Maedi/Visna, a slow virus disease

by

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INTRODUCTION

Maedi and Visna are slowly progressive non febrile contagious diseases of sheep.

When these diseases were first described they were thought to be two different diseases although a certain relationship was anticipated.

Further studies showed, however, that Maedi and Visna should be considered as two different syndromes involving the lung and the central nervous system respectively, caused by infection with a single agent, an ovine retrovirus.

Clinically and pathologically Maedi appears to be similar to other progressive non febrile pneumonias of sheep reported in many sheep-producing countries under various names such as: Chronic Progressive Pneumonia, Lunger Disease, la Bouhite, Zwoegerziekte, Graaf-Reinet Disease, Laikipia Lung Disease.

From the literature it appears that the first descriptions of progressive pneumonias of sheep were given by D.T. MITCHELL (1915) in South Africa and H. MARSH (1923) in Montana.

In the 1940's when Björn SIGURDSSON and his coworkers were studying the sheep diseases, Maedi, Visna, Jaagsiekte and Rida (Scrapie) of Icelandic sheep it became evident that the infective agents of these diseases were causing silent but relentlessly progressive lesions over a long period of time sometimes lasting for the better part of the normal lifespan of the host, finally always resulting in a fatal disease.

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It was thought that these slowly progressive diseases could neither be grouped as acute nor chronic diseases.

In acute infections the disease runs a rather regular course. The causative agent enters the body where it multiplies and spreads rapidly so that clinical signs appear after incubation periods of some few days to few weeks. The host's defences are thereafter mobilized, and unless death of the host has occurred the infecting agent is eliminated and convalescence begins.

Chronic infections on the other hand are not only much more protracted in their course, they are also much less regular, and unpredictable.

In order to characterize this group of the above-mentioned diseases of different origin and nature and probably others of the same kind SIGURDSSON coined the term « peculiarly slow progressive infectious diseases » (annarlega haeggengir smitsjúkdómur), often spoken of as « slow virus diseases ». He characterized such infections by the following criteria:

1) A very long initial period of latency up to several years, during which time there is an active viral proliferation and spread throughout the host in the absence of clinical signs.

2) A fairly regular protracted course after clinical signs of illness have appeared, finally ending in serious disease or death of the host.

3) Limitation of the natural infection to a single host species and localization of anatomical lesions to a single organ or tissue system (SIGURDSSON, 1954).

SIGURDSSON did, however, forecast that this last criterion would perhaps have to be modified in light of further knowledge as later has been found to be the case.

It was underlined that in « slow virus diseases » the appearance of anatomical lesions and progression of the clinical symptoms follow a set pattern, and once clinical signs of disease are recognized they progress continuously to a fatal end; contrary to a chronic disease, where the course is often irregular and unpredictable.

SIGURDSSON was first of all trying to define the interaction between the infective agent and the host in these diseases, not the character of the infective agent itself as some authors seem to maintain. The infective agents had at that time not yet been characterized. When using the word « latency » in the initial period, SIGURDSSON
was not indicating that the infective agent was latent during that period, on the contrary he emphasized as demonstrated in animal experiments that the agent was active, only the lesions it caused were developing so slowly that it took a long time before clinical signs became apparent. This also sometimes seems to have been misunderstood.

The intention of introducing the term « slow virus disease » was by no means done from the taxonomic point of view but simply to try to define the peculiar virus-host interaction of some rather important diseases.

I think time has shown that the term SIGURDSSON introduced has proven to be useful.

*Geographical occurrence*

Slowly progressive pneumonias of sheep which are pathologically similar to Maedi and characterized clinically by gradually progressing dyspnoea, emaciation and weakness have been reported in various breeds of sheep and goats.

Since the first tissue culture isolations of Maedi and Visna virus were made in Iceland 1957-1958 related viruses have been isolated from sheep in many countries, Zweegerziekte virus in Holland (DE BOER, 1970), Progressive Pneumonia in the U.S.A. (KENNEDY et al., 1968), Maedi virus in Germany, Denmark and Norway (STRAUB, 1970; HOFF-JØRGENSEN, 1971; KROGRUD, 1974) and in sheep and goats in India (HAJELA et al., 1975).

Studies of these viruses in tissue culture have shown that most of them have identical properties (THORMAR et al., 1974).

Geographically Maedi or Maedi-like pneumonias, although not all verified by virus isolation have been reported in sheep and goats in India, sheep in East and South Africa, America and many European countries. Therefore this group of Maedi-like pneumonias must be considered one of the most important sheep diseases causing unthriftiness, emaciation and sometimes heavy losses.

*Etiology and pathogenesis*

The chemical and physical properties of Maedi and Visna virus have been found to be almost identical (THORMAR, 1965). They have been classified as ovine retrovirus, and resemble the oncogenic viru-
ses. Oncogenicity of Maedi virus has never been observed in sheep nor in sheep tissue cultures.

The virus replicates in the cytoplasm of host cells and matures by budding from the cell membrane. The virion is enclosed, contains a core and is on the average 85 μ in diameter (Thormar, 1961). The virus is sensitive to chloroform and ethyl ether and is inactivated in 10 minutes by a temperature of 56° and by pH 4.2, and remains infectious outside the host for a short time only.

