

Review article

Histogenesis of the pulmonary lesions in the course of visna maedi virus-induced pneumonia

JL Cadoré *, T Greenland, G Cordier, F Guiguen, JF Mornex

Laboratoire associé de recherches sur les lentivirus chez les petits ruminants, Inra and École vétérinaire de Lyon and Laboratoire d'immunologie et de biologie pulmonaire, Inserm CJF 93-08, Faculté de médecine Grange-Blanche, Université Claude-Bernard, Service de pneumologie, Hôpital Louis-Pradel, Hospices Civils de Lyon, France

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Summary — The major characteristic lesion observed following spontaneous infection of sheep by the prototype lentivirus, maedi-visna virus (MVV), is a lymphocytic interstitial pneumonia. Similar lesions may be observed with variable frequency following infection of other species by pathogenic lentiviruses, for example in children infected by HIV-1. Further, lentivirus-induced lesions involving organs other than the lungs frequently involve a comparable cellular infiltration. The cellular composition of broncho-alveolar lavage specimens from naturally- or experimentally-infected sheep has been examined with a view to describing the pathological progression of lentivirus-induced lung lesions. The naturally-infected sheep presented advanced lesions typical of 'maedi', while the experimentally-infected newborn lambs permitted the study of early lesions which we refer to as 'pre-maedi'. In both cases there was a considerable infiltration of lymphocytes, predominantly CD8+ in maedi, but with nearly equal numbers of CD4+ cells in pre-maedi. A large proportion of the alveolar lymphocytes in spontaneous maedi, but not in experimentally-infected lambs, express high levels of MHC class II antigen, suggesting an activated phenotype. Activated macrophages, the chief target cells for MVV infection, are also present at this advanced stage of the disease suggesting the involvement of mediators such as IL-8 in the cellular interactions leading to the localization of particular lymphocyte sub-populations in the pulmonary parenchyma during lentiviral disease.

visna maedi / lentivirus / pneumonitis / sheep / activated lymphocyte

* Correspondence and reprints: École vétérinaire de Lyon, 1, av Bourgelat, 69280 Marcy-l'Étoile, France

Résumé — Mécanismes des lésions pulmonaires au cours de l'infection du mouton par le virus visna maedi. *Au cours de l'infection spontanée du mouton par le prototype des lentivirus, le virus visna maedi, une pneumonie interstitielle lymphoïde représente une caractéristique lésionnelle majeure. Les lésions pulmonaires lentiviro-induites chez le mouton sont identiques à celles décrites dans d'autres espèces, en particulier l'espèce humaine au cours de l'infection par le virus de l'immunodéficience humaine de type 1 ; plus encore ces lésions sont identiques à celles retrouvées dans d'autres tissus ou organes au cours d'autres lentiviroses humaines ou animales. Afin de proposer les étapes pathogéniques de ces lésions pulmonaires lentiviro-induites, des études cytologiques du liquide de lavage bronchoalvéolaire ont été réalisées dans deux situations différentes : d'une part, l'infection spontanée du mouton par le virus visna maedi au cours de laquelle les lésions pulmonaires sont importantes et qualifiées de «maedi» ; d'autre part, l'infection expérimentale d'agneaux nouveau-nés par le virus visna maedi au cours de laquelle les lésions pulmonaires sont mineures et qualifiées de «pré-maedi». Si dans les deux situations une alvéolite lymphocytaire à fort contingent de lymphocytes ayant un phénotype CD8 dans l'infection spontanée, à contingent comparable de lymphocytes ayant un phénotype CD4 et CD8 dans l'infection expérimentale ont été montrées, une activation lymphocytaire révélée par l'expression d'antigène du complexe majeur d'histocompatibilité de type II n'a été mise en évidence qu'au cours de l'infection spontanée. L'activation lymphocytaire accompagnant l'activation macrophagique au cours de l'infection spontanée en fin d'évolution laisse penser que des médiateurs comme l'IL-8 sont des acteurs dans l'interaction entre ces deux populations cellulaires aboutissant à une compartimentation de l'infection lentivirale dans le parenchyme pulmonaire accompagnant une distribution particulière des sous-populations lymphocytaires.*

lentivirus / visna maedi / mouton / pneumonie / activation lymphocytaire

INTRODUCTION

Lymphocytic interstitial pneumonitis (LIP) may be a direct consequence of infection of patients by human immunodeficiency virus type 1, even in the absence of any opportunist infection such as pneumocystosis (Travis et al, 1992). While this manifestation may be observed in adults, it is particularly important in children born of infected mothers (Joshi et al, 1985). The interstitial lymphocytic infiltration typical of LIP is similar to that observed in other human pulmonary affections of poorly-known aetiology, such as disseminated idiopathic fibrosis and sarcoidosis.

