000$, the total estimated number of U.K. cattle potentially infected with BSE is in excess of 2 million (67). Approximately 750,000 BSE-infected cattle were estimated to have been slaughtered between 1980 and 1996 (35) and potentially consumed by millions of U.K. residents. A more recent statistical analysis incorporating data from surveillance of asymptomatic cattle >30 months of age indicated that the number of BSE-infected cattle slaughtered for human consumption in the United Kingdom may have been about twice as high as the previous estimate (32).

As the U.K. BSE outbreak progressed, several important public health preventive measures were implemented before and after evidence of BSE transmission to humans surfaced in 1996. These measures included a 1989 specified risk material ban for human food, a 1996 prohibition of the processing of cattle ≥ 30 months old for human food, and total ban on the feeding of mammalian protein to any farmed animals (67). The measures introduced in 1996 were intended to contain the BSE outbreak aggressively by keeping potentially BSE-contaminated feed off the farms and to remove as many BSE-infected materials as possible from the human food supply system. Unfortunately, BSE continued to be detected, albeit at a very low rate, in cattle born after the 1996 ban. The source of BSE infection in these cattle is

not fully understood. Exposure to residual or imported contaminated feed or feed ingredients and unidentified nonfeed sources of transmission (e.g., maternal transmission) have been proposed as possible explanations for the occurrence of BSE among cattle born after the 1996 ban (67). Exposure to residual BSE-contaminated feed is the most favored hypothesis because as little as 10 mg of infected material has been shown to be infectious in experimental animal models.

In Other European Countries

In 1989, BSE was identified for the first time outside of the United Kingdom in the Republic of Ireland. Because many other countries, mostly within Europe, had imported cattle and meat-and-bone meal from the United Kingdom, the spread of BSE to these countries was not surprising. By the end of 1999, BSE among domestic cattle was detected in seven other European countries (Portugal and Switzerland in 1990; France in 1991; Belgium, Luxembourg, and The Netherlands in 1997; and Liechtenstein in 1998). During 2000 and 2002, indigenous BSE was reported in 11 additional European countries and, for the first time outside of Europe, in Japan and Israel (Table 1). Improved BSE surveillance particularly in the European Union contributed to the rapid increase in the number of countries with confirmed BSE. Currently, BSE surveillance in European Union countries targets all downer (nonambulatory) cattle, fallen stock (cattle who die of nonspecific causes), cattle >24 months of age slaughtered on an emergency basis, and all slaughtered cattle >30 months of age (67). The large volume of cattle tissues in these surveillance schemes are tested using rapid BSE assays, several of which were evaluated and licensed by the European Commission (58).

North America

For years, the North American continent was considered to be free of indigenous BSE primarily because of the coordinated and proactive measures taken by Canada, Mexico, and the United States to prevent introduction of the disease (45). These measures had included banning the importation of cattle and cattle products from countries known to have BSE or to be at risk of BSE and institution of ruminant feed bans, which were introduced in 1997 in Canada and the United States. BSE in a beef cow imported from the United Kingdom had been identified in 1993 in the province of Alberta, Canada. Members of the herd of the positive cow were culled and incinerated.

On May 20, 2003, BSE was confirmed in an approximately six-year-old Canadian-born Angus cow from a herd in Alberta, heralding the first report of a confirmed indigenous BSE case in North America (15). The cow had been condemned when it was presented for slaughter in January 2003 because of pneumonia. Meat from this cow did not get into the human food supply, but parts of the animal were rendered for animal feed, most likely poultry and pet food. Relevant cattle herds with potential identified risk in the trace-back and trace-forward investigations were quarantined, culled, and tested for BSE. No additional BSE cases were detected. The source of the BSE-contaminated feed likely responsible

TABLE 1 Countries with reported number of bovine spongiform encephalopathy (BSE) cases by year of first detection[a]

Country	Number of BSE cases[b]	Year BSE first detected[c]
Austria	1	2001
Finland	1	2001
Greece	1	2001
Israel	1	2002
Liechtenstein	2	1998
Luxembourg	2	1997
Canada[d]	3	1993
Slovenia	5	2001
Japan	11	2001
Czech Republic	12	2001
Denmark	14	1992
Slovakia	15	2001
Poland	16	2002
Netherlands	76	1997
Italy	117	1994
Belgium	126	1997
Germany	337	1992
Spain	462	2000
Switzerland	455	1990
Portugal	909	1990
France	914	1991
Ireland	1435	1989
United Kingdom	183,972	1986

[a]BSE cases reported to the Office International des Epizooties as of August 23, 2004; data for the United Kingdom are as of June 30, 2004 (http://www.oie.int/eng/info/en_esb.htm).