In the laboratory the virus grows in cultures of cells from sheep choroid plexus (Gudnadóttir and Pálsson, 1967), lungs (Kennedy et al., 1968), testes and adrenal glands (Staub, 1970), where it forms characteristic multinucleated giant cells (Sigurdardóttir and Thormar, 1964).

Although Maedi/Visna virus has been shown to multiply in bovine and human tissue cultures, there is no indication that the virus is infectious to these species (Thormar and Sigurdardóttir, 1962). In the sheep host Maedi virus is found in various organs, e.g. lung, nervous tissue, lymphoid tissue, bone marrow and leucocytes of the blood, but apparently always in low titers.

Infection with Maedi/Visna virus provokes the formation of antibodies at various times after infection, and they seem to remain detectable for years, probably throughout the lifespan of the animal.

In experimental cases neutralizing antibodies emerge usually 2-3 months after infection (Gudnadóttir and Pálsson, 1965). Complement-fixing antibodies can often be detected 3-4 weeks after infection (Gudnadóttir and Kristinsdóttir, 1967; De Boer, 1970).

Antibodies detectable by immunofluorescence have been reported both in experimental and natural cases of Maedi and Zweegerziekte (Thormar, 1969; De Boer, 1970).

Terpstra and De Boer (1973) have demonstrated precipitating antibodies in agar gel immunodiffusion test. Precipitating activity could be detected within 2 to 8 weeks after infection and appears to be more sensitive than the complement-fixation test. The use of this test in the field has been reported (Cultip et al., 1977).

It is thought that natural transmission of Maedi is by droplet infection by the respiratory route.
In the preclinical stage, Maedi is apparently rarely transmitted except from the mother to its lamb, but both colostrum and pharyngeal secretion of affected ewes can carry the virus and could play a role in early infection of lambs (De Boer, 1970; Guðnadóttir, 1974).

On common pastures communicability of Maedi appears to be low even in the clinical stage. When affected sheep are housed together with healthy ones, even for a short period, it usually results in spreading of the disease.

Although it is believed that the disease has been transmitted indirectly by feeding faecal material from diseased sheep to healthy ones indirect spread is apparently extremely rare.

Vertical transmission of Progressive Pneumonia from an infected ewe to her lamb has been reported but was apparently not confirmed by virus isolation (Cross et al., 1975).

The pathogenesis of Maedi/Visna is still poorly understood. The infection is a systemic one affecting spleen and lymph nodes, although lungs and the central nervous system are the target organs where pathological lesions are found.

The early lesions produced by Maedi/Visna virus are small infiltrates of lymphocytes and monocytes, just as produced by a number of other viruses. These cells which apparently are carrying the virus are stimulated to accumulate, gradually resulting in the characteristic lesions found in advanced cases in the lungs and the central nervous system.

The cause of the extreme slowness of Maedi/Visna disease of sheep is still obscure. And still no answer can be given to the question why the defence mechanism constantly fails to overcome the Maedi infection and eliminate the virus. By applying immunosuppression to sheep when experimentally infected with Visna virus Nathanson et al. (1976) could demonstrate suppression of the central nervous system inflammatory response, without apparent effect on virus replication.

These results indicate that the lesions of Visna are immunologically mediated.

*Clinical features (Maedi s. dyspnoea)*

In infected flocks Maedi is found only in adult animals more than 3-4 years old. The onset of the disease is very insidious.
The main clinical features are progressive loss of weight, rapid and laboured respiration which in advanced cases is aided by the accessory muscles and usually accompanied by rhythmic jerks of the head and flanks.

Dry coughing is sometimes observed, body temperature and pulse rate remain within normal range. Affected ewes often give birth to small and weak lambs. If the sheep meet with no hardship they may be expected to survive for 3-8 months after the clinical signs become apparent.

Within a flock the spread of Maedi is at first very slow and usually no losses are observed for the first five to six years after the infection has been introduced.

During the following three to four years the mortality rate in the flock increases rapidly until an annual mortality rate of 20 to 30% is reached. Affected sheep frequently succumb to a secondary bacterial pneumonia which often makes the diagnosis of Maedi difficult.

Visna s. wasting was only found in sheep more than two years of age, and only in flocks where Maedi had been prevalent for some time.

The first sign noted is that the sheep lag behind, incoordination becomes apparent when the sheep is made to trot. Despite a persisting appetite the animal looses weight. Gradually the paresis of the limbs progresses, walking becomes difficult. Tremors of the head and facial muscles are occasionally seen. Mononuclear cells of the cerebrospinal fluid are found in increased number. Paresis slowly progresses to paralysis, prostration and death (SIGURDSSON et al., 1957).

