

Biology of Feline Leukemia Virus in the Natural Environment¹

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Summary

The feline leukemia virus (FeLV) was discovered in 1964 in a cluster of cats with lymphosarcoma. The observed clustering of cases of feline lymphosarcoma suggested that FeLV was an infectious agent for cats. The development of a simple immunofluorescent test for FeLV permitted a sero-epidemiological study to be undertaken on the distribution of the virus in cats living in their natural environment. Over 2000 cats were tested, and the results showed conclusively that FeLV is an infectious agent for cats. This finding has now been independently confirmed using three different test procedures. After the infectious nature of FeLV was discovered, a simple FeLV test and removal program was devised to control the spread of the virus in the natural environment. The spread of FeLV was controlled in 45 households by removing the FeLV-infected cats, while in 25 households, where the infected cats were left in contact with the uninfected cats, 12% of the uninfected cats became infected. The ultimate control of FeLV awaits the development of an effective FeLV vaccine, which now seems feasible since we have already experimentally immunized some cats with attenuated FeLV. Although FeLV is infectious for cats there is no evidence that FeLV can infect humans.

Introduction

The cat is an excellent animal model for the study of viral carcinogenesis in man (9). It is a random-bred species that lives in the same environment and is subject to the same stresses as man. Moreover, the most common of all feline hematopoietic cancer, LSA,⁴ is known to be caused by an oncornavirus, the FeLV (2).

FeLV was discovered in a cluster of cats with LSA in 1964 by Jarrett *et al.* (22, 24) and was first isolated and purified from the plasma of an infected cat with LSA by Kawakami *et al.* (25) in 1967. The discovery of a viral etiology for feline LSA led to extensive research into the nature and mode of transmission of the virus. In 1969, Jarrett *et al.* (19, 21) discovered that FeLV could infect cat, human, and canine tissue culture cells and Rickard *et al.* (29) reported that Mitchell and coworkers showed that FeLV could cause LSA when injected into newborn puppies. These findings further stimulated interest in the ways that FeLV was spread from cat to cat. Huebner and Todaro (18) proposed the oncogene theory, which was based mostly on observations made with inbred laboratory rodents and which stated that the genetic information of oncornaviruses was incorporated into the host cell genome and was transmitted via the gametes to the offspring (vertical transmission). However, there was no evidence for the vertical transmission of FeLV in cats in the natural environment, and the applicability of the oncogene theory to a nonlaboratory outbred species was uncertain.

The 1st anti-FeLV serum was produced in 1969 by Hardy *et al.* (11), thus enabling the development of serological tests for FeLV that greatly facilitated epidemiological studies of the virus. In 1970, a simple IFA test for the detection of FeLV in the peripheral blood was developed by Hardy *et al.* (12), enabling large numbers of both healthy and diseased cats to be tested for the virus. The relative importance of both vertical and horizontal (infectious) transmission of FeLV in the natural environment could therefore be studied. There is now overwhelming evidence, from several different sources, that FeLV is infectious in its natural environment (7, 15, 23). There is epidemiological evidence from (a) clusters of feline LSA cases and (b) the distribution of FeLV in the environment (1, 15, 31). There are also seroepidemiological data showing that antibodies to FeLV and FeLV-induced cell surface antigens develop in some healthy uninfected cats exposed to FeLV-infected cats. There is further evidence of the infectious nature of FeLV from studies that have shown that it is possible to control the spread of FeLV in the environment by the simple techniques used to control other infectious agents (14). This paper will review the data that have now accumulated in each of these quite separate areas showing that FeLV is infectious for cats and will present new data showing that FeLV can be controlled in the environment.

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⁴ The abbreviations used are: LSA, lymphosarcoma; FeLV, feline leukemia virus; IFA, indirect immunofluorescent antibody; gs, group specific; FOCMA, feline oncornavirus-associated cell membrane antigen; MuLV, murine leukemia virus.

