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Lentivirus-induced interstitial lung disease: pulmonary pathology in sheep naturally infected by the visna-maedi virus

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Summary — Visna-maedi virus is a lentivirus that causes a chronic disease in sheep affecting, among other organs, the lungs. Interstitial pneumonitis is similar to that in man associated with the infection by the human immunodeficiency virus type-1. We have compared the pathological features of lungs of sheep naturally infected with visna-maedi virus with the results obtained from bronchoalveolar lavage and virus isolation. Semi-quantitative grading of the lesions was performed on 147 sheep lungs obtained from the slaughterhouse. Seventy-seven were macroscopically and histologically normal, 39 had typical lesions of interstitial lung disease (maedi), and 13 had minor lesions of the same type. Eighteen of the affected lungs were heavily infested with parasites. Of these parasite-infected lungs, 9 showed typical maedi lesions and 4 showed minor lesions; parasite infection had no obvious effect on the development of maedi. In keeping with pathological findings, bronchoalveolar lavage disclosed an alveolitis process in the maedi lungs with increased macrophage, lymphocyte and neutrophil numbers. Cytopathic virus was detected from alveolar macrophage coculture with fibroblasts more often from maedi lungs (10/12) than from normal lungs (9/39). Electron microscopy of bronchoalveolar lavage cocultures revealed typical lentiviral particles. Animals with minor lesions may be at an early stage of the disease.

lentiviruses / visna-maedi virus / interstitial pneumonitis / progressive interstitial pneumonitis in sheep

Résumé — *Pneumonie interstitielle induite par les lentivirus. Pathologie pulmonaire chez le mouton naturellement infecté par le virus visna-maedi. Le lentivirus visna-maedi est l'agent étiologique d'une affection chronique du mouton qui atteint, entre autres organes, les poumons. Cette pneumonie interstitielle du mouton est semblable à celle associée chez l'homme à l'infection par le virus de l'immunodéficience humaine-1. Nous avons comparé les particularités histologiques des poumons*

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de moutons naturellement infectés par le virus visna-maedi avec les résultats obtenus des lavages broncho-alvéolaires et de l'isolement de virus. Une évaluation semi-quantitative des lésions a été effectuée sur 147 poumons de moutons obtenus à l'abattoir. Soixante-dix-sept poumons étaient macroscopiquement et histologiquement normaux, 39 avaient des lésions caractéristiques de pneumonie interstitielle (maedi) et 13 avaient des lésions mineures du même type. Dix-huit poumons étaient infestés de parasites de manière importante. Parmi ces poumons parasités, 9 ont montré des lésions typiques du maedi alors que 4 n'ont montré que des lésions mineures ; l'infection parasitaire n'a pas eu d'effet manifeste sur le développement du maedi. En accord avec les résultats histologiques, le lavage broncho-alvéolaire a révélé un processus d'alvéolite dans les poumons maedi avec accumulation de macrophages, lymphocytes et neutrophiles. L'effet cytopathogène du virus a été détecté par coculture des macrophages alvéolaires avec des fibroblastes plus souvent à partir de poumons maedi (10/12) que de poumons normaux (9/39). La microscopie électronique des cocultures de lavages bronchoalvéolaires a révélé des particules lentivirales caractéristiques. Les lésions mineures pourraient représenter une étape précoce de la maladie.

lentivirus / virus visna-maedi / pneumonie interstitielle / pneumonie progressive ovine

INTRODUCTION

Lentiviruses, a sub-family of retroviruses, infect a wide range of mammalian hosts, and generally induce chronic inflammatory and/or degenerative disease (for reviews, see Haase, 1986; Narayan and Clements, 1989). Several, notably the human immunodeficiency virus type-1 (HIV-1), induce an immunodeficiency syndrome. Apart from the immune system, target organs include the central nervous system, the joints, the mammary glands and the lungs. Involvement of these tissues may follow infection by HIV-1 in humans, simian immunodeficiency virus in monkeys, visna-maedi virus in sheep, caprine arthritis encephalitis virus in goats, equine infectious anemia virus in horses, bovine and feline immunodeficiency viruses in bovidae and felidae. The mechanism of lentiviral pathogenesis is not well understood at present, but persistent infection of mononuclear phagocytes is a common feature. Emphasis has been placed mainly on the mechanisms of viral persistence (Narayan and Clements, 1989) and induction of the immune dysfunction (Fauci *et al*, 1991).

