CHRONIC WASTING DISEASE OF DEER AND ELK: A REVIEW WITH RECOMMENDATIONS FOR MANAGEMENT

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CHRONIC WASTING DISEASE OF DEER AND ELK: A REVIEW WITH RECOMMENDATIONS FOR MANAGEMENT

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Abstract: Chronic wasting disease (CWD) has emerged as an important disease of wild and farmed cervids in North America. Of the transmissible spongiform encephalopathies (TSEs), or prion diseases, CWD is the only 1 found in free-ranging species. Because the TSEs include infamous diseases like bovine spongiform encephalopathy (BSE) of cattle and variant Creutzfeldt-Jakob disease of humans, CWD by association has become a disease of interest beyond the parochial concerns where it is found. Consequently, wildlife managers are faced with developing programs for addressing CWD. Mule deer (*Odocoileus hemionus*), white-tailed deer (*O. virginianus*), and Rocky Mountain elk (*Cervus elaphus nelsoni*) are the only species known to be naturally susceptible to CWD. Although implications of CWD are not entirely clear at this time, we know that CWD is a fatal, contagious disease of mature reproductive segments of deer and elk populations. It has been endemic in free-ranging cervids in a core area of contiguous portions of southeastern Wyoming and northeastern Colorado, USA, for a minimum of 20 years and probably longer. The known geographic distribution of endemic CWD is relatively limited at this time, although as results of intensified surveillance become available, this may change. Foci of CWD in free-ranging deer have been identified distant from the core endemic area as far east as Wisconsin. Distribution has greatly expanded in the last decade or more via commerce in infected farmed elk; as a result, CWD recently has been found in multiple jurisdictions of the plains, foothills, and Rocky Mountains of western North America, and in South Korea. Studies of the biology and natural history of CWD over the last few years have resulted in a better understanding of its pathogenesis and epidemiology. Chronic wasting disease is transmitted horizontally from infected to susceptible cervids. Early involvement of alimentary tract-associated lymphoid tissues during incubation suggests plausible routes for transmission via feces or saliva. Residual environmental contamination also appears to be important in sustaining epidemics. Studies of CWD epidemiology led to development of models to help explain the history of CWD as well as forecast its impacts on deer and elk populations. Improved tests allow CWD to be diagnosed early in incubation, long before clinical signs appear. Where CWD is not known to occur, managers should be, and in some cases are, developing surveillance programs and regulations that prevent or reduce the likelihood that CWD will be introduced into their jurisdictions. Where CWD is already endemic, responsible agencies are conducting surveillance to assess status and trends in prevalence and geographic distribution, managing deer and elk populations to limit spread, and developing and evaluating techniques for further controlling and perhaps eradicating CWD. Programs for addressing the challenges of CWD management will require interagency cooperation, commitment of funds and personnel, and applied research.

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Chronic wasting disease (CWD) recently emerged as a disease of considerable interest and concern to wildlife managers throughout North America. This naturally occurring prion disease of deer (*Odocoileus* spp.; Williams and Young 1980) and Rocky Mountain elk (Williams and Young 1982) is the only transmissible spongiform encephalopathy (TSE), or prion disease, known to affect free-living species (Spraker et al. 1997, Miller et al. 2000). Chronic wasting disease is contagious, and epidemics are self-sustaining in farmed and free-ranging deer and elk populations (Miller et al. 1998, 2000). Although to date the geographic extent of endemic CWD in free-ranging wildlife is relatively limited and natural rate of expansion has been slow, it now appears

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that CWD also has been spread much more widely through market-driven movements of infected, farmed elk. (For the remainder of this paper, "farmed" cervids will refer to privately owned, commercial elk or deer and "captive" cervids will refer to publically owned deer and elk maintained in enclosures for research purposes.) Ecological consequences of CWD and its spread remain to be determined, but CWD epidemics could be detrimental to native deer and elk resources (Gross and Miller 2001). Moreover, other prion diseases of domestic ruminants (e.g., scrapie of domestic sheep and goats, bovine spongiform encephalopathy [BSE]) have had substantial economic and, in the case of BSE, public health impacts. Consequently, it seems prudent for wildlife managers to limit both the distribution and occurrence of CWD before it becomes so widespread that containment becomes infeasible. Here, we review present understanding of CWD, its ecology, and its management.

HISTORY

As has been the case with many other undocumented ecological events, the precise time and place of emergence of CWD cannot be determined with certainty. Based on contemporary distribution and occurrence data (Miller et al. 2000), it appears most plausible that CWD in free-ranging deer and elk first arose somewhere in north-central Colorado or southeastern Wyoming, USA. A "chronic wasting disease" was first recognized in the late 1960s as a clinical syndrome of unknown cause among captive mule deer at wildlife research facilities in Colorado (Williams and Young 1980). Deer in these facilities originated from several sources, including free-ranging populations, and were routinely interchanged with a wildlife research facility in Wyoming. In 1978, "chronic wasting disease" was first diagnosed as a form of spongiform encephalopathy by histopathologic examination of brains from symptomatic animals (Williams and Young 1980). Shortly thereafter, CWD was recognized among captive mule deer in Wyoming (Williams and Young 1980). Diagnosis of CWD in elk from these same facilities quickly followed (Williams and Young 1982). Infected deer or elk in 2 zoological parks—1 in the USA and 1 in Canada—also were detected in subsequent years (Williams and Young 1992), but CWD apparently did not persist in these locations.