Infectious (Horizontal) Transmission of FeLV

Evidence from Clustering of Cases of Feline LSA. Clusters of LSA (2 or more cats contracting the disease in the same household) have been observed by veterinarians for many years. The 1st reported cluster concerned a household of 34 cats in which 6 cats developed LSA during a 3.5-year period (31). However, 5 of the 6 cats were related and it was thus possible that, in this household, vertical transmission took place. A detailed study of another 15 household clusters provided strong evidence of the infectious nature of FeLV (1). A total of 38 of the 64 cats living in these households developed LSA, although only 2 of the 38 cats were related. In another study of 38 households, 117 cats developed LSA, two-thirds of the cases occurring in unrelated cats (15). There were associations of cases between neighboring household clusters, where there was intermingling of cats, and between distant household clusters, where exchanges of cats for breeding purposes took place. In addition to the epidemiological FeLV studies, the IFA test was used to determine the FeLV status of both the diseased and healthy cats in these households. The results showed that cats living in cluster households were twice as likely to be infected with FeLV than those from noncluster LSA households. These FeLV-infected healthy cats were much more likely to develop an FeLV-related disease than were uninfected cats. These findings showed that FeLV was spread infectiously in pet cats.

Evidence from Seroepidemiological Studies. There are 3 classes of antigens associated with FeLV and the cells it infects (10). These antigens are: (a) type-specific antigens, associated with the viral envelope [these antigens can be demonstrated by neutralization of infectivity *in vivo* or *in vitro* (30)]; (b) FeLV *gs* antigens, or internal virion antigens [which are produced in excess in the cytoplasm of the infected cell (12)]; and (c) a viral-specified nonvirion cell surface antigen (FOCMA) that appears in the membrane of FeLV-transformed cells (6). Detection of FeLV *gs* antigen and the finding of antibodies to FeLV envelope and FOCMA antigens in cats have been used to demonstrate the infectious transmission of FeLV.

Results from the IFA Test. Since the IFA test for FeLV *gs* antigen is simple, requiring only 1 drop of peripheral blood from the cat, many cats can be easily tested for FeLV. Over 2000 healthy cats from 5 different environments have been tested for the virus (15). The environments were classified

as follows: (a) multiple-cat households with a history of FeLV-related diseases; (b) multiple-cat households with no history of FeLV-related diseases; (c) single-cat households; (d) stray cats; and (e) experimental cat colonies (Tables 1 and 3). The results showed a striking correlation between the environmental exposure to FeLV-related diseases and FeLV infection. About 33% of the healthy cats exposed to cats with FeLV-related diseases were infected with FeLV while all the cats known not to have been exposed to these diseases were uninfected. However, 0.31% of the stray cats, with an unknown history of exposure, were infected with FeLV. These results are conclusive evidence that FeLV is an infectious agent for cats in their natural environment. Experiments in cat colonies, where the virus was introduced and the environment was controlled, have supported this finding (23, 24). A more detailed analysis of our results has shown that a higher percentage of healthy FeLV-infected cats (43%) occurs in households with 1 or 2 healthy exposed cats (Table 2). In households with more than 3 healthy exposed cats, the percentage is lower (34%). These findings may be explained by the fact that, in a 2- or 3-cat household (with 1 or 2 healthy exposed cats and 1 FeLV-diseased cat), there is more intimate and constant contact between the cats than in a large household where some cats may not mingle with others. Thus, while these findings support the concept of infectious transmission of FeLV, they are not compatible with the FeLV activation theory, which states that stress or other factors are responsible for the high percentage of FeLV-infected cats in multiple-cat households.

Table 2

FeLV spread based on the number of cats exposed in households
All households had at least 1 cat with an FeLV-related disease.

