The First Five (or More) Decades of Chronic Wasting Disease: Lessons for the Five Decades to Come

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Chronic Wasting Disease: Lessons Learned from the First Five Decades

Chronic wasting disease (CWD), an infectious prion disease of at least five cervid species, has run the gamut from minor scientific curiosity to national crisis since the syndrome's first recognition in the late 1960s (Williams and Young 1980; Williams 2005; Norwegian Veterinary Institute 2016). Moving forward, we believe this wildlife disease merits attention somewhere between those extremes. Collective experiences and observations made over the last five decades can serve—for better or worse—as a solid foundation for wildlife and animal health professionals to build upon in addressing anticipated challenges posed by CWD in the decades to come. Here we overview what we regard as the key lessons learned over the first five or more decades of North America's experience with CWD.

Longer Than You Think: Brief History and Known Distribution of Chronic Wasting Disease

That the duration of an outbreak often is underestimated seems perhaps the most important overarching lesson about CWD. Despite its likely occurrence in multiple locations since the 1960s or earlier (Williams and Young 1992; Miller et al. 2000; Wasserberg et al. 2009), many wildlife and animal health professionals, as well as our lay and media publics, perceive CWD as having emerged and spread rapidly only since the early 2000s (e.g., see Saunders, Bartelt-Hunt, and Bartz 2012). This perception has fostered the broader notion that newly discovered disease foci are truly "new" (i.e., very recent) occurrences. To the contrary, given imperfect surveillance approaches, incomplete or inaccurate knowledge about local exposure risks, and the insidious progression of an outbreak in its early stages, the first case *detected* in a locale is rarely *the* first case that has occurred. Consequently, on further investigation, "new" foci tend to have larger spatial dimensions and higher prevalence than expected, thereby perpetuating misconceptions about the speed of "spread." This lesson has been illustrated by experiences in Colorado and Wyoming, Saskatchewan, Wisconsin, and most recently Arkansas where expanded surveillance disclosed 79 additional cases within two months after their "first" case was diagnosed in February 2016 (Miller et al. 2000; Bollinger et al. 2004; Argue et al. 2007; Wasserberg et al. 2009; Holsman, Petchenik, and Cooney 2010; Arkansas Game & Fish Commission 2016).

Chronic wasting disease history (Table 1) remains incompletely documented. The "chronic wasting" syndrome first was recognized in captive mule deer (*Odocoileus hemionus*) held for research in Colorado in the 1960s, but unrecognized cases could have occurred in Colorado or elsewhere before that time (Williams and Young 1980; Williams and Miller 2003). Clinical cases also were recognized in captive mule deer in the Denver and Toronto zoos in the 1970s, and in captive Rocky Mountain elk ("wapiti" hereafter; *Cervus elaphus nelsoni*) in research and zoological collections in Colorado and Wyoming (Williams and Young 1992; Dubé et al. 2006). Undocumented involvement of other private collections or menageries during the 1960s and 1970s seems likely. Within little more than the first two decades after its characterization as a transmissible spongiform encephalopathy, CWD cases were diagnosed in wild mule deer, white-tailed deer (*Odocoileus virginianus*), and wapiti in northeastern Colorado and southeastern Wyoming (1980s to 1990s); in commercial captive wapiti facilities in

Saskatchewan (1996) and in South Dakota (1997); in commercial captive white-tailed deer facilities in several jurisdictions (2001 to 2002); and eventually in moose (*Alces alces*) (Williams and Young 1980; Williams and Young 1992; Spraker et al. 1997; Miller et al. 2000; Williams, Miller, and Thorne 2002; Williams and Miller 2003; Williams 2005). Cases from what have become recognized as large foci in Saskatchewan-Alberta and Wisconsin-Illinois also were first detected in the early 2000s (Williams, Miller, and Thorne 2002). As of April 2016, cases of CWD had been reported in captive and/or free-ranging cervids in 24 U.S. states (75 captive herds in 16 states and free-ranging cervids in 22 states), three Canadian provinces (including Ontario's Toronto Zoo in the 1970s), and South Korea (Figure 1) (Williams and Young 1992; Williams, Miller, and Thorne 2002; U.S. Geological Survey 2016; R. Pritchard personal communication). In addition, at the time of this writing in early April 2016, a single case in a free-ranging reindeer (*Rangifer tarandus*) in Norway in March 2016 had just been reported (Norwegian Veterinary Institute 2016). Based on experience to date, the true geographic distribution of CWD likely remains underestimated.

