

# Scrapie

*Tremblante de mouton, Rida, Traberkrankheit (trotting disease), Gnubberkrankheit (nibbling disease)*

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## Importance

Scrapie is a neurodegenerative disease, caused by a prion, that affects sheep and occasionally goats. In sheep, the animal's genotype strongly influences the incidence of disease. Genetically susceptible sheep do not become ill for several years; however, scrapie is progressive and fatal once the symptoms develop. Typically, scrapie results in production losses and an annual mortality rate of 3-5% in a flock; in severely affected flocks, the annual mortality rate can reach 20%. The presence of this disease can result in trade sanctions, and many countries are conducting control or eradication programs.

As a result of scrapie surveillance, an atypical form of this disease has recently been detected in many countries in Europe, as well as in the United States. This novel form of scrapie, which was first reported from Norway in 1998, is called Nor98. Nor98 scrapie can occur in sheep that are genetically resistant to classical scrapie. The tissue distribution of the Nor98 prion differs from that of the classical prion protein, and some testing protocols must be modified to detect this form. Other atypical forms of scrapie have also been found in some countries.

## Etiology

Scrapie is a member of the transmissible spongiform encephalopathies (TSEs), a group of neurodegenerative disorders caused by unconventional disease agents. These agents are resistant to the treatments that ordinarily destroy bacteria, spores, viruses and fungi. They are generally thought to be prions, although a minority opinion suggests that TSEs may be caused by virinos or retroviruses. Prions are infectious proteins that seem to replicate by converting a normal cellular protein into copies of the prion. This cellular protein, which is called PrPc, is found on the surface of neurons. The scrapie prion, which is a pathogenic isoform of PrPc, is designated PrPSc. Strain variations occur in the scrapie prion. Atypical scrapie prions including the Nor98 agent have also been found.

## Species Affected

Scrapie affects sheep, goats, and moufflon (*Ovis musimon*). Rats, mice, hamsters, monkeys and a variety of other laboratory and wild animals can be infected experimentally.

The Nor98 form of scrapie has been reported in sheep and goats.

## Geographic Distribution

Scrapie can be found worldwide. This disease has been reported in Europe (including the United Kingdom), the Middle East, Japan, Canada, the United States, Kenya, South Africa, Colombia and parts of Asia. The scrapie status of many countries is not known because they have no surveillance for this disease. Australia and New Zealand have remained free of scrapie; although outbreaks occurred in these two countries, the disease was eradicated by slaughtering the imported sheep and their flockmates soon after they were released from quarantine.

The Nor98 form of scrapie was first reported from Norway in 1998. Since 2002, Nor98 and other atypical scrapie agents have been detected in a number of European countries. Nor98 was diagnosed for the first time in U.S. sheep in March 2007.

## Transmission

Transmission of scrapie is best understood in sheep. Infected animals carry the scrapie prion for life, and can transmit the agent even if they remain asymptomatic. Most animals become infected from their dam, either at or soon after birth. In genetically susceptible, infected ewes, prions may be found in the reproductive tract, including the placenta, during pregnancy. These ewes can produce either prion-positive or prion-negative placentas, depending on the genotype of the fetus (for details, see **Genotype and Scrapie Susceptibility in Sheep**, below). Neonatal animals become infected when they lick or ingest fetal membranes and fluids. In confined lambing areas, the disease can also spread to the offspring of uninfected

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sheep. Uninfected adult ewes may be infected from this source, although they are more resistant. Vertical transmission *in utero* might be possible, but current evidence suggests that transmission mainly occurs after birth.

Transmission can also occur by direct contact between sheep. The scrapie agent has been detected in the nervous system, salivary glands, tonsils, lymph nodes, nictitating membrane, spleen, distal ileum, proximal colon and muscles. Urinary excretion has recently been reported in mice with nephritis, and also in hamsters, but it has not been documented in sheep. The importance of environmental contamination is controversial. A recent report suggests that the scrapie agent persisted in a sheep barn in Iceland for 16 years. This prion has also been isolated from an experimentally contaminated soil sample after three years. Transmission via contaminated fomites such as knives is theoretically possible, and transmission has been reported in a contaminated vaccine.

