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BOVINE SPONGIFORM ENCEPHALOPATHY AND ITS RELATIONSHIP TO CREUTZFELDT-JAKOB DISEASE

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INTRODUCTION

Single cases of bovine spongiform encephalopathy (BSE), or mad cow disease, were detected in both Canada and the United States in 2003. These discoveries have increased concerns for the safety of the North American beef supply. However, the question of how mad cow disease might infect humans, if they eat contaminated meat, is rarely discussed in significant detail. This paper will look at the relationship between BSE and its human equivalent, Creutzfeldt-Jakob disease (CJD).

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY

BSE and CJD fall within a category of related diseases known as transmissible spongiform encephalopathies (TSEs), which are fatal in 100% of cases. All TSEs appear to involve prions, which are infectious protein molecules that somehow cause the formation of small, sponge-like holes in brain tissue. Prions are thought to transform normal, benign protein molecules into infectious, deadly ones by altering the shape of the healthy molecules to the dangerous conformation. This transformation then induces a chain reaction to alter the shape of other benign protein molecules into the deadly form. The prion thought to be responsible for scrapie (a TSE affecting sheep and goats) and other spongiform encephalopathies is hypothesized to be a modified form of PrP^{c} and is labelled PrP^{Sc}. PrP^{c} is a normal protein anchored to the outer surface of neurons and, to a lesser extent, the surfaces of other cells, including lymphocytes.

CJD is not the only TSE that affects humans. Other known TSEs include kuru, Gerstmann-Straussler-Scheinker disease and fatal familial insomnia. Kuru, virtually eradicated now, was found in members of the Fore Tribe in Papua New Guinea who consumed the brains of deceased relatives. Gerstmann-Straussler-Scheinker disease and fatal familial insomnia are predominantly hereditary disorders.

TSEs that have been characterized in animals other than cattle include scrapie in sheep and goats; transmissible mink encephalopathy; chronic wasting disease of mule deer and elk; and feline (cat) spongiform encephalopathy. TSEs have also been identified in some exotic zoo animals.

VARIETIES OF CREUTZFELDT-JAKOB DISEASE

A. Sporadic CJD

Classic CJD, a sporadic disease, was first described in the 1920s and represents the majority of cases, approximately 85%. Sporadic CJD refers to those cases in which there is no known infectious source and no family history. The average age at onset of sporadic CJD is 55-75 years, and the illness characteristically lasts 4-6 months with rapidly advancing dementia in all cases. The disease is quite rare and is considered to occur at a rate of one person per million population worldwide.

B. Familial CJD

The inherited form of CJD accounts for the majority of remaining cases of all CJD, some 10-15%. Familial CJD strikes at an earlier age, and the disease course is somewhat longer than for sporadic CJD.

C. CJD Through Infection

Although there is as yet no evidence that suggests that casual contact with an infected individual can cause transmission of the disease, there is evidence that CJD can be transmitted during medical procedures involving the use of tainted human tissue or surgical instruments (iatrogenic transmission). Such transmissions have occurred during corneal transplants, the implantation of electrodes in the brain using contaminated surgical instruments, and the injection of human growth hormone that was derived from cadaveric brain tissue.

D. New Variant CJD

In 1996, a previously unrecognized disease pattern for CJD was identified as New Variant CJD, now called variant CJD or vCJD. The disease is distinct from the sporadic variety in that the average age at onset is considerably lower, just 27 years. Other differences include

vCJD patients' presentation of prominent psychiatric symptoms such as depression; the delayed onset of neurological abnormalities; and a more extended duration of illness, lasting 13-14 months. Microscopic examination of the brain tissue of vCJD patients also revealed a different pattern from that seen in the sporadic form of the disease. As the vCJD patients examined had no family history of CJD or previous exposure to CJD patients or their tissues, researchers were able to eliminate infections and familial transmission as possible modes of transmission of the vCJD variety of the disease.

EVIDENCE FOR TRANSMISSION OF BOVINE SPONGIFORM ENCEPHALOPATHY TO HUMANS

While the cause of sporadic CJD remains unknown, current evidence suggests that vCJD is acquired from consumption of BSE-infected beef.(1) There is still some controversy over this theory,(2) but it has become generally accepted.

From 1986 through 2001, more than 98% of the BSE cases worldwide were reported from the United Kingdom, where this disease was first described. It was determined that the spread of BSE among cattle was facilitated through the practice of including rendered beef products in cattle feed. In this way, infected beef was entering feed and transmitting the disease to the cattle that consumed it. The United Kingdom banned the use of rendered meat products in cattle feed in 1988, and the number of detected BSE cases has been decreasing since that time.(3)

Between 1995 and 2002, 124 cases of vCJD were reported in the United Kingdom, 6 in France and 1 each in Ireland, Italy and the United States. The patients in Ireland and the United States had each spent a prolonged period in the United Kingdom during the BSE epidemic. The number of vCJD cases in the United Kingdom increased by least 18% per year during this period.

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(1) Recent speculation suggests that some sporadic (classic) cases of CJD may also be traced to contaminated beef. See Chris Morris, "Research raises new human-BSE fears," 18 January 2004; available at http://cnews.canoe.ca/CNEWS/Canada/2004/01/18/pf-317283.html.

(2) George A. Venters, "New variant Creutzfeldt-Jakob disease: the epidemic that never was," *British Medical Journal*, Vol. 323, 2001, pp. 858-861.

