No. 12, 1993

Cornell Feline Health Center
Information Bulletin

Feline Leukemia Virus

Jeffrey E. Barlough, D.V.M., Ph.D.
Fred W. Scott, D.V.M., Ph.D.

The feline leukemia virus (FeLV) is the causative agent of the most important fatal infectious-disease complex of American domestic cats today. It is a horizontally transmitted (i.e., contagious), ribonucleic-acid (RNA) virus belonging to the family Retroviridae. Retroviruses causing lymphoid tumors have been identified in a number of animal species, including cats, cattle, domestic fowl, nonhuman primates, and rodents. A retrovirus known as the *human T-lymphotropic virus* (HTLV) has been isolated from people with certain aggressive lymphoid malignancies; data indicate that this virus is indeed involved in the development of these tumors.

The oncogenic retroviruses are collectively referred to as the *RNA tumor viruses*, or *oncornaviruses* (*onco*genic *RNA viruses*). In addition, there are other members of the Retroviridae family, the *lentiviruses*, that induce nonmalignant disease processes such as progressive pneumonia of sheep, arthritis-encephalitis of goats, infectious anemia of horses, and acquired immunodeficiency syndrome of human beings (AIDS). A new and unique lentivirus, the *feline immunodeficiency virus* (FIV), was isolated and characterized in the mid-1980s. FIV causes an immunodeficiency syndrome in cats similar in many respects to that produced by human immunodeficiency virus (HIV) in people. Retroviruses not yet associated with any recognized disease process also exist, such as the *syncytium-forming* ("foamy") viruses that have been recovered from a number of species, including cats.

Replication-competent retroviruses carry with them an enzyme called *reverse transcriptase*, which is capable of making a deoxyribonucleic-acid (DNA) copy of the retroviral RNA. The DNA copy can be inserted into the chromosomal DNA of the infected cell. This alien intruder, known as a *provirus*, or *proviral DNA*, is replicated whenever the host cell divides and can serve as a template for the production of new virus particles. The new particles are assembled in the cytoplasm of the cell and then are released by budding through the cell membrane. During this budding process from the cell, the virus particles or *virions* acquire an outer lipid *envelope* and surface projections known as *knobs*, *spikes*, or *peplomers*. The peplomers are composed of glycoprotein and have specific *epitopes* or regions that attach in a specific way to receptors on the surface of susceptible cells, enabling the new virions to infect these cells and thus perpetuate the virus infection cycle.

At present there is no practical method of removing, or excising, integrated proviruses from infected cells of living organisms. A cell infected with an integrated retrovirus is infected for the length of its lifetime, as are all of its progeny cells. This is of importance in latent FeLV infections and in the persistence of intracellular FeLV during an active immune response. Because a version of their genetic material can become a part of the total genetic information of the cells they infect, retroviruses are among the most intimate parasites known in nature.

FELINE RETROVIRUSES

There are three subfamilies of viruses within the Retroviridae family; Oncovirinae, Lentivirinae, and Spumavirinae. Each of these subfamilies contains one or more viruses that infect cats.

Oncoviruses. Several members of the Oncovirinae subfamily of retroviruses are of significance in this discussion: FeLV, the feline sarcoma virus (FeSV), the endogenous virus known as *RD-114*, and the endogenous FeLV-related sequences (enFeLV). Of this group only FeLV is a truly *exogenous* agent; that is, infection is spread from cat to cat as a contagion, so that unexposed cats are free of FeLV proviral DNA.

RD-114 is a true endogenous virus. Multiple RD-114 proviruses are present within the chromosomal DNA of cells of all domestic cats and are transmitted vertically through the germ line (i.e., they are inherited). However, the production of virus is usually repressed, so that the agent is not contagious. The RD-114 retrovirus does not appear to be related to FeLV and has not been shown to cause any recognized disease in cats.