No. of remaining healthy cats	No. of households	No. of cats tested	No. of FeLV-infected cats	% of healthy cats infected	
1 Cat household	135	135	61	45.1	} 43
2 Cat household	72	144	59	40.9	
3 Cat household	41	123	32	26	} 34
4 or more cat household	81	876	307	35.4	
Total	329	1278	459	35.9	

Table 1

Detection of FeLV in healthy cats from different environments (15)

Environment	History of FeLV or FeLV-associated disease in environment	No. of cats tested	FeLV-infected cats	
			No.	%
Multiple-cat households	Yes	543	177	32.6
Multiple-cat households	No	130	0	0
Single-cat households	No	497	0	0
Stray cats	Unknown	638	2	0.31
Experimental colonies	No	197	0	0
Total		2005	179	8.9

Results from the FOCMA Test. The development of FOCMA antibody can be used as an indication of past FeLV infection since many healthy cats infected with FeLV develop a low (nonprotective) FOCMA antibody titer (3). The development of FOCMA antibody in cats is one of the clearest examples of the importance of immune surveillance as a protective mechanism against naturally occurring cancer. Serum samples from 182 healthy cats living in multiple-cat households with a history of LSA were examined for the presence of FOCMA antibody (4). The incidence of FOCMA antibody in these cats was markedly higher than in cats from the same geographical area that had no known exposure to FeLV (Table 3). A total of 256 healthy cats from pet households with no history of LSA and 191 cats from cat colonies free of LSA were tested for FOCMA antibody (3). A low incidence of FOCMA antibody was found in cats from these environments, especially in single-cat apartment habitats, where the cats were usually not exposed to any other cats. These results are compatible with the results obtained with the IFA test and are further evidence that FeLV is an infectious agent.

Results from the Neutralization Test. Some cats living with FeLV-infected cats never become persistently infected with the virus because they develop a protective neutralizing antibody titer (10). The development of neutralizing antibody, like the development of FOCMA antibody, can be used as an indication of past FeLV exposure (Table 4). None of the 62 FeLV-infected diseased cats and none of the 79 healthy FeLV-infected cats studied were found to have neutralizing antibody. However, of 212 uninfected cats living with FeLV-infected cats, 94 (44.3%) developed FeLV-neutralizing antibody and were thus resistant to FeLV infection. However, only 2 of the 74 cats with no exposure, or with an unknown exposure, had neutralizing antibody. The development of neutralizing antibody is thus dependent on the environmental exposure to FeLV and provides still further evidence of the infectious nature of FeLV.

Results from FeLV Serotyping. Three immunological specificities of the FeLV envelope antigens are known, giving rise to 3 FeLV strains or serotypes (A, B, and C) (20, 30). To simplify the description of cats infected with different FeLV serotypes, we propose the following nomenclature based on that established for the MuLV serotypes. Friend, Molo-

Table 3
FeLV status and neutralizing and FOCMA antibody responses in cats in their natural environment

Cat classification	% of cats FeLV infected (gs positive)	% of cats with neutralizing antibody (≥1:2)	% of cats with FOCMA antibody (≥1:8)
Diseased cats			
Lymphosarcoma	90	0	1
Healthy cats			
Exposed cats	35	44	49
FeLV infected	100	0	36
FeLV uninfected	0	44	61
Unexposed cats	0.1	0	0.8
Unknown exposure			
Stray cats	0.3	5	

Table 4
Occurrence of FeLV-neutralizing antibody in cats in the natural environment

Classification of FeLV exposure	No. of cats tested	Cats with neutralizing antibody titer (≥1:10)	% of cats with neutralizing antibody (≥1:10)
Diseased cats			
FeLV infected			
Lymphosarcoma	40	0	0
Anemia	12	0	0
Other	10	0	0
FeLV uninfected			
Lymphosarcoma	10	0	0
Other	15	1	6.6
Exposed healthy cats			
FeLV infected	79 ^a	0	0
FeLV uninfected	212	94	44.3
FeLV + → -	3	3 ^b	100
Unexposed healthy cats	34	0	0
Unknown exposure (healthy)			
Stray cats	40	2	5
Undomesticated cats	7	0	0
Total	462	100	21.6

^a 3 cats developed LSA.