[b]Because BSE surveillance methods and testing requirements vary by country, the number of reported cases may not be comparable among the different countries.

[c]Year first BSE was detected in imported or domestic cattle.

[d]One of the BSE-positive cows was identified in the United States but was later confirmed to have been imported from Canada.

for the Canadian BSE case was not clearly identified. However, the possibility was proposed that rendered cohorts of the 1993 imported BSE cow may have been the source of infection. Rendered parts of the 1993 cohort may have entered the Alberta feed system in greater volume than it did elsewhere in Canada (15). In response to the detection of BSE in the cow, Canadian authorities implemented additional preventive measures, including a specified risk material ban for humans and increased surveillance for BSE.

Almost immediately, the identification of a native BSE case in Canada raised concern about the possible occurrence of BSE in the United States because of the continuous flow of cattle and cattle products across the U.S.-Canadian border. On the basis of the commercial flow of cattle, possible extension of BSE into the northwestern United States, rather than eastern Canada, had been suspected (15). On December 23, 2003, seven months after the identification of indigenous BSE in Canada, the U.S. Department of Agriculture (USDA) announced the preliminary diagnosis of BSE in a 6.5-year-old nonambulatory cow that was slaughtered for human food on December 9th of that year (25). On December 25th, the BSE diagnosis was confirmed by an international reference laboratory in Weybridge, England. The USDA's investigation traced the birth of the cow to a farm in Alberta, Canada. DNA testing later confirmed the Canadian origin of the cow. At the time of slaughter, meat from the BSE-positive cow had been released for human consumption, but tissues considered to be at high risk for BSE transmission (e.g., brain, spinal cord, and small intestine) were considered unfit for human consumption and, thus, sent to be rendered for other uses (e.g., to produce nonruminant animal feed) (25). The USDA issued a recall of beef from cattle slaughtered in the same plant on the same day as the BSE-positive cow. Meat products manufactured from the recalled meat were distributed primarily in Oregon and Washington, with smaller quantities distributed in California, Idaho, Montana, and Nevada. All known potentially infectious rendered products from the BSE-positive cow were located and removed from commercial distribution.

In response to the identification of BSE, the USDA announced additional safeguards to further minimize the risk of human exposure to BSE in the United States (25). These safeguards included prohibition of the use of downer cattle for human food, removal of specified risk materials from cows $\geq$30 months old, and withholding of the USDA "inspected and passed" mark until negative BSE results are received for any cattle tested. The USDA also proposed the implementation of a national identification system to track animals of various species through the livestock marketing chain and announced its enhancement of current BSE surveillance efforts.

VARIANT CREUTZFELDT-JAKOB DISEASE

BSE captured worldwide attention because of its impact on the farming industry and international trade and, more importantly, because strong evidence indicated its transmission to humans, causing a variant form of CJD (72, 74). The cross-species transmission of BSE was heralded by the identification in the United Kingdom of

