CHAPTER 3

The Feline Immunodeficiency Virus

NIELS C. PEDERSEN

I. PROPERTIES OF FELINE IMMUNODEFICIENCY VIRUS

Feline immunodeficiency virus (FIV) was first isolated from a large multiple cat household in Petaluma, California, in 1986 (Pedersen *et al.*, 1987). The discovery was prompted by an outbreak of acquired immunodeficiency-like disease among a large group of feline-leukemia-virus-negative cats housed in the same pen (Pedersen *et al.*, 1987). Plasma and whole blood from three cats in this group were inoculated into two specific pathogen-free cats. The inoculated cats developed fever, leukopenia, and generalized lymphadenopathy after 4 to 6 weeks. A lentivirus was isolated in normal feline T-lymphocyte-enriched peripheral blood mononuclear cell cultures co-cultivated with similar cells from the two experimentally infected animals.

A. Physical Properties

Feline immunodeficiency virus is morphologically identical to lentiviruses that cause acquired immunodeficiency syndrome (AIDS) in man and primates (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1988a,b). The virus buds from the plasma membrane of infected cells in the same manner as other retroviruses. The complete virion is 105 to 125 nm in diameter, spherical to ellipsoid in shape, and possesses short, poorly defined envelope projections (Fig. 1). Budding viruses have the typical crescent-shaped appearance of C- and D-type retroviruses, except that the developing viral core is not separated

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J. A. Levy (ed.), *The Retroviridae*

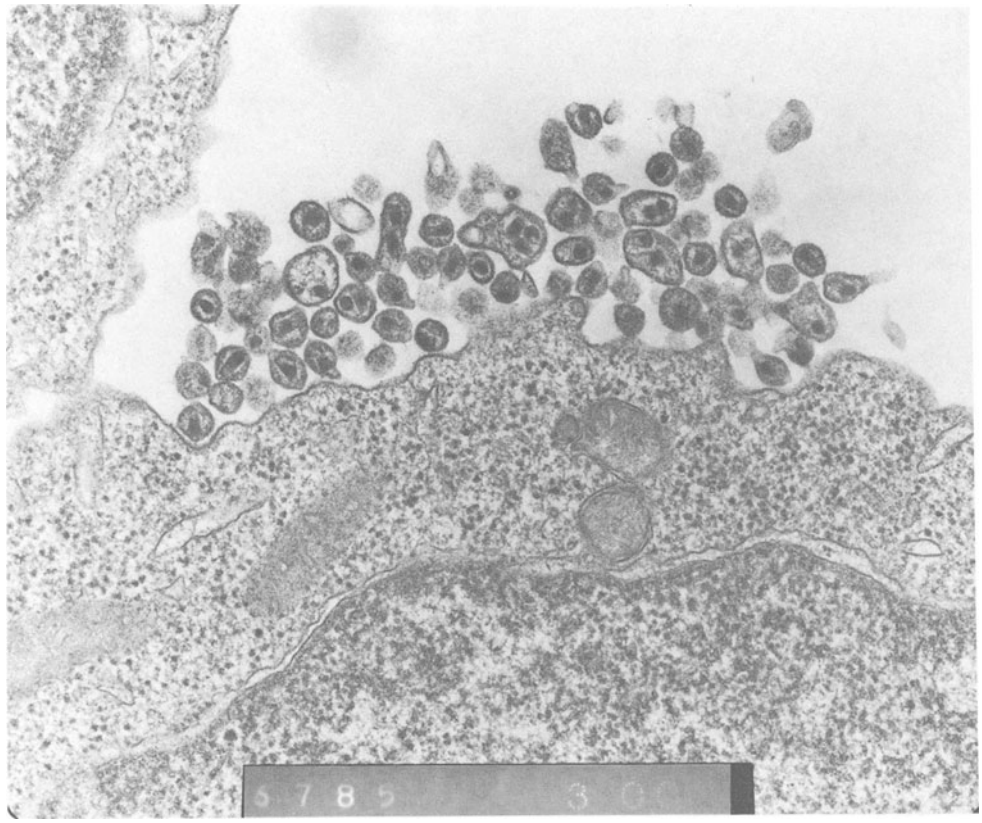

FIGURE 1. Transmission electron photomicrograph of FIV-PPR grown in feline T-lymphoblastoid cells (Elf cells). Numerous lentivirus particles have congregated together along the cell membrane. Uranyl acetate and lead citrate stains, ×68,000. Photomicrograph courtesy of Dr. John Elder, Scripps Clinics and Research Institute, La Jolla, California.

from the overlying plasma membrane by an electron-lucent space. The viral core is composed of a conical shell that is surrounded by an electron-dense nucleoid. A polygonal electron-lucent space is seen between the core shell and the granular layer just inside the outer viral membrane.

Feline immunodeficiency virus has a buoyant density in sucrose of 1.15–1.17 g/cm^3, typical of other retroviruses. It is readily destroyed by common virucidal concentrations of disinfectants such as chlorine, quaternary ammonium compounds, phenolic compounds, or alcohol, and is inactivated by heating to 60°C for a few minutes. It has survived for over 2 years in tissue culture media at −70°C.

B. Biological Properties

1. Antigenic Relatedness to Other Lentiviruses

The proteins of FIV are not recognized by human antisera to human immunodeficiency viruses, types 1 and 2 (HIV-1 or HIV-2), rhesus monkey

antisera to simian immunodeficiency virus (SIV) (macaque and sooty mangabey isolates), goat antisera to caprine arthritis-encephalitis virus (CAEV), sheep antisera to Visna-Maedi virus (V-MV), or bovine serum to bovine immunodeficiency-like virus (BIV) (Pedersen *et al.*, 1987; Steinman *et al.*, 1989) (Table I; see also Chapter 4). Horse antisera to equine infectious anemia virus (EIAV) will immunoprecipitate to some extent the major core protein (p24), the core precursor polyprotein (pr50), and the major envelope glycoprotein (gp95) (Steinman *et al.*, 1989; see also Chapter 5). Rabbit antiserum to EIAV will precipitate all of the *gag* proteins and *gag* precursor polyproteins of FIV (Egberink *et al.*, 1990b; Steinman *et al.*, 1989). Rabbit antiserum to CAEV and V-MV will react with FIV-p24, while rabbit antisera to BIV and HIV-1 are nonreactive (Olmsted *et al.*, 1989).

2. Cell Tropism

Feline immunodeficiency virus replicates in primary feline blood mononuclear cells, thymus cells, and spleen cells that have been stimulated initially with concanavalin A (ConA) and then maintained on human recombinant interleukin-2 (IL-2) (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1988b). Feline immunodeficiency virus will not replicate in nonfeline cell lines such as the Raji continuous human B-lymphoblastoid cells, primary ConA- and IL-2-stimulated canine blood mononuclear or BALB/c mouse spleen cells, mouse IL-2-dependent HT-2c T-lymphoblastoid cells, or in sheep normal fibroblast cultures sensitive to V-MV (Yamamoto *et al.*, 1988b). There is evidence that FIV will infect some human cell lines *in vitro* but no virus replication occurs (L. Sparger, University of California, Davis, unpublished observation, 1990).

TABLE I. Major Structural Proteins, as Determined by Polyacrylamide Gel Electrophoresis (PAGE) or Genetic Sequence Analysis, of Feline Immunodeficiency Virus and Their Antigenic Relationship by Serology to Other Known Lentiviruses

Protein	Size (kDa)		Antigenic relationship to other lentiviruses by serology
	PAGE	Sequence analysis	
gag precursor	52	49.5	horse anti-EIAV, rabbit anti-EIAV
Capsid	28	24.5	horse anti-EIAV, rabbit anti-EIAV, rabbit anti-CAEV, rabbit anti-V-MV
Matrix	15	14.9	rabbit anti-EIAV
Nucleocapsid	10	9.6	rabbit anti-EIAV
Major envelope			
glycosylated	95	—	no cross-reactivity
nonglycosylated	—	75.0	no cross-reactivity
Transmembrane	41	—	no cross-reactivity
Polymerase			
protease	—	13.4	no cross-reactivity
reverse transcriptase	62	61.4	no cross-reactivity
integrase	—	30.7	no cross-reactivity

FIV will co-infect and replicate in permanent feline leukemia virus (FeLV) infected cat T-lymphoblastoid cell lines such as LSA-1 and FL74 (Yamamoto *et al.*, 1988b). Some isolates of FIV such as the Petaluma strain can be adapted to replicate constitutively on Crandell feline kidney (CrFK) cells (Yamamoto *et al.*, 1988b), although adaptation to CrFK cells lowers infectivity toward T lymphocytes. Recently, Miyazawa and co-workers (1989b, 1992) and Kawaguchi and colleagues (1990) chronically infected an IL-2-dependent retrovirus-free feline T-lymphocyte cell line (MYA-1 cells) with the Petaluma and TM-1 strains of FIV. The MYA-1 cell cultures infected with FIV-Petaluma died out after 45 days, while cell cultures chronically infected with FIV-TM-1 survived for over 90 days.

A feline thymus (FeT) IL-2-dependent cell line has been chronically and productively infected with FIV-Petaluma (F4 and F6 cells) (Yamamoto *et al.*, 1991a). The F4 and F6 cells are transformed in morphology, IL-2 independent, and constitutively produce large amounts of their respective strains of FIV. The F4 cells express pan-T, CD4, and CD8 cell surface antigens, while F6 cells express pan-T and CD8.

The feline immunodeficiency virus is tropic *in vivo* for macrophages (Brunner and Pedersen, 1989), and brain macrophages and astrocytes (Dow *et al.*, 1990). Using the polymerase chain reaction on tissues of FIV-infected cats, proviral DNA is most abundant in mesenteric lymph nodes and bone marrow, and less abundant in blood mononuclear cells, spleen, and brain. When tissues are screened by *in situ* hybridization, viral RNA is found mainly within a small proportion of macrophages and lymphocytes in lymph

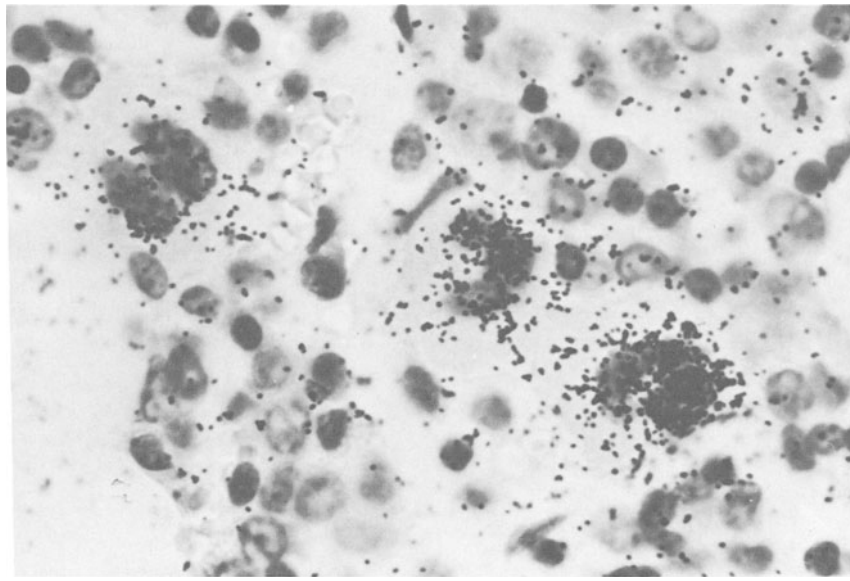

FIGURE 2. Photomicrograph of bone marrow taken from an FIV-infected cat and prepared for *in situ* RNA hybridization using a probe specific for FIV. FIV RNA, as evidenced by overlying grains, is seen mainly in large multinucleated cells (megakaryocytes). Photomicrograph courtesy of Dr. Satya Dandekar, School of Medicine, University of California, Davis, California.

nodes, spleen, and brain (Dandekar *et al.*, 1990) (Fig. 2), while in bone marrow, viral RNA is also seen within a small proportion of megakaryocytes and macrophages (Beebe *et al.*, 1992).

3. Cytopathic Effect

The FIV replicates optimally in peripheral blood mononuclear cell (PBMC) cultures that are initially stimulated with a T-cell mitogen such as ConA and maintained on human recombinant IL-2 (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1989). A characteristic cytopathic effect consisting of balloon degeneration, syncytium formation, and cell death appears in such PBMC cultures within 2 to 4 weeks, associated with the appearance of virion-associated reverse transcriptase and FIV-p24 protein. This cytopathic effect (CPE) is variable, and most evident upon initial isolation. The CPE is often transient, and cultures that are periodically re-fed with fresh cultured PBMC can remain productively infected for many weeks.

A chronic IL-2-dependent feline T-lymphoblastoid cell line (MYA-1 cells) has been produced by Miyazawa and co-workers (1989b, 1992). This cell line has reportedly been superior for FIV propagation than normal feline PBMC cultures. The cytopathic effect of FIV on MYA-1 cells was reportedly limited to cell death, without balloon degeneration or syncytium induction. Presumably, chronically FIV-infected MYA-1 cultures can be maintained with periodic additions of fresh cells.

Tochikura and co-workers (1990) recently described the infection of the chronic 3201 feline T-lymphoblastoid cell line with FIV. The 3201 T-lymphoblastoid cell line is a non-FeLV producer derived from a cat with a thymic lymphoma. They also found that the 3201 cells would undergo an early lytic infection with FIV, but that surviving cells would establish themselves as a chronic producer cell line. Although the 3201 cells in the report were reportedly $CD4^+$, no mention was made of their status to other cell-surface antigens. FIV will also productively infect cultures of U-373 human astrocytoma cells (Dow *et al.*, 1990), which is the only human cell that has been productively infected with the virus. Infected U-373 cells elaborated low levels of reverse transcriptase and viral antigens but showed no cytopathic effect.

4. Viral Receptor

It is still uncertain whether FIV is selectively tropic for cells bearing the feline equivalent of the human $CD4^+$ cell-surface antigen. The virus will infect CD4-antigen-negative FL74 and LSA-1 T-lymphoblastoid cells, and can be adapted to CrFK cells, which are also CD4-negative. Recent studies with a monoclonal antibody have suggested a 24 kDa cell surface protein could be an FIV receptor (Hosie *et al.*, 1993). Initial studies suggest that FIV can infect and replicate within purified populations of either $CD4^+$ or $CD8^+$ T lymphocytes, again suggesting that FIV does not necessarily require a $CD4^+$ receptor to enter cells (W. C. Brown *et al.*, 1991). Although FIV may not enter cells only through a CD4-like receptor, like HIV and SIV, the greatest cytopathic

effect and highest level of virus replication *in vitro* occurs in $CD4^+$ T lymphocytes.

C. Molecular Properties

1. Genomic Size and Organization

Infectious molecular clones of FIV have been recently reported and their genetic sequences elucidated (Olmsted *et al.*, 1989; Talbot *et al.*, 1989; Miyazawa *et al.*, 1991; Siebelink *et al.*, 1992). FIV has the typical *gag-pol-env* organization of retroviruses and the genomic size of lentiviruses, about 9.4 kbp (Fig. 3A). In addition to the major structural genes, the FIV genome contains open reading frames (ORFs) that potentially encode for two large (ORFs 1 and 2) and five smaller (L, D, F, I, and H ORFs) proteins.

2. Major Structural Genes and Gene Products

The precursor polyprotein of the viral core (*gag*) proteins (Pr50) migrates as a 47–52 kDa protein by polyacrylamide gel electrophoresis (PAGE) (Yamamoto *et al.*, 1988b; O'Connor *et al.*, 1989) (Table I). The predicted molecular weight based on genetic sequence data is 49.5 kDa (Talbot *et al.*, 1989). The major core (capsid) protein has a molecular weight by PAGE of 26–28 kDa (Yamamoto *et al.*, 1988b; O'Connor *et al.*, 1989). Based on sequencing data, the actual size of this protein is 24.5 kDa (Talbot *et al.*, 1989). Smaller viral structural proteins of 15–17 (matrix) and 10 (nucleocapsid) kDa have also been identified by PAGE (Yamamoto *et al.*, 1988b; O'Connor *et al.*, 1989). The actual sizes of these proteins are 14.9 and 9.6 kDa, respectively (Talbot *et al.*, 1989). The gene encoding the FIV-Pr50 protein will produce viral-like particles when expressed in baculovirus vectors (Morikawa *et al.*, 1991). The carboxy-terminal part of Pr50 was essential for such assembly.

The envelope (*env*) gene of FIV codes for the surface (SU) and transmembrane (TM) glycoproteins. The SU glycoprotein of FIV was initially reported

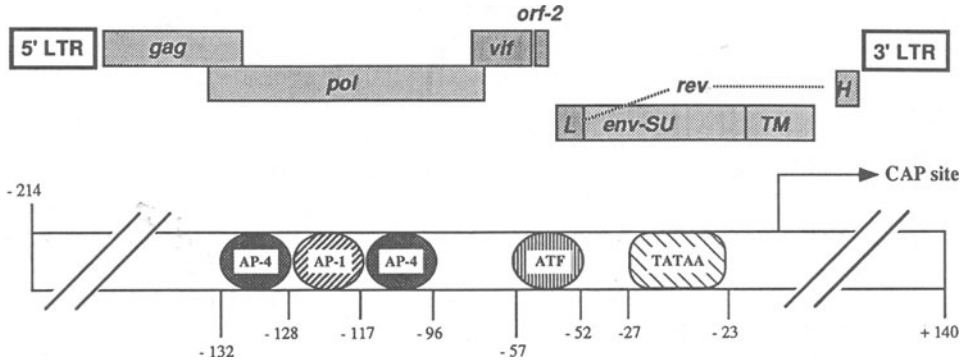

FIGURE 3. (A) The genomic organization of the "Peeper" strain of FIV, and (B) its long terminal repeats (genomic graphs courtesy of Dr. Liz Sparger, University of California, Davis).

to be about 120 kD by radioimmunoprecipitation in its glycosylated form (Egberink *et al.*, 1990b; O'Connor *et al.*, 1989). However, its actual weight may be about 95 kDa. Pulse-chase analyses indicate that the entire SU/TM glycoprotein is synthesized as a 145,000-kDa precursor that is rapidly trimmed to a protein of 130,000 kDa, with nearly one-half of this weight consisting of endo-H sensitive glycans (Stephens *et al.*, 1991). Longer chase periods revealed two glycoprotein species of 40 and 95 kDa, the respective SU and TM glycoproteins. The entire FIV SU gene consists of approximately 750 base pairs, and contains 17 potential sites for N-linked glycosylation prior to the predicted processing site for the transmembrane glycoprotein (Talbot *et al.*, 1989). The potential size of the nonglycosylated SU protein based on sequence data and tunicamycin inhibition studies is 75 kDa (Egberink *et al.*, 1990b; Talbot *et al.*, 1989).

The TM glycoprotein of FIV has a molecular weight by PAGE of about 41 kDa (Yamamoto *et al.*, 1988b; O'Connor *et al.*, 1989). The genetic coding region of the transmembrane protein contains four potential N-linked glycosylation points and a hydrophobic spanning region of 71 bases (Talbot *et al.*, 1989).

The entire polymerase (*pol*) gene region of FIV is comprised of 3371 bases and overlaps the 3′ end of the gene coding for the *gag* proteins (Talbot *et al.*, 1989). The predicted sizes of the protease and reverse transcriptase (RT) are 13.5 and 61.5 kDa, respectively. The 3′ end of the *pol* gene is predicted to encode an integrase of 30.7 kDa. A region of approximately 400 base pairs between RT and integrase was initially identified that would code for a then unknown protein of 14.6 kDa (Talbot *et al.*, 1989). In common with other nonprimate lentiviruses and type-D retroviruses, this segment has been recently shown to encode a functional dUTPase (Elder *et al.*, 1992). The significance of this enzyme in virus replication is unknown at this time.