Knowledge of the specific pulmonary pathology following lentiviral infections in other species can lead to a better understanding of the pathogenesis of the human disease. In particular, lymphoid interstitial pneumonia is the major manifestation of disease in sheep infected by the prototype lentivirus, maedi-visna virus (MVV). A study

of the development of lung lesions in these animals, and the ability to study lesions in experimentally-infected lambs suggests that it might be a useful model of the pathogenesis of lentivirus-induced pneumonia and of idiopathic interstitial pneumonia in general.

HOSTS AND TARGET CELLS OF LENTIVIRUSES

Lentiviruses constitute a genus of the retrovirus family. They are complex retroviruses whose genomes code not only for the constitutive viral genes *gag*, *pol* and *env*, but also for additional peptides which play important roles in regulating both viral and cellular gene expression. Lentiviruses have been found to infect primates, ungulates and felids in the wild and to cause permanent infection of individuals (Narayan and Clements, 1989; Narayan, 1990; Petursson et al, 1991) (table I). The consequences of infection range from mild to unapparent in

Table I. Diseases observed during spontaneous infection by lentiviruses in different species.

Virus	Species	Interstitial pneumonitis	Lesions of central nervous system	Immunodeficiency	Reference
UNGULATES					
Visna maedi virus	sheep	+	+	-	Dawson, 1988
Caprine-arthritis-encephalitis virus	goats	+	+	-	Dawson, 1988
Equine infectious anemia virus	horses	+	nd	nd	Joag et al, 1996
Bovine immunodeficiency virus	cows	nd	nd	nd	Joag et al, 1996
PRIMATES					
Human immunodeficiency virus 1	man	+	+	+	Travis et al, 1992
Human immunodeficiency virus 2	man	-	-	+	Joag et al, 1996
Simian immunodeficiency virus	monkeys	nd	+	+	Baskin et al, 1991
CARNIVORES					
Feline immunodeficiency virus	cats	+	+	+	Joag et al, 1996 Cadore et al, 1996 Hurtrel et al, 1992

+ : Observed in spontaneous disease; - : absence of lesions; nd: not determined.

some naturally-infected primates or felids, to severe and fatal disease, generally appearing after a prolonged latency. Clusters of similar viral types naturally infect some related target species, but individual isolates tend to correlate with the host species in nature. Various isolates of simian immunodeficiency virus from Old World monkeys are clearly similar, but cluster according to host species. A similar situation is observed with feline immunodeficiency virus in domestic cats and various wild felids. A curious relative of the generally mildly-pathogenic bovine immunodeficiency virus causes fulminant disease in Javanese cattle (Chadwick et al, 1995). The equine infectious anaemia virus causes severe recurrent disease in horses and related species. The ovine lentivirus, MVV, and its relative affecting goats, caprine arthritis-encephalitis virus, are widespread in some domestic small ruminant populations and can cause economically-significant disease (Pekelder et al, 1994); it usually occurs some years after viral infection, often induced by ingestion of colostrum or milk from infected dams.

All lentiviruses studied appear to be capable of infecting macrophages (Gendelman et al, 1985; Narayan, 1990), whereas only some of them infect lymphocytes (Gallo,

1990). Immunodeficiency is a striking feature of disease caused by infection by some lymphocytotropic lentiviruses, but does not feature in other infections (table II). One disease manifestation seen with variable frequency after infection by most, if not all, lentiviruses is lymphoid interstitial pneumonia. LIP occurs irrespective of whether the virus infects lymphocytes or not and is seen typically in sheep infected by visna maedi virus; sheep are thus a suitable model for a study of lentiviral lung pathogenesis (Carey and Dalziel, 1993).

LENTIVIRAL OVINE PNEUMONITIS

Small ruminants infected with lentiviruses rapidly develop a disseminated infection with virus-positive cells of the macrophage/monocyte lineage present in small numbers throughout the body. Eventual development of lesions is, however, restricted to a few target organs. The central nervous system is sometimes affected with inflammatory infiltrates and demyelination (Cork et al, 1974a,b; Cutlip et al, 1979; Narayan and Cork, 1985). Arthritis may develop in the carpal or tarsal joints with

Table II. In vivo target cells of lentiviruses.