In 1981, CWD was recognized in a free-ranging elk in Colorado (Spraker et al. 1997). Subsequently, it was found in free-ranging elk in Wyoming, and in free-ranging mule deer (1985) and white-tailed deer (1990) in both states (Williams and Miller 2002*a*). However, surveillance data and epidemic modeling suggest that CWD may have been present in some free-ranging deer populations for 2 decades or more before it was first detected (Miller et al. 2000). Although geographic proximity of research facilities with CWD-infected animals and affected free-ranging deer and elk populations suggests a common origin, it is not possible to discern retrospectively whether CWD arose first in captive or free-ranging populations.

Concern about potential dissemination of CWD via movement of farmed elk in commerce was expressed well before it was identified in the industry (Williams and Young 1992). Although CWD was first diagnosed in farmed elk in Saskatchewan, Canada, in 1996, subsequent epidemiologic investigations point to South Dakota as the source of that infection. Although there is no documentation, the ultimate source likely is somewhere in the Wyoming–Colorado endemic area. To date, CWD has been diagnosed in farmed elk from South Dakota (6 herds), Nebraska (3 herds), Oklahoma (1 herd), Colorado (9 confirmed), Montana (1 herd), Kansas (1 herd), USA, Alberta (1 herd), Canada, as well as 39 Saskatchewan herds (U.S. Animal Health Association 2001, Canadian Food Inspection Agency 2002). Infected elk also were exported from Saskatchewan to South Korea in 1997, representing the first known extension of CWD distribution beyond North America. Based on initial epidemiologic investigations, it appears likely that CWD has been in the North American farmed cervid industry since at least the late 1980s.

During 2000–2002, cases of CWD in free-ranging deer were diagnosed in west-central Saskatchewan, northwest Nebraska, southwest South Dakota, and on the western slope of the Rocky Mountains in northwestern Colorado. In 3 of these cases, a CWD-infected elk farm may have served as a source of infection for the local deer population; the origin of the disease in the Colorado deer is still under investigation. The epidemiologic data from Nebraska are especially compelling that CWD in free-ranging deer originated in farmed elk (Nebraska Game and Parks Commission 2002). In 3 states (South Dakota, Nebraska, Colorado), publically owned deer with CWD have been culled from within the confines of elk farms. Chronic wasting disease was diagnosed in free-ranging white-tailed deer harvested in 2001 in

south-central Wisconsin (J. Langenberg, Wisconsin Department of Natural Resources, personal communication). A case of CWD was found in a mule deer in southern New Mexico in spring 2002 (K. Mower, New Mexico Game and Fish Department, personal communication). The origin and extent of these CWD foci are under active investigation.

CURRENT DISTRIBUTION

There are 2 contemporary CWD epidemics: 1 in a core of free-ranging cervids (Fig. 1A) and another in farmed elk (Fig. 1B). These epidemics are essentially independent and have little geographic overlap. The most parsimonious explanation of their origins is a common root, but it probably dates back several decades, and the exact relationships may never be determined. In free-ranging deer and elk, CWD has been diagnosed in contiguous portions of northeast Colorado, southeast Wyoming, and more recently, in the extreme southwest corner of the panhandle of Nebraska, USA; this is considered the core CWD endemic area. This endemic focus spans about 40,000 km^2 of native habitats ranging from mountains and foothills in the western portions to river bottoms and shortgrass prairie tablelands in the eastern portions (Miller et al. 2000). Natural geographic spread of the free-ranging endemic focus is predictable and appears to follow natural movements of deer and elk in affected areas (Miller et al. 2000; M. M. Conner and M. W. Miller, Colorado Division of Wildlife, unpublished data).

Geographically distinct foci of infection recently reported in free-ranging deer in western Saskatchewan, northwestern Nebraska, and southwestern South Dakota most likely represent spillover from infected farmed elk facilities near each of these cases (Fig. 1), though surveillance and epidemiologic investigations are not yet completed in these sites. The origin of the recently recognized foci of CWD in south-central Wisconsin, northwestern Colorado, and southern New Mexico are not yet determined.

In the North American farmed elk industry, most infected herds have been depopulated within several months of being detected, but as of March 2002, some infected game farms remain. Based on recent trends, surveillance programs may well uncover new CWD-infected farmed cervid herds in the coming years; at present, however, uniformity and consistency in surveillance for CWD among farmed cervids is lacking. In contrast to the predictable pattern of natural spread in free-ranging cervids, CWD spread via farmed elk has been highly unpredictable because animal movements are commercial, essentially random, and inadequately regulated in many locations. Undetected spread via trade of infected animals will likely continue until more rigorous and uniform surveillance programs are adopted and enforced.