FeSV, a replication-defective mutant of FeLV, apparently arises within individual cats by a recombinational event in which a segment of host chromosomal DNA is erroneously incorporated into a FeLV provirus. The

resulting FeSV is unable to replicate without assistance from replication-competent FeLV ("helper" virus), because a portion of its genetic information is lost during recombination. The chromosomal DNA acquired by the virus endows it with the ability to induce certain types of tumors. (See "Mechanisms of Tumor Induction" and "The FeSV-associated Diseases.")

FeLV is classified into three distinct subgroups designated A, B, and C, of which FeLV-A is the most common. All FeLV-positive cats have FeLV-A, while approximately 50% of FeLV-positive cats are also infected with FeLV-B. Fewer than 1% of FeLV-positive cats have FeLV-C (always with either FeLV-A or FeLV-A plus FeLV-B). FeLV-A is the virus subgroup that is transmitted cat-to-cat and that produces viremia and latent infections. The pathogenic effects of FeLV-A, however, are slow to develop; disease often occurs only after some recombinational, mutational, or activation event has occurred during FeLV-A replication within host cells. FeLV-B is a replication-defective mutant of FeLV-A that arises when FeLV-A recombines with enFeLV in an infected cell. The enFeLVs are gene sequences of varying length that, like RD-114, are present in all cat cells; however, the enFeLVs show marked similarities to portions of the genetic material of FeLV. Subsequent replication of FeLV-B (with the assistance of FeLV-A as helper virus) can lead to the development of lymphoid malignancies or myeloproliferative disease. FeLV-C probably arises by recombination or mutation involving FeLV-A; its replication is associated with the development of aplastic anemia (AA), one of the most frustrating of all the FeLV-related diseases to treat. (See "The FeLV-associated Diseases.") Thus the outcome of FeLV infection appears to be determined, at least in part, by the subgroup(s) of FeLV found in the cat.

FeLV-FAIDS is an unusual isolate of FeLV in which the onset of disease is associated with the appearance of a mutant form, *variant A*, in infected cells. Variant A is a replication-defective FeLV that, like FeSV, requires helper FeLV to replicate. Unlike FeSV, however, variant A does not cause cancer. Instead variant A exerts a cytolytic effect, killing infected cells in the bone marrow, lymphoid tissues, and intestine. Because these cells consist in large measure of components of the immune system, their destruction leads to a fatal immunodeficiency syndrome. (This syndrome is distinct from that produced by FIV.)

Lentivirus. FIV, the only feline lentivirus identified to date, is present in 1% to 2% of domestic cats in the United States, and in a much higher percentage of sick cats. FIV also infects nondomestic felids in both zoological gardens and wild populations. This virus has a predilection for infecting T lymphocytes, producing a decrease in $CD4^+$ T cells and, consequently, a progressive immunodeficiency syndrome characterized by chronic secondary infections. FIV and FIV infections are discussed in *Feline Information Bulletin No. 10*, published by the Cornell Feline Health Center.

Spumavirus. The feline spumavirus, feline syncytium-forming virus (FeSFV), causes a common, persistent infection in cats. While FeSFV can be isolated from cats afflicted with a variety of conditions, it has not been shown to be the cause of any disease.

HOST RANGE OF FELV INFECTION

In nature FeLV infection appears to be restricted to members of the cat family, including domestic breeds as well as some exotic cats: sand cats, European wild cats, jungle cats, cougars, and possibly leopard cats.

MECHANISMS OF TUMOR INDUCTION

The precise biochemical mechanisms by which normal, healthy cells are transformed into tumor cells unresponsive to cellular control mechanisms are not yet known. However, studies in the last two decades involving oncornaviruses from a number of animal species have begun to reveal some of the complex molecular interactions responsible for the induction and maintenance of malignancy.

Many oncogenic retroviruses carry with them a transforming gene, or *viral oncogene* (*v-onc*), that plays a major role in the development of cancer in the cells the viruses infect. These oncogenes appear to be derived from normal cellular genes, which the viruses have acquired, or *transduced*. In the process the genes are subjected to alteration and placed under the control of viral regulatory genes. The normal cellular genes (*proto-oncogenes* or *cellular oncogenes* [*c-onc*]) acquired by the viruses are highly conserved. The ability of their virus-modified counterparts to produce abnormal cellular growth indicates that c-onc gene products are involved in the regulation of very basic cellular processes of growth and differentiation.