All of the viruses above can cause an interstitial lung disease (for reviews, see Haase, 1986; Mornex *et al*, 1990). It is

known as 'maedi' in visna-maedi virus-infected sheep and 'lymphocytic interstitial pneumonitis' or 'non-specific interstitial pneumonitis' in HIV-1-infected humans (Solal-Celigny *et al*, 1985; Travis *et al*, 1992). The progression of the HIV-associated lesions is not yet defined. Maedi can provide a convenient model for analysis of the pathogenesis of lentivirus-induced pneumonitis, where macrophages and lymphocytes appear to play a central role (Cordier *et al*, 1990, 1992; Watt *et al*, 1992), and to study the stages of pulmonary involvement.

Although ovine progressive pneumonia (also known as maedi) was described as early as 1923 (Marsh, 1923), the typical pulmonary pathology has been studied in only limited series of naturally or experimentally infected animals (Georgsson and Palsson, 1971; Cutlip *et al*, 1979; Oliver *et al*, 1981; Lairmore *et al*, 1988). The role of parasites in the induction of disease has caused some controversy. In this context we have analysed the pulmonary pathology of a large series of slaughterhouse sheep including cases of maedi, lungworm infestation and normal animals. A proportion of the specimens were also studied by bronchoalveolar lavage and coculture for visna-maedi virus detection. The typical lesions seen in maedi are described together with minor lesions

associated with visna-maedi virus infection. Simultaneous parasite infestation has no effect on the development of the lesions.

MATERIALS AND METHODS

Sheep lungs and bronchoalveolar lavage

One-hundred-and-forty-seven lungs, with no evidence of blood inhalation or lung lesions other than maedi, except minimal parasitic infection, were obtained from freshly slaughtered sheep in 2 slaughterhouses. The slaughterhouses corresponded to 2 infection areas: one with high and one with low incidence of maedi (selected on the basis of gross pathology monitoring of the lung conducted by the *Groupement d'Intérêt Economique ovin du Sud Est*). About half of the lungs came from each area. The macroscopic appearance was recorded and bronchoalveolar lavage was always performed on the right lung. The lesions were always bilateral and equal in severity for both lungs (Georgsson and Palsson, 1971). The alveolar cells were obtained and analysed as previously described (Cordier *et al*, 1990).

Light microscopy

Three tissue blocks, collected from the outer of middle part of the left lung, were fixed in Bouin's solution, routinely processed and embedded in paraffin wax. Five- μ m sections were stained with a combination of haematoxylin, phloxin and safran. Slides were examined for the presence of parasites and maedi-related lesions. Parasites were identified in tissue sections (Li, 1946). As previously reported (Georgsson and Palsson, 1971; Cordier *et al*, 1990), the following elements were considered to contribute to the diagnosis of maedi: peribronchiolar, perivascular and/or parenchymal lymphoid nodules (with or without germinal centers), alveolitis (*ie* a luminal intra-alveolar and mural interstitial inflammatory cellular infiltrate), myomatosis, and fibrosis. The severity of the lesions were evaluated by a single examiner on a numerical scale (Olson *et al*, 1990) as follows: 0 = negative; 1 = present but minor; 2 = significant; and 3 = predominant.

Virus isolation

Alveolar cells obtained by lavage from 59 cases were co-cultured with ovine skin fibroblasts as indicator cells (ID05, obtained from Rhône Mérieux, France) as previously described (Cordier *et al*, 1990). These cells were free of mycoplasma at the time of their use. The presence of visna-maedi virus was demonstrated by the appearance after 10–30 d of co-culture of syncytia with more than 8 nuclei/cell observed after staining with May-Grunwald-Giemsa (Cordier *et al*, 1990). Cultures with no syncytia after at least 60 d of co-culture and/or 10 passages were considered negative.

Reverse transcriptase activity

The anticipated retroviral nature of the cell culture infection was investigated by measurement of reverse transcriptase activity in the supernatants of cultures with a positive cytopathic effect and of macrophages cultured alone. The assay was performed as described elsewhere (Lyon and Hupper, 1983), except that 10 mM magnesium acetate was used instead of 1 mM manganese acetate.