^b All 3 cats had no neutralizing antibody while infected with FeLV but developed titers after rejecting the virus.

ney, and Rauscher MuLV serotypes have been designated MuLV-FMR and Gross MuLV serotype has been designated MuLV-G. We propose, therefore, that the 3 known FeLV serotypes be designated FeLV-A, FeLV-B, and FeLV-C. Mixtures of FeLV serotypes will be designated FeLV-AB, FeLV-ABC, and FeLV-AC. Mixtures of FeLV-BC serotypes have not been found in cats under natural conditions. The FeLV serotypes from 74 cats have now been isolated by us and identified by Jarrett *et al.* (20) using the viral interference test (Ref. 30; Table 5). We have found that about 54% of cats tested carried FeLV-A and 44% carried a mixture of FeLV-AB. FeLV-ABC was found in only 1 cat. Our preliminary data on the distribution of different serotypes within a household suggest that the occurrence of FeLV serotypes is affected by the type of household environment. In closed households, where the cats are isolated from contact with outside cats, all cats in the same house have the same FeLV serotypes (either FeLV-A or FeLV-AB). This is presumably because the original FeLV serotype(s) was brought into the household by a cat carrying that particular serotype or mixture of serotypes that was then spread infectiously to the other cats. If the virus arose "spontaneously" from vertically transmitted virogenes in cats as a result of stress or other factors, then an approximately equal distribution of FeLV-A and FeLV-AB like that found in the natural environment would have been found. In "open" households, where cats are allowed to enter and leave, different cats living in the household carry different serotypes (FeLV-A or FeLV-AB). This indicates that

Table 5
Prevalence of FeLV serotypes in naturally infected cats

Diagnosis	Total FeLV iso-lates	Serotypes		
		FeLV-A	FeLV-AB	FeLV-ABC
Lymphosarcoma	23	9	13	1
Nonregenerative anemia	3	1	2	0
Myeloproliferative diseases	1	0	1	0
Feline infectious peritonitis	1	0	1	0
Fibrosarcoma	2	0	2	0
Other diseases	4	2	2	0
Healthy cats	40	28	12	0
Total	74	40	33	1

FeLV-A- and FeLV-AB-carrier cats independently infected susceptible cats in these open households.

The Response of Cats to FeLV. The fate of an FeLV-exposed cat depends on how it responds to the viral and viral-induced antigens (FOCMA). Some cats are capable of producing protective neutralizing antibody titers to FeLV under natural conditions and are thus resistant to infection (W. D. Hardy, Jr., unpublished observations). Most cats not exposed to FeLV do not have neutralizing antibody titers and are susceptible to FeLV infection. Some cats are capable of producing FOCMA antibodies and are then resistant to disease development (4-8). The FOCMA antibody response is the best example of the immune surveillance system functioning in the natural environment. However, most cats do not have protective FOCMA antibody titers and are thus susceptible to disease development. Based on their FeLV status and neutralizing and FOCMA antibody responses, healthy cats can be put into 1 of 6 classes as follows: Class 1, those that are FeLV uninfected but susceptible to both FeLV and LSA; Class 2, those that are FeLV uninfected and susceptible to FeLV but resistant to LSA; Class 3, those that are resistant to FeLV infection but susceptible to LSA; Class 4, those that are resistant to both FeLV and LSA; Class 5, those that are FeLV infected and susceptible to LSA; and Class 6, those that are FeLV infected but resistant to the development of LSA (FeLV carrier cats) (10) (Table 6). Cats belonging to each of these 6 categories have been found in the natural environment. We have been able to predict the consequences of FeLV infection in many cats by determining their response to FeLV infection.