<i>Virus</i>	<i>Lymphocytes</i>	<i>Mononuclear phagocytes</i>	<i>Glial cells</i>	<i>References</i>
Visna maedi virus	nd	+	+	Gendelmann et al, 1985
Caprine arthritis-encephalitis virus	nd	+	+	Cork et al, 1974b
Equine infectious anemia virus	nd	+	nd	Narayan, 1990
Bovine immunodeficiency virus	+	nd	nd	Joag et al, 1996
Human immunodeficiency virus 1	+	+	+	Fauci, 1988
Human immunodeficiency virus 2	+	+	nd	Joag et al, 1996
Simian immunodeficiency virus	+	+	nd	Joag et al, 1996
Feline immunodeficiency virus	+	+	+	Joag et al, 1996

+: Demonstration in vivo; nd: not determined.

infiltration of the synovium (Dawson, 1988), and mammary lesions, often with frank mastitis, are not unusual (Houwens et al, 1988; Lujan et al, 1993). The most typical lesions are seen in the lungs (Dawson, 1987, 1988; Lujan et al, 1991; Watt et al, 1992; Brodie et al, 1992) and progressively lead to debilitating disease with severe respiratory dysfunction called 'maedi' or ovine progressive pneumonia (Marsh, 1923; Sigurdsson et al, 1952).

Macroscopically the lungs are swollen, dense and firm to the touch. They are greyish brown in colour and do not deflate on opening the thoracic cavity. The mediastinal and tracheo-bronchial lymph nodes are grossly enlarged (Sigurdsson et al, 1952; Georgson and Palsson, 1971; Dawson, 1987). Microscopically, there is a constant thickening of the alveolar septa due to an infiltration of mononuclear leukocytes (lymphocytes and macrophages), causing mural alveolitis and leading in some instances to the obliteration of the alveolar space. Macrophages may be seen to accumulate within open alveoli, sometimes fused into di- or trinucleated cells, but with no true giant multinucleated cells. Zones of smooth muscle hyperplasia, chiefly around the broncho-alveolar axes, and spreading into the adjacent septa, are frequently present, but there is usually only little fibrosis with sparse fibroblasts and collagen fibers. A considerable proliferation of lymphoid cells is regularly seen, both as unstructured septal infiltrates and as structured nodules, typically in peribronchial and perivascular connective tissue and in the parenchyma. While similar nodules may be observed after parasitic infection, their abundance and wide dissemination is typical of the maedi lung. The alveolar epithelium may become cuboid in zones of major thickening and fibrosis of the septa, and the bronchial epithelium is often hyperplastic with mucoid metaplasia of the goblet cells sometimes becoming adenomatous. Similar lesions may be observed

to a greater or lesser degree in the lungs of human (White and Matthay, 1989), feline (Cadoré et al, 1996) or equine victims of infection by the corresponding lentiviruses (Mornex et al, 1990).

Although these lesions are common to many lentiviral infections, the mechanism by which the virus induces the pathological changes is not obvious. In lungs with frank maedi lesions, only a small number of alveolar macrophages show the presence of replicating virus. Lentiviral infections, even those which do not induce immunodeficiency, are commonly associated with opportunistic infections which may well contribute to pathogenesis. Early lesions can give useful clues as to the disease process, and lungs of naturally-infected sheep that do not show the typical pattern of full-blown maedi can present discrete characteristic lesions.

PRE-MAEDI LESIONS

In a series of 147 lungs sampled from slaughterhouses and biased towards maedi-infected animals (Mornex et al, 1994), there were 39 lungs with typical maedi histology, 77 normal lungs and 13 with minor lesions, most frequently including peribronchovascular lymphoid nodules sometimes associated with myomatosis or luminal alveolitis. Virus could be recovered from the lungs with minor lesions as often as from lungs with typical maedi, so the alterations were considered to be specific and termed 'pre-maedi'. Signs of other respiratory infections were uncommon.

Attempts have been made to induce early lesions under controlled conditions by the experimental infection of newborn lambs (Cadoré et al, 1994). Intratracheal injection of a suspension of virus obtained by low-passage culture of recent isolates into colostrum-deprived newborn lambs from seronegative dams is similar to natural infec-

tion by the oral and respiratory route. In previous experiments (Lairmore et al, 1986, 1988a) the infected lambs, but not the controls, developed clinical symptoms of a cough and weight loss some 3 weeks post infection; anatomo-pathological examination of animals sacrificed at various times post infection showed the sequential development of typical lesions of 'pre-maedi' with peribronchovascular lymphoid infiltration preceding the development of pneumonia. The severity of the lesions correlated well with the intensity of the clinical symptoms. In a similar way, the lesions typical of 'pre-maedi' have been reproduced in inoculated lambs (Cadoré et al, 1994). After 12 weeks the infected lambs showed peribronchovascular lymphoid nodules (50%), mural alveolitis (30%), myomatosis (25%) and lymphoid nodules in the mediastinal lymph nodes (50%). Although the lesions were not of sufficient intensity to be qualified as maedi, tomodensitometric scans showed that identifiable macroscopic lesions were present.

