

June 2003

LWDR 03-05



Livestock and Wildlife Disease Report

Colorado
State
University

Extension

Department of Agricultural and Resource Economics, Fort Collins, CO 80523-1172
<http://dare.colostate.edu/pubs>

CHRONIC WASTING DISEASE & THEORIES OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY TRANSMISSION

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Introduction

Chronic Wasting Disease (CWD) is a fatal brain and nervous system disease that affects certain cervidae, such as white tail deer, black tail deer, mule deer, and elk. CWD is in the family of diseases called Transmissible Spongiform Encephalopathies (TSEs). It was first observed in 1967 at a Ft. Collins, Colorado research facility in a mule deer specimen. The principal clinical signs of CWD include staggering, listlessness, abnormal behavior, loss of fear of humans, excessive drooling and drinking, frequently urination, drooping ears, and rough coat in addition to weight loss. Researchers who observed the destructive effects of the disease coined the term CWD due to the rapid weight loss common in infected animals.

The transmissible agent that causes CWD is a relatively open area of research for medical science. While the transmissible agent(s) of other TSEs has been examined for approximately 50 years, definitive conclusions remain elusive. Moreover, until 1996, CWD had only affected a small area of Northeastern Colorado, Southeastern Wyoming and the Panhandle of Nebraska. The recent and rapid spread of CWD to new

areas and the similarities of this disease to Bovine Spongiform Encephalopathy (BSE), or “mad cow disease,” have caused a great deal of public concern. Hunters, wildlife enthusiasts, ranchers, and broader society have a vested interest in CWD. People need to know what the disease is, how it is contracted, what causes it, whether or not there is a human health concern, how to treat it and, of course, how to prevent the disease from occurring and spreading.

CWD and Other TSE Diseases

TSEs are neurological diseases, characterized by microscopic empty spaces in brain matter that create a spongy mass. Although CWD was observed in 1967, it was not diagnosed as a TSE until 1978. Cervidae are not the only animal species to have been affected by TSEs. Cattle famously suffer from BSE. Sheep are known to have been susceptible to scrapie for at least the last 400 years. Cats are vulnerable to Feline Spongiform Encephalopathy (FSE) and mink are prone to Transmissible Mink Encephalopathy (TME). Importantly, humans are vulnerable to several TSEs, including; Creutzfeldt-Jakob disease (CJD), New Variant Creutzfeldt-Jakob disease (nvCJD), and Kuru.

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The principal concerns over TSEs in general and CWD in particular are in understanding where it comes from and how it moves from one species to another. Only four members of the deer and elk family are known to be susceptible to CWD: elk, mule deer, black tailed deer, and white-tailed deer. Out of these species, research reveals that whitetail deer seem to be the most susceptible to the disease (United States Geological Service, 2003). Transmission of CWD among cervid species is believed to occur from direct contact with infected animals and from living in highly contaminated habitat. The exact mode of CWD transmission in the wild is still not known, but it is thought that the infectious agent is passed from infected animals in feces, urine or saliva (USGS, 2003). No universally accepted theory on the genesis of CWD exists. Some experts contend that deer and elk contracted it from sharing grazing land with scrapie-infected sheep along the front range of Colorado (Michaels, 2003). Others believe CWD is a naturally occurring disease of deer and elk (Connecticut Department of Environmental Protection, 2003).

Concern over the potential transmission of CWD from cervidae to other animal species and humans is well grounded in the science of other TSEs. The development of BSE came from the feeding of scrapie infected feed meal to cattle and nvCJD developed in humans from the consumption of BSE infected tissue (Bruce *et al.*, 1997). Kuru was the first documented TSE in humans and it developed from the cannibalism of CJD infected humans. TME's development is allegedly from the feeding of downer cattle to farm raised mink, while FSE supposedly resulted when cats consumed BSE infected meat.

The agent that transmits TSEs is extremely hard to eliminate through the conventional decontamination procedures. For example, an electrode that had been inserted in the cortex of an unrecognized CJD patient was subjected to a normal hospital decontamination process. It was then used in succession on two patients and cleaned in the same fashion after each surgery. Both of the patients developed CJD after their surgeries. Then in an attempt to see if the electrode had been the source of infection it was used on a chimpanzee two years after the first surgery. The chimpanzee also developed a spongiform encephalopathy as a result of the experiment (Weissmann *et al.*, 2002).

