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# A Brief Review of Scrapie

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## History

Accounts of scrapie have been published in northwestern Europe since 1750.<sup>2</sup> Available evidence suggests the prevalence and occurrence of scrapie is closely connected with the breed and genetic structures of the sheep population to which the affected animals belong.<sup>2</sup> After 1700, ovine nutritional and environmental housing conditions improved in Europe with the exception of Spain.<sup>2</sup> Interest in phenotype improvement by genetic selection began at this time also, leading to a system of closer inbreeding. The Spanish merino studs of Germany and France in the late eighteenth century adopted a program of closer inbreeding with catastrophic results. Within 20 years, scrapie had become so prevalent that certain stud flocks were almost lost, as losses from this disease outnumbered increases in the herd.<sup>4</sup> Without individual animal identification and well kept mating and lambing records, it was difficult to control any genetic predisposition to this disease. This is especially true with scrapie, which does not manifest itself until middle age, often halfway through an animal's reproductive life. Unfortunately such records were not always kept under European 18th century farming conditions.

The Spanish fine-wooled sheep, or merinos, are considered one of the four main sources from which the British sheep population was derived, though it is no longer considered a standard British breed. The first recorded occurrences of scrapie in Germany, France, and the Danube Basin of central Europe were associated with, and frequently attributed to, the importations of the Spanish merino, among whose descendants the disease occurred in

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epidemic form in Germany and France.<sup>4</sup> Yet these sheep were used as an out-cross to control scrapie in native breeds in Britain from 1795 to 1810. Paradoxically, scrapie had not been reported in the merinos and their descendants in Australia, New Zealand, South Africa, and the Americas, although some of these were derived from European stocks affected at the time of the original importations.<sup>2</sup> This may be partly explained by examining the history of the merino sheep in Spain.

The Spanish merino sheep was a product of, and a key element in, the agrarian economy of the semi-arid regions of the Iberian peninsula for over five centuries beginning in AD 1273.<sup>5-7</sup> The merino flocks were transhumate, or migratory. They traveled continuously through non-settled, unenclosed country under the care of a group of men who traveled without their families. The shepherds of these migratory flocks were socially a world unto themselves and were isolated from the people of the permanent settlements. This is an interesting observation as scrapie was reported only in these migratory merino flocks and never in the common settled native Spanish sheep.<sup>8</sup> Introduction of these animals to central Europe after 1760 was associated with a marked increase of scrapie, especially in the descendants of the finest-wooled strains of Escorial and Electoral breeds, but not in the Negretti breed.<sup>2</sup>

## Clinical signs

Scrapie is considered to be the representative type disease for a group of neurological disorders known as the subacute spongiform encephalopathies. These diseases share a number of characteristics. All of them have an insidious onset without prior ill health, appearing most commonly in middle age. Histopathologically, development of non-inflammatory degeneration that is bilaterally symmetrical, which affects specific portions of the nervous system, is characteristic. Other changes include the disappearance of nerve cells, which

may exhibit cytoplasmic vacuolation, and spongiform changes in the neuropil, associated with glial proliferation. Tissue homogenates, but not blood, secretions, or excreta, show the presence of an experimentally transmissible agent for the factor capable of inducing, upon injection, a similar neurocytopathic disease in some species of laboratory animals. Finally, the pattern of occurrence is frequently familial which suggests hereditary predisposition.

Scrapie manifests itself as a disorder of behavior, locomotion, and body homeostasis.<sup>2</sup> It usually appears between the ages of two and five years, with a slow progression over a period of three to six months, leading to a fatal conclusion. Both sexes seem to be equally prone to develop the disease, with males manifesting usually six months earlier than females. The disease presents with clearly recognizable syndromes based on combinations of five main functional disturbances. These disturbances include inanition, ataxia, compulsive rubbing or nibbling of specific areas of the body, changes in mentation and loss of fine control of body homeostasis.<sup>2</sup> Development and progression of these disturbances are gradual, continuous, and frequently slight in slowly progressive cases.

The earliest signs are often behavioral, including slight apprehensiveness, general restlessness, distrust of humans, failure to respond to a dog, staring, and an elevated head posture known as "shrugginess". These signs are often overlooked, except by the experienced observer.

Occasional rubbing of certain body regions is seen next. These areas include the base of the tail, the lateral thorax, the poll of the head and later, the lower portion of the legs.

Clumsy movement, especially involving the hind quarters, is the third stage of scrapie. This is seen most commonly when the animal is turning and leads to a "trotting" gait. The animal exhibits rear limb palsy without loss of tendon reflexes.

The next stage involves fine muscular trembling of the body and/or head, associated with an inability to maintain body posture, with coarse postural muscle adjustments.

The final stage is wasting, without loss of appetite or an obviously diminished feed intake. Exercise intolerance progresses, water and salt intake becomes abnormal, and drinking habits become distorted.

Atypical symptoms have occurred often enough in scrapie-affected kinships to be con-

sidered part of the scrapie complex.<sup>2</sup> These syndromes include an acute rear limb palsy or paraplegia, acute myasthenia, defective vision, motor seizures of a grand-mal type, slow, progressive inanition or ill-thrift, and strictly localized segmental rubbing.

