Chronic Wasting Disease and Animal Agriculture

Elizabeth S. Williams
Department of Veterinary Sciences and Wyoming State Veterinary Laboratory, University of Wyoming, Laramie, WY 82070

Abstract

Chronic wasting disease (CWD), a member of the transmissible spongiform encephalopathies (TSEs), is only known to naturally affect mule deer (*Odocoileus hemionus*), white-tailed deer (*O. virginianus*), and Rocky Mountain elk (*Cervus elaphus nelsoni*). It has been recognized in an endemic focus along the front range of the Rocky Mountains in northern Colorado and in the hills of southeastern Wyoming for more than 30 years. Since 1996, CWD has been identified in free-ranging and farmed cervids in 15 western and midwestern states and Canadian provinces and elk imported to Korea from Canada. Surveillance for a TSE in cattle sympatric with deer and elk with CWD began in the early 1990s and has been ongoing since then. Experiments to determine host range of CWD in livestock began in the 1980s. Since that time cattle, domestic sheep and domestic goats have been exposed to the CWD agent by various means. All of these species are susceptible to CWD by intracerebral inoculation but, to date, CWD has not been found to affect traditional domestic livestock species when exposed by natural routes. Chronic wasting disease is of concern in farmed elk and white-tailed deer. Control of this disease in the cervid industries is based in state, provincial, and federal regulations. Surveillance of domestic livestock for TSEs in parallel with surveillance for CWD in farmed and free-ranging cervids will need to be continued into the foreseeable future.

Introduction

Chronic wasting disease, along with bovine spongiform encephalopathy (BSE), scrapie, and transmissible mink encephalopathy, comprise the animal members of the transmissible spongiform encephalopathies (TSEs). These diseases are thought to be caused by prions, infectious agents lacking nucleic acids derived from normal cellular prion proteins (PrP^c). Disease-associated prions (PrP^d) are abnormal, highly stable, isoforms of PrP^c[18] that are partially protease-resistant and sometimes denoted as PrP^{res}. Recent studies lend strong support for the prion-only hypothesis for causality of the TSEs; a synthetic protein was shown to contain infectivity that could be transmitted through passage in mice.[14]

While scrapie has been known for hundreds of years and has been the subject of scientific interest and eradication efforts in domestic sheep, it took emergence of BSE and the associated variant Creutzfeldt-Jacob disease (CJD) in people to focus attention of the public and the broader scientific community on the TSEs in general. Bovine spongiform encephalopathy has killed several hundred thousand cattle; caused severe economic losses to cattle industries in many nations of the world; resulted in significant and expensive changes in how cattle are raised, fed, slaughtered and tested; and altered how some people view the cattle industry and the animal health agencies that regulate the beef industries. It is within the context of these realities and concerns about the TSEs that CWD is being investigated.

The origin of CWD is not known and may never be known. Three hypotheses have been suggested. Perhaps the most plausible is that CWD is derived from scrapie. Support for this hypothesis comes from moderate ability of PrP^{res} derived from CWD-affected deer and elk to convert PrP^c from sheep to the abnormal isoform,[20] and from comparisons of glycoform patterns on western blots of PrP^{res} derived from CWD-affected deer and elk and sheep scrapie.[19] In addition, scrapie agent inoculated intracerebrally causes a disease in elk similar to scrapie.[10,11] However, CWD is unlike any characterized scrapie strain in rodent models,[2,3] does not appear to be transmissible to raccoons (*Procyon lotor*) as is scrapie,[12] and incubation period in an intracerebrally inoculated goat was longer than expected for scrapie.[22] Alternatively, CWD may be a disease of mule deer following spontaneous alteration of PrP^c, resulting in formation of an infectious prion protein. Although spontaneous generation of prions may be theoretically possible, and has been suggested as the origin of some cases of classical CJD of humans,[7] it would be exceedingly difficult if not impossible to prove retrospectively. A third possibility is that CWD is derived from another, currently unidentified source of infection.