The incubation period may be quite prolonged (months to years) for some oncornaviruses, such as FeLV, but may be quite short (weeks) for others, such as FeSV. The vast majority of oncornaviruses with short incubation periods (such as FeSV) are replication-defective; those with prolonged incubation periods are fully capable of replication without the assistance of helper viruses. Most of the defective oncornaviruses that have been closely examined share a common feature: the replacement of genetic information necessary for replication by a v-onc gene sequence that apparently mediates the swift transformation of infected host cells into tumor cells. The v-onc genes present in defective oncornaviruses such as FeSV probably have been acquired by transduction involving a nondefective oncornavirus (in this case, FeLV) and a host chromosomal DNA sequence containing a c-onc gene or other regulatory element.

The mechanisms by which nondefective oncornaviruses with prolonged incubation periods (such as FeLV) induce malignancy are less clear, but it may be that the location in the host-cell chromosome at which

their proviral DNA inserts is critical. Thus insertion of proviral DNA near a c-onc gene may either activate or disrupt that gene in some manner that results in malignant transformation of the host cell. This may in part explain the lengthy incubation period, because it may require many proviral insertions during repeated cycles of infection before alteration of a critical c-onc gene takes place. In other cases the virus may persist in an animal for a prolonged period before transducing a c-onc gene, so that a new recombinant viral mutant is generated *de novo* (an event similar to that which gives rise to FeSV). Disrupted regulation of expression or genetic rearrangement of the *myc* gene, whose gene product is an important regulator of cell proliferation, appears to be responsible for a significant number of the lymphoid malignancies produced by FeLV in cats. By constantly activating the myc gene, the virus showers infected lymphocytes with proliferative signals that generate repeated and uncontrolled cell division. In some cases it appears that secondary mutational events in addition to c-myc activation are required for the full expression of malignancy. Alternatively, other factors in addition to the oncornavirus may be required to produce certain tumors.

IMMUNOGENIC IMPORTANCE OF FELV STRUCTURAL COMPONENTS

Individual particles, or virions, of FeLV consist of two distinct morphologic components: a dense inner core (the *nucleoid*) and an outer envelope. The envelope contains an immunologically important glycoprotein known as *gp70*. This protein is the principal *antigen* (substance against which an immune response can be generated) present in the virus surface receptors, which are responsible for attachment of the virus to cells during infection. Virus-neutralizing antibody (VNA) directed against gp70 is an essential component of a successful immunologic response to FeLV, and the presence of anti-gp70 VNA in the blood is an indication of past FeLV exposure, either from natural infection or vaccination. Most cats with *persistent viremia*—the prolonged presence of FeLV in the bloodstream—produce little or no VNA. In addition, most cats in the general feline population that have not been vaccinated against FeLV do not have levels of VNA that are protective against infection, probably because they have not been exposed recently or at all to an infective dose of FeLV. On the other hand, about 40% to 50% of healthy cats in FeLV-infected multiple-cat households have protective VNA titers. These cats are generally believed to be resistant to subsequent FeLV infection, and most will not become persistently viremic. All FeLV vaccines available at the time of this writing rely on stimulation of VNA against gp70 as the principle for providing protection against FeLV infection.

The second major antigen of the FeLV particle is the core protein *p27*, which is a structural component of the inner viral nucleocapsid. This protein can be found in great abundance in the cytoplasm of infected white blood cells and platelets and in soluble form in plasma and serum of viremic cats. The significance of the immunologic response of the cat to p27 is at present uncertain, because antibodies directed against it are not protective, preventing neither viremia nor FeLV-related disease. The primary importance of p27 lies in its identification as the major FeLV antigen detected by the IFA and ELISA tests. (See "Diagnostic Aids for FeLV Infection.")