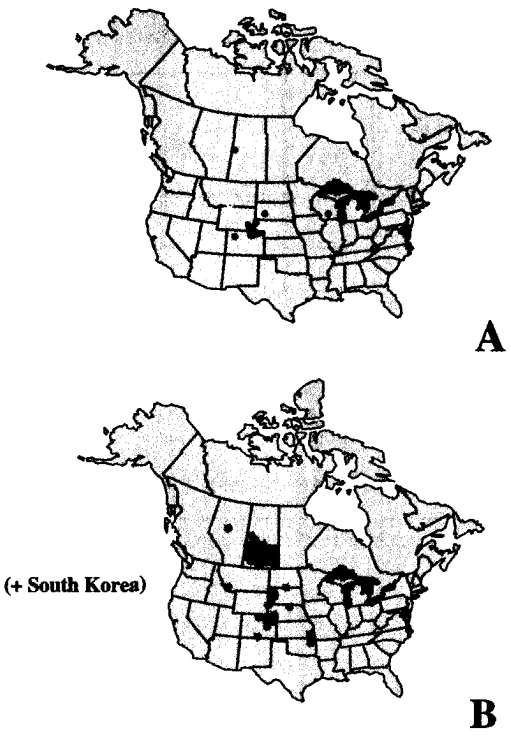

Fig. 1. Known geographic distribution of chronic wasting disease (CWD). (A) Free-ranging deer and elk in North America. The outlines show the core CWD endemic area (Colorado, Wyoming, Nebraska) and foci of CWD in Saskatchewan, Nebraska, South Dakota, Colorado, and Wisconsin. (B) Farmed elk in North America (shown) and South Korea (not shown). Stars indicate affected herds depopulated, quarantined, or released from quarantine without depopulation as of Apr 2002. Added in press: A single case of CWD in a free-ranging mule deer was found in southern New Mexico.

CAUSATIVE AGENT

Chronic wasting disease is 1 of a group of unusual neurological diseases, the TSEs. Only a few recognized TSEs exist, and these naturally affect only a handful of mammalian species (Table 1). All of the known TSEs appear to be caused by prions, proteinaceous infectious agents that are devoid of nucleic acids (Prusiner 1982, 1999). Despite some continued debate (Chesebro 1998, Farquhar et al. 1998), most available data

Table 1. Recognized transmissible spongiform encephalopathies (TSE; prion diseases) and their reported natural host ranges. Of these, only scrapie and chronic wasting disease are considered contagious diseases among susceptible hosts.

Disease	Natural host(s)	References
Animal TSE		
Scrapie	Domestic sheep, domestic goats, mouflon	Parry 1983, Detwiler 1992, Wood et al. 1992
Transmissible mink encephalopathy	Domestic mink	Hartsough and Burger 1965, Hadlow and Karstad 1968
Chronic wasting disease	Mule deer, white-tailed deer, Rocky Mountain elk	Williams and Young 1980, 1982; Spraker et al. 1997
Bovine spongiform encephalopathy	Domestic cattle, captive exotic bovids, captive exotic felids, domestic cat, laboratory primates	Wells et al. 1987, Jeffrey and Wells 1988, Pearson et al. 1992, Bons et al. 1996, Williams et al. 2001
Human TSE		
Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Shenker syndrome, fatal familial insomnia	Humans	Prusiner and Hadlow 1979, Prusiner et al. 1992
variant Creutzfeldt-Jakob disease[a]	Humans	Will et al. 1996

[a] Bovine spongiform encephalopathy in humans is commonly called variant CJD.

support the hypothesis that TSEs are caused by abnormal, protease-resistant forms (PrP^{res}) of cellular prion protein (PrP^{c}; Prusiner 1991). PrP^{c} is normally synthesized in central nervous system and lymphoid tissues (Prusiner 1991). PrP^{res} is thought to arise through posttranslational modifications in tertiary structure of PrP^{c} that decrease α-helical content and increase amounts of β-sheet (Prusiner 1997). In humans, PrP^{res} seems to arise most commonly via sporadic somatic mutations or spontaneous conversion of PrP^{c} to PrP^{res}, although cases resulting from familial germline mutations in the PrP gene (*PRNP*) or iatrogenic infections occur (Prusiner 1997). In animals, TSEs are infectious; spontaneous and familial forms have not been identified, but may occur.

Except for a few laboratory studies, prions have not been propagated successfully in vitro, and consequently are less well characterized than viruses and bacteria. Distinct prion strains with specific host affinities, pathotypes, and glycoform patterns (molecular profiles) have been recognized from studies of infected animals or tissues (Bruce et al. 1994, 1997, 2000; Raymond et al. 1997, 2000; Safar et al. 1998, 2000; Race et al. in review). The nature of these strain differences remains controversial. In addition to natural strain variation, prions have remarkable resistance to environmental conditions and a range of treatments such as heat, most disinfectants, and ionizing and ultraviolet radiation that typically kill or inactivate conventional infectious agents (Millison et al. 1976, Brown and Gajdusek 1991, Ernst and Race 1993, Taylor et al. 1995, Taylor 2000). However, strong sodium hydroxide and sodium hypochlorite solutions are effective disinfectants (see below under Public Health Concerns).