Pathological features

At necropsy overt changes found in Maedi are confined to the thoracic cavity, lungs and associated lymph nodes. The lungs are enlarged weighing in advanced cases 2-3 times more than normal lungs. Their shape remains normal but the affected tissue is of firm and fleshy consistency. The normal pinkish-red colour of a healthy sheep lung is replaced by a characteristic grayish-brown colour. The most advanced lesions are usually in the diaphragmatic lobes, and are less pronounced in the cardiac and apical lobes. A distinct borderline between healthy and affected lung tissue is never found. The lymph nodes associated with the lung are always greatly enlarged, weighing 3-5 times more than normal.
The main histopathological lesions found in advanced cases of Maedi is chronic inflammation with diffuse thickening of the interalveolar septa, sometimes leading to total obliteration of some of the alveoli. The thickening of the interalveolar septa is caused by a cellular infiltration of lymphocytes, monocytes and a few plasma cells. Often hyperplasia of smooth muscles in the interalveolar septa is observed with thickening at the opening of the alveoli into alveolar ducts. Proliferation of lymphoid tissue in the lung is usually marked (Georgsson and Palsson, 1971).

In uncomplicated cases of Visna no macroscopic lesions are found. In cases of long duration some muscular atrophy is sometimes observed.

Histopathological lesions of Visna are confined to the central nervous system, where meningeal and subependymal infiltrations consisting of lymphocytes, monocytes and some plasma cells are found. Often the infiltrations are small, but in severe cases large areas with intensive inflammation sometimes accompanied by necrosis are observed. Around these lesions extensive, perivascular cuffs of lymphocytes, monocytes and a few plasma cells are found (Sigurdsson et al., 1962; Georgsson et al., 1976).

Diagnosis

The clinical signs and post mortem findings in sheep suffering from Maedi/Visna are not pathognomonic. The diagnosis can therefore be difficult especially if lesions are restricted and the disease only little advanced, or if some concurrent unrelated infections have intervened. It is therefore very often necessary to confirm the diagnosis by positive serological tests, virus isolation and histopathological findings.

Methods of disease control

In countries where Maedi/Visna are known sheep farmers should try to avoid exposure of their healthy sheep flocks to diseased animals.

Flock additives should be carefully restricted to healthy, preferably tested flocks.

Because of the long silent preclinical period of Maedi, and the insidious onset in the flock after the infection has been introduced this can often be quite difficult. Often it has been found that Maedi
has been present in a particular flock for years, before it was noticed by the shepherd or the farmer.

When Maedi/Visna has gained foothold within a flock most sheep succumb to the disease at the age of 4 to 6 years. Males and females seem to be equally susceptible.

Sheep in affected flocks should therefore be culled before they become too old.

In some cases the clinical course of Maedi can apparently be retarded, but only for a while, by liberal feeding and careful nursing. So far no therapeutic methods tested have proved of any value.

Animals infected with Maedi/Visna virus form antibodies that seem in most cases to be detectable throughout the course of the disease. Under experimental conditions they become detectable several weeks to several months after infection. These various serological tests have been used for diagnostic purposes with encouraging results.

It is, however, still an open question whether repeated tests of animals in a particular flock and disposal of all positive reactors will, with the present technique, in the long run rid the flock of the infection.

So far, the slaughter of all animals in an infected flock is the only known method of eradicating the disease. Whether such a drastic method is feasible or not depends on the losses caused by Maedi/Visna.

Addendum

In order to illustrate the difficulties met with when dealing with «slow virus diseases» the introduction, spread and eradication of Maedi/Visna in Iceland is a good example.

Maedi/Visna was apparently introduced into Iceland in the year 1933 by an import of 20 sheep of Karakul breed, purchased from a self-contained flock in Germany where this disease was unknown.

On arrival these sheep were kept in quarantine for two months, and since apparently healthy they were sent to 14 farms in different districts of the country.

In retrospect at least two of the rams of the imported flock carried the infection of Maedi, and gave rise to two widespread epizootics in
two different parts of the country wide apart. Almost six years passed, however, before this insidious disease was diagnosed.

In spite of costly preventive measures the disease spread to more and more farms, and when the epizootics were at their peak in the year 1945, about 60% of the sheep farming districts were affected and the number of wintered sheep had declined from 700,000 to 450,000 sheep, mostly because of losses from Maedi. In individual flocks, the annual losses could reach 20-30% (GISLASON, 1966).

Sheep farming practices in Iceland were conducive to this rapid and widespread spread of Maedi/Visna. The sheep flocks are housed during the winter, and during the summer months sheep from different farms used to roam freely on common unfenced pastures in the hills.

As sheep farming became economically a hopeless task under these conditions the authorities decided to make an attempt to eradicate the disease by slaughtering all sheep on every farm within affected districts of the country and replace them with young sheep purchased in still unaffected districts. This program took, however, almost 10 years (1944-1954) to accomplish, owing to the limited number of healthy young sheep available and limited funds.

In most parts this program was carried out with success. However, in a few districts Maedi reappeared in the new stock, and again slaughtering of the flock had to be carried out but only in comparatively small districts.

The last recurrence of Maedi restricted to one farm only was in the year 1965 (FRIDRIKSSON, 1970; PÁLSSON, 1976).

Since then the country has been free of Maedi. The successful campaign against it had lasted for thirty years. More than 650,000 sheep had to be slaughtered in order to eradicate the disease from the country.

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REFERENCES


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