Two Good Stories: The Drivers of Chronic Wasting Disease "Spread"

A second overarching lesson—a corollary to the first—is that new CWD foci often can be explained by two or more equally plausible (and equally undeniable) "origin stories." Distorted temporal perceptions on the likely timing of introduction underlie the plurality of origin stories, as do sociopolitical motivations to deflect or lay blame elsewhere when "new" cases arise. But perhaps most pervasive is the lack of complete information on contributory events, particularly for outbreaks involving free-ranging cervids. Although the lack of a singular explanation can be dissatisfying, failing to consider plausible alternative timelines and exposure sources may be more problematic when disease prevention and control efforts are misinformed or misled. For example, the widely held belief that all CWD occurrences can be traced back to a single Colorado research facility has precluded wildlife and animal health professionals from considering that some outbreaks may be arising from unrecognized exposure events that occur repeatedly over time (e.g., Williams and Miller 2003; Greenlee et al. 2015). The recent Norwegian reindeer case may stimulate broader thinking.

In fact, both natural and anthropogenic factors have contributed to the geographic spread and persistence of CWD over the last five decades. Regardless of the ultimate origin, much of the geographic "spread" of CWD appears attributable to natural movements in some jurisdictions: Wyoming, for example, has only one private game farm and consequently commercial enterprise is unlikely to have driven the widespread distribution there. Alternatively, the role of commercial wapiti operations in CWD outbreaks in Saskatchewan and South Korea was well documented, with inadvertent spillover also giving rise to a large free-ranging focus spanning the Saskatchewan-Alberta shared border (Williams, Miller, and Thorne 2002; Kim et al. 2005; Argue et al. 2007; Bollinger et al. 2004). In Colorado, a combination of natural and anthropogenic factors likely contributed in different measures to separate outbreaks along the Front Range and on the Western Slope.

Natural factors contributing to persistence and geographic spread include prolonged incubation, multiple routes of agent shedding, the agent's environmental persistence, and movements of free-ranging cervids. Infected cervids likely shed prions for most of the disease course, thus affording ample opportunities for transmission within and among social groups (Tamgüney et al. 2009; Henderson et al. 2015). Migration movements also have potential for contributing to longer-distance jumps in distribution. Because infectivity can be harbored in some environments for an extended time, transmission occurs on overlapping ranges even in the absence of direct interactions between infected and uninfected animals. Indirect transmission also increases the likelihood of interspecies transmission.

The primary anthropogenic factor identified in the dissemination of CWD is human-facilitated movement of live animals (Williams and Miller 2003), and to date, this is the only confirmed contributing activity linked to CWD's spread between distant locations. These animal movements typically are fostered by other highly artificial wildlife management activities, such as captive wildlife propagation and high-fenced shooting enclosures (Fischer and Davidson 2005). Although spared from implication thus far,

translocating free-ranging cervids from an infected source also would present a similar risk for spreading CWD. Local wildlife may be exposed to CWD if infected captive animals escape, or if there is ingress/egress of free-ranging cervids with exposure to infected captive animals or to contaminated environments. Fence-line contact offers another opportunity for direct transmission. (We note that these transmission opportunities are a two-way street, i.e., CWD can move in either direction between captive and wild cervids.) Other possible modes for the anthropogenic spread of CWD include transport of infected carcasses, products manufactured or contaminated with prion-laden deer or wapiti urine, saliva, or feces, and movement of hay or grain crops contaminated with the CWD agent. None of these has been documented in the field, although proof of concept has been demonstrated experimentally.

