Pathological Features of Lymphoid Tissues in Cats with Natural Feline Immunodeficiency Virus Infection

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Summary

A range of tissues from a total of 17 cats naturally infected with the feline immunodeficiency virus was examined histologically. In 11 cases, chronic inflammatory lesions were present in various tissues including, most commonly, the intestine, brain and lung. Extensive inflammation in the intestinal wall was present in seven of the cats. No particular bacterial organisms were demonstrated in these inflammatory lesions. A range of changes was present in the lymph nodes, including hyperplasia, atrophy or a mixed pattern. Erythrophagocytosis was a consistent feature. The changes resembled those reported in human acquired immunodeficiency syndrome as a result of infection with human immunodeficiency virus.

Introduction

Human immunodeficiency virus (HIV) has been recognized as the cause of the acquired immunodeficiency syndrome (AIDS). The earlier manifestations of HIV infection, collectively known as the AIDS-related complex (ARC), include lymphadenopathy, fever, weight loss and diarrhoea, but the eventual outcome in most, if not all, cases of HIV infection is a profound depression of cell-mediated immunity leading to full-blown AIDS (Millard, 1984). This syndrome is characterized by the development of multiple unusual opportunistic infections and uncommon tumours, particularly Kaposi's sarcoma (Waisman, Rotterdam, Niedt, Lewin and Racz, 1987).

An AIDS-like disease, with lymphadenopathy, profound T lymphocyte dysfunction and the development of opportunistic infections occurs in macaques infected with another similar T lymphocytotropic virus—Simian immunodeficiency virus (SIV) (Letvin, Daniel, Sehgal, Desrosiers, Hunt, Waldron, MacKay, Smidt, Chalifoux and King, 1985).

Feline immunodeficiency virus (FIV) was first reported in America in 1987 by Pedersen, Ho, Brown and Yamamoto and in the United Kingdom in 1988 by Harbour, Williams, Gruffydd-Jones, Burbridge and Pearson. Subsequent epidemiological studies have shown that FIV infection is not uncommon in the British cat population (Hosie, Robertson and Jarrett, 1989). Studies at the University of Bristol Veterinary School have shown that, while a small proportion of FIV-infected cats are clinically normal or have minor problems, the majority are diseased (Hopper, Sparkes, Gruffydd-Jones, Crispin, Muir,

Harbour and Stokes, 1989). A recent survey in Japan showed that only 10 per cent of FIV-infected cats were healthy (Ishida, Washizu, Toriyabe and Motoyoshi, 1988). The clinical signs of FIV have been described in a series of 46 cases referred to the University of Bristol Veterinary School (Hopper *et al.*, 1989); chronic or recurrent problems such as gingivitis, rhinitis and diarrhoea were common in these cats.

This report describes the post-mortem findings in 17 FIV-infected cats. Thirteen infected cats were killed as a result of chronic disease and two because they were considered by the owner to be a risk to other in-contact cats. One died unexpectedly without showing signs of illness and another was killed in a road traffic accident.

Pathological changes were detected in a range of tissues and the changes in the lymphoid tissues in particular are compared with the changes reported in AIDS in man.

Materials and Methods

Animals

Details of age, breed and sex of the 17 cats are shown in Table 1.

FIV Status

FIV infection was diagnosed either by virus isolation (Harbour *et al.*, 1988) or by demonstration of antibody to FIV with a commercially available ELISA kit (Petcheck FTLV; Idexx Corporation, Portland, Maine, U.S.A.). Sera from 15 cats were tested for feline leukaemia virus (FeLV) antigen by an ELISA method (Leukassay F-II; C-Vet). The results of virus isolation and serology are given in Table 1.

Clinical Features

Details of major clinical signs (if any) reported in the cats are shown in Table 1. Those most commonly present included weight loss (11 of 17) and diarrhoea (7 of 17); gingivitis/stomatitis (4 of 17) and nervous signs (3 of 17) were less frequent. The most frequent haematological abnormalities were leucopenia and/or neutropenia (6 of 17) and anaemia (4 of 17).