Methods of FeLV Transmission. Horizontal (infectious) transmission may occur by 2 routes: (a) epigenetic or (b) contact. Epigenetic transmission includes transmission *in utero* and via the milk. FeLV has been isolated from the milk of 3 viremic queens. In 1 litter, the kittens developed infection 7 weeks after birth and 2 weeks after weaning. There is substantial evidence that FeLV can be transmitted by epigenetic routes since FeLV-infected fetuses have not been found in uninfected queens and have only been found in FeLV-infected queens. For infection through contact, the virus must be shed from infected cats by routes other than

via the milk. FeLV is present in many tissues and has been found in the urine and saliva of infected cats (15). Saliva is a likely medium for spreading FeLV since cats often groom each other. The significance of FeLV in the urine is obvious considering the widespread use of communal litter pans in urban households. FeLV is also found in the peripheral blood of infected cats and thus blood-sucking insects could act as vectors for the virus, but this has yet to be proved (11, 12, 15, 25-27). Charts 1 and 2 illustrate epigenetic and contact FeLV transmission together with the possible disease consequences of these types of horizontal transmission.

The Development of Disease after FeLV Infection. FeLV causes 3 other diseases in addition to LSA (12, 13, 15, 17,

Table 6
Classes of healthy cats based on FeLV status and neutralizing and FOCMA antibody response

Class of healthy cat	FeLV status	FeLV neutralizing antibody	FOCMA antibody
1. Cat susceptible to FeLV and LSA	-	-	-
2. Cat susceptible to FeLV but resistant to LSA	-	-	+
3. Cat resistant to FeLV but susceptible to LSA	-	+	-
4. Cat resistant to FeLV and LSA	-	+	+
5. Cat very susceptible to develop LSA	+	-	-
6. Cat FeLV carrier but resistant to LSA	+	-	+

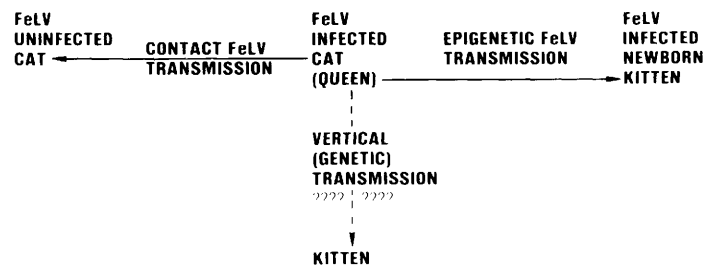


Chart 1. Infectious (horizontal) transmission of FeLV in cats.

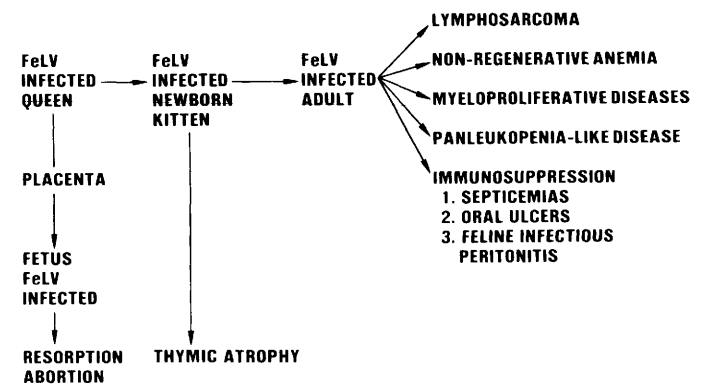


Chart 2. Sequence of epigenetic FeLV infection and disease development in cats.

28). They are (a) nonregenerative anemia; (b) a panleukopenia-like syndrome; and (c) thymic atrophy or fading-kitten syndrome. FeLV is also associated with but not yet proved to be the cause of other diseases such as myeloproliferative disorders and fetal abortions and resorptions (Refs. 13 and 16; Charts 1 and 2).