In addition, other anthropogenic factors can substantially increase the likelihood of establishing, maintaining, and disseminating CWD and other diseases in free-ranging wildlife. In particular, artificial management activities, such as wildlife baiting and feeding or other practices that congregate normally dispersed wild animals, enhance pathogen transmission opportunities (Fischer and Davidson 2005).

Things We Now Know: Chronic Wasting Disease Biology and Ecology

Many facets of CWD biology and ecology that were mysteries even into the early 2000s (e.g., see Williams, Miller, and Thorne 2002) now are well understood. For example, notable advances have been made in diagnostics and in our understanding of transmission routes and host factors modulating disease progression that have application in CWD detection and control. These and other advances have been reviewed thoroughly elsewhere (e.g., see Williams 2005; Sigurdson 2008; Smith, Booth, and Pedersen 2011; Saunders, Bartelt-Hunt, and Bartz 2012; Haley and Hoover 2015). We offer here only a brief synthesis of findings most relevant to detection and control, referring interested readers to the aforementioned reviews and numerous original papers referenced therein for greater details on and sources of specific points highlighted in our synopsis.

Chronic wasting disease appears to be caused by one or more strains of infectious prions. Although the ultimate historical origin never will be known with certainty, we regard exposure of native cervids to the sheep scrapie agent at one or more times and locations as a parsimonious explanation. Regardless of their origin(s), sustained outbreaks now occur as large and small foci and in captive wildlife facilities (Figure 1). Natural cases of CWD have occurred in five host species: mule deer, white-tailed deer, wapiti, moose, and reindeer/caribou. No immunity, recovery, or absolute resistance to infection has been documented in any of the susceptible species. However, natural variation in the host gene encoding for cellular prion protein (the *PRNP* gene) does modulate disease progression, thereby extending survival times and perhaps lowering infection probabilities for "relatively resistant" genotypes. The disease course typically is measured in years. Clinical signs—altered behavior initially, with body condition declining much later—become progressively apparent relatively late in the disease course. Infection can be detected in carcasses as well as in live animals, and diagnostic tests become increasingly reliable in individual animals as the disease progresses. Chronic wasting disease is infectious. Infected individuals shed prions from several routes during most of the disease course, exposing others either directly or through contamination of shared resources or environments. Shed prions can persist for years in the environment, and their binding to soil elements (e.g., clay) enhances persistence and infectivity. The uncoupling of transmission from the immediate presence of infected animals greatly complicates CWD control.

Looking Hard, Hardly Looking: Detecting Chronic Wasting Disease

A third key lesson relates to the difficulty in detecting CWD foci in captive and wild settings despite the considerable effort expended. Most North American jurisdictions have, at least for a time since the early 2000s, engaged in extensive if not intensive surveillance to seek out such foci. Although all of these efforts were well intentioned, many were too flawed or too short-lived to provide reliable information on disease absence. We briefly review common shortcomings of CWD surveillance as widely practiced to provide a basis for improving the efficiency and effectiveness of future efforts.

Preferred approaches for seeking out new foci (termed "surveillance" here) differ from approaches for following epidemic trends over time ("monitoring;" concepts reviewed in greater detail by Samuel et al. 2003). We recommend that CWD surveillance be an ongoing activity in jurisdictions or areas where foci have not been detected previously; monitoring may be a more episodic undertaking (e.g., at multi-year intervals) where support resources are limited because infection rates tend to change slowly compared to more conventional infectious diseases. Regardless of the purpose, CWD surveillance and monitoring should be undertaken at biologically relevant spatial scales and inferences drawn only in the appropriate spatial context in view of the highly patchy distribution of CWD in wild cervids. In our experience, statements exhorting that examination of a few hundred (or even a few thousand) harvested animals has proven a jurisdiction's freedom from CWD rarely are supported by the data in hand.