Chronic Wasting Disease and Cattle

Investigations of cattle susceptibility to CWD have been carried out on multiple scales. Raymond *et al*[19] determined that PrP^{res} from CWD-affected mule deer, white-tailed deer, and elk had minimal ability to con-

vert PrP^c from cattle to PrP^{res} *in vitro*, indicating poor compatibility between these molecules and suggesting that cattle were unlikely to be readily susceptible to CWD infection. This *in vitro* model of molecular compatibility seems to be useful in predicting potential experimental host range of the TSEs. However, the natural host range of the TSEs depends on many other biological factors beyond molecular compatibility, including potential routes of exposure, uptake and organ distribution.

Intracerebral inoculation of experimental animals has been used extensively in the study of the TSEs: hamster and mouse models of scrapie serve as the primary laboratory systems for studying the biology of the TSEs. Although this unnatural method of exposure may be useful for determining the clinical and pathologic features of disease that might occur if a host is susceptible to a particular strain of TSE, this route of exposure is not reliable in determining natural host range.

Some cattle are susceptible to CWD agent derived from mule deer by intracerebral infection. Hamir *et al*[9] (personal communication) transmitted CWD by intracerebral inoculation to five of 13 (38%) head of mixed beef-breed cattle. Affected animals had minimal-to-mild clinical signs (loss of body condition, equivocal behavioral changes) and some had intercurrent disease. There was little to no spongiform encephalopathy found by histopathology, but PrP^d was detected in brains of all affected animals by immunohistochemistry, PrP^{res} was found by immunoblotting, and scrapie-associated fibrils (markers of the TSEs) were found by negative-stain electron microscopy. These findings must be kept in perspective relative to the potential for natural infection of cattle by CWD. Similar studies using scrapie agent inoculated into brains of cattle resulted in nine of nine (100%) cattle developing evidence of scrapie infection after more than one year.[5,6] This is in contrast to the strong epidemiologic evidence that under natural conditions scrapie is not transmissible to cattle. In addition, scrapie was not transmissible to cattle fed raw brain or rendered protein supplements derived from scrapie-affected sheep.[4] However, epidemiologic investigations in the United Kingdom strongly suggested a scrapie strain was the origin of BSE when rendered protein supplements containing scrapie agent were fed to cattle.[21]

Of more direct relevance to what might occur in the field, cattle have been exposed to CWD agent by oral exposure to CWD agent in raw brain derived from mule deer (Williams *et al*, unpublished data). Oral exposure appears to be the most normal route of exposure of hosts to the TSE agents, however, other routes, such as peripheral inoculation through the skin or tongue[1] are also possible, although poorly investigated. Ten head of orally inoculated cattle remain clinically normal more than seven years post-exposure. Due to the known lengthy incubation periods, these studies are designed to continue for a total of 10 years.

As a more realistic challenge, beef cattle are living in CWD-endemic animal facilities where they are continually exposed to CWD-incubating and clinically affected deer and elk. These cattle have lived more than seven years in these facilities, and they also remain clinically normal with no evidence of CWD (Williams *et al*, unpublished data).

Surveillance for evidence of a TSE in cattle has been conducted in areas where CWD is endemic in deer and elk beginning in 1991, in conjunction with the US Department of Agriculture's surveillance of BSE. This has centered on examination of the brains of cattle submitted to veterinary diagnostic laboratories with clinical neurologic signs or other signs suggestive of a TSE (targeted surveillance). Hundreds of cattle have been examined from endemic areas, and no evidence of a TSE has been found. In addition, examination of brains from a group of several hundred cull cattle that lived in CWD-endemic areas found no evidence of a TSE.[8]

Taken together, these studies provide substantial reassurance that CWD is not readily transmissible to cattle under normal conditions. However, the research is not yet completed and surveillance and studies of bovine susceptibility to CWD are being continued.