3. Regulatory Genes

A putative viral infectivity factor (*vif*) gene was initially ascribed to ORF 1, which is a large open reading frame overlapping the 3′ end of the *pol* gene (Talbot *et al.*, 1989). Although this gene corresponds in size and position to the *vif* of the primate lentiviruses, there is no significant genetic homology. Tomonaga and co-workers (1992) created a deletion mutation of the putative FIV-*vif* gene in an infectious molecular clone of FIV; the mutant virus produced normal levels of virion-associated reverse transcriptase, but the resultant particles were not infectious to $CD4^+$ T cells. Therefore, the putative FIV-*vif* is functionally analogous to the *vif* gene of SIV.

The H and L ORFs of FIV have been shown to encode a protein that is equivalent to HIV-*rev* (Kiyomasu *et al.*, 1991; Phillips *et al.*, 1992). A rev-responsive element (RRE) is mapped by a 243-bp fragment at the 3′ end of the *env*-gene (Phillips *et al.*, 1992). An antibody to an L ORF peptide recognizes a 23-kDa protein in the nucleoli of FIV-infected cells (Phillips *et al.*, 1992). Therefore, FIV possess a *rev* and RRE similar to HIV but the FIV-RRE is in a different position in the *env*-gene (HIV-RRE is found in the junctional region between the envelope and transmembrane genes).

A transactivating (*tat*) gene similar in sequence to that of HIV has not been identified in FIV. However, ORF 2 has been postulated to encode a tat-like protein. Experiments suggest that the transactivating activity encoded by FIV is low compared to the HIV *tat*-gene product, and more resembles the activity observed with Visna-Maedi virus (Sparger *et al.*, 1992).

4. Long Terminal Repeats

The genetic structure of the long terminal repeats (LTRs) of FIV has been reported by Olmsted and co-workers (1989) and Talbot and associates (1989) (Fig. 3B). The length of the LTR is similar to that of CAEV, V-MV, and EIAV, but much shorter than that of HIV or SIV. The LTR contains a purine-rich region for the initiation of plus-strand DNA synthesis and a primer-binding site for the initiation of minus-strand DNA synthesis. Transcription signals present in the LTR of FIV include two TATA boxes, one similar to that of HIV and the second identical to that reported for CAEV, V-MV, and EIAV. A consensus polyadenylation signal is present in the LTR as well as a potential enhancer sequence similar to the NF-KB immunoglobulin gene enhancer. The FIV LTR also contains AP-1, AP-4, and ATF binding sites (Sparger *et al.*, 1992). In transient expression assays, FIV LTR-CAT gene constructs will produce high levels of CAT in response to activation signals induced in human T cells treated with lectins and phorbol esters or cAMP analogs, indicating that the FIV-LTR contains sites responsive to T-cell-induced replication factors. The AP-1 site in the FIV-LTR has been mapped as the target sequence for activation responses mediated by phorbol esters, whereas the ATF site is necessary for responses induced by increased intracellular cAMP. These observations indicate that cellular activation may play a more critical role in FIV gene regulation than the putative FIV-encoded transcriptional transactivator.

5. Genetic Homology and Heterology

Phylogenetic analysis of the conserved polymerase gene indicates that FIV differentiated from other lentiviruses relatively early in evolution, i.e., shortly after the divergence of primate and nonprimate lentiviruses, and before the divergence of EIAV from V-MV and CAEV (Talbot *et al.*, 1989). The genomic structure of FIV, especially in the intergenomic regions, is more closely aligned with V-MV than other lentiviruses.

FIV is genetically related to a group of lentiviruses that infect wild Felidae in Africa and other parts of the world. Two lentivirus isolates have been made from geographically separated subspecies of North American puma (Olmsted *et al.*, 1992). The level of genetic divergence between the two puma lentiviruses (PLV) and various FIV strains was greater than the level of divergence between human and certain simian lentiviruses, suggesting that the evolution of felid lentiviruses parallels that of simian and human counterparts.

The various FIV isolates appear to be genetically diverse, especially in the envelope gene (Olmsted *et al.*, 1989; Talbot *et al.*, 1989; Phillips *et al.*, 1990; Masashi *et al.*, 1990; Maki *et al.*, 1992). A molecular clone of the "Peeper"

strain of FIV (FIV-PPR), which was isolated from a cat in LaJolla, California, had an overall sequence identity of 91% with a molecular clone of the original Petaluma, California, strain of FIV (FIV-34TF10). The envelope genes of the two viruses were least conserved, with a 15% nonhomology at the amino acid level. The LTRs of these two cloned isolates were 7% divergent with a lack of conservation in putative NF-KB, LBP-1, and CCAAT enhancer-promoter sites. Two Japanese isolates, FIV-TM1 and FIV-TM-2, were found to be genetically similar to each other, but showed only 80–90% identities in nucleotide sequences to cloned FIV-34TF10 within the entire *gag-pol* and partial *env* regions of their genomes (Masashi *et al.*, 1990). The LTRs of FIV-34TF10 and FIV-TM-2 were over 80% identical in nucleotide sequences, except that FIV-TM-2 lacked a NF-KB site and an alternative TATA-like sequence.

The RT gene has from 40–65% genetic homology with HIV, SIV, V-MV, CAEV, and EIAV (Olmsted *et al.*, 1989; Talbot *et al.*, 1989). The RT-associated ribonuclease H (RNase H) of FIV and HIV both show a marked preference for poly(dC)·[^{3}H]poly(rG) compared to poly(dT)·[^{3}H]poly9rA) (Cronn *et al.*, 1992b). The FIV RNase H displays a preference of Mg^{2+} over Mn^{2+} for divalent cation, as does the RT as a whole, and 90% of maximum activity can be observed between 10 and 18 mM $MgCl_2$. Both FIV and HIV RNase H's can be inhibited by polyanionic compounds such as dextran sulfate and poly(dC)·oligo$(dG)_{12-18}$.

II. PATHOGENESIS IN NATURAL HOST

A. Epidemiologic Features

1. Host Range

All of the present isolates of FIV have come from domestic cats. However, many sera from wild Felidae, including African lions and cheetahs, Asian lions and tigers, South American jaguars, and North American bobcats and panthers (puma), have cross-reacted with structural antigens of FIV and/or EIAV (Barr *et al.*, 1989; Letcher *et al.*, 1991; Lutz *et al.*, 1992; Olmsted *et al.*, 1992). Asian lions in the wild have tested negative for FIV-related antibodies (Lutz *et al.*, 1992), while some zoo-maintained animals have tested positive (Letcher *et al.*, 1991). This may reflect a geographic difference in where the Asian lions were obtained, or more likely, from infection of the Asian lions with lentiviruses from other felids during zoo contact.

Initial attempts to isolate a lentivirus from African lions in cell culture have been unsuccessful, and whole blood from two geographically different seropositive zoo-kept African lions failed to infect laboratory cats (Lutz *et al.*, 1992; N. C. Pedersen, University of California, Davis, unpublished observation, 1989). Two different infectious isolates of a FIV-like lentivirus have been made from North American pumas (Olmsted *et al.*, 1992). The puma isolates were genetically disparate from each other and from FIV. It is apparent, therefore, that many different species of wild felids are infected with lentiviruses closely or distantly related to FIV.

2. Geographic Distribution

Feline immunodeficiency virus has been subsequently identified in many regions of the United States and Canada, Europe, South Africa, Japan, China, Australia, and New Zealand (Table II). Domestic cats spread from Europe to these various countries with the early traders and explorers thousands of years ago, suggesting that FIV has also infected cats for a long time. Seropositive cats have been identified as far back as stored sera are available, which is 1975–1976 in Europe (Gruffydd-Jones *et al.*, 1988), 1972 in Australia (Sabine *et al.*, 1988), and 1968 in the United States and Japan (Shelton *et al.*, 1989b; Furuya *et al.*, 1990).

TABLE II. Prevalence Rate of FIV Infection among Healthy and Ill Populations of Cats in Various Countries and Regions of the World[a]

	Health Status		
Country	Healthy (%)	Unknown (%)	Ill (%)[b]
US and Canada	1.2	—	14.0
Seattle, US	1.4	—	10.2
North Carolina, US	3.6	—	15.0
Oklahoma, US	8.0	10.0	13.0
Texas, US	2.1	11.8	11.3
Ontario, Canada	0.0	—	14.6
Tokyo, Japan	12.0	—	44.0
Sapporo & Tokyo, Japan	10.4	8.8	3.9
China	1.3	—	—
United Kingdom (1)	0.0	—	12.8
(2)	6.0	—	19.0
(3)	0.0	—	14.0
(4)	—	—	33.3
France (1)	0.0	—	22.1
(2)	13.0	—	25.2
Italy	—	—	24.0
Holland	1.0	—	3.0
Switzerland (1)	2.8	—	3.7
(2)	0.7	—	3.4
Germany	5.0	9.5	—
Austria	—	3.5	—
Denmark	4.1	—	19.1
Queensland, Australia	—	30.0	—
Sydney, Australia	6.7	—	8.1
New Zealand	6.8	0.0	27.3
Finland	0.0	6.6	0.0

[a] Bandecchi *et al.*, 1992; Belford *et al.*, 1989; Bennett *et al.*, 1989; Chan, 1990; Cohen *et al.*, 1990; Furuya *et al.*, 1990; Grindem *et al.*, 1989; Gruffydd-Jones *et al.*, 1988; Hosie *et al.*, 1989; Ishida *et al.*, 1988, 1989; Kölbl and Schuller, 1989; Kristensen *et al.*, 1989; Lutz *et al.*, 1988; Neu *et al.*, 1989a; Povey and Hawkins, 1989; Rodgers and Baldwin, 1990; Sabine *et al.*, 1988; Shelton *et al.*, 1989c; Sakura *et al.*, 1992; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989.

[b] Illness may refer to any chronic illness, regardless of ultimate cause, in some studies, while in other studies, illness refers only to cats with clinical signs that are consistent with FIV infection. This difference probably explains the great variations in the percentages of healthy and ill cats that are FIV-positive in the various studies.

3. Modes of Transmission

Feline immunodeficiency virus can be recovered from the blood, serum, plasma, cerebrospinal fluid, and saliva of experimentally or naturally infected cats either by tissue culture or cat inoculation (Yamamoto *et al.*, 1988b, 1989; Dow *et al.*, 1990; Bandecchi *et al.*, 1992). Although horizontal transmission can occur by contact alone (Pedersen *et al.*, 1987), it is relatively inefficient when compared to the transmission of other feline pathogens. Only 1/25 susceptible cats that were housed in common rooms with infected animals became seropositive over a 4-year period (N. Pedersen, University of California, Davis, unpublished observation). Shelton and associates (1989c) found no evidence of infection among 31 feline housemates of infected cats. However, Hosie and co-workers (1989) found a higher infection rate among healthy contacts of infected animals that lived in the same homes than in healthy animals not having such close contact.

Bites appear to be one of the most efficient and important modes of transmission. A single experimentally administered bite from a naturally or experimentally infected cat will transmit the infection to a susceptible animal (Yamamoto *et al.*, 1989). Biting is infrequent among cats that are kept strictly indoors in stable groups (Hart and Pedersen, 1991). Cats kept strictly indoors express their territorial aggression by nonviolent means, while the same cats will ferociously defend their outdoor territories if allowed to roam free. Biting is more apt to occur between male cats, which may explain why male cats are much more likely to be infected than females.

Venereal transmission from infected toms to noninfected females, and vice versa, does not occur to any extent (N. C. Pedersen, University of California, Davis, unpublished observation, 1989). This observation has been supported by field studies showing no negative effect on the FIV infection rate of male or female cats by neutering (Hosie *et al.*, 1989). This suggests that very little infectious virus is present in the semen or in the vaginal mucus, although this remains to be actually determined. Likewise, *in utero* transmission and neonatal transmission through colostrum, milk, and maternal grooming are apparently uncommon under laboratory (Yamamoto *et al.*, 1988b) and field (Ueland and Nesse, 1992) conditions. However, Callanan and co-workers (1991) demonstrated either *in utero* or perinatal (during birth or from suckling) transmission in 1/8 kittens born to three mothers infected during the first trimester of pregnancy. Milk taken from the infectious mother did not contain culturable virus. A similar occurrence has been observed by another group in England (R. Gaskell, University of Liverpool, personal communication, 1990). Wasmoen and associates (1992) also demonstrated perinatal transmission in 2/3 kittens in two different litters. One queen was infected intravenously with FIV 22 days prior to parturition, while the second queen was infected subcutaneously 2 days prior to the time of delivery. All instances of *in utero* or perinatal transmission occurred in queens that were in the primary stage of FIV infection at the time of parturition and lactation; such queens probably had extremely high levels of plasma and cell-associated virus in their blood and possibly in their milk.

4. Epidemiologic and Pathogenic Relationship of FIV to Other Retroviruses

a. General Considerations

Cat cells can be co-infected *in vitro* with any or all of the known types of feline retroviruses: FIV (subfamily Lentivirinae), feline leukemia virus (FeLV) (subfamily Oncornavirinae), or feline syncytium-forming virus (FeSFV) (subfamily Spumavirinae) (N. C. Pedersen, University of California, Davis, unpublished observation, 1990). Co-infected cultures will express any or all of these retroviruses simultaneously into the culture media. It is not surprising, therefore, that cats can also be co-infected either in nature or experimentally with any or all of these agents (Yamamoto *et al.*, 1988a, 1989; Ishida *et al.*, 1989; Miyazawa *et al.*, 1989b; Cohen *et al.*, 1990; Furuya *et al.*, 1990; Rodgers and Baldwin, 1990). The interrelationships between these three retrovirus infections in cats have interesting epidemiologic and pathogenesis implications.

Infection with FeLV tends to occur earlier in life than FIV, with more than one-half of the infected cats being younger than 5 years of age (Fig. 4) (Hosie *et al.*, 1989; Tenario *et al.*, 1991; Bandecchi *et al.*, 1992). In comparison, FIV infection tends to occur in cats greater than 5 years of age (Hosie *et al.*, 1989; Ishida *et al.*, 1989; Yamamoto *et al.*, 1989; Cohen *et al.*, 1990; Rodgers and Baldwin, 1990). The infection rate for FeSFV rises progressively from 6 months of age onward and continues to rise throughout life, similar to FIV (Pedersen, 1987, 1988).

b. Feline Leukemia Virus

Feline leukemia virus, a member of the oncogenic retroviruses, is transmitted *in utero* from mother to kittens, possibly peripartum from the ingestion of infected colostrum or milk, or later in life by close physical oral con-

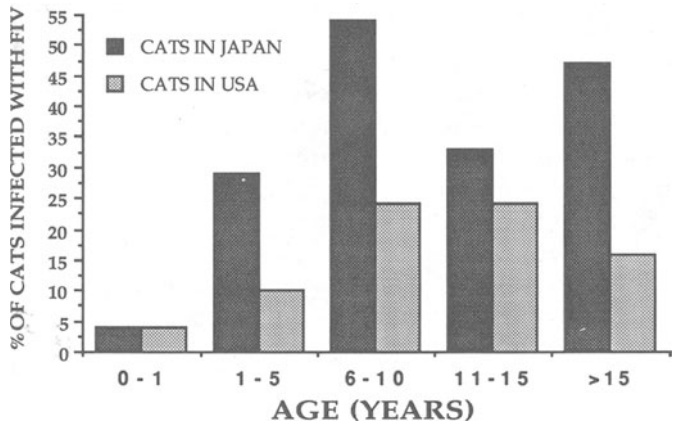

FIGURE 4. Incidence of FIV infection among cats of varying ages in Japan and the United States. Cats tested for this study were considered to be at high risk for FIV infection either because they were demonstrating clinical signs consistent with FIV-related disease or because they were in close contact with known FIV-infected cats.

tact with infectious saliva (mutual grooming, bites), urine, or feces (Pedersen *et al.*, 1977; see Chapter 2). Feline leukemia virus is a cause of a wide range of chronic malignant and degenerative diseases, and it has been associated in the past with acquired immunodeficiency (Pedersen, 1988). Feline leukemia virus infection is endemic at a low level among free-roaming cats, but is most serious as a pathogen when it enters large and closely confined groups of cats, e.g., catteries, multiple cat households (Pedersen, 1988).

About 1/6 to 1/3 of the FIV-infected cats from North America, Japan, France, and the United Kingdom have been co-infected with FeLV (Hosie *et al.*, 1989; Ishida *et al.*, 1989; Yamamoto *et al.*, 1989; Furuya *et al.*, 1990; Moraillon, 1990; Shelton *et al.*, 1990a; Zenger, 1990). There is some question as to whether FIV infected cats are more apt to become infected with FeLV or vice versa. Most studies indicate that FeLV and FIV infections are acquired independently of each other (Sabine *et al.*, 1988; Grindem *et al.*, 1989; Hosie *et al.*, 1989; Ishida *et al.*, 1989; Shelton *et al.*, 1989b,c; Yamamoto *et al.*, 1989; Glennon *et al.*, 1991). However, other studies showed that FeLV-infected cats are 1.5 to 4 times more likely to be infected with FIV than FeLV-negative animals (Cohen *et al.*, 1990; Moraillon, 1990; Zenger, 1990).

Convincing seroepidemiologic evidence shows that dually infected cats have a more severe disease course. Cats co-infected with FeLV in several studies were younger than those infected with FIV alone at the time of diagnosis and tended to have more severe disease and died sooner (Ishida *et al.*, 1989; Zenger, 1990). Although there did not appear to be a distinct difference in the types of diseases that occurred in dually compared cats to singly infected cats, Hosie observed that 87% of the FeLV/FIV-infected animals were present among the cats that were clinically ill at the time of testing (compared with 19% for FIV, and 18% for FeLV, infected alone cats). Moraillon (1990) found that only 0.63% of healthy cats were dually infected compared with 19.9% of sick cats. Grindem and associates (1989) also found that dually infected cats were sicker than cats infected with FIV alone, but they only studied a small group of animals. However, Shelton and co-workers (1989c) found that a similar proportion of dually infected, FeLV-infected, and FIV-infected pet cats were sick at the time their infections were diagnosed.

Pedersen and co-workers (1990) experimentally infected asymptomatic-specific, pathogen-free FeLV carrier cats with FIV and followed their subsequent course of disease. Healthy-appearing FeLV-infected cats that were given FIV developed a much more severe primary form of FIV infection than non-FeLV-infected cats and about one-half of them died within 10 weeks. Following recovery from the primary stage of FIV infection, dually infected cats had severely inverted T4/T8 lymphocyte ratios and were significantly more leukopenic than cats infected with either FeLV or FIV alone. One of these surviving cats died 6 months later of a severe bowel infection and peritonitis associated with an opportunistic infection (*Streptococcus canis*). FeLV-carrier cats that were co-infected with FIV had greatly enhanced levels of FIV RNA and DNA in their tissues by *in situ* RNA hybridization and the polymerase chain reaction compared to cats infected with FIV alone (Pedersen *et al.*, 1990; Torten *et al.*, 1990). Conversely, FeLV expression was not up-regulated by co-infection with FIV (Pedersen *et al.*, 1990). The enhancement of FIV

infection by FeLV infection in cats is analogous to the enhancement of HIV infection of man by HTLV-I infection (Bartholomew *et al.*, 1987). The mechanism by which FeLV infection enhances FIV infection both *in vitro* and *in vivo* has not been precisely determined. There is no evidence that any gene of FeLV will up-regulate FIV gene expression *in vitro* (L. Sparger, University of California, Davis, unpublished observation, 1990). Whether pseudotypes between FeLV and FIV are formed remains to be determined. Enhancement in the reverse order of FeLV/FIV infection is not nearly as pronounced. Healthy FIV infected cats respond much like noninfected cats when subsequently exposed to FeLV (Lehmann *et al.*, 1992).

c. Feline Syncytium-Forming Virus

Feline syncytium-forming virus, a spumavirus (see Chapter 6), is transmitted mainly by bites, with *in utero* transmission being of secondary importance (Pedersen, 1987, 1988). It is the most common retrovirus infection of cats, but chronically infected animals are largely disease free. Feline syncytium forming virus, like FIV, is not readily transmitted by close physical contact alone. Feline immunodeficiency virus and FeSFV are largely infections of free-roaming cats, and the infection rate among confined groups of animals is low. These differences are mainly attributable to the importance of biting as a mode of transmission of FIV and FeSFV; FeLV is much more infectious by close physical contact with infectious secretions.