For surveillance in free-ranging settings, targeting sample sources known to have a relatively high probability of infection in endemic areas (e.g., clinical "suspects," vehicle- or predator-killed adult animals) can be a more cost-effective approach (Miller et al. 2000; Samuel et al. 2003; Walsh and Miller 2010). The effectiveness of so-called "targeted surveillance" assumes relatively even sampling effort over the geographic area of inference. However, this approach does have limitations. For example, clinical disease may not be observed in remote areas, vehicle-kills do not occur in roadless areas, and predator kills may be consumed before sampling can occur. In addition to clinical targeting, spatial targeting via risk-based assessments also may enhance the effectiveness and efficiency of CWD surveillance (Bollinger et al. 2004; Rees et al. 2012; Norbert et al. 2016).

For monitoring, random sampling (e.g., from harvested animals) provides relatively unbiased estimates of infection rates (Samuel et al. 2003). Comparisons over time or between locations should be based on a common denominator (e.g., harvested males aged 2 years or older) to assure that reliable inferences are drawn. Where available, data from lethal and nonlethal sampling can be combined for analysis provided sources are equivalent (e.g., see Geremia et al. 2015). Because foci emerge and grow so slowly, infection rates may be remarkably high on first detection when jurisdictions rely on random sampling for surveillance. Moreover, CWD tends to be unevenly distributed in the wild. The notion that a survey sample of 300 assures 95% probability of detecting at least one case where prevalence greater than or equal to 1% assumes infection is evenly distributed at that rate throughout the entire target population (Samuel et al. 2003). However, CWD distribution typically is uneven within an affected population, and the target population itself often is distributed unevenly.

Toward a Sustained and Sustainable Effort to Control Chronic Wasting Disease

The final overarching lessons learned over the past five decades relate to how wildlife and animal health professionals should (and probably should not) approach the control of CWD. In contrast to advances in our understanding of CWD biology and ecology, the available science informing effective management and control strategies remains relatively incomplete. However, recent insights and modest strides seem to offer a path forward. It follows that adaptive approaches for containing CWD foci and reducing infection and transmission rates deserve further attention.

Eradicating CWD from North America appears infeasible given its extensive distribution and other epidemiological attributes. With few exceptions—the small foci in New York and perhaps Minnesota—CWD in free-ranging cervids has persisted in reporting jurisdictions in the face of widely varied control attempts (New York Department of Environmental Conservation 2015; Minnesota Department of Natural Resources 2014). Faced with the dim prospects for eradication on scales large or small, some affected jurisdictions now seem to have abandoned any further consideration of disease management and some have effectively dismantled surveillance and monitoring as well. In light of myriad wildlife conservation needs and ever-dwindling resources, we appreciate the allure but believe this to be myopic. Instead, we strongly encourage affected jurisdictions to redouble efforts to collectively foster and develop sustained and sustainable approaches for CWD surveillance, monitoring, and control.

In contrast to the apparent success in eliminating New York's small free-ranging focus, well-publicized early attempts to control CWD in Colorado and Wisconsin yielded little evidence of progress

and thus gave initial appearances of failure (e.g., see Conner et al. 2007; Holsman, Petchenik, and Cooney 2010). In recent years, however, evidence from several jurisdictions' control attempts applied across different geographic scales suggest that combinations of intensive deer removal focused around case clusters and more sustained suppression of the affected herd or population may offer some measure of effective disease suppression. A sustained culling program underway since 2003 has stabilized prevalence in northern Illinois white-tailed deer as compared to increasing trends in southern Wisconsin where disease control was suspended in 2007 (Manjerovic et al. 2014). Similar divergence in prevalence among white-tailed and mule deer harvested in Alberta and Saskatchewan may reflect the relative effectiveness of disease suppression approaches in Alberta but also could be an artifact of more recent epizootic emergence in Alberta (Norbert et al. 2016; Pybus 2012). In north-central Colorado, a combination of focal culling and broader, harvest-mediated population reduction (~25%) in the early 2000s appears likely to have contributed to reduced prevalence, whereas estimated prevalence in other Colorado mule deer herds has increased since 2002 (Conner et al. 2007; Colorado Parks & Wildlife, unpubl. data; Geremia et al. 2015).