Transmission electron microscopy

Cells from positive co-cultures were fixed for 1 h in 2.5% glutaraldehyde in 0.1 M cacodylate buffer. After post-fixation in 1% osmium tetroxide in the same buffer, the samples were processed for epon embedding. Thin sections were stained with lead citrate and uranyl acetate and examined under an Elmiscop 102 microscope (Siemens, Germany).

Data analysis

Numerical results are expressed as mean \pm SEM. Statistical tests used were the Mann-Whitney *U* and the χ -square tests with the Statwork™ package (DataMetrics, USA) run on a Macintosh™ computer. Results were considered significant when $P < 0.05$.

RESULTS

Macroscopic appearance of lungs

Of the 147 sheep lungs examined, 93 were macroscopically normal with regard to color and ability to collapse spontaneously. Fifty-four other specimens presented as 'heavy lung' (*ie* a firm, fleshy consistency and did not collapse spontaneously). The associated tracheobronchial and mediastinal lymph nodes were regularly enlarged.

Microscopic findings

The 147 lungs studied were divided into 4 groups according to a semi-quantitative analysis of the pathological findings (table I).

The first group consisted of 77 specimens with normal histology and macroscopic appearance (fig 1).

The second group comprised 39 heavy lungs with typical histological lesions of maedi. Proliferative lymphoid follicles were present in all cases (fig 2), together with one or more of the other typical lesions:

Table I. Macroscopic aspect and semi-quantitative analysis of the pathological findings in 147 lungs.

	<i>Without parasitic infection</i>			<i>With parasitic infection</i>		
	<i>Normal</i>	<i>Maedi</i>	<i>Minor lesions</i>	<i>Normal</i>	<i>Maedi</i>	<i>Minor lesions</i>
<i>Total number</i>	77	39	13	5	9	4
<i>Macroscopic aspect</i>						
Normal	77	0	13	3	0	0
'Heavy' lung	0	39	0	2	9	4
<i>Microscopic aspect</i>						
Lymphoid nodules (grade)	0	39	12	0	9	4
(1)		(3)	(8)		(1)	(3)
(2)		(12)	(3)		(3)	(1)
(3)		(24)	(1)		(5)	(0)
Peribronchovascular nodules	0	39	7	0	4	0
Parenchymal nodules	0	17	0	0	4	0
Myomatosis (grade)	0	38	3	0	9	2
(1)		(25)	(3)		(3)	(2)
(2)		(10)	(0)		(6)	(0)
(3)		(3)	(0)		(0)	(0)
Alveolitis (grade)	0	32	3	0	6	2
(1)		(27)	(3)		(4)	(2)
(2)		(5)	(0)		(2)	(0)
(3)		(0)	(0)		(0)	(0)
Fibrosis (grade)	0	20	2	0	5	1
(1)		(19)	(2)		(3)	(0)
(2)		(1)	(0)		(2)	(0)
(3)		(0)	(0)		(0)	(1)