A strong correlation existed between FeSFV and FIV infections. Seventy-four percent of a group of FeSFV-infected cats in one FIV study group tested positive for FIV infection (Yamamoto *et al.*, 1989). This was compared to a 37% FIV infection rate among a group of FeSFV-negative cats from the same cohort. Bandecchi and associates (1992) were able to identify FeSFV in over 90% of the cats that were infected with FIV. The linkage between FeSFV and FIV infection is probably related to the comparable modes of transmission for these two viruses. The high incidence of FeSFV infection in FIV-infected cats greatly complicates attempts to isolate FIV (Pedersen *et al.*, 1987; Miyazawa *et al.*, 1989a; Bandecchi *et al.*, 1992). It is not known whether FeSFV infection potentiates FIV-related disease, although preliminary studies indicate that FIV/FeSFV co-infected cats are no more likely to become ill than cats infected with FIV alone.

B. Clinical Features

1. Morbidity and Mortality Rates

Immunodeficiency virus infections in Asian macaques (SIV infection), man (HIV infection), and cats (FIV infection) bear strong similarities to each other but differ greatly in morbidity, mortality, distinctness of clinical stages, and the speed of progression. The primate disease is by far the most severe in terms of overall mortality and the speed of progression, with most animals dying within 3 to 18 months. This is probably due to the fact that Asian

macaques are not the natural host species for SIV and have very little evolutionary adaptation to the virus. Primary disease signs are less noticeable in SIV-infected macaques, and animals go from a state of clinical normalcy to severe disease within a brief period of time (days to weeks). The disease of man is much less severe than SIV infection in terms of both mortality and speed of disease progression, and the clinical stages are more distinct. FIV infection of domestic cats more closely resembles HIV infection in terms of clinical staging than SIV infection, but it is the mildest of the three diseases in terms of the speed of disease progression (relative to life span) and overall mortality.

The precise proportion of FIV-affected cats that will die from their infection is not known, nor is the average period of time between infection and death known. Ishida and co-workers (1992) followed 11 asymptomatic FIV-infected cats for 2 years. Four of 11 (36%) showed a progression of the clinical stage of illness. Persistent generalized lymphadenopathy (PGL) was the first sign of illness noted in three cats that were initially in the asymptomatic carrier stage of disease. These three cats showed PGL-like signs for several months before developing ARC-like disease. The fourth cat progressed directly into an ARC-like stage with generalized lymphadenopathy and secondary infections. The ARC-like illness persisted in all four animals for about 10 months and then progressed into AIDS-like illness in 2/4 animals. These latter two cats died within 1 year. The overall mortality in this group of 11 initially asymptomatic cats over a 2-year period was 18%. Specific pathogen-free cats that were experimentally infected with the Petaluma strain of FIV and kept in pathogen-free quarters have remained healthy for as long as 5 years (N. C. Pedersen, University of California, Davis, personal observation, 1991). However, about one-half of the infected cats have significant immunologic abnormalities by 2 to 4 years (Barlough *et al.*, 1991; Torten *et al.*, 1991). At least some of these immunologically impaired animals would presumably become ill if they were exposed to other pathogens in nature.

The time period between infection and illness can be crudely estimated by seroepidemiologic studies of naturally exposed cats. Shelton and co-workers (1989c) found that the median age of healthy-appearing FIV-infected cats was 4 years, while the median age of sick FIV-infected cats was 10 years. Ishida and associates (1989) found that asymptomatic FIV-infected cats had a mean age that was 1 year less than clinically ill animals, 4.3 years versus 5.2 years. Mortality among the index Petaluma cattery dramatically increased 2 to 5 years after the first infected animal was introduced into the household (E. Sparger and N. C. Pedersen, University of California, Davis, unpublished observation, 1989), again suggesting that the time period between infection and serious illness among FIV-infected cats can be as long as 5 years or more.

2. Clinical Staging

An attempt has been made to define the clinical course of FIV infection of cats in five stages, analogous to those of HIV infection of man (Ishida *et al.*, 1990). The five clinical stages of HIV infection of humans are: (1) acute, (2) asymptomatic carrier, (3) persistent generalized lymphadenopathy (PGL), (4)

AIDS-related complex (ARC), and (5) AIDS. A similar classification scheme for FIV-related disease has been advocated by Shelton and colleagues (1990b). This author also favors such a classification scheme, except for the inclusion of a sixth category to cover miscellaneous disorders and the recognition of FeLV as an opportunistic infection. The classification scheme used hereafter contains the following stages: (1) stage 1 infection, (2) stage 2 infection, (3) stage 3 infection, (4) stage 4 infection, (5) stage 5 infection, and miscellaneous disease (Table III). Miscellaneous diseases, e.g., malignancies, ocular, neurologic, or immunologic disorders, were excluded under AIDS-like disease by Shelton and associates (1990b) because they can occur as sole manifestations of FIV infection. Therefore, it is preferable to classify these latter miscellaneous disorders, when not accompanied by ARC-like or AIDS-like signs, in a separate category.

3. Clinical Signs of Disease

a. Stage 1 Infection

Both FIV and HIV infections have a well-defined first stage of illness (Cooper *et al.*, 1985; Yamamoto *et al.*, 1988b; Barlough *et al.*, 1991; Callanan *et al.*, 1992b; Moraillon *et al.*, 1992). The primary phase of the infection is characterized by varying degrees of fever, diarrhea, gingivitis, conjunctivitis, uveitis, jaundice, secondary bacterial sepsis, neutropenia (often associated

TABLE III. Clinical Stages of FIV Infection in Domestic Cats, Their Approximate Duration, and the Major Disease Signs Associated with Each Stage

Clinical state	Duration	Major clinical features
1	0–2 weeks	Varying degrees of generalized lymphadenopathy, fever, leukopenia, neutropenia, diarrhea
2	>1–5 years	No clinical signs of illness
3	months to years	Vague signs of ill-health including fevers, lymphadenopathy, bouts of inappetence and weight loss, arthritis, vague behavioral abnormalities
4	1/2–1 years	Secondary, but not opportunistic, infections of the oral cavity, nasal passages, skin, digestive tract; less than 20% weight loss; hematologic abnormalities (anemia, leukopenia, neutropenia, lymphopenia) in less than one-third of the affected cats, ± miscellaneous signs listed below
5	months	Opportunistic infections, weight loss greater than 20%, hematologic abnormalities (anemia, leukopenia, neutropenia, lymphopenia) in most cases, ± miscellaneous signs listed below
Miscellaneous	months	Neurologic abnormalities, ocular disease, lymphoid or myeloid disorders, malignancies, increased incidence of certain solid tumors, ocular disease, immunologic disease

with a mild to moderate leukopenia), and generalized lymphadenopathy. The fever and other clinical signs persist for a few days to several weeks before disappearing. The generalized lymphadenopathy, which can be pronounced, persists for 2 to 9 months before subsiding. The severity of primary disease signs varies with age; newborn kittens develop the most florid and persistent lymphadenopathy, followed in severity by adolescents. Geriatric cats (>10 years) show minimal primary disease signs (George and Pedersen, 1992), but they progress to stages 3, 4, and 5 much more rapidly (Pedersen, N. C., University of California, Davis, personal observation, 1992).

Mortality during the initial stage of infection is low with good supportive care, e.g., antibiotics to control secondary bacterial infections and fluids to correct dehydration. Secondary bacterial sepsis is particularly troublesome during the primary stage of infection because of the profound neutropenia that occurs in some animals. Only 1 of over 60 specific pathogen-free cats that we have exposed to FIV has died during the primary stage of infection, and this animal died of a myeloproliferative disorder (Yamamoto *et al.*, 1988b). However, 5/10 cats that were asymptomatic FeLV carriers prior to being infected with FIV died within 2 months (Pedersen *et al.*, 1990).

The first stage of FIV infection is reminiscent of the primary stage of FeLV infection, except that cats acutely infected with FIV do not usually become anemic or thrombocytopenic like cats acutely infected with FeLV (Pedersen *et al.*, 1977; Yamamoto *et al.*, 1988b). Furthermore, a majority of cats with acute FeLV infection become aviremic and make a complete recovery within the first 16 weeks of exposure. FIV infection appears to be lifelong in virtually all cats.

b. Stage 2 Infection

Following the disappearance of fever, relative or absolute leukopenia and/or neutropenia, gastrointestinal signs, and generalized lymphadenopathy, experimentally infected cats go into a long period of clinical normalcy (Yamamoto *et al.*, 1988b). The virus can be re-isolated from the blood from all of the infected cats even though they may appear outwardly normal. The length of time between the primary and third stages of infection has not yet been precisely determined. However, a decrease in the absolute numbers of $CD4^+$ T lymphocytes with inversion of the $CD4^+/CD8^+$ T-lymphocyte ratio, a decreased lymphocyte blastogenesis response to pokeweed mitogen and concanavalin-A, and a hypergammaglobulinemia are often evident by 18 to 24 months or more after initial experimental infection (Ackley *et al.*, 1990; Barlough *et al.*, 1991).

The proportion of cats that remain in stage 2 of their infection is unknown. Unlike HIV infection of man, which often progresses to death, there is evidence that a significant proportion (up to 2/3) of FIV-infected cats may carry FIV for life with minimal disease problems. The time period that cats are in stage 2 before progressing to stage 3 is also unknown, but is probably as great as 5 years or more. Thus, FIV-infected cats may spend a much greater proportion of their lives in stage 2 than people infected with HIV. Like man, the stage of life when infection occurs can also influence this time period.

Cats infected when they are 10 years of age or older often progress through stage 2 within 6 to 12 months, whereas animals infected as kittens, adolescents, or young adults take much longer (George and Pedersen, 1992).

c. Stage 3 Infection

About one-third or more of all FIV-infected cats are brought to veterinarians for stage 3 disease. The third stage of FIV infection is probably equivalent to the PGL stage of HIV infection (Ishida *et al.*, 1990). This stage usually precedes stage 4 disease by many months or years.

The third stage is characterized by vague signs of disease and without obvious secondary or opportunistic infection. Signs of illness that cause owners to seek veterinary care include recurrent fevers of undetermined origin, leukopenia, lymphadenopathy, anemia, unthriftiness, inappetence, weight loss, or nonspecified changes in normal behavior (Belford *et al.*, 1989; Hopper *et al.*, 1989; Gruffydd-Jones *et al.*, 1988; Ishida *et al.*, 1989; Kölbl and Schuller, 1989; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989; Lutz *et al.*, 1990; Zenger, 1990). The lymphadenopathy seen in these cats resembles that previously described by Moore and colleagues (1986). Without obvious signs of chronic secondary or opportunistic infections, the diagnosis of FIV infection can be easily missed in this stage.

d. Stage 4 Infection

About one-half of all clinically ill FIV-infected cats present with signs that are reminiscent of the ARC stage of man (Ishida *et al.*, 1990; Shelton *et al.*, 1990b). Cats with ARC-like illness usually present with chronic secondary, but not opportunistic, infections at one or more sites in the body. Secondary infections are usually of bacterial origin. Cats with stage 4 illness will usually exhibit weight loss less than 20% of their body weight, one-third of them have hematologic abnormalities (anemia, leukopenia, neutropenia, or lymphopenia), and some have generalized lymphadenopathy, fevers of inapparent origin, or other signs of illness (Shelton *et al.*, 1990b). Many cats with stage 4 disease and ARC-like signs will develop a terminal AIDS-like syndrome from 6 months to 1 year or more later (Ishida *et al.*, 1992).

Chronic progressive infections of the mouth, including the gingiva, periodontal tissues, cheeks, oral fauces, or tongue are observed in one-half or more of the cats with stage 4 FIV infection (Gruffydd-Jones *et al.*, 1988; Hopper *et al.*, 1989; Ishida *et al.*, 1989, 1990; Knowles *et al.*, 1989; Kölbl and Schuller, 1989; Neu *et al.*, 1989a,b; Shelton *et al.*, 1989c; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989; Zetner *et al.*, 1989) (Fig. 5).

About one-fourth of the FIV-infected cats with stage 4 disease present to the veterinarian with chronic upper respiratory infections involving the lungs (chronic bronchitis, bronchiolitis, pneumonitis), nasal passages (rhinitis), and conjunctival membranes of the eyes (conjunctivitis) (Pedersen *et al.*, 1987; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989; Bennett *et al.*, 1989; Hopper *et al.*, 1989; Ishida *et al.*, 1989; Zenger, 1990) (Fig. 6). Respiratory

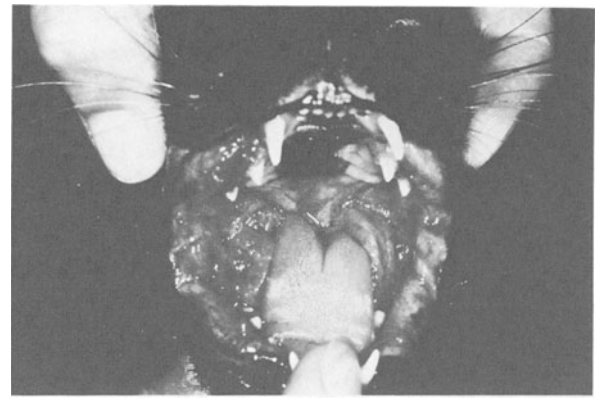

FIGURE 5. The gross appearance of the mouth of an FIV-infected cat with severe ulceroproliferative stomatitis. Photograph courtesy of Dr. Tak Ishida, Nippon Veterinary and Zootechnical College, Tokyo, Japan.

signs can occur by themselves or in association with infections in other areas of the body.

Chronic enteritis, usually manifested by loose or diarrheic stools and some degree of weight loss, is the main clinical complaint in 10% of the cats with ARC-like disease (Pedersen *et al.*, 1987; Ishida *et al.*, 1988, 1989; Belford *et al.*, 1989; Hopper *et al.*, 1989; Gruffydd-Jones *et al.*, 1988; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989; Zenger, 1990). Bowel disease is probably more common than this; many cat owners do not examine their cat's stools and are unaware of any problems.

Chronic bacterial infections of the upper or lower urinary tract are seen in a small proportion of FIV-infected animals (Grindem *et al.*, 1989; Lutz *et al.*, 1990). About 10% or so of clinically ill FIV-infected cats will present with bacterial infections of the skin or subcutis. Skin lesions are usually caused by *Staphylococcus*. Chronic abscesses have been observed in FIV-infected cats by several groups (Grindem *et al.*, 1989; Ishida *et al.*, 1989; Kölbl and Schuller, 1989; Shelton *et al.*, 1989c, 1990b). Abscesses are usually caused by the same types of aerobic and anaerobic bacteria that inhabit the mouths of normal cats. A small proportion of cats with stage 4 illness may also manifest

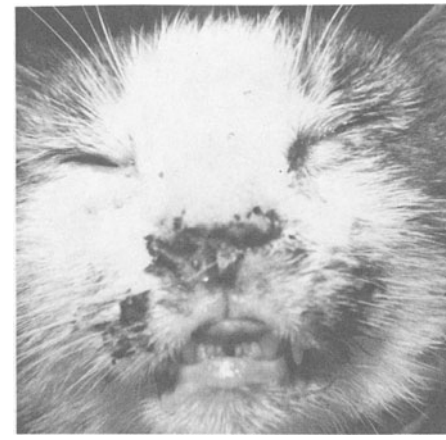

FIGURE 6. A dually FIV- and FeLV-infected cat with severe chronic feline herpesvirus, type 1, keratoconjunctivitis, rhinitis, and stomatitis.

neurologic, ocular, renal, immunologic, or neoplastic disorders (see following discussion of miscellaneous FIV-related disorders).

e. Stage 5 Infection

Less than 10% of clinically ill FIV-infected cats present with a disease syndrome analogous to the AIDS stage of human HIV infection. The proportion would be higher were it not for the common practice of euthanatizing affected cats (usually in stage 4 illness) when they appear to be suffering with no hope of cure. Stage 5 illness usually precedes over a period of many months or several years from stage 4 disease. Cats with AIDS-like illness, like their human counterparts, are often suffering from opportunistic infections in multiple sites of the body; they have lost greater than 20% of their body weight, and most are anemic and leukopenic (Ishida *et al.*, 1989; Shelton *et al.*, 1990b) (Fig. 7). Ishida and associates (1990) and Shelton and colleagues (1990b) excluded cats with concurrent FeLV infections from this category, probably because AIDS-like disease can occur in cats infected with FeLV alone. However, both experimental and laboratory evidence shows that FeLV/FIV-infected cats are more apt to become seriously ill than those infected with FIV alone (see section following). For this reason, this author chooses to place cats with AIDS-like disease and FeLV/FIV co-infections in this category.

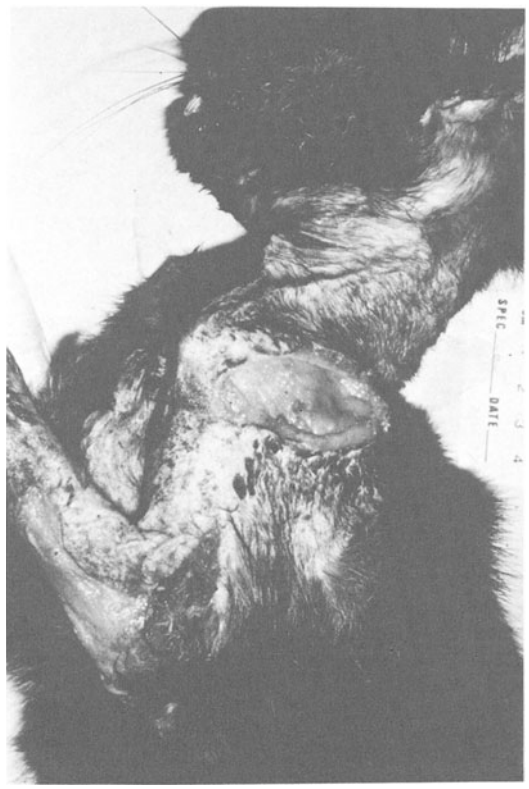

FIGURE 7. A severely cachectic FIV-infected cat with widely disseminated cryptococcosis of the skin and internal organs. Note the extreme degree of emaciation and open wounds over shoulder and foreleg. The stage of FIV-related disease in this cat would be equivalent to the AIDS stage of HIV infection of man. Photograph courtesy of Dr. Tak Ishida, Nippon Veterinary and Zootechnical College, Tokyo, Japan.

Cats with AIDS-like illness usually die within 1 to 6 months, even with the most intense supportive therapy (Ishida *et al.*, 1990; E. Sparger and N. C. Pedersen, University of California, Davis, unpublished observation, 1990).