One of the most common flaws in CWD control efforts to date has been initial underestimation of the affected area (often based on inadequate surveillance and erroneous assumptions about how long disease has been present). The outcome then gave the appearance that the control attempt had "failed" when in fact the approach was biologically sound but the application was either too small (spatially) or too short-lived. It follows that acquiring reliable distribution and prevalence data early in the planning and execution may improve the apparent efficacy of future CWD control efforts. To this end, we encourage jurisdictions to consider and set realistic disease control objectives and to use adaptive management approaches that incorporate existing and prospective field data to refine disease control objectives.

In addition to adopting and adaptively assessing approaches for stabilizing or suppressing CWD epizootics, we encourage jurisdictions to consider how recent trends in cervid management may be contributing to disease emergence. Modeling suggests harvest-based control of CWD may be most effective when focused on male deer, perhaps because infection rates among adult male deer tend to be higher than among adult females (Miller et al. 2000; Grear et al 2006; Rees et al. 2012; Jennelle et al. 2014; Potapov et al. 2016;). Conversely, then, harvest strategies intended to increase male-female ratios or adult male age structure could inadvertently facilitate CWD persistence. This may explain why in Colorado, for example, the dramatic increases in prevalence observed since 2002 in several affected mule deer herds coincide with statewide changes in harvest strategies that have increased male-female ratios over the same period (Bergman et al. 2011). Given the potential for unintended consequences, we encourage broader critical assessment of how this and other harvest strategies (e.g., season timing, baiting, "quality deer management") may be affecting CWD dynamics.

Such pursuits undoubtedly will be more difficult to champion and garner support for in sociopolitical climates ranging from apathetic to combative, particularly when control prescriptions impinge upon or conflict with commercial and sport hunting interests. The human dimensions of managing wildlife diseases in general and CWD in particular present a substantial challenge for those determining the management objectives and actions. For example, surveys of hunters and landowners in Wisconsin identified factors that contributed to hunter opposition to the state's CWD management plan including: opposition to deer population goals (initially zero), conflicts with traditions and consumption norms, uncertainty about the likelihood of success, questions about agency credibility, and no sense of urgency (Holsman, Petchenik, and Cooney 2010).

We believe there are two important motivations for responsible wildlife managers to make progress toward sustainable containment and control strategies for CWD in the coming decades. First, data from several sources suggest that heavily infected cervid populations will not thrive in the long-term (Miller et al. 2000, 2008; Almberg et al. 2011; Edmunds 2013; Monello et al. 2014; Williams, Kreeger, and Schumaker 2014; DeVivo 2015). Second, data on CWD prions and experience with other animal prion diseases suggest minimizing human exposure to these agents would be prudent (Raymond et al. 2000; Belay et al. 2004; Saunders, Bartelt-Hunt, and Bartz 2012; Cassard et al. 2014).

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Table 1. An abbreviated timeline of select chronic wasting disease events. Adopted and from Williams, Miller, and Thorne (2002); updated and compiled by K. Niedringhaus, Southeastern Cooperative Wildlife Disease Study. See text for additional details and references.