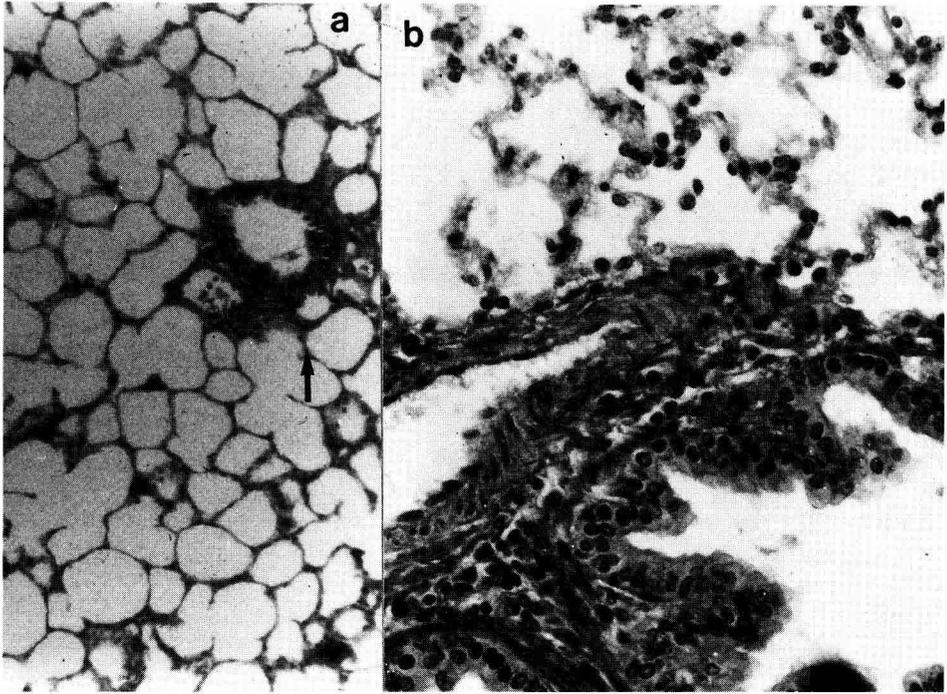


Fig 1. Light microscopic aspect of a normal sheep lung, showing peribronchovascular spaces (arrow) at low (**a**) and higher (**b**) magnification. Staining: haematoxylin, phloxin and safran. Magnification: **a** x 100; **b** x 250.

smooth muscle hyperplasia, diffuse alveolitis and fibrosis (table I). The lymphoid nodules were constantly located in peribronchiolar and perivascular sites, and in a majority of animals (37/39) had typical germinal centers. Alveolitis involved thickening of the alveolar septa by infiltration of chiefly lymphocytes and macrophages and was seen in 32 cases (fig 3). In most instances (24 cases) both mural and luminal infiltration could be seen in the sections; in only 3 cases was luminal involved, and in only 5 instances was mural alveolitis noted.

A third group was made up of 13 lungs with a normal macroscopic appearance, but which showed minor lesions on histological examination. The most frequent finding was

the presence of peribronchovascular lymphoid nodules; alveolitis, fibrosis and myomatosis were rare (table I).

Eighteen lungs had major parasitic infestation. Lungworms (*Protostrongylus rufescens* or *Muellerius capillaris*) were observed on histological examination in the small airways or in non-calcified nodules. Lungs with only minimal infestation or with calcified subpleural parasitic nodules were not included. Only 5 of these lungs had a normal histology, and 2 had the macroscopic aspect of a heavy lung. Nine specimens presented typical lesions of maedi, and all of these had the heavy lung morphology. The 4 remaining lungs had minor histological lesions and all of them were macroscopically

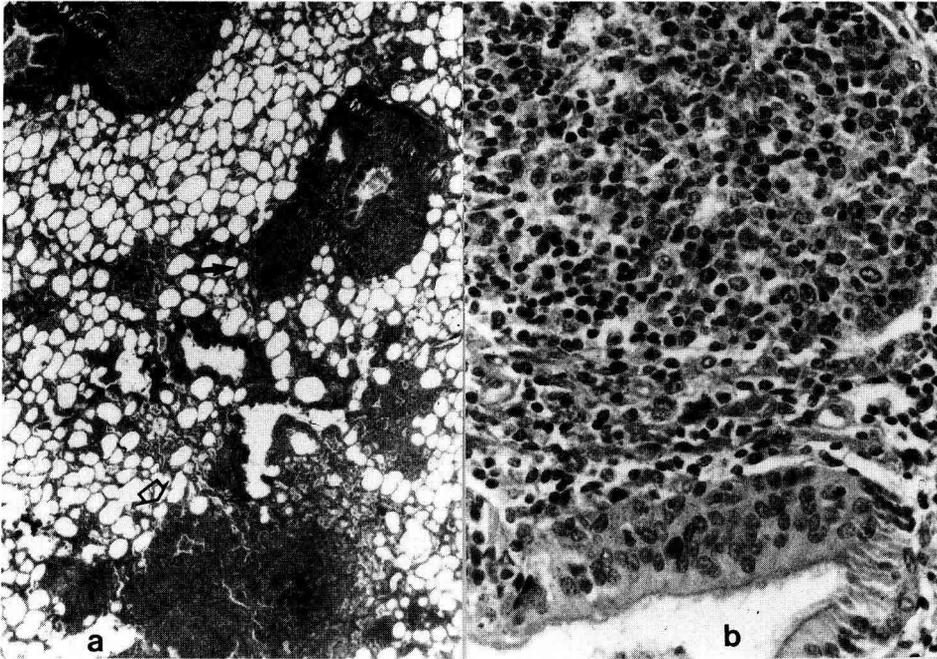


Fig 2. Lymphoid follicles in maedi. **a:** General view of peribronchovascular (arrow) and parenchymal (open arrow) lymphoid follicles. **b:** Typical peribronchial follicle with a germinal center. Staining: haematoxylin, phloxin and safran. Magnification: **a** x 25; **b** x 250.