Research and Theories of the TSE Agent

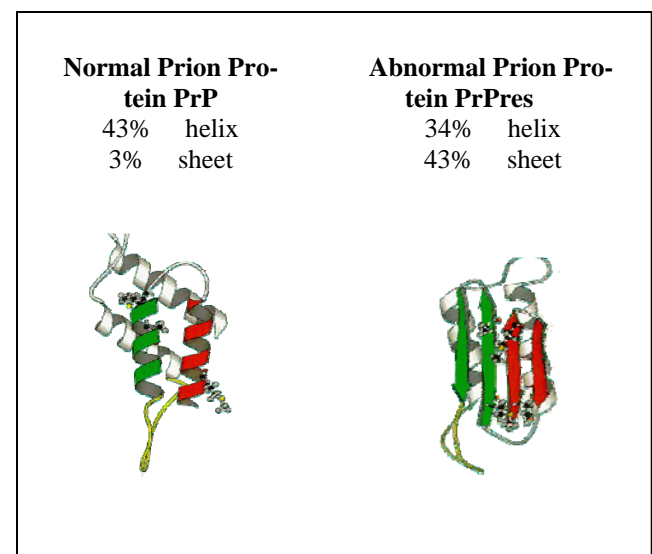
General research on TSEs began in 1955 when British parliament became concerned with the economic

impact of scrapie and its effect on wool production (Giannakenas, 1997). One of scrapie's most notable symptoms is loss of wool, due to the animals rubbing or scraping against whatever they can in order to alleviate the intense itchiness associated with the disease. In the mid-1900's English, French, and British scientists attempted to identify the infectious agent of scrapie to no avail. With limited scientific effort dedicated to scrapie, the disease was marginalized and progress limited. Those few scientists who retained an interest in scrapie competed fiercely for scarce research funds. This contentious environment has carried over into research programs on the other TSE diseases, and many competing theories have resulted (Giannakenas, 1997).

Presently, the causes of TSE diseases are controversial and conclusive evidence has not swayed the scientific community definitively in favor of any one theory. General overviews of the most prevalent theories of the TSE agent are outlined below.

Prion Theory

Both the popular press and the scientific community show the greatest support the "protein only" theory or "prion" theory. Prion is a term coined by Prusiner (1982) to describe a "small proteinaceous infectious particle which is resistant to inactivation by most procedures that modify nucleic acids." It is believed the prions are an irregular protein made from a normal protein-making gene common to all mammals. The normal gene, PrP gene, encodes the formula for the production of a normal protein called the "prion protein", PrP. Once the mutated prion enters the body the normal PrP genes starts the production of the mutated prion protein PrP^{res}. Protease is an enzyme that breaks down protein



(Steevels *et al.*, 2003)

in the brain. The abnormal prion cannot be broken down by protease, while the normal protein can; therefore, the mutated protein accumulates in the brain and causes the degeneration of brain and eventual death of the tissue. It is unknown what function the normal protein performs, but it is typically found in an α -helix formation in healthy brains and in a β -pleated sheet in infected brains.

The infection process of prions has been investigated and it appears that prions use M cells, or intestinal mucosa, to make their way from the digestive tracts to the central nervous system. M cells absorb nutrients and aid in digestion. Gastrointestinal fluids digest most proteins, but normally between 1 in a million and 1 in ten million pass through without being destroyed.

The dissemination of the CWD infection throughout the body of mule deer has been found to be very similar to the dissemination of the scrapie prion in sheep (Sigurdson *et al.*, 1999). In the earliest period of infection, CWD was traced

to the retropharyngeal lymph nodes, tonsils, Peyer's Patches (lymph tissue located in the small intestine) and ileocolic lymph nodes. The dissemination of lymphoid infection is unlike some other TSEs such as BSE, where the infection is only detected in the Peyer's Patches or not at all (Wells *et al.*, 1998; Sigurdson *et al.*, 1999).

Several researchers, including Apler, Griffith, Pattison, Jones, and Prusiner, have advocated the prion theory. Prusiner received much of the credit for the prion theory and the Nobel Prize when he was able to extract a full-length protein (the prion). The magnitude of such discovery is still under scrutiny of medical scientists due to the fact that there has never been any consideration that protein rather than viruses, bacteria, fungi, or parasites could be considered an infectious agent.

Spiroplasma Theory

Spiroplasmas are bacteria that do not have a cell wall and are possibly some of the oldest forms of life on earth. Spiroplasma became suspect as a TSE agent when spiroplasma-like structures were observed in CJD tissues. There are many similarities between spiroplasmas and the TSE agent. Spiroplasmas contain internal proteins that possess the same characteristics as proteins in CJD and scrapie. Spiroplasmas localize in the central nervous system, they show high resistance to disinfectants, and are extremely hard to cultivate in laboratory cultures.