Year	Events
1967	• Wasting syndrome observed in captive mule deer at a Colorado wildlife research facility
1975–81	• Wasting syndrome observed in Toronto Zoo mule deer that came from the Denver Zoo
1978	• Chronic wasting disease (CWD) diagnosed as transmissible spongiform encephalopathy (TSE)
1979	• Recognized in captive mule deer at Wyoming wildlife research facility
1981	• Detected in wild wapiti in Colorado
1985	• Detected in wild mule deer in Colorado & Wyoming
1996	• Detected in a captive wapiti farm in Saskatchewan; 38 other linked farms eventually found positive
1997	• Detected in captive wapiti facilities in South Dakota
1998	• Detected in captive wapiti facilities in Montana & Oklahoma • *Model Program for Surveillance, Control, & Eradication of CWD in Domestic Elk* presented at U.S. Animal Health Association to establish monitoring & control standards
1999	• World Health Organization indicates no evidence CWD is transmissible to humans, but advises that exposure should be avoided nonetheless
2000	• Detected in wild mule deer in Nebraska & Saskatchewan • Research: molecular studies compare host ranges for CWD, scrapie, & bovine spongiform encephalopathy prions; environmental contamination & subclinical infection contribute to transmission; prevalence estimates in wild populations in Colorado & Wyoming
2001	• Detected in captive wapiti in Kansas • Detected in captive wapiti in South Korea imported from Saskatchewan • Detected in wild white-tailed deer in South Dakota • U.S. Department of Agriculture (USDA) declares CWD emergency in captive wapiti; funds available for disease control
2002	• Detected in captive wapiti in Minnesota & captive white-tailed deer in Alberta • Detected in wild & captive white-tailed deer in Wisconsin • Detected in wild white-tailed deer in Illinois, mule deer in New Mexico, wapiti in South Dakota • Joint CWD Task Force of USDA/DOI/States/Universities develops *Plan for Assisting States, Federal Agencies & Tribes in Managing CWD in Wild & Captive Cervids* (National CWD Plan) • Colorado establishes guidelines to minimize transport of high risk carcass materials • 1st International CWD Symposium (Denver, Colorado) • Research: tonsil biopsy as a live animal test; improved high-throughput diagnostics
2003	• Detected in wild mule deer in Utah • APHIS funds available for CWD work in captive & wild cervids (through 2011) • USDA publishes a proposed rule for CWD herd certification & interstate shipping program (HCP) to eradicate CWD from captive deer & wapiti • Research: horizontal transmission of CWD likely important in CWD epidemiology
2004	• Detected in wild wapiti in New Mexico • National CWD plan progress report published & new priorities discussed • Research: environmental sources, decomposed carcasses can contribute to transmission
2005	• Detected in captive & wild white-tailed deer in New York • Detected in wild mule deer in Alberta, moose in Colorado, white-tailed deer in West Virginia
2006	• Detected in captive white-tailed deer in Minnesota

	• Detected in wild white-tailed deer in Kansas • USDA publishes Chronic Wasting Disease Herd Certification Program Final Rule (CWD Final Rule)—never implemented • Research: prions in muscles of infected deer; transmitted in saliva & blood
2007	• Research: prions in environment more infective in particular (clay) soil types
2008	• Detected in captive deer in Michigan • Detected in wild wapiti in Saskatchewan, moose in Wyoming • Research: CWD may be a plausible explanation for local deer population declines in Colorado
2009	• APHIS plans to withdraw 2006 CWD Final Rule, issue a new rule based on 2006 rule & 2009 proposed rule • Research: prions shed in feces from deer in early stages of CWD; prions in urine & saliva
2010	• Detected in captive white-tailed deer in Missouri • Detected in wild white-tailed deer in North Dakota & Virginia
2011	• Detected in wild white-tailed deer in Maryland • Detected in wild white-tailed deer in Minnesota • Severe reduction of USDA funds for CWD work
2012	• Detected in captive white-tailed deer in Iowa & Pennsylvania • Detected in wild white-tailed deer in Missouri • Detected in wild mule deer in West Texas • APHIS Interim Final Rule for CWD Herd Certification & Interstate Movement & CWD Program Standards published • Research: possible link between scrapie & CWD
2013	• Detected in wild white-tailed deer in Pennsylvania
2014	• Detected in captive deer in Ohio • CWD Program Standards revised • APHIS CWD Final Rule implemented • Research: plants may play role in CWD transmission & environmental maintenance; experimental aerosol transmission in white-tailed deer
2015	• Detected in wild white-tailed deer in Michigan • Detected in captive white-tailed deer in Texas • Research: plants can bind prions superficially & uptake prions from contaminated soil
2016	• Detected in wild wapiti & white-tailed deer in Arkansas • Detected in a wild reindeer in Norway

Figure 1. Current known distribution of chronic wasting disease (CWD). In addition to North America, cases have been reported in South Korea (captive only) and Norway (free-ranging only). North America map from U.S. Geological Survey (2016); global maps from Wikipedia.