Pathology

Five of the 17 cats were humanely killed by the referring veterinary surgeon and selected tissues only were submitted for histological examination. In the remaining 12 cats, a complete post-mortem examination was carried out at the University of Bristol Veterinary School; a range of tissues from major systems was examined histologically—salivary gland, oesophagus, stomach, small intestine, large intestine, liver, pancreas, trachea, lung, heart, kidney, bladder, adrenal, thyroid, brain, spinal cord, skeletal muscle, tonsil, spleen and lymph nodes (submaxillary, retropharyngeal, prescapular, mesenteric and popliteal).

The tissues were fixed in 10 per cent neutral buffered formalin, routinely processed and embedded in paraffin wax. Sections were stained with haematoxylin and eosin (HE). Sections of selected tissues were also stained with Gram, Ziehl-Nielsen (ZN) and Periodic acid-Schiff and for reticulin fibres.

Table 1
Age, sex, breed, serology and clinical signs in 17 FIV-infected cats

| Cat | Age (yrs) | Sex | Breed | FIV isolation | Serology | | Diarrhoea | Wt loss | Clinical signs | | Neutro/ | Others |
					FIV	FeLV			Nervous signs	Anaemia	leucopenia	
1	9	FN	DSH	+	+	–	–	+	+	–	+	–
2	7	FN	DSH	+	+	–	+	+	–	+	+	FIA
3	9	FN	DSH	+	+	–	–	+	–	–	–	Abdominal mass
4	4	MN	DSH	+	+	–	+	+	–	–	+	Gingivitis
5	9	FN	DSH	+	ND	ND	–	+	–	–	+	Nasal discharge, cough, sneezing
6	?	MN	DSH	ND	+	–	–	–	+	ND	ND	Gingivitis, pyrexia
7	?6	MN	DSH	+	+	–	+	–	–	–	–	Lymphadenopathy
8	10	MN	DSH	+	+	ND	–	–	–	ND	ND	Malaise
9	6	MN	DSH	+	+	–	+	+	–	–	–	Stomatitis
10	?4/5	M	Siamese	ND	+	–	+	+	–	+	–	Vomiting, pharyngitis
11	?6/8	FN	DSH	+	+	–	+	+	–	+	+	Pyrexia
12	4	MN	DSH	+	+	–	+	+	+	ND	ND	–
13	11	MN	DSH	ND	+	–	–	–	–	–	–	–
14	10	MN	Persian	ND	+	–	–	+	–	+	+	Gingivitis, pyrexia
15	9	FN	DSH	ND	+	–	–	–	–	–	–	Road traffic accident
16	12	MN	DSH	+	+	–	–	+	–	–	–	Keratitis, pyrexia, malaena
17	13	MN	DSH	ND	+	–	–	–	–	–	–	Dermatitis, lymphadenopathy

+/– feature present or absent; ? unknown or doubtful; ND not done.
Sex: FN—Female neutered; MN—Male neutered. Breed: DSH—Domestic short haired.
Virus serology: FIV—Feline immunodeficiency virus; FeLV—Feline leukaemia virus.
FIA—Feline infectious anaemia (*Haemobartonella felis* infection).

Results

Macroscopic and Histological Lesions in Non-lymphoid Tissues

Non-lymphoid tissues in which lesions were noted included the intestine, brain, lung, liver and oral cavity.

In four cats there were macroscopic lesions in the small intestine (cats 3 and 9) or large intestine (cats 2 and 4), with ill-defined areas (up to 5 cm long in the small intestine) of thickening (up to 0·5 cm) of the wall of the intestine by soft, fawn tissue. There was patchy reddening and erosion or ulceration of the mucosal surfaces in areas of thickening. In these cats, and in three others (cats 1, 12 and 13) which were grossly normal, there was, histologically, extensive infiltration by a mixture of chronic inflammatory cells including lymphoid, plasmacytic and histiocytic cells. In many areas, the inflammation extended throughout the thickness of the wall of the intestine to include the muscle layers. In one cat (12) a group of histiocytic and lymphoid cells, with occasional mitoses in the submucosa of the colon, probably represented replacement of a normal colonic lymphoid nodule, rather than a localized area of colitis.