The agent causing CWD is incompletely characterized, but it appears to be a prion. As with other details of CWD emergence, the origin of the prion strain that now causes CWD (PrP^{CWD}) is not known. It is possible that CWD resulted from spontaneous conformational alteration of PrP^{c} to PrP^{res} with subsequent transmission to susceptible deer and elk. The common sporadic form of Creutzfeldt-Jakob Disease (CJD), a human TSE, may arise by this mechanism (Gajdusek 1996); though sporadic forms of TSE have never been documented in animals. Alternatively, CWD could be a strain of scrapie that has adapted to cervids (Race et al. in review). Additional, though relatively weak, evidence for a link between scrapie and CWD is the moderate ability of PrP^{CWD} to convert ovine PrP^{c} in vitro (Raymond et al. 2000) and the susceptibility of goats to intracerebral exposure to the CWD agent (Williams and Young 1992). Chronic wasting disease also could have originated by infection with an unidentified prion strain. The CWD agent differs from the BSE agent, many strains of scrapie, and transmissible mink encephalopathy agent based on mouse strain typing and glycoform pattern comparisons (Bruce et al. 1997, 2000; Race et al. in review). The marked similarity of CNS lesions, epidemiology, and glycoform patterns strongly suggests CWD agent is the same in

farmed, captive, and free-ranging deer and elk (Williams and Young 1993, Spraker et al. 2002*b*), but whether multiple strains of PrP^{CWD} occur in nature remains under study.

SUSCEPTIBLE SPECIES

Only 3 species—mule deer, white-tailed deer, and Rocky Mountain elk—are known to be naturally susceptible to CWD. It is likely that subspecies of these cervid species also are naturally susceptible.

In contrast, a number of wild and domestic species appear to be resistant, or at least much less susceptible to CWD than deer and elk, though the numbers of animals appropriately examined is still small. Moose (*Alces alces*), pronghorn antelope (*Antilocapra americana*), Rocky Mountain bighorn sheep (*Ovis canadensis canadensis*), mouflon (*Ovis musimon*), mountain goats (*Oreamnos americanus*), and a blackbuck (*Antilope cervicapra*) in contact with CWD-affected deer and elk or resident in premises where CWD occurred have not developed the disease. Domestic livestock are not known to be naturally susceptible to CWD. A few cattle, sheep, and goats have resided in research facilities with CWD for prolonged periods without developing the disease. Cattle intensively exposed to CWD-infected deer and elk via oral inoculation or confinement with infected captive mule deer and elk have remained healthy for over 5 years (E. S. Williams, M. W. Miller, and T. J. Kreeger, unpublished data). These observations of apparent species barriers to efficient transmission are supported by molecular and intracerebral challenge studies (Raymond et al. 2000; Hamir et al. 2001; E. S. Williams and S. Young, unpublished data).

Many species are experimentally susceptible to CWD (as well as other TSEs) when exposed via intracerebral inoculation, an unnatural route commonly used in studies of prion diseases. Mink (*Mustela vison*), domestic ferret (*Mustela putorius furo*), squirrel monkey (*Saimiri sciureus*), mule deer, domestic goat, domestic cattle, and laboratory mice were infected with CWD by this route on primary passage (Williams and Young 1992; Bartz et al. 1998; Bruce et al. 1997, 2000; Hamir et al. 2001; R. Marsh, S. Young, and E. S. Williams, unpublished data). Intracerebral transmission of CWD was inefficient on primary passage in goats, cattle, and laboratory mice compared to scrapie or BSE (e.g., Bruce et al. 2000, Hamir et al. 2001).

IMMUNITY AND NATURAL RESISTANCE

There is no known antibody response to the CWD agent. There is some evidence of host response to TSE infections; glial activation occurs in the brain with many TSEs (Hadlow 1996), and an acute phase response has been observed in mice experimentally infected with scrapie (Coe et al. 2001).

The *PNRP* genotype plays a major role in development of natural and experimental scrapie in sheep and mice (Hunter et al. 1992, Bruce et al. 1994, O'Rourke et al. 1997). It is not yet known if particular *PNRP* genotypes confer resistance or increase susceptibility to CWD. Codon 132 methionine homozygotes were overrepresented among free-ranging and farmed CWD-affected elk when compared with unaffected elk (O'Rourke et al. 1999), suggesting potential for differential susceptibility. Resistance associated with *PNRP* genotype has not been recognized in deer, but is still being investigated. Although most captive deer residing in endemic research facilities eventually contract CWD (Williams and Young 1980; M. W. Miller, unpublished data; E. S. Williams and T. J. Kreeger, unpublished data), individuals occasionally survive a lifetime in these facilities without succumbing to CWD.

CLINICAL SIGNS

The most striking clinical features of end-stage CWD in deer and elk are changes in behavior and loss of body condition. Clinical signs of CWD may be more subtle and the clinical course more prolonged in elk than in deer. Signs of CWD are progressive, and in earliest stages often are unrecognizable to casual observers. Caretakers or observers familiar with individual animals often recognize subtle changes in behavior well before those not familiar with the particular animal can detect abnormalities. Not surprisingly, casual inspections of farmed, captive, or free-ranging cervids may fail to detect evidence of clinical CWD. Affected animals may increase or decrease their interaction with conspecifics or handlers. They may show repetitive behaviors (e.g., moving in a set pattern) or periods of somnolence or depression from which they are easily roused, and may carry their heads and ears lowered. Affected animals continue to eat but consume less feed, leading to gradual loss of condition. Serious weight loss occurs well after the earliest behavioral changes arise in most cases; loss in condition is more difficult to discern in free-ranging cervids that naturally undergo a seasonal change in body condition. As CWD progresses, many affected animals display increased drinking and urination, increased salivation with resultant

slobbering or drooling, as well as incoordination, stumbling, subtle trembling, and wide-legged stance. Uncontrollable regurgitation, hyperexcitability, and fainting occasionally are seen. Death is inevitable.