CELLULAR INTERACTIONS IN PATHOGENESIS OF MAEDI

The relatively important functional and histological consequences of an infection, which appears to involve only a minority of the local cells, implies an indirect pathogenic mechanism. One clue to the process is provided by the observation that, while only few alveolar macrophages recovered by broncho-alveolar lavage of infected lungs produce the virus, most of them appear to be activated (Cordier et al, 1990). These cells, which express high levels of MHC class II antigens, liberate several potent mediators such as fibronectin into the supernatant on maintenance culture. They also produce interleukin 8 (IL-8), a chemokine capable of attracting both lymphocytes and neutrophils to the alveoli and so contributing to the alveolitis (Larssen et al, 1989).

The lymphocyte populations in the broncho-alveolar lavage of maedi lungs show a progressive diminution in the CD4+/CD8+ ratio as the disease progresses (Cordier et al, 1992). Differential cell counts suggest that the absolute number of CD4+ cells remains essentially unchanged while CD8+ cells increase dramatically in the late stages of the disease. Infiltration of CD8+ T lymphocytes also characterizes lentiviral lesions in other tissues such as joints and the mammary glands (Kennedy-Stoskopf et al, 1989; Harkiss et al, 1991; Torsteindottir et al, 1992; Demartini et al, 1993). These cells typically comprise cytotoxic lymphocytes, but it is not known what proportion of them may be responding specifically to virus-associated antigens. Within the lung tissues, the lymphoid nodules contain a large proportion of CD4+ cells and relatively few CD8+ lymphocytes, whereas the parenchyma contains predominantly CD8+ cells (Cordier et al, 1992). B Lymphocytes are present in the central portions of some nodules. A large proportion of the T lymphocytes in broncho-alveolar lavage specimens express MHC class II antigens which are not normally expressed by unactivated ovine T cells (Cordier et al, 1990). If these cells are truly activated, they may produce interferon- γ (IFN γ) (Becker, 1985; Lairmore et al, 1988b) and so contribute to the macrophage activation observed. Although some clones of T lymphocytes may be specifically activated through contact with virus-associated antigens, this is unlikely to be the case for all of them. Cytokines secreted by the macrophages present could account for much of the T cell activation, and compose a runaway feedback cycle where each cell type is responsible for maintaining the activated state of the other.

CONCLUSION

A progression can be envisaged leading from 'pre-maedi' in the newly-infected animal

through to the stage of full-blown maedi by a cascade of cellular events. Initially, broncho-alveolar lavage of experimentally-infected animals shows a minor lymphocytic alveolitis with a normal CD4+/CD8+ ratio. The T cells are not activated, in that they express no more class II antigen than cells from control lambs (Cadoré et al, 1994). However, even at this early stage, alveolar macrophages are present, some of which are actively infected and secrete chemotactic molecules capable of initiating the lymphocytic and neutrophilic alveolitis (Lena et al, 1994). The alveolar lymphocyte subpopulations appear normally to exist in dynamic equilibrium with the cells within the lung tissue. Under the influence of the viral infection, this equilibrium progressively shifts to an increase in alveolar CD8+ cells, activation of many alveolar lymphocytes, a build-up of CD8+ cells in the parenchyma, and the formation of fully-structured nodules rich in CD4+ cells. Some other cell types may enter into the process, notably in the formation of non-lymphoid lesions; in vitro experiments show ovine smooth muscle cells to be capable of supporting visna maedi virus replication (Leroux et al, 1995).