Gross lesions affecting the central nervous system were noted in only one cat (13): a small, soft tissue mass within the cranial cavity adjacent to the right tympanic bulla and extending through the orbital fissure and around the optic nerve. Histological examination revealed this mass to be made up of a mixture of histiocytic, lymphoid and plasma cells. There were many mitoses, but the tissue appeared to be inflammatory rather than neoplastic. In three other cats (1, 3 and 9), there was a non-suppurative meningoencephalitis with areas of perivascular and meningeal infiltration by lymphoid and plasma cells.

Macroscopic lesions were noted in the respiratory system of four cats (5, 14, 15 and 16). In cat 15, which died of a road traffic accident, there was haemothorax associated with a ruptured diaphragm and haemoperitoneum. In cats 5 and 14, there was patchy pleural thickening and lung consolidation. In cat 16, a 1·5 cm diameter lozenge-shaped mass of red/fawn tissue was present in the left caudal lung lobe. The lesions in cats 5 and 16 were characterized histologically by infiltration by lymphoid and histiocytic cells, interstitial fibrosis and alveolar epithelial hyperplasia. In cat 14, there was a pneumonia associated with larvae and eggs of *Aeleurostrongylus abstrusus*. In cat 3, histological examination revealed pulmonary arterial muscle hypertrophy typical of the result of infection with *A. abstrusus*. In cat 1, histological examination revealed scattered foci of necrosis suggestive of micro-infarcts, but no thrombi were seen in vessels in the lung or elsewhere.

In only two cats (5 and 15) was the liver grossly abnormal. In cat 5 it contained an irregular friable mass of red/brown tissue within one lobe which was, histologically, a myelolipoma and was considered to be an incidental finding. Cat 15 died after a road traffic accident and there were several tears in the liver and haemorrhage into the abdomen. In sections of liver from five other cats (1, 3, 4, 9 and 17) there were areas of infiltration by a mixture of lymphoid, plasmacytic and histiocytic cells. In three of the cats, only scattered

foci were present while in the other two cats the cellular infiltrate was more extensive, particularly in periportal areas.

Degrees of stomatitis or gingivitis were present in four cats. The lesions were characterized histologically by infiltration by variable numbers of lymphoid, plasmacytic and histiocytic cells. The oral lesions were particularly severe in two cats (4 and 9). In cat 9, the kidneys were small, firm and irregular with narrowed cortices and the oral ulceration could well have been a result of chronic renal failure. In three other cats (6, 7 and 17) scattered foci of infiltration of the kidney by small groups of lymphoid and plasma cells was considered to be an incidental finding; such lesions are not uncommon in older cats.

Description of Lymphoid Tissue Lesions in Spleen, Tonsils or Lymph Node

Macroscopically, lymphoid tissue changes included enlargement and atrophy. In six cats (1, 4, 7, 10, 13 and 17) lymph nodes were enlarged and in three cats (2, 11 and 16) lymph nodes were small. In eight cats (3, 5, 6, 8, 9, 12, 14 and 15) the lymph nodes were not grossly abnormal but there were marked histological abnormalities. Generally, changes were similar in all lymph nodes. Those draining sites of chronic inflammation, for example the retropharyngeal lymph nodes in cats with gingivitis and the mesenteric lymph nodes in cats with chronic enteritis, tended to be enlarged. The histological changes in follicles were essentially similar in different nodes.

Histological lesions in lymph nodes included changes in the capsule, the sinuses, follicles and extrafollicular lymphoid tissues. Lymph node follicular changes were generally associated with similar changes in follicles of tonsils and in the periarteriolar lymphoid sheaths of the spleen.

Three main patterns of lymphoid tissue changes were recognized which reflected similar patterns reported in HIV infection in man (Racz, Tenner-Racz, Kahl, Feller, Kern and Dietric, 1986; Diebold, Audouin and Le Tonneau, 1988). These were: (1) follicular hyperplasia; (2) follicular involution; and (3) a mixture of hyperplasia and involution in the same lymph node.