Healthy FeLV-infected cats have a much greater chance of developing LSA than do healthy cats in the general population where the occurrence of FeLV is low (0.1%). In an average of 6 months from when FeLV was first detected, 16% of the healthy infected cats that were followed developed LSA (15). This incidence is 888 times greater than the expected LSA incidence. If other FeLV-associated diseases are included in the follow-ups, then the percentage becomes higher (33%). The period required for disease development varies from 3 months to 3 years or longer depending on the cat. The percentage of healthy cats developing disease after FeLV infection, therefore, increases the longer these cats are observed. Although most cats are susceptible to disease development, those few that develop high FOCMA antibody titers are resistant to disease and some also act as healthy FeLV carriers. These cats are constantly shedding FeLV and are a source of infection for susceptible cats.

Control of FeLV in the Natural Environment

We have been able to control the spread of FeLV by the IFA test and removal program, which is similar to the programs used to control other infectious disease agents (14). Two types of households must be considered: (a) those containing only 1 cat and (b) those containing several cats. In single-cat households the infected cats should be removed (or at least isolated) and the litter pan and feeding bowl should be discarded. The household should then be cleaned with household detergents, which are capable of inactivating the virus, and an interval of 30 days should be allowed to elapse before another cat is obtained. In multiple-cat households 1 cat usually falls ill or is found to be infected with FeLV before the others. This cat should be removed and all the cats exposed to the infected cat should be immediately tested for FeLV. Any cats found to be infected should be removed (or isolated) in order to protect the remaining healthy uninfected cats. The household should be cleaned as described above and quarantined (*i.e.*, no cats permitted to enter or leave the household). The remaining uninfected cats should be retested for FeLV after a 3-month interval. This is necessary because the incubation period of the virus is fairly long and there is a possibility that an infection just prior to the 1st test would not have been detected. If all the cats remain negative in the 2nd test, then the household is considered virus free and cats can be bought, sold, or given away. All new cats should be tested for FeLV before being introduced into the household.

This program has been successful in controlling the spread of FeLV in many households (Table 7). A total of 70 households have been studied. In 45 households the owners removed (or isolated) their FeLV-infected healthy cats after the initial test, while in 25 households the infected

healthy cats were left with the uninfected cats. In the 45 households where the infected cats were removed, a total of 723 cats were initially tested for FeLV, of which 159 were infected and 564 were uninfected. Of these 564 uninfected cats only 3 (0.53%) subsequently became infected. In the 25 households where there was no removal of the FeLV-infected cats, 397 cats were initially tested, 129 of which were FeLV-infected and 268 were uninfected. Of these 268 uninfected cats, 32 (11.9%) subsequently became infected and 4 have developed LSA. These results show that it is possible to control the spread of FeLV, and the diseases it causes, by relatively simple procedures.

Since FeLV is an infectious agent and since some cats can develop immunity to FeLV under natural conditions, the development of an FeLV vaccine seems feasible. There are 3 possible types of FeLV vaccine: (a) those consisting primarily of live attenuated FeLV, (b) those consisting of killed FeLV, and (c) those composed of FeLV envelope subunits. Each type of vaccine has its own advantages and disadvantages. The advantages of a live attenuated FeLV vaccine are that it is more effective than a killed-virus vaccine in producing a higher neutralizing antibody titer and requires less frequent revaccinations. Its disadvantages are that the possible public health risks are greater than with a killed-virus vaccine and that there is a possibility that a virulent mutant could develop. These problems are reduced with a killed-virus vaccine, but such a vaccine may require higher virus doses and more frequent revaccinations to produce and maintain protective antibody titers. In many respects, an FeLV subunit vaccine, composed of specific viral subunits or proteins free of the viral RNA, would be the best type of vaccine. However, such vaccines are difficult and expensive to produce.

All 3 types of vaccine are currently being studied in order to determine which one would provide the most practical and effective results. A few susceptible cats have already been immunized with attenuated live FeLV in our laboratory but much more work needs to be done before an effective FeLV vaccine will be available for routine veterinary use.