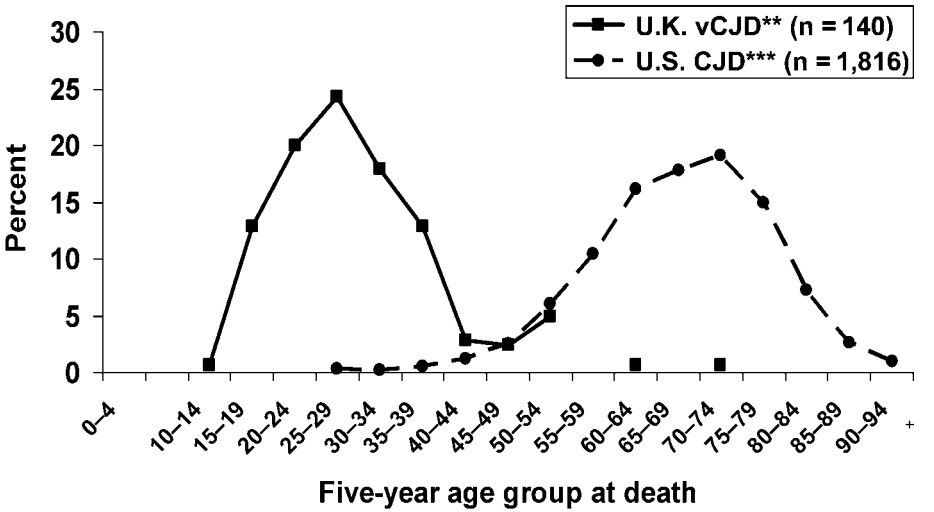
a BSE-like disease in zoo animals beginning in the late 1980s and in domestic cats beginning in 1990 (28). This resulted in the institution of national CJD surveillance in the United Kingdom, which detected an unusual clustering of ten young patients (median age, 28 years) with a unique clinical and neuropathologic profile (74). The unusually young age of the patients and their clinicopathologic homogeneity led U.K. researchers to suspect that the cases may represent an emergence of a new form of CJD resulting from BSE transmission to humans. The occurrence of this variant form of CJD (vCJD) was announced in 1996, approximately nine years after the identification of BSE in the United Kingdom. Absence of similar cases in other countries with comparable surveillance programs, their continued occurrence almost exclusively in the United Kingdom, and additional laboratory studies further strengthened the causal link between vCJD and BSE. As of November 1, 2004, a total of 151 vCJD cases had been reported from the United Kingdom (30). In addition, three cases (one each from Canada, Ireland, and the United States) among persons with potential BSE exposure in the United Kingdom because of their past U.K. residence, 8 vCJD cases from France, and 1 case from Italy have been identified (5, 7, 27).

Clinical Features

The age distribution of vCJD patients is strikingly different from that of classic CJD patients (Figure 1). Over 50% of vCJD patients died before 30 years of age, whereas only <0.2% of U.S. noniatrogenic CJD patients die before this unusually young age of 30 years. The median age at death of vCJD patients is 28 years compared with 68 years for classic U.S. CJD patients (25). In addition to differences in the age groups affected, vCJD patients also differ from classic CJD patients in the progression of clinical signs, illness duration, magnetic resonance imaging (MRI) findings, and neuropathologic lesions (Table 2) (11, 72). Characteristically, the earliest clinical manifestations in vCJD patients include psychiatric symptoms such as anxiety, depression, and withdrawal. The development of frank neurologic signs, such as myoclonus and extrapyramidal dysfunction, is often delayed for several months after illness onset. The most striking early neurologic sign in some vCJD patients is persistent dysesthesia or paresthesia (5, 7, 72). The characteristic EEG finding of periodic triphasic complexes seen in most classic CJD patients has not been reported in any of the vCJD cases to date. However, a diagnostic MRI finding of an abnormal, symmetrical, high signal intensity in the posterior thalamus, relative to that of other deep and cortical gray matter, was reported in about 87% of vCJD patients (29). In the presence of typical neurologic signs and progression, this MRI picture, designated the pulvinar sign, is considered to be highly indicative of a vCJD diagnosis. In addition, the duration of illness for vCJD patients (median, 13–14 months) is more prolonged than that for classic CJD patients (median, 4–5 months).

Neuropathologic Features

A final confirmatory diagnosis of vCJD requires histopathologic or immunodiagnostic testing (e.g., Western blot and immunohistochemistry) of brain tissues



* Excludes blood transfusion–associated vCJD and pituitary hormone- or dural graft–associated CJD

** U.K. vCJD deaths, including U.K.-related nonresident cases, 1995–2003 (R.G. Will, personal communication)

*** U.S. CJD deaths, 1995–2001.

Figure 1 Percent distribution, by age group, of noniatrogenic U.K. vCJD and U.S. CJD deaths, 1995–2003.

preferably obtained at autopsy. Frozen brain tissues are needed for Western blot testing of the protease-resistant prion protein, but immunohistochemical analysis can be done on fixed brain tissues. In addition to the neuropathologic lesions of spongiosis and neuronal loss typical for most human prion diseases, the neuropathologic findings in vCJD are distinguished by the presence of numerous deposits of kuru-type amyloid plaques that are surrounded by a halo of spongiform changes. These daisy-like amyloid deposits are designated florid plaques (44). Marked diffuse accumulation of the protease-resistant prion protein can be demonstrated in many areas of the brain by immunohistochemical staining. For some patients, immunohistochemical analysis of tonsilar biopsy tissue was used to make a premortem diagnosis of vCJD (41, 42). Prion fragments can be detected easily in the tonsils, lymph nodes, spleen, and appendix of vCJD patients but not in those of classic CJD patients (71).