In the present study three cats showed changes of follicular hyperplasia and in five cats there was a mixture of hyperplasia and involution. In the other nine cats there was a range of follicular involution and lymphoid depletion (Table 2).

Follicular Hyperplasia. In the three cats (1, 4 and 7) in which hyperplasia was the only follicular change, the lymph nodes were recognized grossly as being enlarged. The lymph node capsule was normal or sometimes slightly thickened by fibrous tissue and contained occasional scattered mononuclear immunoblastic lymphoid and reticular cells.

The cortical sinuses were hypercellular with a mixture of lymphoid and histiocytic cells and occasional neutrophils; erythrophagocytosis was often present. Germinal centres were enlarged (Fig. 1), and in some cases occupied most of the thickness of the cortex and extended into the medulla. Germinal centres retained polarity but the marginal zones were often attenuated or
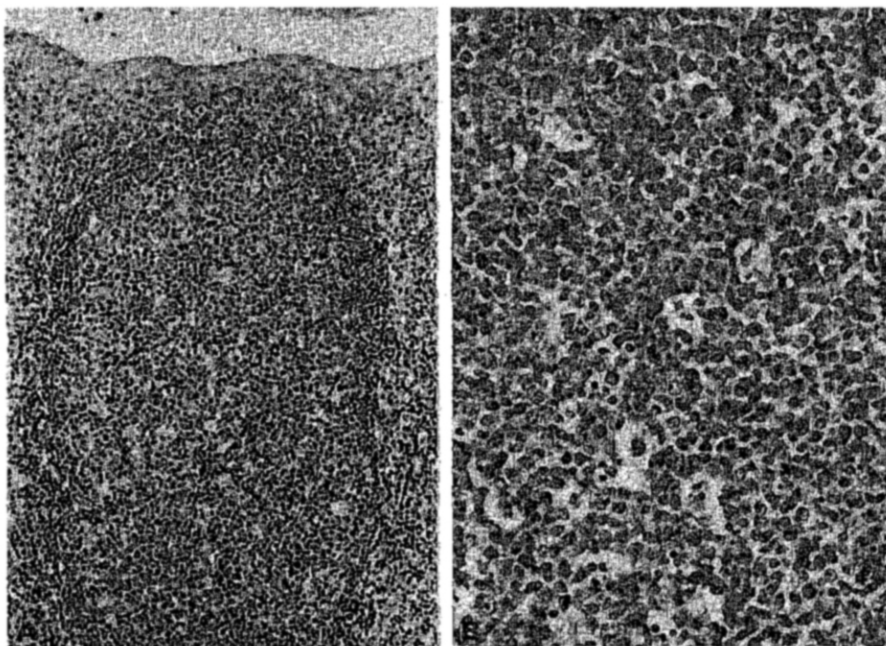
Fig. 1.   Hyperplastic germinal centre in lymph node of an FIV-infected cat. HE (A) × 75, (B) × 225.

disrupted. Many tingible body macrophages and, sometimes, epithelioid macrophages were present in the germinal centres and there was a high mitotic rate and evidence of lymphocytolysis. In extrafollicular lymphoid tissue, medullary cords contained a mixture of cells including some plasma cells. Medullary sinuses contained variable numbers of lymphoblastic cells and histiocytes; there was widespread erythrophagocytosis and variable numbers of macrophages containing haemosiderin were present.

Mixed Hyperplasia and Involution.   In five cats, hyperplastic follicles, as described above were present together with involuted follicles as described below. In three of the cats (10, 13 and 17) the lymph nodes were recognized as being enlarged. In the other two cats (12 and 15) the lymph nodes were grossly normal.