heavy lungs. The semi-quantitative evaluation of the histological lesions indicates that the grading of the different histological parameters in the lungs with typical lesions of maedi or with minor lesions was not altered by the presence of parasitic infestation.

Assessment of luminal alveolitis

The cells recovered by bronchoalveolar lavage were analysed in a total of 75 cases from the different groups (table II). The total cell count was significantly increased over the normal range in all but one of the cases of maedi, and the alveolitis process was characterized by raised numbers of macrophages, lymphocytes and neutrophils.

In the lungs showing minor lesions, a significant increase in the number of neutrophils was the principal finding. Parasitized lungs showed an alveolitis with a notable presence of eosinophils, which were absent from the maedi lungs without major lungworm infestation. Comparison of the results of histological determination of alveolitis and of bronchoalveolar lavage for 61 specimens examined by the 2 techniques revealed a close relationship between the 2 methods (table III).

Virus detection

Bronchoalveolar lavage cells from 59 cases were co-cultured with ovine skin fibroblasts

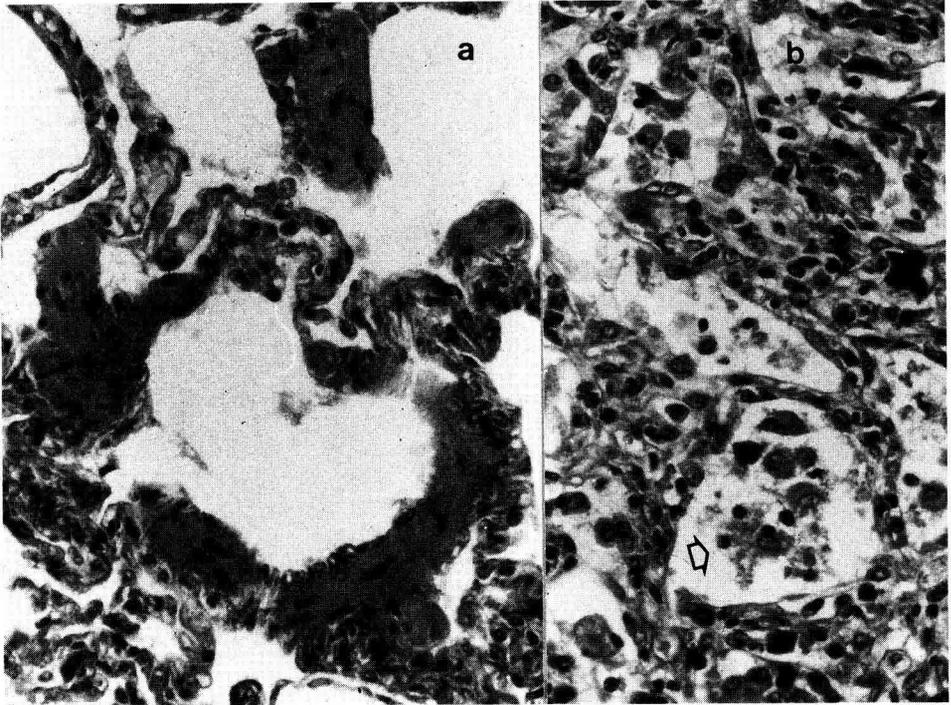


Fig 3. Light microscopic aspect of the alveolar changes observed in maedi. **a:** Thickening of the alveolar walls by smooth muscle cells (arrow). **b:** Mural and luminal alveolitis with intra-alveolar macrophages (open arrow). Staining: haematoxylin, phloxin and safran. Magnification x 250.

for the detection of visna-maedi virus. Virus was detected by syncytium formation in 24 cases. Table IV shows that virus was more often detected in cells from lungs with typical maedi lesions (10/12) than from histologically normal lungs (9/39) ($P < 0.05$). Nevertheless, 4 of the lungs with only minor lesions harbored the virus.