In farmed herds newly experiencing CWD, sporadic cases of prime-aged animals losing condition, being unresponsive to symptomatic treatment, and dying from pneumonia are commonly reported. Aspiration pneumonia, presumably from difficulty swallowing and excess salivation, may lead to misdiagnosis if tissues are not examined specifically for CWD. "Sudden deaths" following handling also have been reported in some situations, as have unusual mortalities (e.g., an elk getting its head caught under a fence). Given this variety in initial presentations of clinical CWD, careful laboratory examinations of all juvenile (>6 months old) and adult cervid mortalities on game farms appears prudent and has been required in some jurisdictions seeking to establish CWD surveillance programs in farmed cervids.

Once signs of CWD appear, the clinical course can vary from a few days to about a year, with most animals surviving from a few weeks to 3–4 months. Although relatively protracted clinical disease is typical, occasionally acute death may occur in deer (M. W. Miller, unpublished data). Clinical courses in free-ranging deer and elk probably tend to be somewhat shorter than in captivity because wild cervids must forage, find water, and are susceptible to predation—all of these factors affect longevity of sick animals in the wild.

DETECTION OF CWD-INFECTED CERVIDS

Because clinical signs of CWD alone are not diagnostic, a confirmed diagnosis is based on examination of the brain for spongiform lesions (Williams and Young 1993) and/or accumulation of PrP^{CWD} in brain and lymphoid tissues by immunohistochemistry (IHC; Miller et al. 2000, Peters et al. 2000, Miller and Williams 2002, Spraker et al. 2002*a*). The latter uses monoclonal antibodies and chromogens to detect accumulation of PrP^{CWD} in various tissues.

A specific portion of the brain, the parasympathetic vagal nucleus in the dorsal portion of the medulla oblongata at the obex, is the most important site to examine for diagnosing CWD (Williams and Young 1993, Peters et al. 2000) because of its early involvement following infection in all 3 known susceptible species. Sampling the correct portion of the brain is critically important for a meaningful test. The segment of the medulla oblongata required for testing can, with practice, be readily removed from the brain through the foramen magnum. Specimens also must be appropriately preserved (the obex in 10% buffered formalin and remaining brain frozen). Because PrP^{CWD} accumulates in lymph nodes and tonsils of deer early in infection (Sigurdson et al. 1999; E. S. Williams and M. W. Miller, unpublished data), examining these tissues via IHC provides a reliable means of antemortem (live animal) and preclinical diagnosis of CWD (Miller and Williams 2002, Wolfe et al. 2002). Tonsils and retropharyngeal lymph nodes are particularly reliable for early detection of CWD using appropriate monoclonal antibodies (Miller and Williams 2002, Spraker et al. 2002*a*). Both organs are readily collected from heads of harvested animals, and can be examined along with brainstem to enhance chances of proper diagnosis. Because the progression of CWD in elk differs from progression in deer, sampling lymphoid tissue in elk does not appear to be sensitive enough to use as a reliable antemortem diagnostic test.

New laboratory tests developed for BSE (e.g., Deslys et al. 2001) are being evaluated for use in CWD diagnostics. If these tests show reliability similar to IHC (e.g., both sensitive and specific in preclinical cervids), then they may afford more rapid testing than is possible with available methods. They are being validated for use on brain, tonsils, and lymph nodes.

Several strategies can be used to detect CWD infections in farmed and free-ranging cervid populations. Surveillance can be accomplished through laboratory screening of individuals showing signs suggestive of CWD (clinically targeted surveillance), of all naturally occurring mortalities, or of randomly sampled individuals from populations of interest. Where adequate records and individual animal identification are available, epidemiologic investigations can identify populations potentially exposed and at risk of infection. Among farmed cervid herds, CWD has been detected through various combinations of mortality-based surveillance and epidemiologic investigations. Although some infected herds have been detected through voluntary or mandated surveillance programs, surveillance data from most farmed cervid herds presently are insufficient to assure that these herds are not infected with CWD. In light of uncertain incubation periods and variation in clinical presentation and course, a minimum of 5 years of complete

surveillance of all juvenile (>6 months old) and adult mortalities seems the minimum standard necessary to provide relative assurance that farmed cervid herds do not have CWD.

Detection of CWD in free-ranging deer and elk has been accomplished through clinically targeted surveillance; this is an efficient approach for detecting new foci of infection (Miller et al. 2000) that should be practiced by all North American wildlife management agencies (Williams and Miller 2002*b*). Geographically based surveillance either through direct examination of hunter-harvested or culled animals in proximity to farmed cervid facilities where CWD has been identified has been very important in several states and provinces.