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REFERENCES

- Baskin GB, Murphey-Corb M, Martin LN, Soikek KF, Hu FS, Kuebler D (1991) Lentivirus-induced pulmonary lesions in Rhesus monkeys (*Macaca mulatta*) infected with simian immunodeficiency virus. *Vet Pathol* 28, 506-515
- Becker S (1985) Interferon- γ accelerates immune proliferation via its effect on monocyte HLA-DR expression. *Cell Immunol* 91, 301-307
- Brodie SJ, Marcom KA, Pearson LD et al (1992) Effects of virus load in the pathogenesis of lentivirus-induced lymphoid interstitial pneumonia. *J Infect Dis* 166, 531-541
- Cadoré JL, Guiguen F, Cordier G et al (1994) Early events in the experimental interstitial lung disease induced in sheep by the visna-maedi virus. *Immunol Lett* 39, 39-43
- Cadoré JL, Loire R, Steiner-Laurent S et al (1996) *Res Vet Sci (in press)*
- Carey N, Dalziel RG (1993) The biology of maedi-visna virus – an overview. *Br Vet J* 149, 437-454
- Chadwick BJ, Coelen RJ, Wilcox GE, Sammels LM, Kertayadnya G (1995) Nucleotide sequence analysis of Jembrana disease virus: a bovine lentivirus associated with an acute disease syndrome. *J Gen Virol* 76, 1637-1650
- Cordier G, Cozon G, Greenland T et al (1990) In vivo activation of alveolar macrophages in ovine lentivirus infection. *Clin Immunol Immunopathol* 55, 355-367
- Cordier G, Guiguen F, Cadoré JL, Cozon G, Jacquier MF, Mornex JF (1992) Characterization of the lymphocytic alveolitis in visna-maedi virus-induced interstitial lung disease of sheep. *Clin Exp Immunol* 90, 18-24
- Cork LC, Hadlow WJ, Crawford TB, Gorham JR, Piper RC (1974a) Infectious leucoencephalomyelitis of young goats. *J Infect Dis* 129, 134-141
- Cork LC, Hadlow WJ, Gorham JR, Piper RC, Crawford TB (1974b) Pathology of virus leucoencephalomyelitis of goats. *Acta Neuropathol* 29, 281-292
- Cutlip R, Jackson T, Lehmkuhl H (1979) Lesions of ovine progressive pneumonia. Interstitial pneumonitis and encephalitis. *Am J Vet Res* 40, 1370-1374
- Dawson M (1987) Pathogenesis of maedi-visna. *Vet Rec* 20, 451-454
- Dawson M (1988) Lentivirus diseases of domesticated animals. *J Comp Pathol* 99, 401-419
- Demartini JC, Brodie SJ, De La Concha-Bermejillo A, Ellis JA, Lairmore MD (1993) Pathogenesis of lymphoid interstitial pneumonia in natural and experimental ovine lentivirus infection. *Clin Infect Dis* 17 (Suppl 1), S236-242
- Fauci AS (1988) The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. *Science* 239, 617-622
- Gallo RC (1990) Mechanisms of disease induction by HIV. *J AIDS* 3, 380-389
- Gendelman HE, Narayan O, Molineaux S, Clements JS, Ghotbi Z (1985) Slow persistent replication of lentiviruses: role of tissue macrophages and macrophage-precursors in bone marrow. *Proc Natl Acad Sci USA* 82, 7086-7090
- Georgsson G, Pålsson PA (1971) The histopathology of maedi. *Vet Pathol* 8, 63-80
- Harkis GD, Watt NJ, King TJ, Williams J, Hopkins J (1991) Retroviral arthritis: Phenotypic analysis of