Follicular Involution.   In three of the nine cats with follicular involution, the lymph nodes were grossly smaller than normal (2, 11 and 16). In the other six cats (3, 5, 6, 8, 9 and 14) they were normal. The lymph node capsule was generally normal or, in some cases, slightly thickened with a scattered mixed cellular infiltrate. Cortical sinuses were mostly rather collapsed and empty but in some cats there was a moderate histiocytosis and some erythrophagocytosis. Follicles varied in appearance. Some were small and indistinct without evidence of germinal centre formation (Fig. 2). Other follicles contained aggregates of hyaline eosinophilic material, and contained only a few cells,
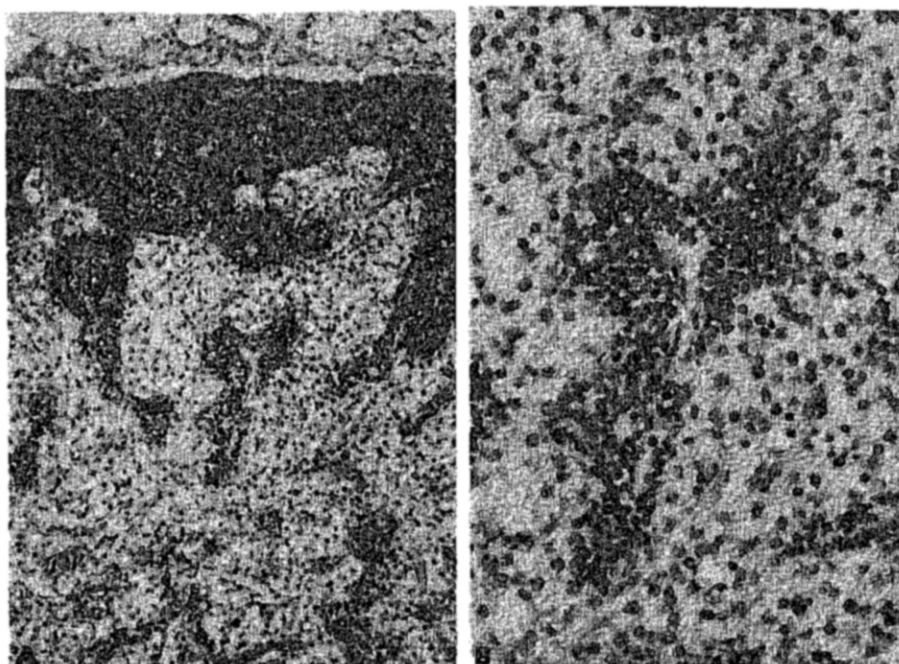
Fig. 2. Follicular involution with lymphoid depletion in a cat infected with FIV. (HE) (A) × 75, (B) × 225.

giving a "burned out" or depleted appearance (Fig. 3). Some follicles contained tingible body macrophages and there was lymphocytolysis in some cases. In only one cat were germinal centres with any obvious marginal zone noted. Changes in extrafollicular tissue varied in different cats. Medullary sinuses contained variable numbers of histiocytes. Even when sinus histiocytosis was not marked there was evidence of erythrophagocytosis and, in many cases, haemosiderin-containing macrophages were also present. Medullary cords were generally hypocellular and contained a mixture of lymphoblastic and histiocytic cells. In five cases (5, 9, 10, 13 and 14) plasmacytoid cells predominated. The connective tissue and vascular skeleton of the lymph node was prominent in those nodes in which involution and lymphoid depletion were most marked.

Discussion

The most consistent finding in this study was the presence of microscopic lesions in the lymphoid tissues. These were present in all 17 cats. In 11 cats, chronic inflammatory lesions were also present in other tissues, including the intestine, brain and lung.