Codon 129 Homozygosity for Methionine

Except for a patient with preclinical vCJD related to bloodborne transmission, all vCJD patients tested to date have been homozygous for methionine at the polymorphic codon 129 of the human prion protein gene (25, 72). Although the scientific basis for this almost exclusive occurrence of vCJD in this subgroup of the population is unknown, investigators have suggested that methionine homozygosity may be associated with a shorter incubation period, younger age distribution, and

TABLE 2 Clinical and pathologic characteristics distinguishing variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom (U.K.) from classic CJD in the United States (U.S.), 1979–2001[a]

Characteristic	vCJD, U.K.	Classic CJD, U.S.
Median age at death (years)	28 (range, 14–74)	68 (range, 23–97)[b]
Median illness duration (months)	13–14	4–5
Clinical presentation	Prominent psychiatric/ behavioral symptoms, painful sensory symptoms, delayed neurologic signs	Dementia, early neurologic signs
Periodic sharp waves on EEG	Absent	Often present
"Pulvinar sign" on MRI[c]	Present in >75% of cases	Very rare or absent
Presence of "florid plaques" on neuropathology	Present in great numbers	Rare or absent
Immunohistochemical analysis of brain tissue	Marked accumulation of PrP-res[d]	Variable accumulation
Presence of agent in lymphoid tissue	Readily detected	Not readily detected
Increased glycoform ratio on immunoblot analysis of PrP-res	Present	Not present
Genotype at codon 129 of prion protein	Methionine/methionine[e]	Polymorphic

[a]Adapted from Reference 25.

[b]U.S. CJD surveillance data 1979–2001.

[c]High signal in the posterior thalamus.

[d]Protease-resistant prion protein.

[e]One patient with preclinical vCJD related to bloodborne transmission was heterozygous for methionine and valine.

specific clinicopathologic profile. If this assumption is correct, vCJD could potentially occur in persons who are heterozygous or homozygous for valine at codon 129 after a possible longer incubation period. Studies conducted in predominantly white populations indicate that methionine homozygosity at codon 129 of the prion protein gene may be present in approximately 35%–40% of the general population (3, 72).

Statistical models have been applied to predict the eventual size of the vCJD epidemic in the United Kingdom. Some of these studies suggested that the epidemic may have already reached its peak and the eventual size may not exceed several hundred clinical cases (43, 70). However, uncertainties still exist about the influence of other factors on the size of the vCJD epidemic. These factors include the emergence of vCJD in persons with a codon 129 genotype other than methionine homozygosity, secondary spread of the vCJD agent via blood products, and the

extent and contribution of subclinical infection to the potential secondary spread of the agent.

Bloodborne Transmission

A highly probable bloodborne, person-to-person transmission of vCJD was reported in the United Kingdom in a 69-year-old man who had vCJD onset in late 2002, 6.5 years after receipt of 5 units of packed red blood cells (51). One of the red blood cell units was obtained from a 24-year-old donor who developed vCJD >3 years after donation. Both the donor and recipient died of pathologically confirmed vCJD. The unusually older age of the recipient, appropriate latency period, and the remote likelihood that confirmed vCJD in a donor and recipient pair would have occurred by chance alone indicates that this episode represents a highly probable bloodborne transmission of vCJD. The patient was identified as part of a cohort study of 48 patients who received blood components during 1980–2003 from 15 donors who subsequently died of vCJD. None of the 27 recipients who died within approximately 10 years after transfusion had a death certificate diagnosis of a neurodegenerative disease (51); the cause of death in 3 recipients was unknown. Of the remaining 17 patients under follow up, one elderly patient was recently diagnosed with preclinical vCJD on the basis of detection of the agent in the spleen and cervical lymph node. The patient died of a ruptured abdominal aortic aneurysm five years after transfusion, and no pathologic lesions were detected in the brain. This latter case represented a second episode of vCJD transmission via blood transfusion, which indicates that this mode of spread may be more frequent than previously appreciated. Most significantly, the patient was the first ever with methionine and valine heterozygosity at the polymorphic codon 129 of the prion protein gene, which indicates that persons who are not homozygous for methionine can be susceptible to infection by the BSE agent.