Transmission has not been studied extensively in goats. Most infected goats have a history of contact with sheep, and are probably infected by contact with the placenta or nasal secretions. Transmission through fomites may also be possible. Experimental infections have been established in goats by feeding prion-containing fetal membranes, as well as by intracerebral or subcutaneous inoculation.

## Incubation Period

The incubation period is usually 2 to 5 years in sheep; cases are rare in sheep less than a year old.

Cases of scrapie have been reported in 2 to 8 year old goats. The incubation period in experimentally infected goats is less than three years, with a range of 30 to 146 weeks.

## Clinical Signs

The symptoms of scrapie are variable in sheep, and can be influenced by the strain of the prion and the sheep's genotype and/or breed. The first symptoms are usually behavioral: affected sheep tend to stand apart from the flock and may either trail or lead when the flock is driven. As the disease progresses, animals usually become hyperexcitable and have a high-stepping or unusual hopping gait and/or a fixed stare, with the head held high. Other symptoms may include ataxia, incoordination, blindness, trembling, or convulsions when being handled. Intense pruritus is common and may lead to rubbing, scraping or chewing. Scratching of the dorsum or pressure over the base of the tail may cause a characteristic nibbling response due to pruritus. Loss of condition is common in the early stages, and significant weight loss or emaciation may be seen late. The fleece may be dry and brittle. Drinking behavior and urination can also change, with affected animals drinking small quantities of water often. Most animals die two to six

weeks after the onset of symptoms, but deaths may occur up to six months later.

In sheep with the Nor98 variant, incoordination and ataxia appear to be major symptoms. Pruritus seems to be minimal or uncommon, although it has been seen in some animals. Loss of body condition, anxiety, tremors, abnormal menace responses or a subdued mental status have been reported in some cases, but not others. Some cases of atypical scrapie have been found by routine surveillance in apparently healthy flocks at slaughter.

Variable clinical signs have been reported in goats with scrapie. In one case, the only symptoms were listlessness, weight loss and premature cessation of lactation. The clinical signs may also resemble scrapie in sheep, with behavioral changes such as irritability and loss of inquisitiveness, as well as hyperesthesia, incoordination, posture abnormalities, unusual alertness, restlessness, tremors, teeth grinding, salivation, impaired vision or regurgitation of rumen contents. Some goats have been reported to stamp and hold their heads down as if they are bothered by nonexistent flies. In late stages, animals may appear drowsy and have difficulty rising. Pruritus is less common in goats than in sheep; if it occurs, it is typically less intense and often localized over the tailhead or withers. As in sheep, the disease is progressive, with prostration and death 1-6 months after the onset of symptoms.

## Post Mortem Lesions [Click to view images](#)

The carcass may be wasted or emaciated. No other gross lesions are found. The characteristic histopathologic lesions include neuronal vacuolation and non-inflammatory spongiform changes in the gray matter of the central nervous system (CNS). Astrocytosis and amyloid plaques may also be seen. These lesions are usually but not always bilaterally symmetrical.

## Morbidity and Mortality

The incidence of scrapie varies with the country. The prevalence of this disease is low in U.S. sheep: in 2002-2003, slaughter surveillance estimated the overall prevalence as 0.20% in mature sheep, with most cases occurring in black-faced sheep. The prevalence of scrapie in different breeds varies with the country. Scrapie is rare in goats; only sporadic cases have been reported worldwide.

Scrapie is always fatal once the symptoms appear. Typically, the annual mortality rate in an affected flock is 3 to 5%. In severely affected flocks, up to 20% of the animals may die each year.