A similar range of lesions affecting lymphoid tissues, intestine, brain and lung is commonly seen in human ARC as a result of HIV infection (Millard, 1984; Waisman *et al.*, 1987). Likewise, in SIV infections there is a lymphadeno-
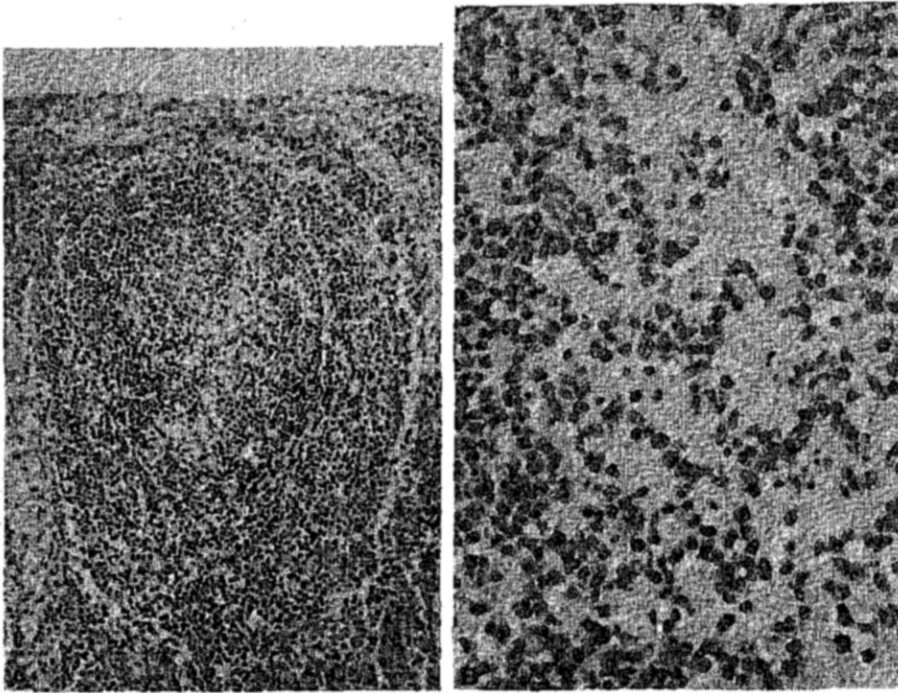
Fig. 3. Follicular involution with hyaline germinal centre in an FIV-infected cat. HE (A) × 75, (B) × 225.

pathy syndrome with the development of opportunistic infections (Letvin *et al.*, 1985).

The precise cause of the intestinal lesions present in seven of the FIV-infected cats is not clear. No pathogens were obvious in Gram- or ZN-stained sections and no inclusion bodies were seen. Similar mural inflammation of the intestine has been reported in a kitten experimentally infected with FIV (Yamamoto, Sparger, Ho, Andersen, O'Connor, Mandell, Lowenstine, Munn and Pedersen, 1988).

Gastro-intestinal disease in human AIDS cases is mainly associated with secondary infections (Waisman *et al.*, 1987). In a survey of intestinal disease in 100 AIDS patients, *Mycobacterium avium intracellulare* was most commonly identified followed by Cytomegalovirus, Cryptosporidium, *Salmonella* spp. and Herpesvirus; no infectious aetiology was found in one-third of all cases (Antony, Brandt, Klein and Bernstein, 1988). *Yersinia pseudotuberculosis* has been isolated from the bowel of some affected cats while in others there may be proliferation of intestinal viruses or protozoa (Pedersen, 1988).

The nervous system lesions present in four cats in this study probably reflect secondary infections, although no obvious specific cause was identified in these cases. The coronavirus responsible for feline infectious peritonitis (FIP) can cause a non-suppurative meningoencephalitis, but none of the lesions was typical of FIP and no antibody to coronavirus was present in the serum of these four cats when tested by immunofluorescence (Hopper, personal communication, 1989). Nervous system lesions in HIV infections are, again, mainly a

result of opportunistic infections, although a subacute encephalitis and vacuolar myelopathy owing to direct involvement by HIV have been described (Waisman et al., 1987; Gray, Gherardi and Scaravalli, 1988).

Respiratory disease in cases of AIDS is mainly a consequence of secondary infection, most commonly Cytomegalovirus or Pneumocystis (Waisman et al., 1987). In one cat in the present study there were scattered foci of necrosis in the lung suggestive of micro-infarcts. Similar microscopic foci of necrosis were present in the liver in three other cats. The cause of these focal lesions is unclear. Endocarditis and vascular lesions were not present and there was no evidence of disseminated intravascular coagulation.

