

# Comments on Classical and Atypical Scrapie in Domestic Sheep and Goats

Terry R. Spraker<sup>1</sup>, DVM, PhD, DACVP; Katherine I. O'Rourke<sup>2</sup>

<sup>1</sup>College of Veterinary Medicine and Biological Sciences, 300 West Drake Road, Colorado State University, Fort Collins, CO

<sup>2</sup>U.S. Department of Agriculture, Agricultural Research Service, Animal Disease Research Unit, 3003 ADBF, Pullman WA 99164

## Abstract

Scrapie is a neurodegenerative disease in domestic sheep and goats. Scrapie has a long incubation period that can vary from two to five years. The etiology is an extremely stable isoform (PrP<sup>Sc</sup>) of the normal cellular prion protein (PrP<sup>C</sup>). The accumulation of this protein in the brain is thought to result in the spongiform encephalopathy that characterizes the disease. Scrapie has been reported in the United Kingdom, Ireland, most European countries, Canada, the United States, India and Japan, but not in Australia and New Zealand. Clinical signs are mostly neurological and diagnosis is usually made with immunohistochemical staining of the brainstem and retropharyngeal lymph nodes. Genetics plays a significant role in the susceptibility and incubation period of the disease and is used in control strategies. The primary method of prevention is maintenance of a closed ewe flock, purchase of sheep from uninfected farms enrolled in an approved flock certification program, or purchase of genetically resistant stock. Following diagnosis of scrapie in a flock, depopulation of genetically susceptible sheep is the only effective control measure at this time. If a sheep or goat flock is diagnosed with atypical scrapie the herd is depopulated.

## Résumé

La tremblante du mouton est une maladie neurodégénérative du mouton et de la chèvre domestique. La tremblante du mouton a une longue période d'incubation pouvant varier entre deux et cinq ans. Une isoforme extrêmement stable (PrP<sup>Res</sup>) de la protéine prion cellulaire normale (PrP<sup>C</sup>) en est la cause. On pense que l'accumulation de cette protéine dans le cerveau entraîne l'encéphalopathie spongiforme qui caractérise la maladie. La tremblante du mouton a été signalée au Royaume-Uni, en Irlande, dans la plupart des pays d'Europe, au Canada, aux États-Unis, en Inde et au Japon, mais pas en Australie ni en Nouvelle-Zélande. Les signes cliniques sont majoritairement neurologiques et le diagnostic est habituellement arrêté par coloration immunohistochimique du tronc cérébral

et des ganglions lymphatiques rétro-pharyngiens. La génétique joue un rôle considérable dans la sensibilité à la maladie et sa période d'incubation et elle est utilisée dans l'élaboration de stratégies de lutte contre la maladie. La principale méthode de prévention demeure le maintien d'un troupeau de brebis fermé, l'achat de moutons de fermes exemptes d'infection inscrites à un programme approuvé d'accréditation du troupeau, ou l'achat d'animaux bénéficiant d'un génotype résistant. Une fois la tremblante du mouton diagnostiquée dans un troupeau donné, le dépeuplement des animaux ayant un génotype sensible représente la seule méthode efficace de maîtrise, pour l'instant. Si la tremblante du mouton atypique est diagnostiquée au sein d'un troupeau de moutons ou de chèvres, il faut procéder à l'abattage intégral du troupeau.

## General Comments

Scrapie is a family of fatal neurodegenerative disorders occurring in domestic sheep and goats. Scrapie was first recognized in domestic sheep in Scotland approximately 200 to 250 years ago. It is speculated that scrapie was actually in Spain in Merino sheep and introduced into Scotland from these sheep. Other names for scrapie include Rida, La Tremblante du mouton, Traberkrankheit and the scrapies.