Random sampling of harvested deer and elk also can be used to survey for CWD in free-ranging populations; however, for such surveys to be meaningful, sample sizes must be sufficient to detect relatively low infection rates (e.g., 1–2%) with considerable confidence in the population of interest. Harvest-based surveys were successful in detecting recent CWD cases in Saskatchewan, Nebraska, South Dakota, and Wisconsin. With the exception of these 4 locations, no CWD-infected free-ranging cervid has been found in examinations of over 10,000 cervids harvested outside the contiguous Wyoming–Colorado–Nebraska core endemic area. Random surveys also provide relatively unbiased estimates of prevalence in infected populations (Conner et al. 2000).

EPIDEMIOLOGY

Chronic wasting disease is both infectious and contagious, but specific details of its transmission remain to be determined. In contrast to BSE (Wilesmith et al. 1988), CWD is not a foodborne disease associated with rendered ruminant meat and bonemeal. Instead, data from CWD epidemics in captive deer and elk provide strong evidence of lateral transmission (Williams and Young 1992; Miller et al. 1998, 2000) more similar to scrapie epidemics (Hoinville 1996); experimental and epidemic modeling data support these observations (Miller et al. 2000; Gross and Miller 2001; M. W. Miller, unpublished data). Maternal transmission, if it occurs, must be relatively rare and cannot explain most cases where complete epidemiologic data are available (Miller et al. 1998, 2000). Some interspecies transmission probably occurs among the 3 naturally susceptible species; suspected transmission from mule deer to elk, mule deer to white-tailed deer, and elk to mule deer and white-tailed deer has been observed.

Accumulation of presumed CWD agent (PrP^{CWD}) in gut-associated lymphoid tissues (e.g., tonsils, Peyer's patches, and mesenteric lymph nodes; Sigurdson et al. 1999, Miller and Williams 2002, Spraker et al. 2002*b*) suggests that shedding through the alimentary tract (feces and saliva) may occur. Because TSE agents are extremely resistant in the environment (Brown and Gajdusek 1991), transmission may be both direct and indirect. Concentrating deer and elk in captivity or by artificial feeding probably increases the likelihood of direct and indirect transmission between individuals. Transmission via contact between susceptible and infectious individuals probably requires more than just transient exposure. Thus, minimal fence-line contact probably does not pose excessive risk of transmission; however, prolonged fence-line contact increases the possibility of transmission. Contaminated pastures appear to have served as sources of infection in some CWD epidemics (Miller et al. 1998; M. W. Miller, unpublished data; E. S. Williams, W. E. Cook, and T. J. Kreeger, unpublished data), although these observations are anecdotal and not yet corroborated by controlled studies. Similar phenomena have been suspected in some outbreaks of sheep scrapie (Greig 1940, Pálsson 1979, Andréoletti et al. 2000). The apparent persistence of PrP^{CWD} in contaminated environments may represent a significant obstacle to eradication of CWD from either farmed or free-ranging cervid populations. However, CWD apparently did not persist in several facilities that experienced a few cases of CWD and presumably were not heavily contaminated.

The overall duration of CWD infection (time from exposure to end-stage clinical disease) has been difficult to measure in natural cases—without clear knowledge of when animals become infected, it is impossible to accurately determine the overall course of disease. Experimental CWD challenge studies based on single-dose, oral exposure to infectious brain tissue have yielded some insights into disease course; however, because the course of infection may be inversely related to exposure dose (i.e., greater exposure results in shorter duration), experimental data probably underestimate the time frames for most natural infections. Experimentally, minimum incubation (time from exposure to onset of clinical disease) was about 15 months, and mean time from oral infection to death was about 23 months (range 20

to >25 months) in mule deer (E. S. Williams and M. W. Miller, unpublished data); the range of incubation observed in orally infected elk was approximately 12–34 months (E. S. Williams, M. W. Miller, and T. J. Kreeger, unpublished data). The maximum disease course is not known, but can exceed 25 months in experimentally infected mule deer and 34 months in elk. Duration is less certain in naturally occurring cases. The youngest animal diagnosed with clinical CWD was 17 months old, suggesting 16–17 months may be the minimum natural incubation period. Among deer and elk residing in facilities with a long history of CWD, most natural cases occur in 2- to 7-year-old animals; however, deer have lived >7 years in heavily infected facilities without succumbing to CWD, and elk >15 years of age have died of CWD.

It is not known when during the course of infection an animal may become infectious, but it appears likely that PrP^{CWD} shedding is progressive through the disease course in deer. The presence of PrP^{CWD} in alimentary tract associated lymphoid tissues early in the incubation period (Sigurdson et al. 1999) suggests that shedding of the agent may begin early. Epidemic models suggest shedding probably precedes onset of clinical disease in both deer and elk (M. W. Miller, unpublished data).