### *Genotype and scrapie susceptibility in sheep*

In sheep, transmission and the development of clinical disease are both influenced by the host's genotype. Susceptibility or resistance to the classical form of scrapie is associated with polymorphisms in the PrP gene at codons 136, 154 and 171. These three codons are located in a part of the protein that may undergo structural changes during the conversion from PrPc to PrPSc. At

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codon 136, alanine (A) is linked to scrapie resistance and valine (V) is associated with susceptibility. At codon 154, histidine (H) is associated with resistance and arginine (R) with susceptibility. At codon 171, arginine (R) is linked to resistance, while glutamine (Q) and histidine (H) are linked to susceptibility. Although other combinations are theoretically possible, only five PrP alleles are common in sheep: A136R154R171 (abbreviated ARR), ARQ, AHQ, ARH and VRQ. Sheep with the ARR/ARR genotype are highly or completely resistant to classical scrapie, while sheep with the VRQ/VRQ genotypes are most susceptible. The remaining genotypes have intermediate susceptibility.

Sheep with resistant genotypes develop clinical disease after longer incubation periods, or not at all. Some experimental studies suggest that the genotype can affect the level of scrapie replication in cells. The genotype also influences transmission. A genetically resistant fetus suppresses the appearance of prions in the placenta of an infected, scrapie-susceptible ewe. Ewes with resistant genotypes do not produce scrapie-positive placentas, regardless of the genotype of the fetus.

Atypical scrapie is also influenced by the genotype; however, it can occur in sheep resistant to classical scrapie. Increased susceptibility to atypical (Nor98) scrapie has been associated with an ARQ allele that contains a phenylalanine residue at codon 141 (AF141RQ) and also with the AHQ genotype. Atypical scrapie has also been reported more often in ARR and/or ARQ genotypes with a leucine at position 141 (AL141RQ). Nor98 scrapie has been seen in ARR/ARR sheep, which are completely resistant to classical scrapie.

## Genotype and scrapie susceptibility in goats

Genetic factors that influence scrapie resistance are poorly understood in goats. However, in one affected herd, polymorphisms at codon 154 (R or H) and 222 (Q or K) were associated with scrapie resistance or susceptibility. In these goats, a lysine (K) at codon 222 was associated with scrapie resistance.

## Diagnosis

### Clinical

Scrapie should be suspected in animals that develop a slowly progressive, fatal neurologic disease. Pruritus strengthens the diagnosis, but the absence of pruritus does not rule it out.

### Differential diagnosis

The differential diagnosis for scrapie includes external parasitism (lice, mange or itch mites), pseudorabies (Aujeszky's disease), maedi-visna, cerebral listeriosis, pregnancy toxemia, rabies, cerebrocortical necrosis (polioencephalomalacia), abscesses or tumors in the brain, louping ill and other tick-borne encephalitides, toxins, hypomagnesemia, focal symmetrical encephalomalacia (chronic enterotoxemia), and other degenerative central nervous system diseases or causes of

pruritus. Bovine spongiform encephalopathy has been reported in experimentally infected sheep and a naturally infected goat, and would look similar to scrapie.

### Laboratory tests

Transmissible spongiform encephalopathies have traditionally been diagnosed by histopathology. Scrapie is usually confirmed by detecting PrP<sup>Sc</sup> in the CNS. Neuronal vacuolation and PrP<sup>Sc</sup> accumulation typically occur in the brainstem at the level of the obex in sheep with the classical form of scrapie. In sheep with Nor98 scrapie, these abnormalities occur mainly in the cerebellar and cerebral cortices; and are much less apparent at the level of the obex. The Nor98 agent has a unique biochemical signature when compared to classical PrP<sup>Sc</sup>. In classical scrapie, PrP<sup>Sc</sup> can sometimes be found in peripheral lymphoid tissues before it appears in the brain, but this is not consistent.

Accumulations of PrP<sup>Sc</sup> can be found in unfixed brain extracts or other tissues by immunoblotting (Western blotting) and in fixed tissues by immunohistochemistry. The diagnosis can also be confirmed by finding characteristic fibrils of PrP<sup>Sc</sup> (scrapie-associated fibrils) with electron microscopy in brain extracts. Some of these tests can be used on frozen or autolyzed brains. A combination of tests may be used to certify flocks as scrapie-negative. Rapid tests are also used in some countries for postmortem screening. These tests include both ELISAs and immunoblot -based tests for PrP<sup>Sc</sup>.