## Etiology

The etiology of scrapie is thought to be the alteration of a normal cellular protein (PrP<sup>C</sup>) of the body. This protein (PrP<sup>C</sup>) is thought to be located in nearly all tissues, but is especially abundant in lymphoid and neural tissues. Its function is not presently known, but is thought to be associated with neural transmission at synaptic junctions. The dogma at the present time is that the scrapie agent (PrP<sup>Sc</sup>) enters the body and is first sequestered by lymphoid cells. The PrP<sup>Sc</sup> in some manner alters the PrP<sup>C</sup>. This same activity next occurs in the brain. The accumulation of this extremely stable isoform (PrP<sup>Sc</sup>) of the normal cellular prion protein (PrP<sup>C</sup>), with the inability of the body to break it down or

metabolize it, is thought to be the pathogenesis of the transmissible spongiform encephalopathies (TSEs).

The infectivity of PrP<sup>Sc</sup> in homogenates of brain from infected sheep is extremely stable and not eliminated by formalin, ultraviolet radiation, normal autoclaving, many disinfectants and many proteases and nucleases. However, infectivity is generally inactivated by 40% household bleach, very high or very low pH (NaOH, formic acid), certain detergents (LpH, SDS), and autoclaving at 280° F (138°C) for prolonged periods of time.

### Susceptible Host

All breeds of domestic sheep and goats appear to be susceptible. The Suffolk breed of sheep appears to be the most susceptible in the US, probably because of increased exposure risk and a high percentage of genetically susceptible sheep. The genetics of the sheep have been shown to have a profound influence on the disease. Scrapie is rare in goats, but no single breed seems to be more susceptible than other breeds.

### Distribution

Scrapie is currently reported in the United Kingdom, Ireland, most European countries, Canada, the United States, India and Japan. Scrapie was first recognized in Canada in 1945 and in the United States in 1947 in Wisconsin. The clinical signs are insidious and often non-specific; the disease may have been in the US before that time, but not recognized. Scrapie has not been reported in Australia and New Zealand.

### Clinical Signs

Scrapie has a long pre-clinical incubation period, and the onset of the disease varies from two to five years in the field. The primary clinical signs of domestic sheep with classical scrapie include weight loss despite normal appetite, behavioral changes, excessive itching and rubbing/wool pulling or biting (hence the name scrapie), lip smacking, loss of coordination, startling at sudden noise or movement, high-stepping gait (front legs), bunny-hop movement (especially in the rear legs), tremors (especially in the head, neck and shoulders), swaying of hind quarters, terminal recumbency, or death with no clinical signs. These clinical signs vary from animal to animal and no single animal shows all of these signs.

There appear to be two different phenotypes of classical scrapie as observed in sheep in the United States. The first phenotype, occurring in sheep with the prion genotype 136V, is relatively rare, has a short incubation period and relatively high transmission rates within a flock (approximately 30-40% in a flock), and trans-

mission appears to be adult to adult as well as from adults to lambs. The second and more common form of scrapie in US sheep, occurring in sheep lacking the 136V genotype, has a longer incubation period three to five years, within-flock prevalence is usually less than 30%, and adult to lamb transmission is more common than adult to adult spread. Although these two phenotypes are thought to represent two different scrapie strains in the US, lesion patterns and PrP<sup>Sc</sup> biochemical profiles (Western blot) are nearly identical.

Atypical or Nor98-like scrapie usually occurs in older sheep and goats ( $\geq$  six years). This novel strain is reported at low prevalence and the pathogenesis, etiology, genetics and transmission modes are poorly understood.

### Genetic Differences in Sheep with Classical Scrapie

Genetic differences are thought to play a significant role in scrapie susceptibility. Sheep with the short incubation period and highly transmissible strain usually have the Prnp gene encoding 136V (136VV or 136AV), indicating the amino acids valine or arginine at position 136 of PrP<sup>c</sup>. Sheep with the more common form (longer incubation period with lower transmission rates) are usually sheep with the Prnp gene encoding 136AA, coupled with the susceptible mutation at position 171; homozygosity (AAQQ) for glutamine (Q) at position 171 confers susceptibility, and sheep with the arginine (R) genotype (AAQR or AARR) are usually resistant.