Chronic wasting disease can reach remarkably high prevalence in captive cervid populations. In 1 infected research facility, more than 90% of mule deer residents for >2 years died or were euthanized due to clinical CWD (Williams and Young 1980). Recently, high CWD prevalence (about 50%) has been demonstrated via IHC in white-tailed deer confined in association with an infected Nebraska elk farm (Nebraska Game and Parks Commission 2002). Among captive elk, CWD was the primary cause of adult mortality (5 of 7, 71%; 4 of 23, 23%) in 2 research herds (Miller et al. 1998); high prevalence (59%) was detected by IHC in a group of 17 elk slaughtered from an infected farm herd (Peters et al. 2000); and 11 (20%) of 54 captive elk in a research herd had IHC evidence of infection (E. S. Williams, W. E. Cook, and T. J. Kreeger, unpublished data).

To estimate prevalence in infected free-ranging populations, tissues from deer and elk harvested by hunters in the CWD-endemic area have been collected and examined at random (Miller et al. 2000). Within the endemic area, prevalence of preclinical CWD, based on PrP^{CWD} IHC, has been estimated at <1–15% in mule deer and <1% in elk (Miller et al. 2000). Modeled CWD epidemics failed to achieve a steady-state equilibrium in infected deer populations, suggesting that CWD may lead to local extinctions of infected deer populations if left unmanaged (Gross and Miller 2001).

CONTROL STRATEGIES

No treatment is available for cervids affected with CWD. Once clinical signs develop, CWD is invariably fatal. Affected animals that develop pneumonia may respond temporarily to treatment with antibiotics, but ultimately the outcome is still fatal. Similarly, no vaccine is available to prevent CWD infection in deer or elk. It follows that controlling CWD is problematic. Long incubation periods, subtle early clinical signs, absence of a practical antemortem diagnostic test, extremely resistant infectious agent, possible environmental contamination, and incomplete understanding of transmission all constrain options for controlling or eradicating CWD.

In farmed facilities, management options currently are limited to (1) prevention of introduction of CWD, (2) quarantine, or (3) depopulation of CWD-affected herds. Some states and provinces, especially in western North America, have developed CWD surveillance and herd certification programs, and a federal program is nearing adoption (U.S. Department of Agriculture 2002). Also, some states have initiated moratoriums on importation or movement of cervids until the extent of the CWD problem in farmed cervids is clearly established.

Two attempts to eradicate CWD from cervid research facilities failed; the causes of these failures were not determined, but residual environmental contamination following depopulation and/or facility clean-up was likely in both cases (Williams and Young 1992, Miller et al. 1998). In contrast, CWD apparently was not maintained in several zoological parks where CWD was diagnosed in a small number of animals, even without significant attempts to disinfect the facilities. Attempts to eliminate CWD from farmed elk populations are more recent, and consequently the efficacy of these attempts remains uncertain. Whether heavily contaminated environments can ever be completely disinfected remains questionable. Until effective cleaning and disinfection procedures are identified, or evidence provided that environmental contamination does not pose a risk, farmed cervids should not be reintroduced into facilities where CWD has occurred; moreover,

free-ranging cervids should be excluded from previously infected premises. Inherent difficulties in managing infected herds and premises underscore the need for aggressive surveillance to prevent movements of infected animals in commerce.

Managing CWD in free-ranging animals presents even greater challenges (Williams and Miller 2002*b*). Long-term, active surveillance programs to monitor CWD distribution and prevalence have been instituted in the Wyoming–Colorado–Nebraska endemic area to determine the extent of the endemic area and to assist in evaluating both temporal changes and effects of management intervention. Management programs established to date focus on containing CWD and reducing its prevalence in localized areas (Miller and Kahn 1999, Colorado Division of Wildlife 2001). Ultimate management goals vary among affected states and provinces. In Saskatchewan, northwest Nebraska, Wisconsin, and northwest Colorado, where CWD may not yet be endemic, eradication is the ultimate goal for CWD management. In contrast, wildlife managers in Colorado and Wyoming have refrained from committing to eradication because it appears unattainable in their endemic CWD situations (Colorado Division of Wildlife 2001).

A variety of specific strategies for managing CWD in free-ranging wildlife have been adopted in affected jurisdictions. Translocating and artificially feeding cervids in endemic areas have been banned in attempts to limit range expansion and decrease transmission. Selective culling of clinical suspects has been practiced throughout endemic portions of Colorado and Wyoming for a number of years, but this approach alone has proven insufficient to reduce prevalence in affected populations. Localized population reduction in an area of high CWD prevalence has been undertaken in Colorado as a management experiment, but efficacy has not been determined. Although it seems intuitive that lowered deer and elk densities should reduce both transmission and likelihood of emigration by affected animals to adjacent areas, historic migration patterns and social behaviors characteristic of some deer and elk populations may diminish the effectiveness of wholesale density reduction in controlling CWD. Models of CWD epidemic dynamics suggest early, aggressive intervention via selective culling or more generalized population reduction show the greatest promise of preventing new endemic foci from being established (Gross and Miller 2001); unfortunately, surveillance limitations (both cost and sensitivity) may delay detection of newly infected free-ranging populations for a decade or more after CWD has been introduced (Miller et al. 2000). In Nebraska, Saskatchewan, and Wisconsin, aggressive reductions of deer numbers in newly identified foci have been undertaken in attempts to eliminate CWD from these areas. In these areas, as well as in South Dakota and Colorado, culling deer near CWD cases outside the core endemic area has been done to provide data on the extent of the local problem. Recent development of tonsil biopsy as an antemortem test for CWD in deer might aid control efforts under some conditions in which lethal sampling may not be possible, but large-scale applications to free-ranging populations seem impractical (Wolfe et al. 2002).