Researchers have shown that when spiroplasmas were injected into rats it produced infection and a spongy change in the brain tissue. Through the aid of electron microscopy in the early stages of infection the spiroplasmas appeared as membrane bound infection in the rats. When it was obvious the tissues were infected using a broth culture there was no evidence of spiroplasma. Therefore, conclusive evidence showing a direct relationship between spiroplasmas and TSE has not been confirmed (Bastian, 1984).

Virus Theory

All viruses contain nucleic acid, either DNA or RNA (but not both), and a protein coat, which encases the nucleic acid. Sigurdson (1954) and his early studies on scrapie resulted with the "slow viruses" theory, due to the long period prior to the appearance of clinical symptoms. Scrapie was labeled a virus because the physical characteristics measurable at the time include size, ability to be transmitted, and that it does multiply during infection.

Diringer, Beeks, and Oberdieck (1994) published the virus theory with two fundamental observations associated with scrapie and other TSE disorders. Firstly, TSE diseases are transmissible and, secondly, a single dominant gene of the host not only controls the disease process, but is also involved in strain selection (e.g., scrapie in sheep, BSE in cattle, and so on). The concept of TSE as a viral disease has led for an extensive search in "infected" tissue for evidence of viruses. Thus far, this avenue of inquiry has not proven successful.

Viroid Theory

Viroids are small, circular, single-stranded RNA's, which replicate autonomously when inoculated into host plants. The viroid theory came from the discovery of properties of the infectious agents of TSEs, which suggested they were smaller and simpler than known viruses and that they resemble protein free infectious RNA molecules that cause diseases in particular plants (Diener, 1974). The viroid concept became obscure when it became clear that protein, which is not found in the infectious RNA molecules, was essential for the infection of TSEs to occur.

Virino Theory

A virino is a hypothetical infectious particle, which consists of nucleic acid in a protective coat of host cell proteins. The virino theory suggests that the scrapie-specific nucleic acid is covered with host protein and may be "sticky", hard to purify from other host

proteins, and would be extremely hard to recognize (Dickinson & Outram, 1979). This agent (virino) would fit in the niche between viruses, which have their own protein, and virioids, which need no protein at all. This concept is a more complex example of the viroid theory with the addition of the protein component that the virino would be unable to make for itself. The virino theory hypothesizes that the life cycle of the TSE agent includes a stage when it is bound to the host protein (a naturally occurring prion protein, PrP). This theory lacks physical supporting evidence and is speculative in nature (Bastian, 2003).

Inter-Species Transfer of TSE Diseases

Generally speaking, inter-species transfers of TSE family diseases are one million times less likely than within species transmissions. However, once inter-species transfer occurs, the new strain can more easily jump from species to species than the original strain. For example, scrapie has a limited number of species it can affect, but once scrapie became BSE in cattle, it could affect a much broader range of species than scrapie could (Weissman *et al.*, 2002).

Inter-species transfer of CWD is still being investigated. Pronghorn antelope, Rocky Mountain bighorn sheep, mountain goats, moose, and an exotic antelope called a blackbuck have been in contact with CWD-affected deer and elk or resided in areas where CWD had occurred but have not developed the disease. Domestic livestock does not appear to be susceptible to CWD, and some cattle, sheep, and goats have resided in research facilities with CWD for long periods without developing the disease (Williams, Kirkwood, and Miller, 2003).

Many species are experimentally susceptible to CWD by cerebral inoculation, or by injection of infected material into the brain, an unnatural but commonly used route for the study of TSE diseases. Mink, domestic ferret, squirrel monkey, mule deer, domestic goat (Williams and Young, 1992), and laboratory mice (Bruce *et al.*, 1997) are susceptible to CWD by this route. For cattle and humans, it is likely that susceptibility to CWD is limited by the lack of conversion compatibility of the respective PrP (Raymond *et al.*, 2000). The National Institutes of Health laboratory in Montana is planning on researching CWD effects on primates. This research should provide great insights on what the likely effects on humans might be.

Conclusion

An understanding of what risk CWD poses to wildlife and the public requires an extensive knowledge of what research has concluded on other TSEs. The public should not only be aware of the leading theories but also what other work has been done in order to give the interested party the background to be critical. The first step in combating CWD is to understand the disease and the process in which it attacks. Conclusive evidence on the agent responsible for CWD and other TSEs is still under investigation by scientists. Despite this, many authorities in the field and members of the popular press have decided that the prion theory is the most likely. Research is ongoing and human health concerns continue to be a focal point of public concern. At this stage, CWD is considered to have no human health implications, but the consumption of infected cervid meat is discouraged. Medical science is working toward a greater understanding of the causes of TSEs, and, hopefully, the appropriate course for their detection, prevention, and eventual elimination from human and animal populations.

Acknowledgments

Without implication, the authors would like to thank Cleon Kimberling and John Balliette for their reviews of an earlier version of this document.

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