PATHOGENESIS OF FELV INFECTION

Exposure of unvaccinated, susceptible cats to FeLV virus may result in (1) a failure of the cat to become infected with virus, (2) a progressive FeLV infection, or (3) a regressive FeLV infection. Those cats that do not become infected following exposure will remain FeLV-negative by IFA and ELISA tests. The outcome for those cats that become infected with the virus depends on host, viral, and environmental factors. FeLV is a lymphotropic retrovirus with a predilection for the T lymphocytes that are responsible for the cell-mediated immune response of the cat. A decrease in both $CD4^+$ and $CD8^+$ T lymphocytes occurs during acute FeLV infection.

In progressive FeLV infections, the incubation period is followed by an acute period of infection with a continuous increase in the degree of replicating virus until a persistent, stable FeLV infection develops. If the viremia lasts for at least twelve weeks, a persistent FeLV infection results, with a lack of immunity or protection against the various FeLV-related diseases. If an effective immune response is mounted by the host, a regressive FeLV infection occurs, with either no virus in the blood or only a transient viremia. The virus may be rejected entirely *(immune infection)* or controlled within bone marrow or other tissue *(sequestered infection)*, or a portion of the virus genome may be incorporated within the genome of the host cell *(latent infection)*.

Initial infection with FeLV occurs in the lymphoid tissues at the site of initial virus penetration (usually the tonsils); the virus then spreads via lymphatics to the local lymph nodes of the head and neck, where viral replication is amplified. Two to twelve days after the initial infection, virus first appears in the blood stream *(primary viremia)* and involves only a small number of infected mononuclear white blood cells. During this brief time, virus is transported to other regions of the body, especially to systemic lymphoid tissue, the intestine, and bone marrow. These sites contain populations of rapidly dividing cells, in which FeLV replication can be enhanced. Infection of white blood cells and platelet precursor cells in the bone marrow and subsequent release of infected cells into the circulation result in a more profound or secondary viremia. In cats that develop an effective immune response following FeLV infection, containment of the virus may occur in the early lymphoid stage of infection, during primary viremia, or during the first few weeks of secondary viremia. This removal of virus

from the blood by the host immune response results in a transient viremia; such cats will progress from a FeLV test-positive status to a FeLV test-negative status. In those cats destined to develop persistent viremia, the host immune response is ineffective in controlling virus replication, and the infection proceeds to involve the bone marrow, pharynx, respiratory tract, esophagus, stomach, bladder, and, importantly, the salivary glands.

TRANSMISSION OF FELV

Persistently viremic cats shed infectious FeLV in their saliva and urine, and most will remain infectious for the rest of their lives. They thus serve as a source of infection for uninfected susceptible cats with which they come into contact. Cats that develop immunity may experience an initial transient viremia lasting from a few days to twelve weeks, during which time they too can shed infectious FeLV.

Excretion of FeLV occurs primarily in salivary secretions, although virus may also be present in respiratory secretions, feces, and urine; the infection is usually acquired by ingestion. Thus the social grooming habits of cats, licking and biting, sneezing, and the sharing of litter boxes and food bowls probably represent the major modes of spread of FeLV among pet cats. In addition, in-utero transfer of virus across the placenta and excretion of FeLV in colostrum and milk are known to occur, so that kittens may become infected either from an infected queen or by close contact with other persistently infected cats. Prolonged close contact (days to weeks, or longer) between cats is usually required for effective transmission of FeLV; "asocial" cats appear to be less readily infected than more "outgoing" cats. Virus can also be spread by blood transfusions when the blood donor cat is viremic. The time period between initial exposure to an infective dose of FeLV and the development of either viremia or immunity is quite variable and may depend in part on the route of virus transmission as well as the amount of virus in the exposure.