Chronic Wasting Disease and Domestic Sheep and Goats

Fewer studies of the potential for sheep to contract CWD have been conducted in comparison to cattle. The *in vitro* studies of molecular compatibility between PrP^{res} from CWD-affected cervids and PrP^c derived from domestic sheep demonstrated that there was moderate ability to convert ovine PrP^{res}.[20] The same caveats apply to interpretation of these findings as apply to similar *in vitro* work with samples derived from cattle and cervids (see above). Suffolk sheep of the most scrapie-susceptible genotype are susceptible to CWD agent when inoculated intracerebrally, reproducing a disease similar to scrapie (A. Hamir, personal communication). Similarly, a single domestic goat developed evidence of CWD infection following intracerebral inoculation. Incubation period in the goat was six years,[22] and the clinical disease was characterized by pruritus and loss of body condition; spongiform encephalopathy was prominent (Williams, unpublished data). The more relevant experiments, to determine if sheep and goats are susceptible to CWD when orally or contact-exposed, have not been conducted, although some studies are planned.

Surveillance for scrapie in domestic sheep and goats, though submissions of suspect animals to veterinary diagnostic laboratories or through surveillance in

flocks using nictitating membrane lymphoid biopsies,[17] have not demonstrated a spatial link between CWD and scrapie in the field, although the numbers of sheep tested are small. Studies of the potential relationship between scrapie and CWD should be continued. If such a relationship were to be identified, there could be significant management implications for both cervids and sheep.

Chronic Wasting Disease and Farmed Cervids

Chronic wasting disease has affected farmed elk and white-tailed deer in multiple jurisdictions (Figure 1) since 1996, when it was found in a farmed elk from Saskatchewan.[13] Subsequent surveillance and epidemiologic investigation resulted in identification of CWD in many herds in the United States and Canada, and resulted in depopulation of thousands of elk. Many more cases have been identified in elk than in white-tailed deer, and CWD has not been identified in farmed mule deer. Many states and provinces have guidelines and regulations in place for managing CWD in farmed cervids; these are posted on most agency web sites and are readily available. Federal regulations have been adopted by Canada (http://www.inspections.gc.ca/english/anima/healsan/disemala/cwdmdc/cwdmde.shtml) and are in the later stages of preparation in the United States (http://www.aphis.usda.gov/vs/nahps/cwd/cwd-history.html). The bases of these regulations are individual animal identification, surveillance, ability to quarantine and pay indemnity, and development of certified herds after five years of participation in the program. Only three herds, one white-tailed deer herd and two elk herds, remain under quarantine for CWD in the United States (http://www.aphis.usda.gov/vs/nahps/cwd/farmed-cwd.html).

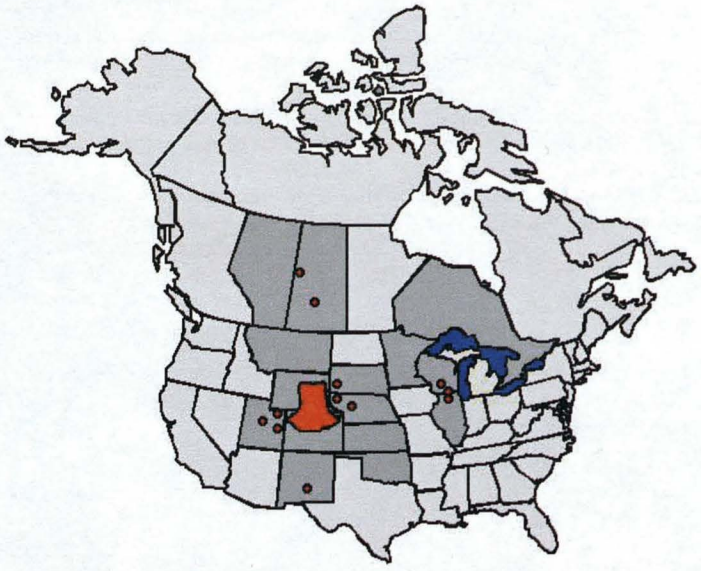

Figure 1. Occurrence of chronic wasting disease in North America 1978-2004. Chronic wasting disease was diagnosed in farmed or captive cervids in states and provinces marked in grey. Currently, farmed herds under CWD quarantine only occur in Wisconsin and Colorado. Dark-grey foci indicate areas where CWD has been identified in free-ranging cervids.