### Transmission

Scrapie transmission is associated with lambing, probably due to contamination of the lambing facility with infectious material in the shed placenta. Accumulation of PrP<sup>Sc</sup> in the placenta of an infected ewe is controlled by the genotype of the fetus; placental cotyledons from a genetically resistant lamb do not have detectable PrP<sup>Sc</sup>. Nor98-like or atypical scrapie is reported in sheep of all genotypes, although mutations at position 142 (leucine to phenylalanine) or 154 (arginine to histidine) appear to predispose sheep to this disorder. The low prevalence of this strain in a flock and the widespread geographic distribution suggest that this may be a sporadic disorder associated with aging in small ruminants.

### Postmortem Lesions/Histopathology

The primary gross lesions of classical scrapie and atypical scrapie are similar and often meager. The primary gross lesion is often muscle wasting with the pres-

ence of a small amount of subcutaneous and abdominal fat. The excessive itching in classical scrapie often produces areas of alopecia over the chest, hindquarters and sometimes head; however, the underlying skin usually shows little evidence of dermatitis. The primary histological lesion is a spongiform encephalopathy in both classical and atypical scrapie, only the neuroanatomical locations that are affected are different. The spongiform degeneration typical of classical scrapie is first found in the motor nucleus of the vagus nerve, but then spreads throughout brain stem, thalamus and hypothalamus, and later can be found throughout the brain and spinal cord. The histological lesions of atypical scrapie are predominately located in the cerebellum and not in the motor nucleus of the vagus nerve as with classical scrapie.

### Diagnosis

Classical scrapie or atypical scrapie can be suspected following a complete physical examination, but other tests are required to make a definitive diagnosis. At the present time tissue biopsy of the palatine tonsil, lymphoid follicles of the nictitating membrane and rectal mucosa followed by immunohistochemical staining can lead to a presumptive ante-mortem diagnosis of most forms of classical scrapie. Postmortem testing of brain and lymph nodes by ELISA, immunohistochemistry or Western blot are definitive.

### Differential Diagnoses

Differential diagnoses for scrapie that should be considered in sheep and goats include Johne's disease, grass tetany (hypomagnesemia), listeriosis (circling disease), milk fever (hypocalcemia), copper deficiency, ketosis (acetonemia), polioencephalomalacia, thiamine deficiency, blunt trauma to the lumbar region and parasitism. These diseases are relatively easy to rule out if they are considered. A gross and histological examina-

tion of tissues with specific immunohistochemical stains can usually rule out these other diseases and confirm scrapie. The most common conditions found in sheep and goats that are suspected of having scrapie and are presented to the Colorado State University Diagnostic Laboratory, Fort Collins, Colorado are Johne's disease and injuries to the spinal column.

### Treatment

At the present time there is no known treatment for classical or atypical scrapie in sheep or goats.

### Prevention and Control

Classical scrapie is a transmissible disease, and the primary method of prevention is maintenance of a closed ewe flock, purchase of sheep from uninfected farms enrolled in an approved flock certification program, or purchase of genetically resistant stock. Following diagnosis of scrapie in a flock, depopulation of genetically susceptible sheep is the only effective control measure at this time. In the absence of prion genotypes conferring resistance in goats, total depopulation or permanent quarantine of exposed goats is the only approved control measure.

### Resources

Excellent downloadable printed information and videos for veterinarians and sheep producers are available at several websites, including:

A producer's guide to scrapie

[http://sheepindustrynews.com/scrapie\\_guide/](http://sheepindustrynews.com/scrapie_guide/)

Eradicate scrapie!

<http://www.animalagriculture.org/scrapie/scrapie.htm>

Scrapie disease information

[http://www.aphis.usda.gov/animal\\_health/animal\\_diseases/scrapie/](http://www.aphis.usda.gov/animal_health/animal_diseases/scrapie/)