### **Histopathological Features of Natural Scrapie**

Natural scrapie appears to be a primary neural system degeneration, of "dying back" type, with three crucial sites of neuronal degeneration. In human neuropathology, the term "system degeneration" denotes a group of disorders in which there is a loss of neurons in specific parts of the nervous system, without inflammatory response, and with no obvious cause.<sup>2</sup> Degeneration is considered to proceed from the peripheral end of the axon towards the cell body.<sup>9,10</sup> The finding, in natural scrapie, of degenerating mossy fibers of the cerebellum as the sole pathological change in preclinical cases is consistent with such a concept.<sup>2</sup> The most prominent lesion is vacuolation of nerve cells in the medulla, pons, and mesencephalon, which consists of single or multiple vacuoles causing ballooning of nerve cells.<sup>11</sup>

The degree of clinical signs of cerebellar disturbance correlates well with the severity of the lesions found in the cerebellum.<sup>2</sup> Pathological changes were found bilaterally in the afferent parts of the cerebellum, while efferent cerebellar pathways were relatively unaffected. Nerve cell losses were most prominent in the granular layer and in the Purkinje cells of the flocculonodular lobe. Animals showing severe or moderate cerebellar signs displayed certain degenerative changes. These included nerve cell loss in both the cerebellar cortex and in the pontine and papilloform nuclei as well as a corresponding reduction of nerve fibers. Myelin breakdown and fibrous gliosis of both gray and white matter in these regions was also seen. In less severe cases the cerebellar cortex displayed nerve fiber degeneration in the form of degenerating mossy endings, retraction bulbs, and torpedoes. Finally, changes in the inferior olivary nuclei were variable, and neuronal vacuolation was found in other brainstem nuclei. There is often interstitial spongy degeneration in the same areas, sometimes particularly prominent in midline regions where it may extend rostrally to include diencephalic

and telencephalic non-cortical regions.<sup>11</sup>

While the correlation between clinical and cerebellar signs and cerebellar lesions is very good, that between metabolic and autonomic disturbances and degeneration in the hypothalamoneurohypophyseal (HNN) system of the individual sheep is less striking.<sup>2</sup> Changes in this system are remarkably similar to changes seen in animals that have undergone hypophysectomy or pituitary stalk section.<sup>12</sup> There is neuron loss in the supraoptic and paraventricular nuclei, with many of the surviving neurons containing neurosecretory material. Nerve fibers in the HNN showed degeneration (and probably regeneration) and excessive deposition of neurosecretory material confirmed as containing neurophysin by immunohistochemistry in the median eminence, in the pituitary stalk, and in the pars tuberalis. It is not usually found in normal animals.<sup>2</sup> Degeneration of this system is considered retrograde also, and reflects initial axonal damage.

### Etiology of Scrapie

The structure of the unusual infectious agent causing scrapie has defied explanation for more than four decades.<sup>13</sup> The infectious nature and resistance to formalin inactivation of the scrapie agent was shown in Scotland in the 1930s. Inadvertently, 18,000 sheep were exposed to the scrapie agent which was contained in a contaminated batch of formalin-inactivated louping ill vaccine. Two years later 1500 sheep developed scrapie in a herd that had been previously unaffected. The agent has several unusual biological properties, such as resistance to nucleases, to irradiation with ultraviolet light, and to divalent cation hydrolysis. It has physicochemical stability and an apparent lack of specific antigenicity. These properties have led to some radical re-thinking about the nature of the scrapie agent and other "slow" viruses.

Over the last 20 years attempts have been made to purify and characterize the scrapie agent but none have succeeded in purifying it to a level free from contamination.<sup>1</sup> A number of hypothetical structures have been suggested, involving every major class of macromolecules as an important component.<sup>1</sup> So far the structure has proven both unusual and difficult to define.<sup>1</sup> It has been suggested that the agent behaves as a conventional neurotropic virus.<sup>14</sup>

Further, it has been known for some years that the agent is an independent pathogen exerting control over a number of characters.<sup>15</sup> Strain variations of the agent have been demonstrated, with different incubation periods and lesion distribution.<sup>16,17</sup>

From these investigations four major hypotheses on the nature of the scrapie agent have emerged.<sup>1</sup> These include the viroid hypothesis, the virino hypothesis, the prion hypothesis, and the hypothesis in which the infectious agent is filamentous in nature and is related to the "scrapie associated fibrils" (SAF) identified by negative staining by electron microscopy.

### Conclusion

Scrapie, as one of the most studied of the subacute spongiform encephalopathies, continues to be a puzzle. Several hypotheses have been proposed for its etiology but none has yet found universal acceptance. Diagnosis of this disease is made on clinical signs and histopathological findings at necropsy.

Because there is no treatment for the disease, control consists of culling of affected animals along with familial lines. As research progresses, new insight into this disease may shed considerable light on the other spongiform encephalopathies.

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