Chronic wasting disease is only known to naturally affect mule deer, white-tailed deer, and elk. However, it seems highly likely that subspecies of *C. elaphus*, including red deer and other North American subspecies, would be susceptible to CWD if exposed. Studies to determine susceptibility of fallow deer (*Dama dama*) to CWD by co-habitation with CWD-incubating and clinically affected mule deer are under way (J. Rhyan and M. Miller, personal communication).

The relationship between CWD of farmed and free-ranging cervids is not completely understood. Epidemiologic investigations are hampered by lack of appropriate tools to readily type CWD strains, in addition to the long incubation period of CWD and inherent difficulties in monitoring disease in individuals and populations of free-ranging cervids. There is some circumstantial evidence that CWD has moved from farmed cervids to free-ranging populations and, as well, evidence that suggests the converse: movement of CWD from free-ranging populations to farmed animals. The concern about the potential for movement between farmed and free-ranging cervids has led to regulations restricting farming cervids in CWD-endemic areas and specifications for fencing to prevent co-mingling of these populations.

A significant concern associated with management of CWD in farmed herds is the potential for horizontal transmission and environmental contamination.[15] Under experimental conditions, pastures housing mule deer with CWD retained infectious agent for approximately two years after affected deer had been removed.[16] Thus, care should be used in assessing whether pastures potentially contaminated with CWD agent should be used for holding susceptible cervids. In addition, free-ranging deer and elk should not have access to these premises.

Summary

Chronic wasting disease is important to domestic animal agriculture because of the general concern about all animal TSEs in the wake of BSE. It is unlikely that CWD will be eradicated from populations of free-ranging cervids, and it is likely that this disease will continue to spread geographically. Although there is currently no evidence that CWD can naturally infect cattle and sheep, the presence of this disease in free-ranging deer and elk on overlapping range suggests that they could be exposed to the CWD agent. Surveillance for TSEs in domestic livestock is necessary as part of

BSE and scrapie regulatory programs, and it is especially important in areas where CWD occurs so as to accumulate convincing evidence that CWD poses no threat to these animals or, if they should be susceptible, to make timely identification of that fact. On the other hand, CWD clearly is a threat to farmed cervids. The CWD problem is being addressed by regulatory agencies and affected industries, and there is reason to believe it can be eradicated in these farmed populations.