A number of infections of an opportunistic nature have been seen in FIV-infected cats in the AIDS-stage of illness. Rodent poxvirus infection (Brown *et al.*, 1989), feline calicivirus (Knowles *et al.*, 1989; Tenario *et al.*, 1990), toxoplasmosis (Witt *et al.*, 1989), *Streptococcus canis* (Pedersen *et al.*, 1991), cryptococcosis and candidiasis (Ishida *et al.*, 1989, 1990; Malik *et al.*, 1992) (Fig. 7), generalized demodectic (Chalmers *et al.*, 1989; Swinney *et al.*, 1989), and notoedric mange (Ishida *et al.*, 1989), mycobacteriosis (Ishida *et al.*, 1989; Swinney *et al.*, 1989), dirofilariasis (Zenger, 1990), and haemobartonellosis (Ishida *et al.*, 1988; Belford *et al.*, 1989; Grindem *et al.*, 1989; Hopper *et al.*, 1989) have all been observed as complicating infections in FIV-infected cats.

f. Miscellaneous FIV-Related Disorders

i. Neurologic Disorders. About 5% of clinically ill FIV-infected cats will have neurological abnormalities as the predominant clinical feature of their disease (Shelton *et al.*, 1989c; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989; Kölbl and Schuller, 1989; Neu, 1989a; Zenger, 1990). Neurological signs can also be an accompanying feature of a more generalized ARC-like or AIDS-like syndrome in a similar proportion of cats (Pedersen *et al.*, 1987; Harbour *et al.*, 1988; Shelton *et al.*, 1989c). Neurological signs can be a direct effect of the virus on brain cells (commonly) (Dow *et al.*, 1990), or a manifestation of some other opportunistic infection (uncommonly) (Heidel *et al.*, 1990). Neurologic abnormalities in FIV-infected cats tend to be more behavioral than motor. Dementia, twitching movements of the face and tongue, psychotic behavior (hiding, rage, over-aggression), loss of toilet training, and compulsive roaming have all been recognized in FIV-infected cats (Harbour *et al.*, 1988; Belford *et al.*, 1989; Shelton *et al.*, 1989c; Yamamoto *et al.*, 1989). Convulsions, nystagmus, ataxia, and intention tremors are also observed in some FIV-infected cats. The author has observed an FIV-infected cat that presented with acute posterior paralysis associated with a spongiform degeneration of the spinal cord (B. Rideout and N. C. Pedersen, University of California, Davis, unpublished observation, 1990). Swinney and colleagues (1989) described an oculomotor nerve paralysis in one FIV-infected cat and a flaccid forelimb paralysis in another.

Even though only 5% or so of FIV-infected cats exhibit abnormal neurologic signs, a much greater proportion of naturally and experimentally infected cats have microscopic lesions in their central nervous system (Dow *et al.*, 1990). Is it possible that many FIV-infected cats have subclinical neurologic abnormalities? Indeed, Wheeler and colleagues (1990) found that many naturally FIV-infected animals without outward neurologic abnormalities had abnormally slow motor and sensory nerve conduction velocities. The pattern of these defects suggested to them that FIV-infected cats had a selective nerve fiber dropout in the peripheral nerves, dorsal roots, and/or ascending spinal cord tracts. They also found evidence of demyelination in the dor-

sal columns of the spinal cord, selective fiber loss in nerve fasicles, and prominent vacuolar changes in myelin sheaths of dorsal and ventral nerve roots.

ii. Ocular Disease. Inflammatory disease of the eye, in particular the anterior uveal tract, has been seen in several FIV-infected cats from the field (English *et al.*, 1990; Gruffydd-Jones *et al.*, 1988). Some eye lesions are caused by other agents, in particular *Toxoplasma gondii* (Lappin *et al.*, 1990). In other cases, no obvious agent can be identified (English *et al.*, 1990). Glaucoma, with or without concurrent uveitis, and a *pars planitis*-like disorder are two other ocular conditions that have been associated with FIV infection (English *et al.*, 1990). *Pars planitis* in humans is a nonpainful and slowly progressive ocular disorder that is manifested by white, nodular infiltrates in the anterior vitreous and is often associated with a peripheral retinal vasculitis and a perivascular mononuclear cell infiltrate. It is thought to be immune-mediated in people.

iii. Renal Disease. Renal disease of an unspecified type has been observed as a complicating feature of FIV infection in some cats (Belford *et al.*, 1989; Ishida *et al.*, 1989; Swinney *et al.*, 1989). Whether this merely reflects the tendency of FIV-diseased cats to be of advanced age (renal disease is common in old cats), or whether there is a definite cause and effect relationship remains to be established. Cystitis of bacterial or unknown origin has been seen in some FIV-infected animals (Gruffydd-Jones *et al.*, 1988; Shelton *et al.*, 1989a,c; Yamamoto *et al.*, 1989).

iv. Immune-Mediated Disease. Several types of immune-mediated diseases may be associated in some way with FIV infection in cats (N. C. Pedersen, University of California, Davis, unpublished observations, 1990). A proportion of anemic FIV-infected cats have a Coomb's positive anemia. Such anemias are common with haemobartonellosis, and because *Haemobartonella felis* is not easy to identify in the blood of some chronically infected animals, it is not always possible to ascribe the anemia solely to immunologic mechanisms when no organisms are seen. The author has treated several cats with immune-mediated thrombocytopenia and/or arthritis. Arthritis has also been observed in FIV-infected cats by Dow and colleagues (1990) and Hopper and associates (1989). *Pars planitis*, a possibly immune-mediated vascular disease of the eye of humans, has also been recognized in FIV-infected cats (English *et al.*, 1990).

v. Neoplasia. There is mounting evidence that FIV-infected cats have a higher incidence of certain types of cancers. It is not yet certain how FIV is associated with these cancers, i.e., is it oncogenic like FeLV, does it increase cancer incidence by decreasing tumor immunosurveillance mechanisms, or does it allow other cancer-causing agents to be activated?

Cancers that appear to be FIV-associated are of several types: (1) lymphoid tumors (lymphosarcoma), (2) myeloid tumors (myelogenous leukemia, myeloproliferative disease), and (3) miscellaneous solid carcinomas and sarcomas. Lymphosarcomas have been observed in a number of FeLV-negative, FIV-infected cats (Alexander *et al.*, 1989; Belford *et al.*, 1989; Gruffydd-Jones *et al.*, 1988; Buracco *et al.*, 1992; Hopper *et al.*, 1989; Ishida *et al.*, 1989; Kölbl and Schuller, 1989; Sabine *et al.*, 1988; Shelton *et al.*, 1989b, 1990a; Yama-

moto *et al.*, 1989). The most convincing study on the relationship between FIV infection and lymphosarcoma has been presented by Shelton and co-workers (1990a). They found that the relative risks for developing leukemia/lymphoma were 5.6, 62.1, and 77.3 times greater in cats infected with FIV, FeLV, or FeLV/FIV, respectively. Lymphoid tumors tended to occur in FeLV-infected cats with a mean age of 3.8 years, and in FIV-infected cats with a mean age of 8.7 years (Shelton *et al.*, 1990a). Lymphoid tumors in FIV-infected cats have been frequently associated with the head and neck (nasopharyngeal lymphomas). Lymphoid tumors in the nasal passages appear to arise out of surrounding plasmacytic-lymphocytic inflammation and to be of the B-cell type.

At least two occurrences of lymphosarcoma have been observed in specific pathogen-free cats inoculated only with FIV. One cat inoculated with FIV as a young adult developed a lymphosarcoma affecting the liver and kidneys 36 weeks later (Callanan *et al.*, 1992a). A second specific pathogen-free cat, which was infected with FIV when 10 years old, died of an intestinal lymphosarcoma 1 year later (N. C. Pedersen, University of California, Davis, personal observation, 1992). Lymphomas were never observed in nonretrovirus-infected cats from both of these laboratories, indicating that FIV alone can in some way cause or enhance these tumors.

Myeloproliferative disorders have also been seen in some FeLV-negative, FIV-infected cats that presented with severe anemias and leukopenias (Belford *et al.*, 1989; Ishida *et al.*, 1989; Pedersen, unpublished observation, 1989; Yamamoto *et al.*, 1989). A myeloproliferative disorder has been induced in a specific pathogen-free cat experimentally infected with just FIV for several months (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1988b), suggesting once again that FIV may be in some way oncogenic. It is interesting to note that myeloid neoplasms and myelodysplasias (preleukemias) are common in cats, and only 70% of them can be directly linked to FeLV infection (Blue *et al.*, 1988). It appears, therefore, that FIV might be another retrovirus cause of myeloid leukemias and myelodysplasias in cats.

Shelton and co-workers (1990) observed feline sarcoma virus-induced fibrosarcomas in two cats that were co-infected with both FeLV and FIV, which seemed unusual. Ishida and colleagues (1989) described FIV-infected cats with FeLV-negative multicentric sarcomas. Hopper and co-workers (1989), Neu (1989a), and Zenger (1990) reported a high incidence of various rare types of tumors in FIV-infected cats. Many of these tumors occur in the head, such as nasal adenocarcinomas. FIV infection has also been diagnosed in some older cats with squamous cell and mammary gland carcinomas (Hopper *et al.*, 1989; Ishida *et al.*, 1989; Kraegel, unpublished observation, 1989; Neu, 1989a). The rate of FIV infection among cats with squamous cell carcinomas of the mouth and skin at the School of Veterinary Medicine, University of California, Davis, has been about 10–20%, which appears higher than chance. However, cats with squamous cell carcinomas tend to be older, more often male, and inevitably outdoor roaming, all of which are risk factors for FIV infection as well. More studies are needed before FIV can be considered either a co-factor or cause of these unusual solid tumors of cats.

C. Diagnostic and Hematologic Factors

1. FIV Antibody Detection

FIV infection is currently diagnosed by detecting antibodies in the blood. Because cats do not usually recover from FIV infection, a direct correlation exists between the presence of antibodies and virus infection (Yamamoto *et al.*, 1989). Antibodies can be detected by an indirect fluorescent antibody (IFA) assay using FIV-infected T-lymphocyte-enriched peripheral blood mononuclear or CrFK cells as a substrate, by ELISAs using specific FIV proteins or peptides produced by recombinant DNA technology (Fotenot *et al.*, 1992; Mermer *et al.*, 1992; Reid *et al.*, 1991), or by ELISA or Western blotting using gradient-purified tissue culture-grown virus as a source of antigen (Pedersen *et al.*, 1987; O'Connor *et al.*, 1989; Yamamoto *et al.*, 1988b). Antibodies usually appear within 2 to 4 weeks of experimental infection and remain at detectable levels more or less for the rest of the animal's life (Yamamoto *et al.*, 1988b; O'Connor *et al.*, 1989). However, a small proportion of experimentally infected cats may not demonstrate antibodies for up to a year following infection (Yamamoto *et al.*, 1988b).

ELISA tests, in particular those using tissue culture propagated whole virus, suffer from a low percentage of false-positives, perhaps on the order of 2% to 20% (Hosie and Jarrett, 1990; N. C. Pedersen, University of California, Davis, unpublished observation, 1990). The rate of false-positives has decreased greatly as the specificity of the commercially available diagnostic tests has been improved. False-positive reactions are particularly troublesome in low-risk groups of cats, such as purebred catteries where testing is often required as a condition for sale. In such environments, the incidence of false-positive serological reactions may greatly exceed the true incidence of the infection. Such cats are heavily vaccinated and often have serum antibodies against cat cell antigens. Cat cell and tissue culture antigens often contaminate antigen preparations used for most ELISAs, because the virus is propagated in cat cell cultures (Barlough *et al.*, 1984).

The Western blot and IFA tests are not quite as sensitive as ELISA, but may be more specific. However, care must be taken in reading weak bands of reaction in the 25 and 70 kDa regions of the immunoblot strips. Many cats have low levels of antibodies that react against nonviral proteins that band in these regions. The IFA test is also not entirely foolproof, because the titer of antibodies in many cat sera is very low and the test is often read at the limits of its sensitivity. If FIV-infected T lymphocytes are used as the substrate, a nonspecific reaction can occur if the sera contains antilymphocyte antibodies.

A small proportion of cats in long-term contact with FIV-seropositive animals never have detectable levels of antibody in their blood, yet have recoverable virus in their peripheral blood lymphocytes (Harbour *et al.*, 1988; Hopper *et al.*, 1988, 1989; Dandekar *et al.*, 1992). These cats may be analogous to the sexual partners of AIDS-patients who have genomic virus in their body by the polymerase chain reaction (PCR) or virus isolation for months or years prior to seroconversion (Imagawa *et al.*, 1989; Pezzella *et al.*, 1989).

2. FIV Antigen Detection

Tests that detect viral antigen in the blood, similar to those used in FeLV testing, are being researched at this time. An ELISA test using two different mouse monoclonal antibodies to FIV-p24, and capable of detecting 0.2 ng/ml of free antigen, has been developed (Tilton *et al.*, 1990). However, the test cannot reliably detect antigen in the blood of FIV-infected cats and has been used mainly to detect viral antigens in tissue culture fluids of peripheral blood mononuclear cell cultures from infected cats.

3. FIV Proviral DNA Detection

The polymerase chain reaction (PCR) has been used to detect FIV proviral DNA in tissues (Pedersen *et al.*, 1990; Dandekar *et al.*, 1992; Hohdatsu *et al.*, 1992). The highest concentration of proviral DNA is found in bone marrow, and mesenteric and peripheral lymph nodes. Intermediate levels of proviral DNA are seen in blood and brain, and very low levels in organs such as the kidney, lungs, and liver. Much higher levels of viral DNA are seen in FIV/FeLV-infected cats than in cats infected with FIV alone (Pedersen *et al.*, 1990).

4. Virus Detection by *In Situ* Hybridization

Viral RNA has been demonstrated in the tissues of FIV-infected cats by RNA *in situ* hybridization (Lackner *et al.*, 1991) (Fig. 2). Viral RNA tends to be concentrated in macrophage-type cells and lymphocytes in lymphoid organs and brain, and macrophage-type cells and megakaryocytes in bone marrow (Beebe *et al.*, 1992). Mucosal and epithelial cells have not contained viral RNA.

5. Virus Isolation

It is relatively easy to isolate virus from plasma and peripheral blood mononuclear cells (PBMC) during the first few months of infection, but more difficult in later stages (Bandecchi *et al.*, 1992; N. C. Pedersen, University of California, Davis, personal observation, 1992). Plasma is co-cultivated directly with ConA and IL-2-stimulated PBMC from uninfected donor cats. In the case of PBMC isolation, host PBMC are first stimulated for several days with ConA and IL-2 before being co-cultivated. Cultures should be maintained for 6 to 10 weeks before being discarded as negative; the higher the amount of input virus the sooner the infection can be detected in the cultures. In cases where virus cannot be isolated *in vitro* from PBMC or plasma, whole blood from the infected individual should be inoculated into susceptible animals and virus isolation performed 4 to 6 weeks later from the blood of the recipient (Pedersen *et al.*, 1987). The best tissues for primary isolation of FIV are the lymph nodes (particularly the mesenteric nodes), bone marrow, and PBMC. The virus is present as a latent infection in peritoneal macrophages and can be rescued by co-cultivation with stimulated PBMC (Brunner and Pedersen, 1989).

6. Hematologic Abnormalities

Although no hematologic abnormalities are pathognomonic for FIV infection, a number of blood changes have been observed in FIV-infected animals. A leukopenia, due mainly to an absolute neutropenia, is commonly seen in the primary stage of FIV infection (Yamamoto *et al.*, 1988b). The neutropenia tends to reach a nadir between 6 to 10 weeks postinfection and then returns to normal or near-normal levels thereafter (Mandell *et al.*, 1992). A relative or absolute neutropenia tends to reappear with time in experimentally infected cats and is often a measure of disease activity. The neutropenia is associated with myeloid hyperplasia and a left shift to promyelocytes (Mandell *et al.*, 1992).

Hematologic abnormalities are also common in naturally FIV-infected cats with advanced ARC-like or AIDS-like disease signs, or in cats with myeloproliferative disorders or immune-mediated hemolytic anemias (Harbour *et al.*, 1988; Ishida *et al.*, 1988, 1989; Belford *et al.*, 1989; Grindem *et al.*, 1989; Gruffydd-Jones *et al.*, 1988; Hopper *et al.*, 1989; Shelton *et al.*, 1989a,c, 1990b; Swinney *et al.*, 1989; Yamamoto *et al.*, 1989; Zenger, 1990). The main abnormalities are leukopenia and anemia. Shelton and co-workers (1990b) recognized anemia, lymphopenia, neutropenia, and thrombocytopenia in 36%, 53%, 34%, and 8%, respectively, in FIV-infected cats in the ARC-like and AIDS-like stages of illness. The leukopenia can be attributable to an absolute granulocytopenia, an absolute lymphopenia, or both. The anemias are usually nonresponsive in nature. Examination of bone marrow often shows either marrow hyperplasia (immune-mediated anemias) or myeloid dysplasia (myeloproliferative disorders). Maturation arrests, particularly in the red blood cell series, are common. Monocytosis and lymphocytosis have been observed in a proportion of FIV-infected cats (Hopper *et al.*, 1989).

Bone marrow cytology was found to be abnormal in 72% of examined cats with ARC-like and AIDS-like diseases (Shelton *et al.*, 1990b). Abnormalities consisted of either hyperplasia of dyspathic changes. Dyspathic changes included abnormal-appearing cells, increased numbers of plasma cells and lymphocytes, increased numbers of eosinophils, maturation abnormalities such as megaloblastic erythropoiesis, neoplastic infiltrates, or necrosis.

Despite the fact that the bone marrow seems to be affected in FIV infection, the level of virus replication (mainly in megakaryocytes and mononuclear cells) in bone marrow is quite low as measured by *in situ* RNA-hybridization (Beebe *et al.*, 1992). However, the numbers of infected cells in the bone marrow increase in proportion to the overall disease severity.

Linenberger and colleagues (1991) demonstrated that the *in vitro* behavior of hematopoietic projenitors is not affected by FIV infection alone. They felt that as in HIV infection, factors associated with the development of progressive immunodeficiency opportunistic infections, nutritional deficiencies, or malignancies may play significant roles in the ceropenias observed in later stages of FIV infection. However, such secondary factors do not explain the profound neutropenia seen in the primary stage of infection.

Hypergammaglobulinemia occurs in about one-third, and elevated levels of serum IgG in about one-half, of all FIV-infected cats presenting with clini-

cal signs of illness (Hopper *et al.*, 1989). The hypergammaglobulinemia is not due just to opportunistic infections. Specific pathogen-free cats that are infected just with FIV, and not exposed to any other pathogens, show a progressive hypergammaglobulinemia with time compared to noninfected littermate controls (Ackley *et al.*, 1990).

III. INFECTION AND IMMUNITY

A. Antiviral Immunity of the Host

1. Humoral Immunity

Antibodies to the 24 (capsid), 41 (transmembrane), and 50 (*gag* precursor) kDa virion proteins are the first to appear in the serum following experimental infection, followed shortly by antibodies to the 10 (nucleocapsid), 15 (matrix), 31 (integrase?), and 62 (reverse transcriptase) kDa proteins (Yamamoto *et al.*, 1988b; O'Connor *et al.*, 1989). Antibodies to the 95-kDa surface glycoprotein measured by RIP-PAGE appear early in the course of infection and tend to remain high throughout the subsequent disease course (O'Connor *et al.*, 1989; Steinman *et al.*, 1989). Antibodies to FIV-gp95 are usually not measurable in Western blots using whole virus. The SU glycoproteins are easily sheared from the virions during the purification and do not transfer well onto the nitrocellulose paper.

Antibodies that will inhibit the *in vitro* activity of the FIV reverse transcriptase appear early after infection but rise only slowly over a period of several years (Fevereiro *et al.*, 1991). Inhibitory activity of serum IgG from experimentally FIV-infected cats was 2.9%, 18.4%, 33%, and 47% at postinfection months 6, 12, 24, and 36, respectively. The inhibitory activity of the antibodies was specific for the RT of FIV and not RTs of other retroviruses. The authors concluded that the level of inhibitory IgG in the serum might be a useful measure of the chronicity of FIV infection in nature, with maximal levels occurring only after 2 years.

Virus-neutralizing antibodies are present at 3 months, and probably earlier, after infection (Tozzini *et al.*, 1992). Neutralizing antibodies have been measured by both conventional infectivity inhibition assays (Yamamoto *et al.*, 1991b) and by the inhibition of syncytium formation (Tozzini *et al.*, 1992).

2. Cell-Mediated Immunity

FIV-specific cytolytic T cells against FIV-infected T lymphocytes can be detected as early as 7 to 9 weeks postinfection (Song *et al.*, 1992). This corresponds with the termination of the primary stage of illness and is several weeks later than the time when serum antibodies appear. Effector cells are composed predominantly of $CD8^+$ T cells, and specific cell killing is histocompatibility class I restricted.