The third eyelid test can be used for live animal diagnosis in some countries, including the U.S. This test detects PrP<sup>Sc</sup> in the nictitating membrane by immunohistochemistry. Similar tests are done on tonsil biopsies in some countries. Antemortem tests do not detect prion proteins in all infected sheep. Other live animal tests are in development, including capillary electrophoresis to detect PrP<sup>Sc</sup> in the blood.

Serology is not useful for diagnosis, as antibodies are not made against the scrapie agent.

### Samples to collect

The third eyelid test, which detects PrP<sup>Sc</sup> in the nictitating membrane, can be used for live animal diagnosis in some countries, including the U.S. Veterinarians in other countries make take tonsil biopsies. The detection of PrP<sup>Sc</sup> in the placenta may be helpful for disease surveillance in some flocks.

At necropsy, the brain should be removed for testing. The cerebral spinal cord with the dorsal root ganglia should be included if possible. Both fixed and unfixed samples are sent. In sheep, the spleen and a variety of lymph nodes should also be collected and sent to the laboratory unpreserved. During necropsy, a standard neuropathologic approach should be followed to rule out other causes of disease.

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## Treatment

There is no treatment for scrapie.

## Recommended actions if a transmissible spongiform encephalopathy is suspected

### Notification of authorities

Scrapie is a reportable disease in the United States. The U.S. has a scrapie eradication program, with the goal of disease eradication by 2010, as well as a flock certification program.

Federal: Area Veterinarians in Charge (AVICS)

[http://www.aphis.usda.gov/vs/area\\_offices.htm](http://www.aphis.usda.gov/vs/area_offices.htm)

State Veterinarians:

<http://www.aphis.usda.gov/vs/sregs/official.html>

## Control

The risk of introducing scrapie can be reduced by maintaining a closed flock or minimizing outside purchases of stock. If replacement animals must be added to the flock, they should be from flocks that are negative for this disease. The use of scrapie-resistant genotypes also decreases the risk for the classical form of scrapie; however, atypical scrapie can occur in these animals, including those with highly resistant ARR/ARR genotypes.

Genotyping is being used to reduce the incidence of the classical form of scrapie in a number of countries. In the U.S. eradication program, codons 136 and 171 are primarily used to classify resistant and susceptible sheep. Genetically susceptible sheep can be removed from infected flocks, and genetically resistant breeding stock should be selected. In particular, the use of resistant rams can decrease or eliminate shedding of prions from the fetal membranes and fluids of genetically susceptible, infected ewes. In addition, the fetal membranes and placenta should be removed immediately after sheep have lambed, and the bedding should be changed between parturitions.

Goats usually become infected after contact with sheep. Goats should not be mixed with sheep of unknown scrapie status. Outside purchases of stock should be minimized.

Scrapie can be contagious, and quarantines may be necessary for its control. The scrapie agent is highly resistant to disinfectants, heat, ultraviolet radiation, ionizing radiation, and formalin. Effective disinfection is possible with a single porous load autoclave cycle of 134-138°C for 18 minutes. Infectious tissues should either be autoclaved under the same conditions or incinerated. Sodium hypochlorite and sodium hydroxide are effective chemical disinfectants; sodium hypochlorite containing 2% available chlorine or 2 N sodium hydroxide should be applied for more than one hour at 20°C. Overnight disinfection is recommended for equipment.

## Public health

There is no evidence that scrapie can be transmitted to humans

## Internet Resources

United States Department of Agriculture Animal and Plant Health Inspection Service [USDA APHIS]

<http://www.aphis.usda.gov/>

USDA APHIS Scrapie Program

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

World Organization for Animal Health (OIE)

<http://www.oie.int>

OIE Manual of Standards

[http://www.oie.int/eng/normes/mmanual/a\\_summry.htm](http://www.oie.int/eng/normes/mmanual/a_summry.htm)

OIE International Animal Health Code

[http://www.oie.int/eng/normes/mcode/A\\_summry.htm](http://www.oie.int/eng/normes/mcode/A_summry.htm)

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