(3) For more information on BSE, see Frédéric Forge and Jean-Denis Fréchette, *Mad Cow Disease and the Bovine Industry in Canada*, PRB 03-01E, Parliamentary Research Branch, Library of Parliament, Ottawa, September 2003.

The increased rate of CJD cases soon after the BSE epidemic led researchers to examine whether BSE might be crossing species to infect humans, even though TSEs were thought to be species-specific. For example, it has been demonstrated that scrapie in sheep and chronic wasting disease in deer cannot be passed on to other types of animals or to humans. However, TSEs were being identified in some exotic animals and wild cats that had been fed rendered meat or uncooked cattle tissues, suggesting that TSEs could indeed be transmissible between species. In addition, it was demonstrated experimentally that BSE and vCJD transmitted to macaque monkeys as well as mice produced similar clinical symptoms. Laboratory studies have since shown that the pathological agent isolated from BSE-infected cattle, PrP^{Sc}, is identical molecularly and biologically to the agent isolated from human cases of vCJD. It has also been determined that there are four distinct types of the disease-causing PrP^{Sc}, based on the three-dimensional conformation and pattern of glycosylation.(4) Sporadic and iatrogenic CJD are associated with PrP^{Sc} types 1-3, while all vCJD cases are associated with a distinct type 4 PrP^{Sc}. (Familial CJD has been characterized by more than 20 coding mutations in the prion protein gene.)(5)

The link between BSE and vCJD, although probable, has not yet been scientifically proven, because not all epidemiological criteria have been met to prove a causal link. In addition, the manner by which the bovine prion is replicated within the human brain to produce the disease has not been established.(6)

THE EFFICIENCY OF TRANSMISSION OF BOVINE SPONGIFORM ENCEPHALOPATHY TO HUMANS

At the peak of the BSE epidemic in the United Kingdom in 1992, there were over 37,000 affected cattle, with 800 new cases being identified each week. Despite the general acknowledgment that vCJD is caused by the consumption of BSE-infected beef, the U.K. Department of Health, which has maintained the U.K. Creutzfeld-Jakob Disease Surveillance Unit since 1990, has reported a total of only 137 cases of vCJD since it became identifiable. Although this number is alarmingly high compared to other countries where vCJD is virtually non-existent, it is not of the magnitude that might have been expected if the link between vCJD and BSE is accepted, given the amount of infected beef in the food supply.

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(4) Glycosylation is the attachment of a glucose molecule or other sugar unit to specific places on a protein.

(5) John Collinge, “Variant Creutzfeldt-Jakob disease,” *The Lancet*, Vol. 354, July 1999, pp. 317-323.

(6) Venters (2001).

Most of the U.K. population consumes beef. It would seem, therefore, that the disease-causing agent is inefficient at infecting and producing the disease in humans, or is easily destroyed in the cooking process, or is not generally found in those cuts of meat consumed by humans.

The efficiency of infectivity does not appear to have been specifically addressed in much research to date. However, recent findings suggest that the infectious prion can be absorbed via abrasions in the tongue.(7) In addition, some studies have suggested that BSE-infected meat may cause disease only in individuals who possess a certain genetic variation of the PrP^c gene. Possibly other genes may affect susceptibility as well, including a gene coding for an immune system protein called HLA-DQ7.(8)

The prion molecule responsible for these diseases is heat-resistant. The rendered meat used in animal feed thus remains infectious even though the rendering process involves extreme heat. It seems unlikely, therefore, that the prion molecules of BSE-infected beef would be destroyed while being cooked for human consumption.

The low rate of infectivity may be attributable largely to the cuts of meat most likely to be eaten by humans. Bioassays have identified the BSE prion in the brain, spinal cord, retina, dorsal root ganglia (nervous tissue near the backbone) and distal ileum (large intestine) of experimentally infected cattle. These tissues may have commonly been used in the rendering process but are not generally consumed by humans, who primarily eat muscle tissue. However, such tissues may have been consumed through their use in hamburger, sausages, wieners, bologna, etc.

CONCLUSION

Although the link between BSE and CJD is still contested by a few, it is generally accepted that BSE can be passed to humans through the consumption of infected meat and be manifested as vCJD. In Canada, all suspect cattle are tested for the disease, as required internationally, and there is no evidence at this time that any BSE-infected beef has reached the Canadian market. In January 2004, the Canadian Food Inspection Agency (CFIA) announced enhancements to Canada's cattle identification system to make it easier to trace the history of an

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(7) J. C. Bartz *et al.*, "Rapid Prion Neuroinvasion following Tongue Infection," *Journal of Virology*, Vol. 77, No. 1, January 2003, pp. 583-591.

(8) Graham S. Jackson *et al.*, "HLA-DQ7 antigen and resistance to variant CJD," *Nature*, Vol. 414, November 2001, pp. 269-270.

animal confirmed to have BSE. The CFIA also announced that the number of cattle to be tested for BSE is to be progressively increased.

SELECTED REFERENCES

The Creutzfeldt-Jakob Disease Foundation Internet site: www.cjdfoundation.org.

The Canadian Food Inspection Agency Internet site: www.inspection.gc.ca.

The BSE and CJD site of the U.S. Centers for Disease Control and Prevention's National Center for Infectious Diseases: www.cdc.gov/ncidod/diseases/cjd/bse_cjd.htm.

The CJD site of the U.K. Department of Health: www.doh.gov.uk/cjd.