PUBLIC HEALTH CONCERNS

No cases of human prion disease have been associated with CWD (World Health Organization 2000, Belay et al. 2001, Food and Drug Administration Transmissible Spongiform Encephalopathy Advisory Committee 2001). Contrary to a widely distributed story that recently circulated in the popular press, none of 3 young people diagnosed with CJD who either hunted or consumed venison were connected epidemiologically to CWD exposure (Belay et al. 2001). The tendency toward a natural species barrier, reducing human susceptibility to CWD and other prion diseases, has been demonstrated by in vitro studies; in those studies, PrP^{CWD} inefficiently converted human PrP^{c} to the abnormal isoform as compared to homologous PrP^{c} to cervid PrP^{CWD} conversions. Human PrP^{c} conversions by cervid PrP^{CWD} were essentially equivalent to conversions of human PrP^{c} by scrapie and BSE PrP^{res} (Raymond et al. 2000). However, lingering uncertainty about interpreting these data and assessing any potential risk that CWD may pose to humans is fostered by differing experiences with 2 more common animal TSEs. Although there is a long history of human exposure to scrapie through handling and consuming sheep tissues, including brain, there is no evidence that this presents a risk to human health. In contrast, massive exposure (Ghani et al. 2000) of British and perhaps other European citizens to the BSE agent has resulted in approximately 117 cases of variant Creutzfeldt-Jakob disease as of April 2002 (The UK Creutzfeldt-Jakob Disease Surveillance Unit 2002).

In the absence of complete information on risk, and in light of similarities of animal and human TSEs, public health officials and wildlife management professionals in the CWD-endemic area inform the hunting public about CWD and where it occurs via the news media, World Wide Web sites, educational publications, and through specific detailed information in hunting license application packets. Hunters harvesting deer and elk in the endemic area, as well as meat processors and taxidermists handling cervid carcasses, should take some common sense measures (Colorado Division of Wildlife 2002, Williams and Miller 2002*b*) to avoid exposure to the CWD agent and to other known zoonotic pathogens. Advice includes avoiding harvest or consumption of sick deer and elk; wearing latex or rubber gloves when dressing a deer or elk from CWD areas; discarding the brain, spinal cord, lymph nodes, spleen, tonsils, and eyes because these organs appear to contain the greatest amount of CWD agent in infected animals; and thoroughly washing knives and other implements. Sodium hypochlorite (household bleach, >2% free chlorine, 280 ml in 720 ml water at room temperature for 1 hr) or sodium hydroxide (caustic soda, soda lye, 38 g in 1 liter water at room temperature for 1 hr) can be used for disinfection, although these solutions may be corrosive to metal utensils. Scrapie PrP^{res} has been demonstrated in skeletal muscle of experimental mouse models (Bosque et al. 2002), but PrP^{CWD} has not been identified in skeletal muscle of natural TSEs of animals including CWD (Spraker et al. 2002*b*). Deboning game meat is recommended as a way to further reduce potential for exposure to the CWD agent. Raw velvet antler, a product unique to the farmed cervid industry, may deserve further evaluation for presence of PrP^{CWD}.

MANAGEMENT IMPLICATIONS

Where it occurs, CWD in farmed and free-ranging cervids represents serious management problems. Farmed populations are quarantined, thus limiting use and value of infected or exposed animals. Indemnity for depopulated cervids has been made available only recently in the United States; in Canada, the magnitude of infection in farmed elk herds detected thus far has cost the Canadian government over CAN$30 million in indemnity and clean-up funds (U.S. Animal Health Association 2001; G. Luterbach, Canadian Food Inspection Agency, personal communication). Guidelines for management of farmed herds with CWD are being developed by state and provincial animal health officials. A national program is nearing adoption in Canada, and a similar program currently is under review in the United States (U.S. Department of Agriculture 2002). Spillover of CWD into local free-ranging cervid populations may have occurred in several locations; further spillover could establish more foci, thereby impairing long-term viability of both cervid farming and wildlife management.

Implications for free-ranging populations of deer and elk may be even more significant. Agencies do not translocate deer and elk from CWD-endemic areas. Ongoing surveillance programs are expensive and draw resources from other wildlife management needs. Perhaps most important, impacts of CWD on population dynamics of deer and elk presently are unknown. Modeling suggests that CWD could substantially harm infected cervid populations by lowering adult survival rates and destabilizing long-term population dynamics (Gross and Miller 2001). Ultimately, public perceptions and concerns about human health risks associated with the TSEs may erode participation in sport-hunting in the endemic area and even impact hunting where CWD is not known to occur. Therefore, CWD could have a dramatic influence on management of free-ranging cervid herds where it is present. It follows that responsible wildlife management and animal health agencies must act to limit distribution and occurrence of CWD in free-ranging and farmed cervids, and should continue working to better understand the biology and potential methods for control of CWD.

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