The nature of the virus responsible for the cytopathic effect observed on the indicator cells was further characterized by reverse transcriptase measurements and electron microscopy. Higher levels of reverse transcriptase activity were found in 12/14 (86%) of the 24 supernatants of co-cultures showing typical cytopathic effects than in supernatant from cultures of unin-

fectured indicator fibroblasts ($5.5 \pm 2.2 \times 10^4$ cpm/ml vs $1.7 \pm 0.4 \times 10^3$ cpm/ml). In another set of experiments (Cadoré *et al*, 1994), reverse transcriptase activity levels were to be found similar in the supernatant of co-cultures of alveolar macrophages and fibroblasts leading to no syncytia formation when compared to fibroblasts alone.

Cells from 10 cultures showing typical cytopathic changes and from 3 cultures which had retained a normal appearance after 60 d co-culture, were examined by electron microscopy. Typical images of lentiviruses with budding particles were observed in 8/10 positive and 0/3 negative cultures.

Table II. Results of 75 bronchoalveolar lavages expressed as cells/ μ l according to lung pathology.

<i>Lung pathology (n)</i>	<i>Total cells</i>	<i>Macrophages</i>	<i>Neutrophils</i>	<i>Lymphocytes</i>	<i>Eosinophils</i>
Normal (49)	1 222 \pm 169	1 018 \pm 138	68 \pm 25	225 \pm 37	1 \pm 1
Maedi (16)	4 456 \pm 715*	2 576 \pm 383*	561 \pm 160*	1 372 \pm 326*	0 \pm 0
Minor lesions (3)	1 313 \pm 690	1 275 \pm 494	386 \pm 265*	146 \pm 42	45 \pm 34*
Parasite (7)	3 700 \pm 1123*	2 461 \pm 984*	463 \pm 200*	537 \pm 215	583 \pm 219*

Data in maedi, minor lesions and parasite groups were each compared to the normal group and significant differences are indicated by an asterisk.

Table III. Results of bronchoalveolar lavages obtained from 61 lungs, expressed as cells/ μ l according to the presence or absence of alveolitis on lung pathology.

	<i>Lung pathology</i>	
	<i>No alveolitis</i> n = 45	<i>Alveolitis</i> n = 16
Total cells	1 841 \pm 224	4 453 \pm 827*
Macrophages	1 329 \pm 531	2 849 \pm 531*
Neutrophils	178 \pm 48	525 \pm 168*
Lymphocytes	349 \pm 67	1 315 \pm 341*
Eosinophils	77 \pm 43	24 \pm 21

Significant differences between the 2 groups are indicated by *.

DISCUSSION

Maedi, the interstitial lung disease observed in sheep naturally or experimentally infected with visna-maedi virus, is a model of tissue damage induced by lentiviruses. The present study involves a large number of animals sampled at slaughter, and enables us to assess the prevalence of the various types of pulmonary lesions. In this study, a lentivirus could regularly be isolated from bronchoalveolar lavage cells from lungs with the characteristic maedi lesions. The presence of associated pathogens, such as lungworms, did not appear to increase the severity of the typical maedi lesions. In

Table IV. Detection of a cytopathic effect in culture of bronchoalveolar lavage cells with ovine fibroblasts (ID05) according to pathology group in 59 lungs.

<i>Lung pathology</i>	<i>Positive</i>	<i>Negative</i>
Maedi	10	2
Minor lesions	4	2
Parasite infection	1	1
No pathology	9	30
Total	24	35

addition to typical cases of maedi, lentivirus could be isolated from sheep with no histological evidence of lung disease, and from sheep with minor but evocative typical lung lesions suggesting an early stage of the disease.