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References

1. Bartz JC, Kincaid AE, Bessen RA: Rapid prion neuroinvasion following tongue infection. *J Virol* 77:583-591, 2003.
2. Bruce M, Chree A, Williams ES, Fraser H: Perivascular PrP amyloid in the brains of mice infected with chronic wasting disease. *Brain Pathol* 10:662-663 Abstract C632-608, 2000.
3. Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, McCardle L, Chree A, Hope J, Birkett C, Cousens S, Fraser H, Bostock CJ: Transmission to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* 389:498-501, 1997.
4. Cutlip RC, Miller JM, Hamir AN, Peters J, Robinson MM, Jenny AL, Lehmkuhl HD, Taylor WD, Bisplinghoff FD: Resistance of cattle to scrapie by the oral route. *Can J Vet Res* 65:131-132, 2001.
5. Cutlip RC, Miller JM, Lehmkuhl HD: Second passage of a US scrapie agent in cattle. *J Comp Pathol* 117:271-275, 1997.
6. Cutlip RC, Miller JM, Race RE, Jenny AL, Katz JB, Lehmkuhl HD, DeBey BM, Robinson MM: Intracerebral transmission of scrapie to cattle. *J Infect Dis* 169:814-820, 1994.
7. Gajdusek DC: The potential risk to humans of amyloids in animals, in Gibbs CJ, Jr. (ed): *Bovine spongiform encephalopathy. The BSE dilemma*. New York, Springer-Verlag, 1996, pp 1-7.
8. Gould DH, Voss JL, Miller MW, Bachand AM, Cummings BA, Frank AA: Survey of cattle in northeast Colorado for evidence of chronic wasting disease: geographical and high-risk targeted sample. *J Vet Diagn Invest* 15:274-277, 2003.
9. Hamir AN, Cutlip RC, Miller JM, Williams ES, Stack MJ, Miller MW, O'Rourke KI, Chaplin MJ: Preliminary findings on the experimental transmission of chronic wasting disease agent of mule deer to cattle. *J Vet Diagn Invest* 13:91-96, 2001.
10. Hamir AN, Miller JM, Cutlip RC, Kunkle RA, Jenny AL, Stack MJ, Chaplin MJ, Richt JA: Transmission of sheep scrapie to elk (*Cervus elaphus nelsoni*) by intracerebral inoculation: Final outcome of the experiment. *J Vet Diagn Invest* 16:316-321, 2004.
11. Hamir AN, Miller JM, Cutlip RC, Stack MJ, Chaplin MJ, Jenny AL: Preliminary observations on the experimental transmission of scrapie to elk (*Cervus elaphus nelsoni*) by intracerebral inoculation. *Vet Pathol* 40:81-85, 2003.
12. Hamir AN, Miller JM, Cutlip RC, Stack MJ, Chaplin MJ, Jenny AL, Williams ES: Experimental inoculation of scrapie and chronic wasting disease agents in raccoons (*Procyon lotor*). *Vet Rec* 153:121-123, 2003.
13. Kahn S, Dube C, Bates L, Balachandran A: Chronic wasting disease in Canada: Part 1. *Can Vet J* 45:397-404, 2004.
14. Legname G, Baskakov IV, Nguyen HO, Riesner D, Cohen FE, DeArmond SJ, Prusiner SB: Synthetic mammalian prions. *Science* 305:673-676, 2004.
15. Miller MW, Williams ES: Prion disease: Horizontal prion transmission in mule deer. *Nature* 425:35-36, 2003.
16. Miller MW, Williams ES, Hobbs NT, Wolfe LL: Environmental sources of prion transmission in mule deer. *Emerg Infect Dis* 10:1003-1006, 2004.
17. O'Rourke KI, Duncan JV, Logan JR, Anderson AK, Norden DK, Williams ES, Combs BA, Stobart RH, Moss GE, Sutton DL: Active surveillance for scrapie by third eyelid biopsy and genetic susceptibility testing of flocks of sheep in Wyoming. *Clin Diagn Lab Immunol* 9:966-971, 2002.
18. Prusiner SB: Novel proteinaceous infectious particles cause scrapie. *Science* 216:136-144, 1982.
19. Race RE, Raines A, Baron TGM, Miller MW, Jenny A, Williams ES: Comparison of abnormal prion protein glycoform patterns from transmissible spongiform encephalopathy agent-infected deer, elk, sheep, and cattle. *J Virol* 76:12365-12368, 2002.
20. Raymond GJ, Bossers A, Raymond LD, O'Rourke KI, McHolland LE, Bryant PK, III, Miller MW, Williams ES, Smits M, Caughey B: Evidence of a molecular barrier limiting susceptibility of humans, cattle and sheep to chronic wasting disease. *EMBO J* 19:4425-4430, 2000.
21. Wilesmith JW, Ryan JBM, Atkinson MJ: Bovine spongiform encephalopathy: Epidemiological studies on the origin. *Vet Rec* 128:199-203, 1991.
22. Williams ES, Young S: Spongiform encephalopathies of Cervidae. *Sci Tech Rev Office Int Epiz* 11:551-567, 1992.

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