The range of changes which occurred in the lymph nodes of the 17 cats reported here match those of hyperplasia and involution described in HIV infection (Racz et al., 1986; Diebold et al., 1988). The lesions are also comparable with those seen in other lymphadenopathy syndromes occurring in macaques infected with SIV (Letvin et al., 1985) and in cattle infected with bovine immunodeficiency virus (Gonda, Braun, Carter, Kost, Bess, Arthur and van der Maaten, 1987). Thus it seems likely that the group of lentiviruses associated with immunodeficiency syndromes may cause a distinct pattern of lymph node pathology. There has been a considerable effort to understand the lymph node changes seen in HIV infection; in man, a four-part classification has been proposed (Racz et al., 1986; Diebold et al., 1988), including follicular hyperplasia, a mixed pattern with both hyperplasia and involuted follicles, and severe follicular involution with lymphoid depletion. These changes are reflected clinically as a progression from lymphadenopathy to lymph node atrophy. These three patterns were seen in the cats in this study. The fourth pattern seen in HIV infection, follicular hyperplasia with hypervascularity, which is associated with cases of Kaposi's sarcoma, was not encountered here although, with lymphoid depletion, the connective tissue and vascular skeleton of lymph nodes appeared prominent in some cases. Human lymphadenopathies are primarily associated with infection of T lymphocytes but they can be associated with B cell hyperplasia accompanied by histiocytic hyperplasia (Diebold et al., 1988). Both SIV (Chalifoux, Ringler, King, Dehgal, Desrosiers, Daniel and Letvin, 1987) and HIV (Boylston and Francis, 1988) typically infect T lymphocytes and macrophages. The potential importance of different cell-types infected with HIV has recently been discussed (Boylston and Francis, 1988) and the histological changes in HIV and SIV infections have been correlated with the presence of viral antigens (Letvin et al., 1985; Diebold et al., 1988) and alterations in the distribution of different lymphocyte (and other) cell populations (Racz et al., 1986; Chalifoux et al., 1987). In this study, follicular hyperplasia, alone or as a mixed pattern, was seen in eight cats. Both follicular hyperplasia and dysplasia of the lymph nodes have been reported in kittens which were experimentally infected with FIV (Yamamoto et al., 1988), and a naturally occurring case of FIV infection showed follicular hyperplasia (Sheton, Abkowitz, Linenberger, Russell and Grant, 1989). Infection with FeLV has also been associated with follicular hyperplasia, possibly reflecting secondary infections (Hardy, 1988), but the dysplasia seen in FIV infection in this and in experimental studies (Yamamoto et al., 1988) was not a feature of

FeLV infection. Lymphoid depletion, in which lymphoid atrophy is most marked in the T cell-dependent paracortical zone of the lymph nodes, and less pronounced in the spleen, has been reported in the FeLV-induced acquired immunodeficiency syndrome in cats (Hardy, 1988). Although atrophic lymph nodes were found in nine cats in this study, none of the 15 cats in which the FeLV status was known showed evidence of FeLV infection. Generalized lymphadenopathy (Mooney, Patnaik, Hayes and MacEwen, 1987) and a distinctive hyperplastic lymphadenopathy (Moore, Emerson, Cotter and DeLellis, 1986) have previously been described in cats. Only some of those cats were infected with FeLV and others may have had a hyperplastic response to FIV infection (Yamamoto *et al.*, 1988). A feature seen in all the cats in this study was erythrophagocytosis. This feature has been reported in AIDS patients (Racz *et al.*, 1986) and is thought to indicate secondary viral infection (Diebold *et al.*, 1988). The phenomenon of haematophagic histiocytosis has recently been reviewed (Reiner and Spivak, 1988). It was a consistent feature in the cats examined in this study, although the precise mechanism is unclear. It is probably not related to the clinical signs of anaemia seen in four cats (2, 10, 11 and 14), which was non-regenerative in type (Hopper, personal communication). Ultrastructural studies to demonstrate FIV particles in lymph nodes from a number of these cats are under way. These studies, together with the use of immunohistochemical methods to detect viral proteins, will enable further comparison with HIV.

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