3. Antiviral Immunity in the Central Nervous System

Dow and co-workers (1990) have investigated the association of FIV with the central nervous system (CNS) of naturally and experimentally infected cats. They detected FIV antibodies in the cerebrospinal fluid (CSF) of 9/10 naturally infected cats and were able to culture the virus from the CSF of 5/9 of these animals. Infection of the CNS of experimentally FIV-infected cats was often associated with pleocytosis in the CSF, increased CSF IgG levels, elevated CSF IgG index, and local FIV antibody production.

4. Immunity of FIV-Infected Cats to Incidental Infectious Diseases

Various studies have been conducted on how experimentally FIV-infected cats handle other common incidental feline infectious diseases. All these studies have involved cats that have been either in the primary or asymptomatic carrier stage of their infections. Cats in the primary stage of FIV infection became more ill than did their non-FIV-infected cohorts after being artificially infected with feline calicivirus, and they had diminished antibody responses (Dawson *et al.*, 1991). FIV-infected cats in a similar stage of infection also became sicker after being infected with *Chlamydia psittaci* var. *felis* than did noninfected animals (O'Dair *et al.*, 1991). A similar finding was also observed for cats in the asymptomatic stage of FIV infection that were artificially infected with feline herpesvirus, type 1 (FHV-1) (Reubel *et al.*, 1992). FIV-infected cats became significantly sicker following FHV-1 infection than their noninfected cohorts but otherwise handled the disease remarkably well and with no mortality. The only immunologic deficiencies in the anti-FHV-1 responses were a decreased primary anti-FHV-1 IgM antibody response and a slight delay in the appearance of virus-neutralizing antibodies in the serum. Studies such as these indicate the importance of the host's immunologic reserves; although FIV-infected cats in the early stages of their infection have significant defects in various immune parameters and one-half the levels of $CD4^+$ T cells, they are still able to respond to common infectious diseases in a reasonably normal manner.

B. Immunopathogenesis

Reports on the immunologic status of both experimentally and naturally FIV-infected cats are only now beginning to appear. These studies were made possible by the recent development of pertinent mouse monoclonal antibodies to feline lymphocyte cell surface markers (Klotz and Cooper, 1986; Ackley *et al.*, 1989, 1990; Tompkins *et al.*, 1990). These reagents have made it possible to study changes in lymphocyte subsets during the course of natural and experimentally acquired FIV infection. Nonspecific phytomitogen-induced lymphocyte blastogenesis studies have also been applied to FIV infection, as well as antigen-induced antibody responses to classical natural and synthetic T-dependent and T-independent immunogens. Table IV summarizes the ma-

jor immunologic abnormalities that have been recognized in domestic cats that have been infected either experimentally or naturally with FIV.

1. Abnormalities in Lymphocyte Subsets

Novotney and associates (1990) found that 13/19 naturally FIV-infected cats had $CD4^+$:$CD8^+$ lymphocyte ratios below the 5th percentile of normal noninfected cats, and 18/19 had ratios below 1. They found that the inverted ratios were due to a decrease in $CD4^+$ cells, while $CD8^+$ and pan-T and pan-B cells remained relatively normal. They concluded that such changes were somewhat specific for FIV infection, because analysis of a group of cats with a variety of chronic diseases, including FeLV infection, did not reveal such pronounced depressions in $CD4^+$ cell numbers and ratio inversions. Although these changes appeared to be characteristic of FIV infection, there was a poor relationship between the degree of $CD4^+$ cell depression in FIV-infected cats and clinical signs of illness. Similar findings have been described for naturally FIV-infected cats in Germany (Hoffmann-Fezer *et al.*, 1991).

The progressive decrease in $CD4^+$ T lymphocytes occurs in two basic stages (Torten *et al.*, 1991) (Fig. 8). A pronounced stepwise decrease is seen within 8 weeks of experimental infection. Thereafter, the decline is more gradual. The decrease in $CD4^+$ T lymphocytes was not associated with any changes in the $CD8^+$ T-lymphocyte population in one study (Barlough *et al.*, 1991), but with slightly increasing $CD8^+$ T-lymphocyte numbers in a second study (Ackley *et al.*, 1990). The absolute numbers of $CD4^+$ T lymphocytes in the blood of FIV-infected cats falls below the minimum range for normal cats by the second year or so of infection. The gradual decrease in the numbers of $CD4^+$ T lymphocytes is associated with an equally gradual inversion of the $CD4^+/CD8^+$ T-lymphocyte ratio (Ackley *et al.*, 1990; Barlough *et al.*, 1991) (Fig. 8).

TABLE IV. Immunologic Abnormalities That Have Been Recognized in FIV-Infected Cats

Leukopenia, neutropenia, lymphopenia
Progressive decline in the absolute numbers of $CD4^+$ T lymphocytes
Gradual inversion of the $CD4^+/CD8^+$ T lymphocyte ratio
Early and progressive decrease in lymphocyte responsiveness to pokeweed mitogen
Late and progressive decrease in lymphocyte responsiveness to concanavalin A
Hypergammaglobulinemia
Decreased primary antibody response to T-dependent, but not T-independent, synthetic antigens
Inhibition in the switch from IgM to IgG antibody synthesis in the primary immune response to natural T-dependent antigens
Decreased interleukin-2 production by concanavalin-A-stimulated peripheral blood mononuclear cell cultures
Diminished proliferative response of peripheral blood mononuclear cell cultures to saturating dosages of interleukin-2
Hyperplasia, atrophy, and dysplasia of lymphoid tissues

2. *In Vitro* Changes in Lymphocyte Mitogenic Responses

Hara and colleagues (1990) found a significant depression in ConA lymphocyte mitogen responsiveness in naturally FIV-infected cats compared to noninfected ones. Taniguchi and associates (1990) found a significant decrease in ConA-induced lymphocyte blastogenesis in the asymptomatic carrier stage of naturally infected cats, and the loss of mitogen responses became more pronounced for cats in the ARC stage of infection. Cats in the AIDS stage of infection had completely lost their mitogen responses. Siebelink and co-workers (1991) observed significantly reduced ConA, pokeweed mitogen (PWM), and lipopolysaccharide lymphocyte blastogenesis responses in five naturally FIV-infected, clinically ill cats compared to normal cats.

Lymphocyte mitogen responses have also been tested in specific pathogen-free cats that were experimentally infected with FIV. Lin and colleagues (1990) found that cats experimentally infected with FIV had significantly lower lymphocyte blastogenesis responses to concanavalin A (ConA), PWM, and phytohemagglutinin (PHA) than did noninfected cats. Siebelink and associates (1991) observed similar decreases in ConA, PWM, and lipopolysaccharide-induced lymphocyte blastogenesis in cats experimentally infected with FIV. Depressed responses to PWM appeared within the first 6 months of experimental FIV infection and became progressively worse with time (Barlough *et al.*, 1991). Lymphocyte blastogenic responses to ConA did not markedly decrease until 2 years or more into the infection, however. The decline in lymphocyte blastogenesis responses to PWM in experimentally infected cats seen during the first 6 months of infection was associated with only minor decreases in absolute numbers of $CD4^+$ T lymphocytes (Barlough *et al.*, 1991). Diminished ConA responses were only seen when $CD4^+$ T lymphocytes are

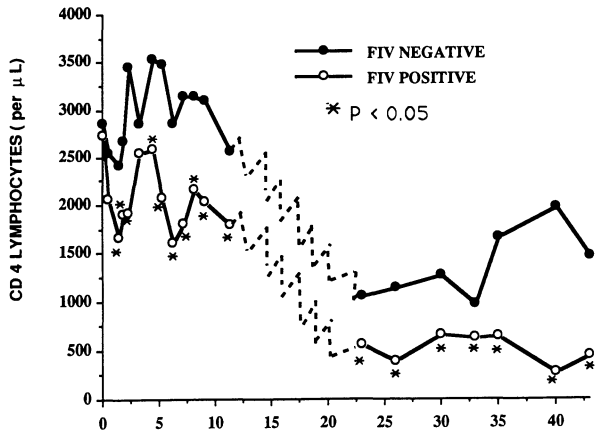

FIGURE 8. The mean absolute $CD4^+$ T-lymphocyte levels in the blood of two groups of cats, each containing 15 cats experimentally infected with FIV and 15 noninfected control cats. One group (right of broken lines) has been infected for almost 4 years, while the other group (left of broken lines) has been infected for 13 months. The cats were from the same parentages, were of mixed sex, and all of them were infected with FIV at 3 to 6 months of age with an injection of contaminated blood taken from an experimentally FIV-infected cat with impaired immunologic functions. The absolute levels of $CD4^+$ T lymphocytes fell precipitously during the first 8 weeks of infection, and then decreased less rapidly thereafter. Impaired immunologic functions are most evident from 18 to 24 months or more after infection when the absolute $CD4^+$ T-lymphocyte levels fall below 1000 cells/µl. The (*) indicates that the values for FIV-infected cats were significantly lower than those of their noninfected cohorts. Also note the normal decline in $CD4^+$ T-lymphocyte levels with aging in the noninfected group of cats.

markedly decreased, which was 2 years or more following infection (Barlough *et al.*, 1991).

Peripheral blood mononuclear cells (PBMC) from cats naturally or experimentally infected with FIV were found to produce significantly less interleukin-2 (IL-2) than noninfected control cats (Siebelink *et al.*, 1991). Mean levels of IL-2 in ConA-stimulated PBMC culture supernatants were 1 IU/ml for symptomatic FIV-infected cats and 13 IU/ml for FIV-negative control cats; asymptomatic naturally and experimentally infected cats had levels of 9–16 IU/ml. Peripheral blood mononuclear cells from clinically ill FIV-infected cats were significantly less responsive to saturating levels of IL-2 (100 IU/ml) than PBMC from healthy noninfected cats (Siebelink *et al.*, 1991). Peripheral blood mononuclear cells from asymptomatic cats with natural or experimentally induced FIV infections had intermediate depressions in their responses to exogenous IL-2.

Lawrence and co-workers (1992) studied lymphocyte mitogenic and cytokine responses during the first 30 days of experimental FIV infection. They demonstrated an early depression in the mitogenic responses of PBMC to ConA, PHA, and PWM. Mitogen responses of splenic lymphoid cells were also depressed at 10 days postinfection, whereas lymphocytes from mesenteric lymph nodes responded normally until 20 days after infection. Depressed mitogenic responses of spleen cells could not be augmented by exogenous IL-2, while IL-2 was partially effective in restoring mitogenic responsiveness of lymphoid cells from the mesenteric lymph nodes. The production of IL-2 was normal in cultured ConA-stimulated PBMC, slightly depressed in mesenteric lymph node cells, and slightly elevated in splenic cells. Tumor necrosis factor-α levels were significantly elevated in the plasma of infected cats by 10 days following inoculation.

3. Changes in Cell-Surface Receptor Expression

FIV appears to infect and replicate within both $CD4^+$ and $CD8^+$ T-lymphocyte cultures *in vitro* (W. C. Brown *et al.*, 1991). The level of virus replication and cytopathicity is somewhat greater, however, in $CD4^+$ than in $CD8^+$ T cells. The $CD4^+$ T-lymphocyte receptor is either down-regulated in some cultures, or left unchanged in others, following *in vitro* PBMC infection. Major histocompatibility complex (MHC-II) receptors are upregulated on T lymphocytes both *in vitro* and *in vivo* (Rideout *et al.*, 1992a).

Ohno and associates (1992) studied cell-surface receptors on naturally FIV-infected cats. The number of circulating PBMCs staining positive for the alpha IL-2 receptor (IL-2Rα) was increased in FIV-infected cats, as were the numbers of MHC-II^+ PBMC. PBMCs from FIV-infected cats, when stimulated *in vitro* with ConA, had depressed IL-2Rα expression.

4. Effect of FIV Infection on Nonspecific Humoral Immune Responsiveness

Cats that are experimentally infected with FIV demonstrate a gradual loss of antibody responsiveness to many T-dependent, but not T-independent

antigens. Specific pathogen-free cats infected with FIV for 5 to 6 months demonstrate relatively normal antibody responses to both synthetic T-dependent and T-independent antigens, whereas cats infected for 26 months or longer respond normally to T-independent but not T-dependent antigens (Torten *et al.*, 1991). FIV-infected cats immunized with tetanus toxoid and diphtheria antitoxin showed diminished antibody responses to primary immunization; the magnitude of antibody suppression was intermediate in FIV-infected cats with normal $CD4^+/CD8^+$ T-lymphocyte ratios and pronounced in cats with inverted ratios (S. Dandekar and J. Barlough, University of California, Davis, unpublished observation, 1990). Cats experimentally infected with FIV responded normally to a genetically engineered and *E. coli*-expressed FeLV envelope protein vaccine (Lehmann *et al.*, 1991). Several studies have been done on the antibody responses of FIV-infected cats to common incidental feline pathogens. FIV-infected cats responded less than normal, especially in primary immune responses, to feline herpesvirus (Reubel *et al.*, 1992) and feline calicivirus (Dawson *et al.*, 1991) infections.

Similar changes have also been observed in naturally FIV-infected cats. Taniguchi and colleagues (1991) found impaired primary, but not secondary, antibody responses to a T-cell-dependent antigen—sheep red blood cells (SRBC). In contrast, primary and secondary antibody responses to a T-cell-independent antigen, tri-nitro phenyl-lipopolysaccharide conjugate (TNP-LPS), were unaffected in FIV-infected cats. The impaired primary antibody response to SRBC was associated with an impairment of IgM to IgG switching.

The defect in the humoral immune responsiveness of FIV-infected cats is most pronounced in the primary immune response (Torten *et al.*, 1991; Reubel *et al.*, 1992) and becomes progressively more severe in proportion to the decline in absolute $CD4^+$ T-cell counts (Torten *et al.*, 1991). Bishop and associates (1992) found that naive $CD4^+$ T cells from FIV-infected cats were significantly impaired in their ability to be primed by key-hole limpet hemocyanin when compared to cells from noninfected control animals.

IV. LATENCY, PERSISTENCE, AND REACTIVATION

A. General Considerations

Virtually all cats infected with FIV remain infected for life (Yamamoto *et al.*, 1988b), although the status of the virus in the body is not known for all stages of the infection. Virus is actively shed in the saliva of most infected cats, regardless of their disease status (Yamamoto *et al.*, 1989). However, saliva from cats with advanced ARC-like or AIDS-like disease appears to be more infectious than saliva from healthy-appearing cats. Although salivary shedding is an active and persistent process, the FIV genome appears to be present in a latent form within peripheral blood mononuclear cells (PBMC). Virus only appears in PBMC cultures after they are stimulated with PHA and

IL-2, and then only after several weeks or more in culture (Pedersen *et al.*, 1987; Yamamoto *et al.*, 1988a).

Virus is present both within the plasma and PBMC components of whole blood (Pedersen *et al.*, 1987), and in the cerebral spinal fluid. The source of this plasma- and CSF-borne virus is not known.

B. Replication and Persistence of FIV within Macrophages

Macrophage or macrophage-like cells, rather than T lymphocytes, appear to be the principal reservoir for FIV in the body as based on a number of studies. Brunner and Pedersen (1989) were the first to demonstrate FIV replication and persistence within macrophages both *in vitro* and *in vivo*. Undifferentiated peritoneal macrophages from normal cats underwent a brief lytic and virus productive infection when infected *in vitro* with FIV. Following this initial infection, the macrophages became activated in morphology following FIV infection, differentiating into larger multinucleated giant cells. Following activation, the FIV infection went latent. Latently infected macrophages often formed huge syncytium cells, which were caused by the fusion of several activated multinucleated giant cells. If the peritoneal macrophages were activated to multinucleated giant cells by yeast prior to FIV infection, the lytic/virus productive stage of *in vitro* FIV infection did not occur. The activated macrophages were latently infected from the onset, but syncytium formation between activated multinucleated giant cells was still observed. FIV could be recovered from latently infected macrophages by stimulation with phorbol myristate acetate and co-cultivation with normal feline T lymphocytes (Brunner and Pedersen, 1989). Peritoneal and bone marrow macrophages from FIV-infected cats were found to be more activated than similar macrophages from normal cats; syncytium formation was observed in the cultures and the FIV infection was latent from the onset (Brunner and Pedersen, 1989).

FIV will infect primary cultures of feline astrocytes and brain macrophages (Dow *et al.*, 1990, 1992). The FIV-infected astrocytes underwent a productive and lytic infection with reverse transcriptase elaboration and FIV-p24 antigen production following 3 to 4 days after syncytium formation. Maximum virus production occurred at days 6 to 8 in culture, and cell death was evident by 7 to 10 days. Primary cultures of feline brain macrophages also produced reverse transcriptase and FIV antigens following infection, but no cytopathic effect was observed. Dow and co-workers (1990) were able to productively infect, at a low level, human U237 astrocyte cells, but no cytopathic effect was observed.

Using *in situ* RNA hybridization techniques, FIV has been localized in the tissues of both naturally and experimentally infected cats. Like HIV infection of man, only a very small proportion of cells in various tissues were found to harbor the viral RNA (Fig. 2). Infected cells were most often of a macrophage type (Dandekar *et al.*, 1990).

V. PATHOLOGY

A. Stages 1 and 2

Gross and histopathologic lesions in the primary stage of infection are concentrated in the peripheral and mesenteric lymph nodes, the lower bowel, and the bone marrow (Yamamoto *et al.*, 1988b; Callanan *et al.*, 1992b). Enlarged mesenteric or peripheral lymph nodes demonstrate a pronounced follicular hyperplasia with less marked increase in paracortical zones (Fig. 9). The follicles are often dysplastic in appearance, being asymmetric and intruding into the pericortex. As in both asymptomatic and diseased naturally FIV-infected cats, experimentally FIV-infected cats often have lymphoid follicles in unusual places such as the bone marrow, thymus, parathyroid glands, salivary glands, kidneys, sclera, and choroid of the eyes (Callanan *et al.*, 1992b). The latter two lesions may be associated with conjunctivitis and uveitis.

Gastrointestinal lesions range from inapparent to severe in kittens with primary FIV infection (Yamamoto *et al.*, 1988b). More severe lesions tend to be seen in FeLV-infected cats that are subsequently infected with FIV (Pedersen *et al.*, 1990). Multiple foci of subacute ulceration are often seen in the wall of the colon and cecum; in severe cases, the necrosis may involve the entire intestinal wall including the serosal surface.

Bone marrow aspirates taken during the neutropenic phase of primary FIV infection usually show myeloid hyperplasia (Mandell *et al.*, 1992). In some cases, evidence of myeloid dysplasia is also observed.

Minimal pathologic changes are seen in tissues during stage 2.

B. Stages 3 and 4

There are no pathognomonic gross or histologic changes in the tissues of FIV-infected cats in more advanced stages of disease (Rideout *et al.*, 1992b). Furthermore, the types of lesions vary greatly depending on the stage of infection, the form of disease, and the presence or absence of opportunistic infections.