The bloodborne transmission of vCJD had long been suspected as possible because of some unusual features of the disease. These features included the ease by which the vCJD agent was detected in lymphoid tissues, raising the possibility that it could also be found in circulating lymphocytes, and the existence of a possible blood phase, or prionemia, of the agent as it travels from the original site of infection in the gut to the brain (71). The FDA, on recommendation from its Transmissible Spongiform Encephalopathy Advisory Committee and with support from the CDC and the National Institutes of Health, had recommended a blood donor deferral policy to exclude donors who have spent specific periods of time in the United Kingdom and other European countries (7). This policy was implemented in 1999 despite considerable criticism by people who focused more on the potential negative impact on the blood supply and on the mere theoretical nature of the risk of bloodborne transmission of vCJD. In hindsight, the reports of bloodborne spread of vCJD in the United Kingdom appear to justify the precautionary deferral policy recommended by the FDA.

Multiple BSE Strains

Unlike scrapie or classic CJD, BSE is likely caused by a single strain of an infectious agent that has a strikingly stable molecular property after natural or experimental transmission to other species. In 2004, however, researchers in Italy reported that the brain lesions of two of eight cattle they studied were distinguished from BSE by the presence of amyloid plaques and distribution of protease-resistant prion protein in the brain (16). On Western blot analysis, the prion fragment in the two cases had a lower molecular mass than that of the classic form of BSE. The researchers suggested that the difference in neuropathology and molecular mass indicates the existence of a second strain of BSE. To distinguish the disease in the two cows from the classic form of BSE, the researchers coined the name bovine amyloidotic spongiform encephalopathy (BASE). Three BSE cases with distinct molecular phenotype among cattle routinely diagnosed in a BSE surveillance system were independently reported in France also (9). Whether the findings from Italy and France do or do not represent new strains of widely circulating BSE should be confirmed through identification of more cases and additional laboratory studies.

No scientific evidence exists to causally link any form of BSE with a sporadic CJD-like illness in humans. Concerns about BSE causing a sporadic CJD-like illness have persisted after BSE-infected transgenic mice expressed prions with a molecular phenotype consistent with a subtype of sporadic CJD (2). The transgenic mice were designed to produce the human prion protein, which is homozygous for methionine at codon 129. If BSE causes a sporadic CJD-like illness in humans, an increase in sporadic CJD cases would be expected to occur in the United Kingdom first, where the vast majority of vCJD cases have been reported. However, in the period following the first published description of vCJD in 1996, there was no increasing trend in the reported annual number of U.K. sporadic CJD deaths (52). Furthermore, surveillance in the United Kingdom has shown no increase in the proportion of sporadic CJD cases that are homozygous for methionine.

CHRONIC WASTING DISEASE

Distribution

CWD (chronic wasting disease), a prion disease of North American deer and elk, was first identified as a fatal wasting syndrome of captive mule deer in the late 1960s in research facilities in Colorado (76). It was first recognized as a TSE in 1978. The occurrence of CWD among wild cervids was first identified in 1981 when a free-ranging elk from Colorado was diagnosed with the disease. Subsequent surveillance studies demonstrated the endemic occurrence of CWD among free-ranging deer and elk in a contiguous area in northeastern Colorado, southeastern Wyoming, and, most recently, in western Nebraska (76). Epidemic modeling suggested that CWD might have been present among free-ranging animals in some portions of the endemic area several decades before it was initially recognized (55).

After 2000, new foci of CWD have increasingly been identified in Illinois, New Mexico, South Dakota, Utah, Wisconsin, and non-CWD-endemic areas of Colorado and Wyoming (6, 76). The identification of CWD in these new areas seems to be related to increased surveillance and spread of the disease as a result of natural migration of deer and elk or translocation of infected cervids by humans. Currently, two largely independent outbreaks, one in free-ranging deer and elk and another in the captive elk and deer industry, are occurring in Canada and the United States (6).