The Possible Public Health Risks of FeLV

FeLV can grow in the cells of other species including human cells grown in tissue culture (19). FeLV grows in canine tissue culture cells and experiments have shown that it can also cause LSA in newborn puppies (29). There are therefore questions as to whether FeLV can infect humans living or working with FeLV-infected cats. In one survey, veterinarians were checked for serological evidence of FeLV infection (*i.e.*, for antibodies to FOCMA) but none was found (32). Over 500 humans, including some with malignant disease, have been tested by us for FeLV *gs* antigens and FeLV-neutralizing antibody. The detection of FeLV *gs* antigens would indicate current infection while the detection of neutralizing antibody would indicate past infection. One hundred seventy-nine people who had been exposed to FeLV and 326 people with an unknown FeLV exposure were tested for the presence of FeLV *gs* antigens. No one was found to be infected with FeLV (Tables 8 and 9). About 100 people were tested for FeLV-neutralizing antibody. No anti-

Table 7
FeLV test and removal program to control the spread of FeLV

	Total households	No. of FeLV diseases	FeLV status	Total healthy cats in households	No. of healthy cats		No. of cats remaining uninfected 3 mo. later	No. of cats becoming infected	% of cats becoming infected	
					Infected	Uninfected				
Removal of infected cats	45	39 LSA 13 FIP ^a 4 anemia 12 other	32 + 13 NT	723	723	159	564	561	3 ^b	0.53
					22%					
No removal of infected cats	25	37 LSA 9 FIP 2 anemia 6 other	23 + 2 NT	397	397	129	268	236	32	11.9
					32.5%					

^a FIP, feline infectious peritonitis; NT, not tested.

^b May have been incubating virus at 1st test (no 3-month retest performed).

Table 8
Search for FeLV gs antigens in humans known to be exposed to FeLV-infected cats

Diagnosis	No. tested	No. FeLV gs antigen positive
Healthy		
Cat owners	63	0
Severely bitten by FeLV-infected cat	4	0
Child, exposed <i>in utero</i> to FeLV-infected cat	1	0
Veterinarians	52	0
Veterinary hospital employees	41	0
FeLV laboratory personnel	6	0
Total	167	
Diseases		
Lymphosarcoma	2	0
Acute lymphoblastic leukemia	2	0
Hodgkin's disease	3	0
Nonlymphoid cancers	5	0
Total	12	

Table 10
Search for FeLV-neutralizing antibody in humans

Diagnosis	No. tested	FeLV titer > 1:2
<i>Exposed to FeLV or FeLV infected cats</i>		
Healthy		
Cat owners	11	0
Cat breeders	54	0
Veterinarians	8	0
FeLV laboratory personnel	4	0
Exposed to massive FeLV spill	1	0
Diseases		
Lymphoid tumors	6	0
Nonlymphoid tumors	1	0
Veterinarian with lymphosarcoma	1	0
Total	86	0
<i>No known FeLV exposure</i>		
Healthy		
Non-cat owners	18	0
Total	18	0

Table 9
Search for FeLV gs antigens in humans with unknown exposure to FeLV-infected cats

Diagnosis	No. tested	No. FeLV gs antigen positive
Healthy		
Cat breeders	24	0
Cat owners	36	0
Cancer laboratory personnel	7	0
Total	67	
Diseases		
Lymphosarcoma	49	0
Acute lymphoblastic leukemia	66	0
Chronic lymphoblastic leukemia	38	0
Hodgkin's disease	47	0
Nonlymphoid cancers	59	0
Total	259	

body was found in any individual including those who had been exposed to FeLV and had also developed cancer (Table 10). These results indicate that FeLV did not infect those individuals tested, however, more work with more sensitive techniques must be done before it can be concluded that FeLV does not infect man. Immunosuppressed individuals and fetuses, which are more susceptible to viral infections than are adults, might well have a higher risk of FeLV infection than healthy adults.

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