Lymphoid tissue changes in FIV-infected cats have been reported by P. J. Brown and associates (1991), Dieth and co-workers (1989), and Rideout and associates (1992b). Except for the tendency of lymphoid tissues from FIV-infected cats to manifest a greater degree of plasmacytosis, there are no lymphoid changes in FIV-infected cats that cannot also be seen in cats ill with non-FIV-related illnesses. Lymph node changes may vary widely between individual animals and within the same cat. Some nodes are grossly enlarged and show mild to severe follicular hyperplasia. Other lymph nodes may appear remarkably normal and inactive, even though they are in the drainage area of obvious sites of inflammation. Some nodes may be small and inconspicuous. Follicular architecture can also vary from atrophic, to markedly hyperplastic and/or dysplastic, to normal. In general, cats in the initial and

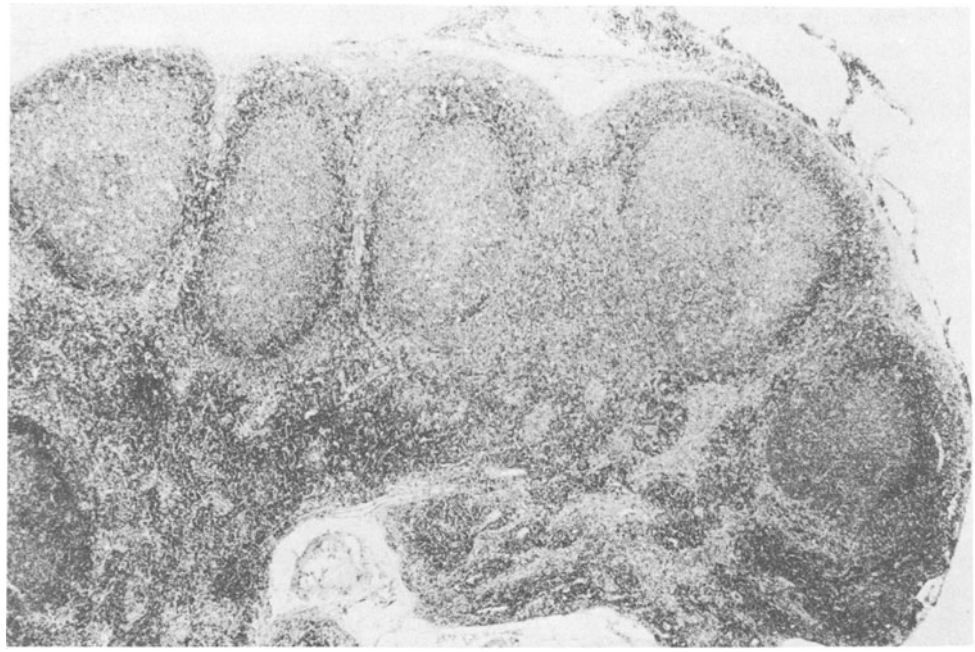

FIGURE 9. A photomicrograph of a mesenteric lymph node taken from a kitten in the primary stage of experimentally induced FIV infection. There is exuberant follicular hyperplasia. The follicles are also dysplastic in appearance, being asymmetric and intruding into the pericortex. H&E stain, ×7.5.

ARC stages of illness tend to have hyperplastic or hyperplastic/involuting lymphoid tissues, whereas lymphoid depletion is frequent in the AIDS stage (Rideout *et al.*, 1992b). Atrophic lymph nodes often demonstrate pronounced pericortical lymphoid depletion with total follicular collapse and hyalinization (Fig. 10). Splenic changes parallel those of the lymph nodes, ranging from normal, to hyperplastic, to atrophic. The thymus glands may show atrophy with depletion of lymphoid follicles, plasmacytosis, and perivascular lymphoid cell infiltration.

Oral cavity lesions in cats with stomatitis are usually of an ulceroproliferative appearance grossly. Histologically, there is varying degrees of pyogranulomatous inflammation and necrosis in the surface and center of the lesions and intense plasma cell/lymphocyte infiltration with perivascular orientation in the deeper tissues surrounding the lesions.

FIV-infected cats with chronic diarrhea and wasting often show a characteristic severe and diffuse villous atrophy that is particularly evident in the lower half of the small intestine, and focal areas of mural necrosis with fibrosis in the wall of the intestine. Lymphoid tissue within the intestinal wall is often hyperplastic with a pronounced increase in the numbers of B lymphocytes and plasma cells. Intestinal lesions are reminiscent of those caused by acute panleukopenia virus (feline parvovirus) infection, but they are chronic rather than acute in nature.

Lesions in parenchymatous organs are less flamboyant than those of mucous membranes. A characteristic, although not pathognomonic feature, of advanced FIV infection is the presence of diffuse interstitial infiltrates of lymphocytes and plasma cells in many organs, in particular the lungs, liver, pancreas, and kidneys. A diffuse cholangiohepatitis with mixed periportal lymphocyte/plasma cell infiltrates, periportal fibrosis, biliary stasis has been observed in a number of chronically ill FIV-infected cats (Dieth *et al.*, 1989).

Central nervous system lesions in cats with uncomplicated FIV infection are common with or without clinical signs of CNS disease. Dow and colleagues (1990) and Hurtrel and associates (1992) described perivascular mononuclear cell infiltrates, diffuse gliosis, discrete glial nodules, and vacuolation of white matter in naturally and experimentally infected cats. Lesions tend to be concentrated in the thalamus, midbrain, and cerebellar peduncles. Multinucleated giant cells, which are characteristic of HIV and SIV infections, have not been seen in either naturally or experimentally infected cats (Hurtrel *et al.*, 1992). Spinal cord lesions of uncomplicated FIV infection usually consist of demyelination of the dorsal columns, vacuolar changes in myelin sheaths of dorsal and ventral nerve roots, decreased density of nerve fibers in fasicles, and focal mononuclear cell infiltrates (Wheeler *et al.*, 1990). Virus has been localized by *in situ* hybridization in the brain of FIV-infected cats to mononuclear cells within and surrounding blood vessels and in a rare unidentified cell type (Lackner *et al.*, 1991).

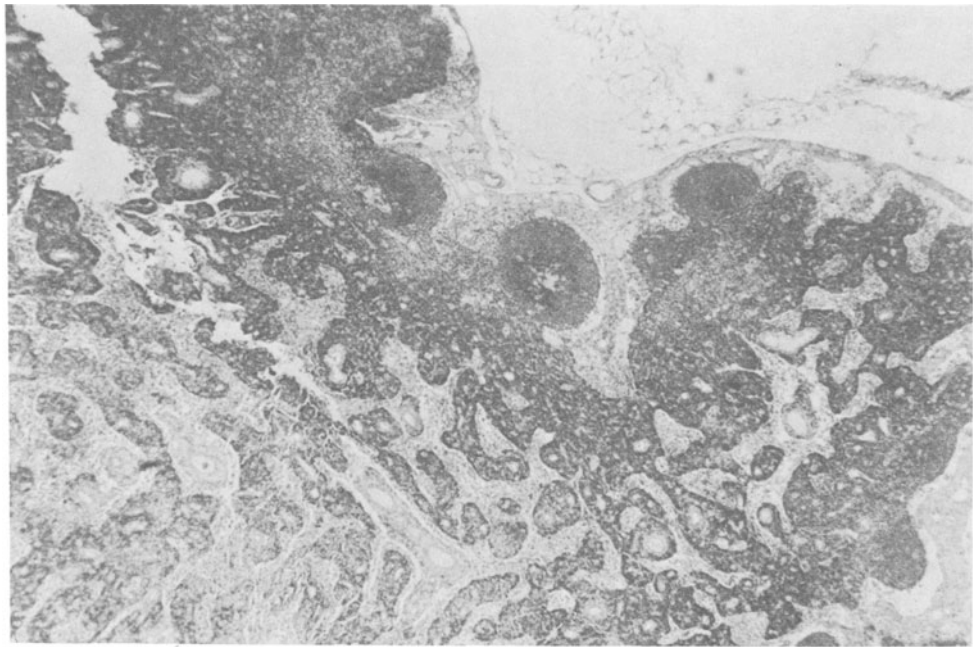

FIGURE 10. A photomicrograph of a mesenteric lymph node taken from a 10-year-old cat in the terminal AIDS-like stage of naturally acquired FIV infection. There is pronounced atrophy of the node with follicular collapse and hyalinization, and depletion of pericortical lymphoid cells. H&E stain, ×7.5.

VI. CONTROL OF INFECTION

A. Nonspecific Treatment

Most FIV-infected cats in the clinical stages of illness are treated symptomatically and supportively. Secondary and opportunistic infections often respond well to specific antimicrobial therapy in the early stages of infection, but become more and more refractory to treatment with time. This probably reflects the steady deterioration of the immune system that is occurring in the face of therapy.

Corticosteroid therapy may be helpful in controlling certain immune-mediated complications in FIV-infected cats without obvious opportunistic infections. *Pars planitis* and anterior uveitis have been controlled with topical steroid therapy in FIV-infected cats (English *et al.*, 1990). The author has also successfully treated one FIV-infected cat with autoimmune thrombocytopenia and polyarthritis, and one cat with polyarthritis, with corticosteroids alone.

B. Antiviral Drug Therapy

1. *In Vitro* Testing

The RTs of FIV and of HIV have similar sensitivities to various RT inhibitors (North *et al.*, 1989, 1990a,b; Hardy *et al.*, 1990; Tanabe-Tochikura *et al.*, 1992) (Table V). The two RTs have similar inhibition sensitivities to five nucleoside analogs of ddTTP, 3′-azido-3′-deoxythymidine 5′-triphosphate, 2′,3′-dideoxythymidine 5′-triphosphate, 2′,3′-dideoxy-2′,3′-didehydrothymidine 5′-triphosphate, 3′-amino-3′-deoxythymidine 5′-triphosphate, and 3′-fluoro-3′-deoxythymidine 5′-triphosphate (North *et al.*, 1989, 1990a,b) (Table III). The RT of FIV is also more susceptible to inhibition by phosphonoformate than the RT of HIV, except it is much more active with poly(rA)-oligo(dT) as a template primer than with poly(rC)-oligo(dG) or poly(rI)-oligo(dC). Dextran sulfate (mol. wt. 500,000) will noncompetitively inhibit the RNase H's of FIV and HIV to similar levels, 0.12 and 0.13 nM, respectively (Cronn *et al.*, 1992b).

The RT of FIV is also inhibited by the 2′-deoxyadnosine-5′-triphosphate analogs 9-(2-phosphonomethoxyethyl)adenine (PMEA) and 2′,3′-dideoxyandenosine (ddA) when primed with phage ϕ174 DNA (Egberink *et al.*, 1990a; Cronn *et al.*, 1992a). Both compounds were more potent inhibitors of FIV-RT than HIV-RT when ϕX-174 DNA was used as the primer (Cronn *et al.*, 1992a). However, they were poor inhibitors when the system was primed with poly(rU)-oligo(dA). The reaction of FIV-RT with poly(rU)-oligo(dA) was not highly processive, resulting in short nucleotide transcripts and a low inhibitory potential for the presumed active forms, 2′,3′-dideoxyaenosine (ddATP) and PME-diphosphate (PMEApp). High molecular transcripts were produced when ϕX-174 DNA was substituted for poly(rU)-oligo(dA) in the reaction.

TABLE V. Inhibition of FIV and HIV Reverse Transcriptases by Analogs of dTTP

	Mean K_i/K_m ratio	
Inhibitor	FIV	HIV
N_3dTTP	0.0010	0.0011
ddTTP	0.0020	0.0010
D4TTP	0.0005	0.0014
3′-F-dTTP	0.0009	0.0010
3′-NH_2-dTTP	0.0005	0.0012

Less conventional viral inhibitors that have been shown to be effective *in vitro* against HIV have also shown similar inhibitory activity against FIV (Tanabe-Tochikura *et al.*, 1992). Dextran sulphate (mol. wt. 5000) completely inhibited FIV-antigen expression and cytopathicity at concentrations as low as 0.1 μg/ml, as did pradimicin A and heparin at levels greater than 10 μg/ml.

2. *In Vivo* Testing

Antiviral drugs, such as azidothymidine (AZT), have been used successfully in HIV-infected AIDS patients (Fischl *et al.*, 1987). Reports of the successful use of AZT in FIV-infected cats are just now starting to appear (Smyth *et al.*, 1990). The antiviral drug PMEA has also been used successfully to treat several naturally FIV-infected cats (Egberink *et al.*, 1990; Hartmann *et al.*, 1992). PMEA has also been tested as a prophylactic for FIV infection (Philpott *et al.*, 1992). Cats that were treated with PMEA beginning 24 hours before infection and for 7 weeks thereafter still became infected. However, their virus burdens in blood and tissues were significantly lower 1 year after drug cessation when compared to nontreated animals that were similarly infected and monitored. Azidothymidine-resistant mutants of FIV have been produced *in vitro* (Remington *et al.*, 1990). Mutants have the same pattern of cross-drug resistance as do AZT-resistant mutants isolated from humans.

C. Therapy with Biologic Response Modifiers

The therapy of FIV infection using biologic response modifiers has just begun to be studied. Acemannan, a complex carbohydrate that stimulates IL-1, TNF-α, and prostaglandins, as well as having a direct antiviral effect, has been used to treat 49 naturally FIV-infected cats in various stages of illness (Yates *et al.*, 1992). Animals were treated weekly for 12 weeks by oral or subcutaneous routes and then put on indefinite maintenance therapy; 13 cats died during treatment, usually from neoplasia, pancreatic, or renal disease. Among the survivors, lymphocyte counts significantly increased and the incidence of sepsis decreased. Unfortunately, a parallel placebo group was not included in the study and the trial was not blinded.

D. Prevention

The disease can best be prevented by keeping cats out of environments that encourage high-risk behavior. Basically, cats should be neutered, kept indoors whenever possible, and not exposed to new homeless, feral, abandoned, or stray cats without those animals being first tested for the virus.

Research on FIV vaccines is currently underway. Cats inoculated with either inactivated whole virus or whole cell vaccine developed detectable levels of virus-neutralizing antibodies but appeared to be more sensitive to challenge-exposure with virulent virus (Hosie *et al.*, 1992). In contrast, Yamamoto and co-workers (1993) were able to protect cats against a low level of virulent whole virus with inactivated FIV-infected T-lymphoid cell or whole virus vaccines. Whether such immunity will prove effective and sustainable in the field remains to be determined. One complication of such vaccines is that vaccinated cats are rendered positive to currently employed FIV diagnostic tests.

VII. PUBLIC HEALTH CONSIDERATIONS

There is no evidence that would link FIV infection to any human disease, and most specially AIDS. The virus is antigenically and genetically distinct from HIV and appears to be highly species adapted (Pedersen *et al.*, 1987; Egberink *et al.*, 1990b; O'Connor *et al.*, 1989; Olmsted *et al.*, 1989; Steinman *et al.*, 1989; Talbot *et al.*, 1989; Yamamoto *et al.*, 1988b). Species adaptation is characteristic of all retroviruses, including lentiviruses, and although there is some evolutionary evidence based on genomic DNA analysis that retroviruses do cross species, this adaptation gradually occurs over eons of time. Once retroviruses adapt themselves to a new host, they become species specific. There is no evidence that a lentivirus infection of one species of animal readily transmits itself back and forth to another. Limited studies have failed to identify FIV antibodies in people that have had intimate contact with FIV-infected cats and people that have been bitten by infected animals or inadvertently injected themselves with virus-containing material (Yamamoto *et al.*, 1989; Childs *et al.*, 1990).

VIII. REFERENCES

Ackley, C. D., Hoover, E. A., and Cooper, M. D., 1989, Identification of a CD4-like homologue in the cat, *Tissue Antigens* **35**:92.

Ackley, C. D., Yamamoto, J. K., Levy, N., Pedersen, N. C., and Cooper, M. D., 1990, Immunologic abnormalities in pathogen free cats experimentally infected with feline immunodeficiency virus, *J. Virol.* **64**:5652.

Alexander, R., Robinson, W. F., Mills, J. N., Sherry, C. R., Sherard, E., Paterson, A. J., Shaw, S. E., Clark, W. T., and Hollingsworth, T., 1989, Isolation of feline immunodeficiency virus from three cats with lymphoma, *Aust. Vet. Pract.* **19**:93.

Bandecchi, P., Matteucci, D., Baldinotti, F., Guidi, G., Tozzini, F., and Bendinelli, M., 1992, Prevalence of feline immunodeficiency virus and other retroviral infections in sick cats in Italy, *Vet. Immunol. Immunopathol.* **31**:337.

Barlough, J. E., Jacobson, R. H., Pepper, C. E., 1984, Role of recent vaccination in production of false-positive coronavirus antibody titers in cats, *J. Clin. Microbiol.* **19**:442.

Barlough, J. E., Ackley, C. D., George, J. W., Levy, N., Acevedo, R., Moore, P. F., Rideout, B. A., Cooper, M. D., and Pedersen, N. C., 1991, Acquired immune dysfunction in cats with experimentally induced feline immunodeficiency virus infection: Comparison of short-term and long term infections, *J. Acquir. Immune Defic. Syndr.* **4**:219.

Barr, M. C., Calle, P. P., Roelke, M. E., and Scott, F. W., 1989, Feline immunodeficiency virus infection in nondomestic felids, *J. Zoo Wild. Med.* **20**:265.

Bartholomew, C., Blattner, W., and Cleghorn, F., 1987, Progression to AIDS in homosexual men co-infected with HIV and HTLV-I in Trinidad, *Lancet* **2(8573)**:1469.

Beebe, A. M., Gluckstern, T. G., George, J., Pedersen, N. C., and Dandekar, S., 1992, Detection of feline immunodeficiency virus infection in bone marrow of cats, *Vet. Immunol. Immunopathol.* **35**:37.

Belford, C. J., Miller, R. I., Mitchell, G., Rahaley, R. S., and Menrath, V. H., 1989, Evidence of feline immunodeficiency virus in Queensland cats: Preliminary observations, *Aust. Vet. Pract.* **19(1)**:4.

Bennett, M., McCracken, C., Lutz, H., Gaskell, C. J., Gaskell, R. M., Brown, A., and Knowles, J. O., 1989, Prevalence of antibody to feline immunodeficiency virus in some cat populations, *Vet. Rec.* **124**:397.

Bishop, S. A., Williams, N. A., Gruffydd-Jones, T. J., Harbour, D. A., and Stokes, C. R., 1992, Impaired T-cell priming and proliferation in cats infected with feline leukemia virus, *AIDS* **6**:287.

Blue, J. T., French, T. W., and Kranz, J. S., 1988, Non-lymphoid hematopoietic neoplasia in cats: A retrospective study of 60 cases, *Cornell Vet.* **78**:21.

Brown, A., Bennett, M., and Gaskell, C. J., 1989, Fatal poxvirus infection in association with FIV infection, *Vet. Rec.* **124**:19.

Brown, W. C., Bissey, L., Logan, K. S., Pedersen, N. C., Elder, J. H., and Collisson, E. W., 1991, Feline immunodeficiency virus infects both $CD4^+$ and $CD8^+$ T lymphocytes, *J. Virol.* **65**:3359.

Brown, P. J., Hopper, C. D., and Harbour, D. A., 1991, Pathological features of lymphoid tissues in cats with natural feline immunodeficiency virus infection, *J. Comp. Pathol.* **104**:345.

Brunner, D., and Pedersen, N. C., 1989, Infection of peritoneal macrophages in vitro and in vivo with feline immunodeficiency virus, *J. Virol.* **63**:5483.

Buonavoglia, C., Tempesta, M., Pestaboza, S., Di Trani, L., Titti, F., Pennisi, M. G., Catarsini, O., and Compagnucci, M., 1990, Isolamento in Italia del virus dell'immunodeficienza del gatto (FIV), *Selezione Vet.* **31**:121.

Buracco, P., Guglielmino, R., Abate, O., Bocchini, V., Cornaglia, E., DeNicola, D. B., Cilli, M., and Ponzio, P., 1992, Large granular lymphoma in an FIV-positive and FeLV-negative cat, *J. Small Anim. Pract.* **33**:279.

Callanan, J. J., Hosie, M. J., and Jarrett, O., 1991, Transmission of feline immunodeficiency virus from mother to kitten, *Vet. Rec.* **128**:332.

Callanan, J. J., McCandlish, I. A., O'Neil, B., Lawrence, C. E., Rigby, M., Pacitti, A. M., and Jarrett, O., 1992a, Lymphosarcoma in experimentally induced feline immunodeficiency virus infection, *Vet. Rec.* **130**:293.