Studies have demonstrated that age at the time of infection and the amount and strain of the infective dose are important determinants of the outcome of FeLV exposure. Whereas most young kittens exposed to FeLV become persistently viremic, most cats older than four to six months of age do not, suggesting that age-related maturational changes in the immune system are involved. Evidence indicates that these changes occur in cats between two and four months of age. However, it does appear that some older animals may become persistently viremic if the duration of exposure to the virus is lengthy, or if the exposure is to certain highly virulent virus strains such as the FeLV-FAIDS.

In common with many enveloped viruses, FeLV is labile once outside the cat and is rapidly inactivated by alcohol and most common household detergents and disinfectants. The infectivity of virus in saliva left to dry at room temperature has been shown to decline to inconsequential levels within three to four hours. However, the infectivity of FeLV suspended in liquid (blood serum, tissue culture medium) at room temperature may persist for several days and for even longer periods at refrigerator temperature.

THE FELV-ASSOCIATED DISEASES

Cats persistently infected with FeLV are susceptible to diseases that are directly or indirectly caused by the virus. Those directly caused by FeLV include lymphoid malignancies, myeloproliferative disorders, anemias, the panleukopenia-like and thymic atrophy syndromes, at least one form of kidney disease, and certain reproductive disorders. Diseases indirectly caused by FeLV include a myriad of conditions that develop secondarily to FeLV-mediated suppression of the immune system. The prognosis for survival of persistently viremic cats is poor; approximately 50% die within six months of detection of their infection, and over 80% die within three and a half years. Some persistently viremic cats can live for many years, however.

Lymphoid malignancies. *Lymphosarcoma* (LSA) and *lymphocytic leukemia* are among the most common tumors occurring in American domestic cats. Several forms of LSA have been identified, and their classification is based most commonly on their anatomic distribution. The tumors consist primarily of solid masses of abnormally proliferating lymphocytes and constitute the majority of the malignancies caused by FeLV.

The *thymic,* or *mediastinal, form* is characterized by the presence of a large tumor mass (or masses) infiltrating the thymus gland and spreading to regional lymphoid tissues and sometimes to structures outside the chest. Clinical signs reflect pressure effects of the mass and the severe intrathoracic fluid accumulation that frequently accompanies the tumor. Physical examination may reveal labored respiration, cyanosis, muffled heart sounds, coughing, difficulty in swallowing, and incompressibility of the chest wall.

The *alimentary form* of LSA is characterized by tumor-cell infiltration of the gastrointestinal tract and other organs, such as the intestinal lymph nodes, liver, kidneys, and spleen. Common presenting signs include inappetence, weight loss, vomiting, diarrhea, bloody stool, and jaundice. Occlusion of the bowel lumen by the proliferating tumor results in constipation or obstipation.

The *multicentric form* is characterized by primary involvement of many lymphoid tissues of the body and additional involvement of other structures, such as the bone marrow, liver, kidneys, spleen, and lungs. Presenting signs are variable and dependent on the precise anatomic distribution of the tumor. They often include painless swelling of peripheral lymph nodes and enlargement of the spleen and liver and often of the intestinal lymph nodes, accompanied by inappetence and weight loss. When peripheral lymph node enlargement is the primary sign, the tumor may be mistaken for the initial stage of FIV infection unless a lymph node smear or biopsy is prepared. (See *Feline Infor-*

mation Bulletin No. 10—Feline Immunodeficiency Virus.)

Atypical forms of LSA also occur and consist usually of solitary tumor masses involving primary sites of origin in nonintestinal, nonlymphoid structures. These include the kidneys, central nervous system, nasal passages, eyes, and, rarely, the skin or bones. Presenting signs vary according to the location of the tumor.

Lymphocytic leukemia is characterized by the presence of cancerous lymphocytes in the blood or bone marrow. It may precede the development of LSA or it may be associated secondarily with LSA. Presenting signs usually consist of inappetence, depression, and weight loss. More specific signs include anemia, fever, jaundice, and enlargement of the liver, spleen, and lymph nodes.

Lymphoid tumors occur in cats of all ages, but certain age-related tendencies have been observed. Thus the thymic form of LSA and lymphocytic leukemia occur most commonly in younger cats, the multicentric form of LSA in middle-aged cats, and the alimentary form in middle-aged and older cats.