- cells in the synovial fluid of sheep with inflammatory synovitis associated with visna virus infection. *Clin Immunol Immunopathol* 60, 106-117
- Houwens DJ, Pekelder JJ, Akkermans JW, Van Der Molen EJ, Schreuder BE (1988) Incidence of indurative lymphocytic mastitis in a flock of sheep infected with mædi-visna virus. *Vet Rec* 122, 435-437
- Hurtrel M, Ganière JP, Guelfi JF *et al* (1992). Comparison of early and late feline immunodeficiency virus encephalopathies. *AIDS* 6, 399-406
- Joag SV, Stephens EB, Narayan O (1996) Lentiviruses. In: *Virology Fields* (PM Knipe, DM Howley *et al*, eds), 3rd edition, Raven, Philadelphia, 1977-1995
- Joshi V, Oleske J, Minnefor B *et al* (1985) Pathologic pulmonary findings in children with acquired immunodeficiency syndrome: a study of ten cases. *Hum Pathol* 16, 241-246
- Kennedy-Stoskopf S, Zink MC, Narayan O (1989) Pathogenesis of ovine lentivirus-induced arthritis: phenotypic evaluation of T lymphocytes in synovial fluid, synovium, and peripheral circulation. *Clin Immunol Immunopathol* 52, 323-330
- Lairmore MD, Rosadio RH, DeMartini JC (1986) Ovine lentivirus lymphoid interstitial pneumonia: rapid induction in neonatal lambs. *Am J Pathol* 125, 173-181
- Lairmore MD, Poulson JM, Adducci TA, DeMartini JC (1988a) Lentivirus-induced lymphoproliferative disease. Comparative pathogenicity of phenotypically distinct ovine lentivirus strains. *Am J Pathol* 130, 80-90
- Lairmore MD, Butera ST, Callahan GN, DeMartini JC (1988b) Spontaneous interferon production by pulmonary leukocytes is associated with lentivirus-induced lymphoid interstitial pneumonia. *J Immunol* 140, 779-785
- Larsen CG, Anderson AO, Appella E, Oppenheim JJ, Matsushima K (1989) The neutrophil-activating protein (NAP-1) is also chemotactic for T lymphocytes. *Science* 243, 1464-1466
- Lena P, Freyria AM, Lyon M *et al* (1994) Increased expression of tissue factor mRNA and procoagulant activity in ovine lentivirus-infected alveolar macrophages. *Res Virol* 145, 209-214
- Leroux C, Cordier G, Mercier I *et al* (1995) Ovine aortic smooth muscle cells allow the replication of visna mædi *in vitro*. *Arch Virol* 140, 1-11
- Lujan L, Garcia Marin JF, Fernandez de Luco D, Vargas A, Badiola JJ (1991) Pathological changes in the lungs and mammary glands of sheep and their relationship with mædi-visna infection. *Vet Rec* 129, 51-54
- Lujan L, Begara I, Collie DDS, Watt NJ (1993) Phenotypic analysis of cells in bronchoalveolar lavage fluid and peripheral blood of mædi visna-infected sheep. *Clin Exp Immunol* 91, 272-276
- Marsh H (1923) Progressive pneumonia in sheep. *J Am Vet Med Assoc* 15, 458-473
- Mornex JF, Ecochard D, Greenland T *et al* (1990) Diffuse interstitial pneumonias due to lentivirus infection in man (HIV-1) and animals. *Rev Mal Resp* 7, 517-528
- Mornex JF, Lena P, Loire R *et al* (1994) Lentivirus-induced interstitial lung disease: pulmonary pathology in sheep spontaneously infected by the visna-mædi virus. *Vet Res* 25, 478-488
- Narayan O, Cork LC (1985) Lentiviral diseases of sheep and goats: chronic pneumonia leukoencephalitis and arthritis. *Rev Infect Dis* 7, 89-98
- Narayan O, Clements JE (1989) Biology and pathogenesis of lentiviruses. *J Gen Virol* 70, 1617-1639
- Narayan O (1990) Immunopathology of lentiviral infections in ungulate animals. *Curr Opin Immunol* 2, 399-402
- Pekelder JJ, Veenink GJ, Akkermans JP, Van Eldik P, Elving L, Houwers DJ (1994) Ovine lentivirus induced indurative lymphocytic mastitis and its effect on the growth of lambs. *Vet Rec* 134, 348-350
- Petursson G, Andresdottir V, Andresson O, Torsteindottir S, Georgsson G, Pálsson PA (1991) Human and ovine lentiviral infections compared. *Comp Immunol Microbiol Infect Dis* 14, 277-287
- Sigurðsson B, Grimsson H, Pálsson PA (1952) Mædi, a chronic progressive infection of sheep's lungs. *J Infect Dis* 90, 233-241
- Torsteindottir S, Georgsson G, Gisladdottir E, Rafnar B, Pálsson PA, Petursson G (1992) Pathogenesis of central nervous system lesions in visna: cell-mediated immunity and lymphocytes subsets in blood, brain and cerebrospinal fluid. *J Neuroimmunol* 41, 149-158
- Travis WD, Devaney KO, Weiss LM *et al* (1992) Lymphoid pneumonitis in 50 adult patients infected with the human immunodeficiency virus: lymphocytic interstitial pneumonitis versus nonspecific interstitial pneumonitis. *Hum Pathol* 23, 529-541
- Watt NJ, King TJ, Collie D, McIntyre N, Sargan D, McConnel I (1992) Clinicopathological investigation of primary, uncomplicated mædi-visna virus infection. *Vet Rec* 131, 455-461
- White DA, Matthay RA (1989) Non infectious pulmonary complications of infection with the human immunodeficiency virus. *Am Rev Respir Dis* 140, 1763-1787