Callanan, J. J., Thompson, H. T., Toth, S. J., O'Neil, B., Lawrence, C. L., Willett, B., and Jarrett, O., 1992b, Clinical and pathological findings in feline immunodeficiency virus experimental infection, *Vet. Immunol. Immunopathol.* **35**:3.

Chalmers, S., Schick, R. O., and Jeffers, J., 1989, Demodicosis in two cats seropositive for feline immunodeficiency virus, *J. Am. Vet. Med. Assoc.* **194**:256.

Chan, S. G., 1990, The feline population and the existence of feline immunodeficiency virus and feline leukemia virus in Guangzhou (Canton) China. Master of Preventive Veterinary Medicine thesis, University of California, Davis.

Childs, J. E., Witt, C. J., Glass, G. E., Bishop, B. D., and Moensch, T. R., 1990, Feline immunodeficiency virus: A survey in Baltimore, *Feline Practice* **18(2)**:11.

Cohen, N. D., Carter, C. N., Thomas, M. A., Lester, T. L., and Eugster, A. K., 1990, Epizootiologic association between feline immunodeficiency virus infection and feline leukemia virus seropositivity, *J. Am. Vet. Med. Assoc.* **197**:220.

Cooper, D. A., Maclean, P., Finlayson, R., et al., 1985, Acute AIDS retrovirus infection, *Lancet* **1**:537.

Cronn, R. C., Remington, K. M., Preston, B. D., and North, T. W., 1992a, Inhibition of reverse transcriptase from feline immunodeficiency virus by analogs of 2′-deoxyadenosine-5′-triphosphate, *Biochem. Pharmacol.* **44**:1375.

Cronn, R. C., Witmer, J. D., and North, T. W., 1992b, RNase H activity associated with reverse transcriptase from feline immunodeficiency virus, *J. Virol.* **66**:1215.

Dandekar, S., Martfeld, D. J., Torten, M., Rideout, B., Luciw, P. A., and Pedersen, N. C., 1990, Tissue distribution of FIV and relationship to pathogenesis in cats and comparison with SIV model, in: Proc. 6th Intl. Conf. AIDS, June 20–24, San Francisco, Abstract Th.A.286.

Dandekar, S., Beebe, A. M., Barlough, J., Phillips, T., Elder, J., Torten, M., and Pedersen, N. C., 1992, Detection of feline immunodeficiency virus (FIV) nucleic acids in FIV-seronegative cats, *J. Virol.* **66**:4040.

Dawson, S., Smyth, N. R., Bennett, M., Gaskell, R. M., McCraken, C. M., Brown, A., and Gaskell, C. J., 1991, Effect of primary-stage feline immunodeficiency virus infection on subsequent feline calicivirus vaccination and challenge in cats, *AIDS* **5**:747.

de Thé, G., 1988, HIV-1 and HIV-2 epidemiology and disease association in Ivory Coast, in: Proc. 2nd Colloque des Cent Gardes, Retroviruses of Human A.I.D.S. and Related Retrovirus Diseases, Marnes-La-Coquette/Paris, France, October 28–30, 1987, pp. 51–54.

Dieth, V., Lutz, H., Hauser, B., and Ossent, P., 1989, Pathologische Befunde bei mit lentiviren infezierten Katzen, *Schweiz. Arch. Tierheilkd* **131**:19.

Dow, S. W., Poss, M. L., and Hoover, E. A., 1990, Feline immunodeficiency virus: A neurotropic lentivirus, *Acquir. Immune Defic. Syndr.* **3**:658.

Dow, S. W., Dreitz, M. J., and Hoover, E. A., 1992, Feline immunodeficiency virus neurotropism: Evidence that astrocytes and microglia are the primary target cells, *Vet. Immunol. Immunopathol.* **35**:23.

Egberink, H. E., Ederveen, J., Montelaro, R. C., Pedersen, N. C., Horzinek, M. C., and Koolen, M. J. M., 1990b, Intracellular proteins of feline immunodeficiency virus (FIV) and their antigenic relationship to equine infectious anemia virus (EIAV), *J. Gen. Virol.* **71**:739.

Egberink, H. E., Borst, M., Niphuis, H., Balzarini, J., Neu, H., Schellekens, H., De Clercq, E., Horzinek, M., and Koolen, M., 1990a, Suppression of feline immunodeficiency virus infection in vivo by 9-(2-phosphonomethoxyethyl)adenine, *Proc. Natl. Acad. Sci. USA* **87**:3087.

Elder, J. H., Lerner, D. L., Hasselkus-Light, C. S., Fotenot, D. J., Hunter, E., Luciw, P. A., Montelaro, R. C., and Phillips, T. R., 1992, Distinct subsets of retroviruses encode dUTPase, *J. Virol.* **66**:1791.

English, R. V., Davidson, M. G., Nasisse, M. P., Jamieson, V. E., and Lappin, M. R., 1990, Intraocular disease associated with feline immunodeficiency virus infection in cats, *J. Am. Vet. Med. Assoc.* **196**:1116.

Fevereiro, M., Ronekar, C., and de Noronha, F., 1991, Antibody response to reverse transcriptase in cats infected with feline immunodeficiency virus, *Viral Immunol.* **4**:225.

Fischl, M. A., Richman, D. D., Grieco, M. H., Gottlieb, M. S., Volderding, P. A., Laskin, O. C., Leedon, J. M., Groopman, J., Mildran, D., Schooler, R. T., Jackson, G. G., Durack, D. T., King, D., and the AZT Collaborative group, 1987, The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: A double-blind, placebo controlled trial, *N. Engl. J. Med.* **317**:185.

Fotenot, J. D., Hoover, E. A., Elder, J. H., and Montelaro, R. C., 1992, Evaluation of feline immunodeficiency virus and feline leukemia virus transmembrane peptides for serological diagnosis, *J. Clin. Microbiol.* **30**:1885.

Furuya, T., Kawaguchi, Y., Miyazawa, T., Fujikawa, Y., Tohya, Y., Azetaka, M., Takahashi, E., and Mikami, T., 1990, Existence of feline immunodeficiency virus infection in Japanese cat population since 1968, *Jpn. J. Vet. Sci.* **52**:891.

George, J. W., and Pedersen, N. C., 1992, The effect of age on the course of experimental feline immunodeficiency virus infection in cats, *AIDS Res.* (in press).

Glennon, P. J., Cockburn, T., and Stark, D. M., 1991, Prevalence of feline immunodeficiency virus and feline leukemia virus infections in random-source cats, *Lab. Anim. Sci.* **41**:545.

Grindem, C. B., Corbett, W. T., Ammermann, B. E., and Tomkins, M. T., 1989, Seroepidemiologic survey of feline immunodeficiency virus infection in cats of Wake County, North Carolina, *J. Am. Vet. Med. Assoc.* **194**:226.

Gruffydd-Jones, T. J., Hopper, C. D., Harbour, D. A., and Lutz, H., 1988, Serological evidence of feline immunodeficiency virus infection in UK cats from 1975–76, *Vet. Rec.* **123**:569.

Hara, Y., Ishida, T., Ejima, H., Tagawa, M., Motoyoshi, S., Tomoda, I., Shimizu, M., and Shichinohe, K., 1990, Decrease in mitogen-induced lymphocyte proliferative responses in cats infected with feline immunodeficiency virus, *Jpn. J. Vet. Sci.* **52**:573.

Harbour, D. A., Williams, P. D., Gruffydd-Jones, T. J., Burbridge, J., and Pearson, G. R., 1988, Isolation of a T-lymphotropic lentivirus from a persistently leucopenic domestic cat, *Vet. Rec.* **122**:84.

Hardy, W. D. Jr., Zuckerman, E. E., Boecker, J., Corbishley, J., Kong, X.-B., Wantanabe, K. A., Polsky, B. W., Gold, J. W. M., Baron, P., Chou, T.-C., Fox, J., and Armstrong, D., 1990, The pyrimidine nucleoside 3′-deoxy-3′-fluorothymidine (FLT) inhibits the replication of feline onco- and lenti-retroviruses in vitro and in vivo, in: Proc. 6th Intl. Conf. AIDS, June 20–24, San Francisco, abstract Th.A.255.

Hart, B., and Pedersen, N. C., 1991, Behavior, In *Feline Husbandry: Disease and Management in the Multiple Cat Environment*, pp. 287–322. American Veterinary Publications, Goleta, Calif.

Hartmann, K., Donath, A., Beer, B., Egberink, H. F., Horzinek, M. C., Lutz, H., Hoffmann-Fezer, G., Thum, I., and Thefeld, S., 1992, Use of two virustatica (AZT, PMEA) in the treatment of FIV and of FeLV seropositive cats with clinical symptoms, *Vet. Immunol. Immunopathol.* **35**:167.

Heidel, J. R., Dubey, J. P., Blythe, L. L., Walker, L. L., Duimstra, J. R., and Jordan, J. S., 1990, Myelitis in a cat infected with *Toxoplasma gondii* and feline immunodeficiency virus, *J. Am. Vet. Med. Assoc.* **196**:316.

Hoffmann-Fezer, G., Thum, I., Herbold, M., Ackley, C., Mysliwietz, J., Hartmann, K., and Kraft, W., 1991, T-helper and T-suppressor lymphocyte subpopulations in peripheral blood of spontaneously FIV-positive cats, *Tierarztl. Prax.* **19**:682.

Hohdatsu, T., Yamada, M., Okada, M., Fukasawa, M., Watanabe, K., Ogasawara, T., Takagi, M., Aizawa, C., Hayami, M., and Koyama, H., 1992, Detection of feline immunodeficiency virus proviral DNA in peripheral blood lymphocytes by the polymerase chain reaction, *Vet. Microbiol.* **30**:113.

Hopper, C., Sparkes, A., Gruffydd-Jones, T. J., and Harbour, D. A., 1988, Feline T-lymphotropic virus infection (Letter). *Vet. Rec.* **122**:590.

Hopper, C. D., Sparkes, A. H., Gruffydd-Jones, T. J., Crispin, S. M., Harbour, D. A., and Stokes, C. R., 1989, Clinical and laboratory findings in cats infected with feline immunodeficiency virus, *Vet. Rec.* **125**:341.

Hosie, M. J., and Jarrett, O., 1990, Serological responses of cats to feline immunodeficiency virus, *AIDS* **4**:215.

Hosie, M. J., Robertson, C., and Jarrett, O., 1989, Prevalence of feline leukaemia virus and antibodies to feline immunodeficiency virus in cats in the United Kingdom, *Vet. Rec.* **125**:293.

Hosie, M. J., Reid, G., Neil, J. C., and Jarrett, O., 1992, Enhancement after feline immunodeficiency virus vaccination, *Vet. Immunol. Immunopathol.* **35**:191.

Hurtrel, M., Ganiére, J.-P., Guelfi, J.-F., Chakrabarti, L., Maire, M.-A., Gray, F., Montagnier, L., and Hurtrel, B., 1992, Comparison of early and late feline immunodeficiency virus encephalopathies, *AIDS* **6**:399.

Imagawa, D. T., Lee, M. H., Wolinsky, S. M., Sano, K., Morales, F., Kwok, S., Sninsky, J. J., Nishanian, P. G., Giorgi, J., Fahey, J. L., Dudley, J., Visscher, B. R., and Detels, R., 1989, Human immunodeficiency virus type 1 infection in homosexual men who remain seronegative for prolonged periods, *N. Engl. J. Med.* **320**:1458.

Ishida, T., and Tomoda, I., 1990, Clinical staging of feline immunodeficiency virus infection, *Jpn. J. Vet. Sci.* **52**:645.

Ishida, T., Washizu, T., Toriyabe, K., and Motoyoshi, S., 1988, Detection of a feline T-lymphotropic lentivirus (FTLV) infection in Japanese domestic cats, *Jpn. J. Vet. Sci.* **50**:39.

Ishida, T., Washizu, T., Toriyabe, K., Motoyoshi, S., and Pedersen, N. C., 1989, Feline immunodeficiency virus (FIV) infection in Japan. *J. Am. Vet. Med. Assoc.* **194**:221.

Ishida, T., Taniguchi, A., Kanai, T., Kataoka, Y., Aimi, K., Kariya, K., Washizu, T., and Tomoda, I., 1990, Retrospective serosurvey for feline immunodeficiency virus infection in Japanese cats, *Jpn. J. Vet. Sci.* **52**:453.

Ishida, T., Taniguchi, A., Matsumura, S., Wahizu, T., and Tomoda, I., 1992, Long-term clinical observations on feline immunodeficiency virus infected asymptomatic carriers, *Vet. Immunol. Immunopathol.* **35**:15.

Kawaguchi, Y., Miyazawa, T., Tohya, Y., Takahashi, E., and Mikami, T., 1990, Quantification of feline immunodeficiency virus in a newly established feline T-lymphoblastoid cell line (MYA-1 cells), *Arch. Virol.* **111**:269.

Kiyomasu, T., Miyazawa, T., Furuya, T., Shibata, R., Sakai, H., Sakuragi, J.-I., Fukasawa, M., Maki, N., Hasegawa, A., Mikami, T., and Adachi, A., 1991, Identification of feline immunodeficiency virus *rev* gene activity, *J. Virol.* **65**:4539.

Klotz, F. W., and Cooper, M. D., 1986, A feline thymocyte antigen defined by a monoclonal antibody (FT2) identifies a subpopulation of non-helper cells capable of specific cytotoxicity, *J. Immunol.* **136**:2510.

Knowles, J. O., Gaskell, R. M., Gaskell, C. J., Harvey, C. E., and Lutz, H., 1989, Prevalence of feline calicivirus, feline leukaemia virus and antibodies to FIV in cats with chronic stomatitis, *Vet. Rec.* **124**:336.

Kölbl Von S., and Schuller, W., 1989, Serologische Untersuchungen zum Vorkommen des Felinen Immunodefizienzvirus (FIV) bei Katzen in Osterreich, *Wien. Tierärztl. Mschr.* **76**:185.

Kristensen, T. S., Petersen, S. F., and Hoff-Jorgensen, R., 1989, Feline AIDS (FAIDS) of feline immunodeficiency virus (FIV), *Dansk Vet. Tidsskr.* **72**:447.

Lackner, A. A., Dandekar, S., and Gardner, M. B., 1991, Neurobiology of simian and feline immunodeficiency virus infections, *Brain Pathol.* **1**:201.

Lane, H. C., and Fauci, A. S., 1985, Immunologic abnormalities in the acquired immunodeficiency syndrome, *Annu. Rev. Immunol.* **3**:477.

Lappin, M. R., Greene, C. E., Winston, S., Toll, S. L., and Epstein, M. E., 1990, Clinical feline toxoplasmosis, *J. Vet. Int. Med.* **3**:139.

Lawrence, C. E., Callanan, J. J., and Jarrett, O., 1992, Decreased mitogen responsiveness and elevated tumor necrosis factor production in cats shortly after feline immunodeficiency virus infection, *Vet. Immunol. Immunopathol.* **35**:51.

Lehmann, R., Franchini, M., Aubert, A., Wolfensberber, C., Cronier, J., and Lutz, H., 1991, Vaccination of cats experimentally infected with feline immunodeficiency virus, using a recombinant feline leukemia virus vaccine, *J. Am. Vet. Med. Assoc.* **199**:1466.

Lehmann, R., Joller, H., Lutz, H., and Haagmans, B. L., 1992, Tumor necrosis factor α levels in cats experimentally infected with feline immunodeficiency virus: Effects of immunization and feline leukemia virus infection, *Vet. Immun. Immunopath.* **35**:61.

Letcher, J. D., and O'Connor, T. P., 1991, Incidence of antibodies reacting to FIV in a population of Asian lions, *J. Zoo. Wildl. Med.* **22**:324.

Lin, D. S., Bowman, D. D., Jacobson, R. H., Barr, M. C., Fevereiro, M., Williams, J. R., Noronha, F. M. O., Scott, F. W., and Avery, R. J., 1990, Suppression of lymphocyte blastogenesis to mitogens in cats experimentally infected with feline immunodeficiency virus, *Vet. Immunol. Immunopathol.* **26**:183.

Linenberger, M. L., Shelton, G. H., Persik, M. T., and Abkowitz, J. L., 1991, Haematopoiesis in asymptomatic cats infected with feline immunodeficiency virus, *Blood* **78**:1963.

Lutz, H., Egberink, H., Arnold, P., Winkler, G., Wolfensberger, C., Jarrett, O., Parodi, A. L., Pedersen, N. C., and Horzinek, M. C., 1988, Felines T-lymphotropes Lentivirus (FTLV): Experimentelle Infektion und Vorkommen in einigen Ländern Europas, *Kleintierpraxis* **33**:445.

Lutz, H., Isenbügel, E., Lehmann, R., Sabapara, R. H., and Wolfensberger, C., 1992, Retrovirus infections in non-domestic felids: Serological studies and attempts to isolate a lentivirus, *Vet. Immunol. Immunopathol.* **35**:215.

Lutz, H., Lehmann, R., Winkler, G., Kottwitz, B., Dittmer, A., Wolfensberger, C., and Arnold, P., 1990, Das Feline Immunshwachevirus in der Schweiz: Klinik und Epidemiologie im Verliech mit dem Leukamie- und dem Coronavirus, *Schweiz. Arch. Tierheilkd.* **132**:217.

Maki, N., Miyazawa, T., Fukasawa, M., Hasegawa, A., Hayami, M., Miki, K., and Mikami, T., 1992, Molecular characterization and heterogeneity of feline immunodeficiency virus isolates, *Arch. Virol.* **123**:29.

Malik, R., Wigney, D. I., Muir, D. B., Gregory, D. J., and Love, D. N., 1992, Cryptococcosis in cats: Clinical and mycological assessment of 29 cases and evaluation of treatment using orally administered fluconazole, *J. Med. Vet. Mycol.* **30**:133.

Mandell, C. P., Sparger, E. E., Pedersen, N. C., and Jain, N. C., 1992, Long-term haematological changes in cats experimentally infected with feline immunodeficiency virus, *Comp. Haematol. Intl.* **2**:8.

Masashi, F., Hasegawa, A., Maki, N., Miyazawa, T., Kawamura, M., Takahashi, E., Mikami, T., and Hayami, M., 1990, Molecular cloning of the Japanese isolates of feline immunodeficiency virus (FIV), in: Proc. 6th Intl. Conf. AIDS, June 20–24, San Francisco, Abstract Th.A.284.

Mermer, B., Hillman, P., Harris, R., Krogman, T., Tonelli, Q., Palin, W., and Andersen, P., 1992, A recombinant-based feline immunodeficiency virus antibody enzyme-linked immunosorbent assay, *Vet. Immunol. Immunopathol.* **35**:143.

Miyazawa, T., Furuya, T., Itagaki, S., Tohya, Y., Nakano, K., Takahashi, E., and Mikami, T. 1989a. Preliminary comparisons of the biological properties of two strains of feline immunodeficiency virus (FIV) isolated in Japan with FIV Petaluma strain isolated in the United States, *Arch. Virol.* **108**:59.

Miyazawa, T., Furuya, T., Itagaki, S., Tohya, Y., Takahashi, E., and Mikami, T. 1989b. Establishment of a feline T-lymphoblastoid cell line highly sensitive for replication of feline immunodeficiency virus, *Arch. Virol.* **108**:131.

Miyazawa, T., Fukasawa, M., Hasegawa, A., Maki, N., Ikuta, K., Takahashi, E., Hayami, M., and Mikami, T., 1991, Molecular cloning of a novel isolate of feline immunodeficiency virus biologically and genetically different from the original U.S. isolate, *J. Virol.* **65**:1572.

Miyazawa, T., Toyosaki, T., Tomonaga, K., Norimine, J., Ohno, K., Hasegawa, A., and Mikami, T., 1992, Further characterization of a feline T-lymphoblastoid cell line (MYA-1 cells) highly sensitive for feline immunodeficiency virus, *Jap. J. Vet. Sci.* **54**:173.

Moore, F. M., Emerson, W. E., Cotter, S. M., and DeLellis, R. A., 1986, Distinctive peripheral lymph node hyperplasia of young cats, *Vet. Pathol.* **23**:386.