The typical features of maedi have been described as lymphoid hyperplasia, hyperplasia of smooth muscle cells, alveolitis and fibrosis (Marsh, 1923; Georgsson and Pals-son, 1971; Cutlip *et al*, 1979). They have been observed in the lungs of animals and humans infected by lentiviruses (Solal-Celigny *et al*, 1985; Haase, 1986; Narayan and Clements, 1989; Mornex *et al*, 1990; Travis *et al*, 1992). In the present report,

the most constant pathological finding was lymphoid hyperplasia, which was present in all cases; this feature may be considered as a hallmark of maedi. In maedi, the lymphoid tissue is organized in nodules surrounding the bronchioles and vessels, and, in all but 2 of 39 cases, the presence of germinal centers suggests a sustained immunological response which may be related to the hypergammaglobulinaemia which is observed in natural cases of ovine progressive pneumonia (Molitor *et al*, 1979). This lymphoid hyperplasia extended to the lung parenchyma in 44% of cases. The next most constant finding was hyperplasia of smooth muscle cells which was seen in all but one case, and may be considered another typical feature of the disease. The possibility of an association between maedi and lungworm infestation has been reported and the attribution of distinctive pathological lesions to either of the 2 causative agents has been the subject of controversy (Georgsson and Palsson, 1971; Cutlip *et al*, 1979; Oliver *et al*, 1981; Zink *et al*, 1990). None of the lungworms found in the present study can induce the spectrum of lesions we describe here. At the most, *Protostrongylus* or *Muellerius* sp can induce bronchiolar smooth muscle hyperplasia (Li, 1946; Georgsson and Palsson, 1971; Rose, 1973). No smooth-muscle hyperplasia was observed in lungworm-infested animals without maedi and some of these infested lungs had a normal histology. The incidence of major infestation appeared to be much higher in maedi-positive animals than in normal animals but there was no difference in the semi-quantitative evaluation of maedi-related lesions in the 9 animals where maedi was associated with major lungworm infestation and the 39 where it was not. Apart from possible sampling bias, it is conceivable that lungworms activate latent maedi, or, alternatively, that animals with maedi have decreased resistance to parasites. The incidence of parasitic infestation associated with Maedi lesions was slightly more

elevated in the lung group obtained from the area with the higher Maedi incidence.

Infection of alveolar macrophages by visna-maedi virus was demonstrated by cytopathic effect in co-cultures, in 24/59 attempts from lungs with various degrees of lesions. As indicated in previous smaller studies (Georgsson and Palsson, 1971; Cutlip *et al*, 1979; Oliver *et al*, 1981; Quérat *et al*, 1984), virus could be recovered from most frank cases of maedi. The retroviral nature of the isolate was confirmed by measurement of reverse transcriptase activity (12/14) and/or by electron microscopic identification of typical lentiviral particles (8/10).

Although the most constant feature of maedi is a lymphoid hyperplasia, visna-maedi virus replicates in cells of the monocyte-macrophage lineage and not in lymphocytes (Haase, 1986; Narayan and Clements, 1989; Gorrell *et al*, 1992). This suggests that viral replication in infected sheep initiates events leading to T and B cell proliferation, forming typical peribronchovascular lymphoid nodules with germinal centers with an accumulation of CD4 T cells (Cordier *et al*, 1992; Watt *et al*, 1992). These germinal centers may relate to the interaction of lymphocytes with dendritic cells that are infected by visna-maedi virus (Gorrell *et al*, 1992) and HIV-1 (Fox *et al*, 1991; Spiegel *et al*, 1992).

In addition to animals with typical lesions of maedi a number of cases presented lesser microscopic lesions resembling a more moderate pathology of the same type. The success of viral isolation was as high in such lungs as those with obvious maedi but virus load has not been assessed. Visna-maedi virus is a typical lentivirus, with a long lag period between infection and disease manifestation. The minor lesions, typically the presence of bronchovascular lymphoid nodules without alveolitis, might represent an early stage in the disease process or a minor form of disease (Lairmore *et al*, 1988).

An early lesion-free phase of natural infection is suggested by the isolation of virus from histologically normal lungs in this study and other reports (Cutlip *et al*, 1977; Cadore *et al*, 1994), and by the observation of numerous seropositive animals with no lung lesions (Houwens and Nauta, 1989; Ecochard *et al*, 1990; Lujan *et al*, 1991). A later step may be the recruitment and activation within the alveolar spaces of macrophages (Cordier *et al*, 1990), neutrophils (this work; Cordier *et al*, 1990, 1992) and T lymphocytes (Cordier *et al*, 1992; Watt *et al*, 1992).

In conclusion, there seem to be stages or degrees of development of visna-maedi virus-induced interstitial pneumonitis. Initially present as peribronchovascular lymphoid nodules, it progresses to an alveolitis associated with a myomatosis.

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