Risk to Humans

The increasing spread of CWD in the United States and the zoonotic transmission of BSE raised concerns about the possible transmission of CWD to humans (6). Several CJD cases or apparent CJD clusters with suspect CWD transmission have been reported in the United States (4, 6, 23). Epidemiologic and laboratory investigations of these isolated cases and clusters did not provide convincing evidence for a link between CWD and the patients' illnesses. However, the studies seeking evidence for a possible link between CWD and human illness have been limited. Additional epidemiologic and laboratory studies should be conducted before the CWD agent can be exonerated as a possible human pathogen. Because persons who hunted deer and elk in the known CWD-endemic areas of Colorado and Wyoming are more likely to have been exposed to the CWD agent over many years, a follow-up study of these hunters has been initiated to monitor the possible zoonotic transmission of CWD. A transgenic mice study, involving humanized and cervidized mice, is also in progress to determine the susceptibility of these mice to the CWD agent (6).

CONCLUSION

Three distinct prion disease–related human health risks from environmental sources of infection can be identified in the United States. These include the iatrogenic transmission of CJD, occurrence of vCJD from exposure to BSE-contaminated cattle products in the United States or other countries with BSE, and possible transmission of CWD to humans. The iatrogenic transmission of CJD appears to be on the decline following appropriate preventive measures that were instituted as the different iatrogenic modes of spread were identified. Additional iatrogenic CJD cases, however, can be anticipated primarily because of the long incubation period associated with prion diseases.

To date, only one vCJD patient has been identified as a resident of the United States (25). This patient is believed to have contracted the disease while growing up in her native country of Britain during the height of human exposure to the BSE outbreak. Although the public health preventive measures recently instituted by the USDA should further reduce the risk of BSE exposure to the U.S. population, the possibility that domestically acquired vCJD may appear in the

United States cannot be totally dismissed. However, this possibility is probably much smaller than the risk of contracting vCJD as a result of BSE exposure during any previous travel or residence in countries where a much higher rate of BSE has been documented. Recent reports of vCJD transmission via blood products obtained from donors who were incubating the disease are of concern because of a potentially large number of blood donors who might have been exposed to BSE and are incubating the disease. Theoretically, these persons might transmit the vCJD agent if they donate blood while they are clinically asymptomatic. The blood donor deferral policy instituted by the FDA is expected to greatly minimize this possible risk of bloodborne transmission of vCJD in the United States. The findings of vCJD transmission in a patient who was heterozygous at codon 129 may have implications for the eventual size of the vCJD outbreak. Heterozygous patients may develop vCJD after a longer incubation period and at an older age than methionine homozygous patients, potentially resulting in a more protracted course for the vCJD outbreak.

To date, no convincing evidence of CWD transmission to humans has been reported. Because the decade-long occurrence of CWD had been relatively limited to a small geographic area, it is possible that not enough human exposure with the appropriate latency period has occurred for the agent to overcome the species barrier and cause disease in humans. There is a concern that the level of human exposure to CWD might increase over time with the increasing spread of CWD to new areas. Continued surveillance for possible human CWD among high-risk populations (e.g., persons hunting for many years in the CWD-endemic areas of Colorado and Wyoming) and evaluation of the zoonotic potential of the CWD agent in transgenic animal models should be conducted to monitor the possibility that the CWD agent can cause disease in humans.

Suspected cases of iatrogenic CJD, vCJD, or human CWD cases should be reported to the CDC through local and state health departments. To facilitate surveillance for emerging forms of prion diseases such as vCJD and human CWD, the CDC, in collaboration with the American Association of Neuropathologists, established a National Prion Disease Pathology Surveillance Center. This pathology center is located at Case Western Reserve University, in Cleveland, Ohio, and provides state-of-the-art diagnostic support free of charge to U.S. physicians and develops laboratory methods to detect emerging human prion diseases. Autopsies should be sought in all clinically suspected and diagnosed human prion disease cases. Brain tissues from these cases should be sent to the National Prion Disease Pathology Surveillance Center to confirm the diagnosis of CJD and determine the CJD subtype. Increased testing of brain tissues from suspected case-patients would facilitate detection of the emergence of any new prion diseases, such as vCJD or possible human CWD, in the United States.

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Annual Review of Public Health
Volume 26, 2005

CONTENTS

SOCIAL ENVIRONMENT AND BEHAVIOR

HEALTH SERVICES

INDEXES

ERRATA

An online log of corrections to *Annual Review of Public Health* chapters may be found at http://publhealth.annualreviews.org/