Moraillon, A., 1990, Feline immunodepressive retrovirus infections in France (letter), *Vet. Rec.* **126**:68.

Moraillon, A., Barre-Sinoussi, F., Parodi, A., Moraillon, R., and Dauguet, C., 1992, In vitro properties and experimental pathogenic effect of three strains of feline immunodeficiency virus (FIV) isolated from cats with terminal disease, *Vet. Microbiol.* **31**:41.

Morikawa, S., Booth, T. F., and Bishop, D. H. L., 1991, Analyses of the requirements for the synthesis of virus-like particles by feline immunodeficiency virus *gag* using baculovirus vectors, *Virology* **183**:288.

Neu, H., Moenning, V., Leidinger, K., and Bussian, E., 1989a, Erste Ergebnisse uber die Verbreitung FIV-(FTLV-) seropositiver Katzen in Deutchland und Interpretation der Ergebnisse. *Der Praktische Tierarzt* **70**:38.

Neu, H., 1989b, FIV(FTLV)-infektion der Katze. 11 Fälle-Beitrag zur Epidemiologie Klinischen Symptomatologie und zum Krankheitsverlauf, *Kleintierpraxis* **34**:373.

North, T. W., North, G. L. T., and Pedersen, N. C., 1989, Feline immunodeficiency virus, a model for reverse transcriptase-targeted chemotherapy for acquired immune deficiency syndrome, *Antimicrob. Agents Chemother.* **33**:915.

North, T. W., Cronn, R. C., Remington, K. M., and Tandberg, R. T., 1990a, Direct comparisons of inhibitor sensitivities of reverse transcriptases from feline and human immunodeficiency viruses, *Antimicrob. Agents Chemother.* **34**:1505.

North, T. W., Cronn, R. C., Remington, K. M., Tandberg, R. T., and Judd, R. C., 1990b, Characterization of the reverse transcriptase from feline immunodeficiency virus, *J. Biol. Chem.* **265**:5121.

Novotney, C., English, R. V., Housman, J., Davidson, M. G., Nasisse, M. P., Jen, C-R., Davis, W. C., and Tompkins, M. B., 1990, Lymphocyte population changes in cats naturally infected with feline immunodeficiency virus, *AIDS* **4**:1213.

O'Connor, T. P., Jr., Tanguay, S., Steinman, R., Smith, R., Barr, M. C., Yamamoto, J. K., Pedersen, N. C., Andersen, P. R., and Tonelli, Q. J., 1989, Development and evaluation of immunoassay for detection of antibodies to feline T-lymphotropic lentivirus (feline immunodeficiency virus), *J. Clin. Microbiol.* **27**:474.

O'Dair, H. A., Gruffydd-Jones, T. J., and Hopper, C. D., 1991, Co-infection of cats infected with feline immunodeficiency virus (FIV) with *Chlamydia psittaci.* Proc. First Intl. Conf. FIV Researchers, Davis, California, p. 28.

Ohno, K., Watari, T., Goitsuka, R., Tsujimoto, H., and Hasegawa, A., 1992, Altered surface antigen expression on peripheral blood mononuclear cells in cats infected with feline immunodeficiency virus, *J. Vet. Med. Sci.* **54**:517.

Olmsted, R. A., Barnes, A. K., Yamamoto, J. K., Hirsch, V. M., Purcell, R. H., and Johnson, P. R., 1989, Molecular cloning of feline immunodeficiency virus, *Proc. Natl. Acad. Sci. USA* **86**:2448.

Olmsted, R. A., Langley, R., Roelke, M. E., Goeken, R. M., Adger-Johnson, D., Goff, J. P., Albert, J. P., Packer, C., Laurenson, M. K., Caro, T. M., Scheepers, L., Wildt, D. E., Bush, M., Martenson, J. S., and O'Brien, S. J., 1992, Worldwide prevalence of lentivirus infection in wild feline species: Epidemiologic and phylogenetic aspects, *J. Virol.* **66**:6008.

Pedersen, N. C., 1987, Feline syncytium-forming virus infection, In: *Diseases of the Cat* (J. Holzworth, ed.), pp. 268–278. W. B. Saunders, Philadelphia.

Pedersen, N. C., 1988, *Feline Infectious Diseases,* American Veterinary Publications, Goleta, Calif.

Pedersen, N. C., Theilen, G. H., Keane, M. A., Fairbanks, L., Mason, T., Orser, B., Chen, C., and Allison, C., 1977, Studies on naturally transmitted feline leukemia virus infection, *Am. J. Vet. Res.* **38**:1523.

Pedersen, N. C., Ho, E., Brown, M. L., and Yamamoto, J. K., 1987, Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome, *Science* **235**:790.

Pedersen, N. C., Torten, M., Rideout, B., Sparger, E., Tonachini, T., Luciw, P., Ackley, C., Levy, N., and Yamamoto, J., 1990, Feline leukemia virus infection as a potentiating cofactor for the primary and secondary stages of experimentally induced feline immunodeficiency virus infection, *J. Virol.* **64**:598.

Pedersen, N. C., Hosie, M. J., Willett, B. J., Dunsford, T. H., Jarrett, O., and Neil, J. C., 1993, A monoclonal antibody which blocks infection with feline immunodeficiency virus identifies a possible non-CD4 receptor, *J. Virol.* **67**:1667.

Pezzella, M., Mannella, E., Mirolo, M., Vanesch, N., Macchi, B., Rosci, M. A., Miceli, M., Marace, G., Rapicetta, M., Angeloni, P., and Sorice, F., 1989, HIV genome in peripheral blood mononuclear cells of seronegative regular sexual partners of HIV-infected subjects, *J. Med. Virol.* **28**:209.

Phillips, T. R., Talbott, R. L., Lamont, C., Muir, S., Lovelace, K., and Elder, J. H., 1990, Comparison of two host cell range variants of feline immunodeficiency virus, *J. Virol.* **64**:4605.

Phillips, T. R., Lamont, C., Konings, D. A. M., Shacklett, B. L., Hamson, C. A., Luciw, P. A., and Elder, J. H., 1992, Identification of the rev transactivation and rev-responsive elements of feline immunodeficiency, *J. Virol.* **66**:5464.

Philpott, M. S., Ebner, J. P., and Hoover, E. A., 1992, Evaluation of 9-(2-phosphonylmethoxyethyl) adenine therapy for feline immunodeficiency virus using a quantitative polymerase chain reaction, *Vet. Immunol. Immunopathol.* **35**:155.

Povey, R. C., and Hawkins, G. J., 1989, Feline immunodeficiency virus: A commentary, *Can. Vet. J.* **30**:559.

Reid, G., Rigby, M. A., McDonald, M., Hosie, M. J., Neil, J. C., and Jarrett, O., 1991, Immunodiagnosis of feline immunodeficiency virus infection using recombinant p17 and p24, *AIDS* **5**:1477.

Remington, K. M., Cheseboro, B., Wehrly, K., Pedersen, N. C., and North, T. W., 1990, Mutants of feline immunodeficiency virus resistant to 3′-azido-3′-deoxythymidine, *J. Virol.* **65**:308.

Reubel, G. H., George, J. W., Barlough, J. E., Higgins, J., Grant, C. K., and Pedersen, N. C., 1992, Interaction of acute feline herpesvirus-1 and chronic feline immunodeficiency virus infections in experimentally infected specific pathogen free cats, *Vet. Immunol. Immunopathol.* **35**:95.

Rideout, B. A., Moore, P. F., and Pedersen, N. C., 1992a, Persistent upregulation of MHC class II antigen expression on T lymphocytes from cats experimentally infected with feline immunodeficiency virus, *Vet. Immunol. Immunopathol.* **35**:71.

Rideout, B. A., Lownstine, L. J., Hutson, C. A., Moore, P. F., and Pedersen, N. C., 1992b, Characterization of morphologic changes and lymphocyte subset distribution in lymph nodes from cats with naturally acquired feline immunodeficiency virus infection, *Vet. Pathol.* **29**:39.

Rodgers, S. J., and Baldwin, C. A., 1990, A serologic survey of Oklahoma cats for antibodies to feline immunodeficiency virus, coronavirus, and *Toxoplasma gondii* and for antigen to feline leukemia virus, *J. Vet. Diagn. Invest.* **2**:180.

Roy, S., and Wainberg, M. A., 1988, Role of the mononuclear phagocyte in the development of the acquired immunodeficiency syndrome (AIDS), *J. Leukoc. Biol.* **43**:91.

Sabine, M., Michelsen, J., Thomas, F., and Zheng, M., 1988, Feline AIDS, *Aust. Vet. Pract.* **18**:105.

Sakura, A., Salminen, T., and Lindberg, L.-A., 1992, A survey of FIV antibodies and FeLV antigens in free-roaming cats in the capital area of Finland, *Acta. Vet. Scand.* **33**:9.

Shelton, G. H., Abkowitz, J. L., Linenberger, M. L., Russell, R. G., and Grant, C. K., 1989a, Chronic leukopenia associated with feline immunodeficiency virus infection in a cat, *J. Am. Vet. Med. Assoc.* **194**:253.

Shelton, G. H., McKim, K. D., Cooley, P. L., Dice, P. F., Russell, R. G., and Grant, C., 1989b, Feline leukemia virus and feline immunodeficiency virus infections in a cat with lymphoma, *J. Am. Vet. Med. Assoc.* **194**:249.

Shelton, G. H., Waltier, R. M., Connor, S. C., and Grant, C. K., 1989c, Prevalence of feline immunodeficiency virus infections in pet cats, *J. Am. Anim. Hosp. Assoc.* **25**:7.

Shelton, G. H., Grant, C. K., Cotter, S. M., Gardner, M. B., Hardy, W. D., Jr., and DiGiacomo, R. F., 1990a, Feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) infections and their relationships to lymphoid malignancies in cats: A retrospective study (1968–1988), *J. Acquir. Immune Defic. Syndr.* **3**:623.

Shelton, G. H., Linenberger, M. L., Grant, C. K., and Abkowitz, J. L., 1990b, Hematologic manifestations of feline immunodeficiency virus infection, *Blood* **76**:1104.

Siebelink, K. H. J., Chu, I.-H., Rimmelzwaan, G. F., Weijer, K., Herwijnen, R., Van, Knell, P., Egberink, H. F., Bosch, M. L., and Osterhaus, A. D. M. E., 1991, Feline immunodeficiency virus (FIV) infection in the cat as a model for HIV infection in man: FIV induced impairment of immune function, *AIDS* **6**:1373.

Siebelink, K. H. J., Chu, I.-H., Rimmelzwaan, G. F., Weijer, K., Osterhaus, A. D. M. E., and Bosch, M. L., 1992, Isolation and partial characterization of infectious molecular clones of feline immunodeficiency virus obtained directly from bone marrow DNA of naturally infected cats, *J. Virol.* **66**:1091.

Smyth, N. R., Gaskell, R. M., Brown, A., and Gaskell, C. J., 1990, Treatment for FIV? (letter), *Vet. Rec.* **126**:409.

Song, W., Collisson, E. W., Billingsley, P. M., and Brown, W. C., 1992, Induction of feline immunodeficiency virus-specific cytolytic T-cell responses from experimentally infected cats, *J. Virol.* **66**:5409.

Sparger, E. E., Shacklett, B. L., Renshaw-Gregg, L., Barry, P. A., Pedersen, N. C., Elder, J. H., and Luciw, P. A., 1992, Regulation of gene expression directed by the long terminal repeat of the feline immunodeficiency virus, *Virology* **187**:165.

Steinman, R., Dombrowski, J., O'Connor, T., Tonelli, Q., Montelaro, R., Lawrence, K., Seymour, C., Goodness, J., Pedersen, N., and Andersen, P. R., 1989, Biochemical and immunological characterization of the major structural proteins of feline immunodeficiency virus, *J. Gen. Virol.* **71**:701.

Stephens, E. A., Monck, E., Reppas, K., and Butfiloski, E. J., 1991, Processing of the glycoprotein of feline immunodeficiency virus: Effect of inhibitors of glycosylation, *J. Virol.* **65**:1114.

Swinney, G. R., Pauli, J. V., Jones, B. R., Wilks, C. R., 1989, Feline T-lymphotropic virus (FTLV) (feline immunodeficiency virus infection) in cats in New Zealand, *N. Z. Vet. J.* **37**:41.

Talbot, R. L., Sparger, E. E., Lovelace, K. M., Fitch, W. M., Pedersen, N. C., Luciw, P. A., and Elder, J. H., 1989, Nucleotide sequence and genomic organization of feline immunodeficiency virus, *Proc. Natl. Acad. Sci. USA* **86**:5743.

Tanabe-Tochikura, A., Tochikura, T. S., Blakeslee, J. R., Jr., Olsen, R. G., and Mathes, L. E., 1992, Anti-human immunodeficiency virus (HIV) agents are also potent and selective inhibitors of feline immunodeficiency virus (FIV)-induced cytopathic effect: Development of a new method for screening of anti-FIV substances in vitro, *Antiviral Res.* **19**:161.

Taniguchi, A., Ishida, T., Konno, A., Washizu, T., and Tomoda, I., 1990, Altered mitogen response of peripheral blood lymphocytes in different stages of feline immunodeficiency virus infection, *Jpn. J. Vet. Sci.* **52**:513.

Taniguchi, A., Ishida, T., Washizu, T., and Tomoda, I., 1991, Humoral immune response to T-cell dependent and independent antigens in cats infected with feline immunodeficiency virus, *Jpn. J. Vet. Sci.* **54**:333.

Tenario, A. P., Franti, C. E., Madewell, B. R., and Pedersen, N. C., 1991, Chronic oral infections of cats and their relationship to persistent oral carriage of feline calici-, immunodeficiency, or leukemia viruses, *J. Vet. Immunol. Immunopathol.* **29**:1.

Tilton, G. K., O'Connor, T. P., Jr., Seymour, C. L., Lawrence, K. L., Cohen, N. D., Andersen, P. R., and Tonelli, Q. J., 1990, Immunoassay for detection of feline immunodeficiency virus core antigen, *J. Clin. Microbiol.* **28**:898.

Tochikura, T. S., Hayes, K. A., Cheney, C. M., Tanabe-Tochikura, A., Rojko, J. L., Mathes, L. E., and Olsen, R. G., 1990, *In vitro* replication and cytopathogenicity of the feline immunodeficiency virus for feline T4 thymic lymphoma 3201 cells, *J. Virol.* **179**:492.

Tomanaga, K., Norimine, J., Shin, Y.-S., Fukusawa, M., Miyasawa, T., Adachi, A., Toyosaki, T., Kawaguchi, Y., Kai, C., and Mikami, T., 1992, Identification of a feline immunodeficiency virus gene which is essential for cell-free virus infectivity, *J. Virol.* **66**:6181.

Tompkins, M. B., Gebhard, D. H., Bingham, H. R., Hamilton, M. J., Davis, W. C., and Tompkins, W. A. F., 1990, Characterization of monoclonal antibodies to feline T lymphocytes and their use in the analysis of lymphocyte tissue distribution in the cat, *Vet. Immunol. Immunopathol.* **4**:305.

Torten, M., Sparger, E. E., Rideout, B. A., Pedersen, N. C., and Luciw, P. A., 1990, Coinfection of cats with FIV and FeLV affects both quantity and distribution of FIV DNA in various tissues, in: *Vaccines 90: Modern Approaches to New Vaccines Including Prevention of AIDS*, pp. 375–378, Cold Spring Harbor Press, Cold Spring Harbor, N.Y.

Torten, M., Franchini, M., Barlough, J. E., George, J. W., Mozes, E., Lutz, H., and Pedersen, N. C., 1991, Progressive immune dysfunction in cats experimentally infected with feline immunodeficiency virus, *J. Virol.* **65**:2225.

Tozzini, F., Matteucci, D., Bandecchi, P., Baldinotti, F., Poli, A., Pistello, M., Siebelink, K. H. J., Ceccherini-Nelli, L., and Bendinelli, M., 1992, Simple in vitro methods for titrating feline immunodeficiency virus (FIV) and FIV neutralizing antibodies, *J. Virol. Meth.* **37**:241.

Ueland, K., and Nesse, L. L., 1992, No evidence of vertical transmission of naturally acquired feline immunodeficiency virus, *Vet. Immun. Immunopath.* **33**:301.

Wasmoen, T., Armiger-Luhman, S., Egan, C., Hall, V., Chui, H.-J., Chavez, L., and Acree, W., 1992, Transmission of feline immunodeficiency virus from infected queens to kittens, *Vet. Immunol. Immunopathol.* **35**:83.

Wheeler, D. W., Whalen, L. R., Gasper, P. W., and Overbaugh, J., 1990, A feline model of the AIDS dementia complex (ADC), in: Proc. 6th Intl. Conf. AIDS, June 20–24, 1990, San Francisco, Abstract Th.A.286.

Witt, C. J., Moench, T. R., Gittelsohn, A. M., Bishop, B. D., and Childs, J. E., 1989, Epidemiologic observations on feline immunodeficiency virus and *Toxoplasma gondii* coinfection in cats in Baltimore, Md., *J. Am. Vet. Med. Assoc.* **194**:229.

Yamamoto, J. K., Pedersen, N. C., Ho, E. W., Okuda, T., and Theilen, G. H., 1988a, Feline immunodeficiency syndrome-A comparison between feline T-lymphotropic lentivirus and feline leukemia virus, *Leukemia* **2**(suppl.):204S.

Yamamoto, J. K., Sparger, E., Ho, E. W., Andersen, P. R., O'Connor, P., Mandell, C. P., Lowenstine, L., Munn, R., and Pedersen, N. C., 1988b, The pathogenesis of experimentally induced feline immunodeficiency virus (FIV) infection in cats, *Am. J. Vet. Res.* **49**:1246.

Yamamoto, J. K., Hansen, H., Ho, E. W., Morishita, T. Y., Okuda, T., Sawa, T. R., Nakamura, R. M., Kau, W. P., and Pedersen, N. C., 1989, Epidemiologic and clinical aspects of feline immunodeficiency virus infection in cats from the continental United States and Canada and possible mode of transmission, *J. Am. Vet. Med. Assoc.* **194**:213.

Yamamoto, J. K., Ackley, C. E., Zochlinski, H., Louie, H., Pempbroke, E., Torten, M., Hansen, H., Munn, R., and Okuda, T., 1991a, Development of IL-2-independent feline lymphoid cell lines chronically infected with feline immunodeficiency virus: Importance for diagnostic reagents and vaccines, *Intervirology* **32**:361.

Yamamoto, J. K., Okuda, T., Ackley, C. D., Louie, H., Rembroke, E., Zochlinski, H., and Gardner, M. B., 1991b, Experimental vaccine protection against feline immunodeficiency virus infection, *AIDS Res.* **7**:911.

Yamamoto, J. K., Hohdatsu, T., Olmsted, R. A., Pu, R., Loule, H., Zochlinski, H. A., Acevedo, V., Johnson, H. M., Soulds, G. A., and Gardner, M. B., 1993, Experimental vaccine protection against homologous and heterologous strains of feline immunodeficiency virus. *J. Virol.* **67**:601–605.

Yates, K. M., Rosenberg, L. J., Harris, C. K., Bronstad, D. C., King, G. K., Biehle, G. A., Walker, B., Ford, C. R., Hall, J. E., and Tizard, I. R., 1992, Pilot study of the effect of acemannan in cats infected with feline immunodeficiency virus, *Vet. Immunol. Immunopathol.* **35**:177.

Zenger, E., 1990, Clinical findings in cats with feline immunodeficiency virus, *Feline Practice* **18**(4):25.

Zetner, K., von, Kampfer, P., Lutz, H., and Harvey, C., 1989, Vergleichende immunologische und virologische Untersuchungen von Katzen mit chronischen oralen Erkrankungen, *Wien. Tierärztl. Mschr.* **76**:303.