FeLV-negative lymphoid malignancies. During the course of investigations into the biology of FeLV, it has become apparent that approximately one-third of lymphoid malignancies in cats are negative for FeLV-related material, such as virus particles, viral structural proteins, or proviral DNA. Most of these FeLV-negative tumors are of the alimentary type and occur proportionally more often in older cats than in younger ones. It appears that FeLV (probably the result of a latent infection) ultimately is responsible for the development of many of these FeLV-negative malignancies. Recently, however, it has become apparent that FIV may also play a role in the production of some of these tumors, perhaps as a result of the virus's immunosuppressive properties.

Myeloproliferative disorders. Myeloproliferative disorders are a group of primary bone marrow diseases characterized by abnormal proliferation of one or more *hemopoietic* (blood-forming) cell lines. *Granulocytic* (myelogenous) *leukemia, erythroleukemia, erythremic myelosis, megakaryocytic leukemia, polycythemia rubra vera,* and *reticuloendotheliosis* are all terms that have been applied to various forms of these disorders. Classification relies on identification of the cell line(s) of origin. Clinicopathological differentiation among the different forms is sometimes difficult if not impossible, however, because more than one hemopoietic cell line may be involved, either sequentially or simultaneously. Presenting signs can include inappetence, depression, weight loss, relentless and progressive anemia, fever, jaundice, peripheral lymph node enlargement, and enlargement of the liver and spleen secondary to massive infiltration by abnormally proliferating hemopoietic cells.

Aplastic anemia. Aplastic anemia (AA) is one of the more common manifestations of FeLV infection and is often associated with FeLV-C infections. This type of anemia, also known as nonregenerative or depression anemia, is characterized by a severe reduction in the number of red blood cell precursors in the bone marrow, resulting in a failure to produce adequate numbers of circulating red cells. (Sometimes there may be a pancytopenia, in which red-cell, white-cell, and platelet precursors are all affected). AA may occur alone or in conjunction with LSA or a myeloproliferative disorder, or it may precede the development of an FeLV-induced malignancy. Because many cats severely ill with AA are euthanized, the true incidence of subsequent malignancy cannot be accurately determined. Unfortunately, because of the stoic nature of cats, clinical signs often are not detected until the anemia is well advanced. Common signs include inappetence, depression, weight loss, lethargy, respiratory distress, and increased heart rate. Co-infection of such cats with *Haemobartonella felis,* the red blood cell parasite causing *feline infectious anemia,* may contribute to the severity of the anemia.

Other anemias. In addition to AA, other types of anemia may occur in cats in association with FeLV infection. These include (1) *leukoerythroblastic anemia,* characterized by the simultaneous presence of circulating immature red blood cells in numbers out of proportion to the severity of the anemia, and of certain immature white blood cells (this type of anemia has been observed in some cases of LSA); (2) *megaloblastic anemia* (similar to the anemia of vitamin B12/folate deficiency), sometimes seen in cats with myeloproliferative disorders; (3) *hemolytic anemia,* characterized by premature destruction of circulating red blood cells by an immunologic process; and (4) *anemia of chronic disease,* due to ineffective reutilization of iron for synthesizing hemoglobin.

Panleukopenia-like syndrome. A syndrome resembling *feline panleukopenia* (feline parvovirus infection) has been observed in some FeLV-infected cats known to be immunized against panleukopenia. Presenting signs often include inappetence, depression, dehydration, weight loss, fever, vomiting, diarrhea (which may be bloody), and a profound reduction in the number of circulating white blood cells. Anemia may also be present. Although affected cats may respond transiently to supportive therapy, the disease is progressive and always fatal.

Thymic atrophy syndrome. Kittens born to persistently viremic queens often develop a syndrome of lethargy, inappetence, wasting, stunted growth, atrophy of the thymus and other lymphoid structures, and enhanced susceptibility to infection with other disease-producing agents ("fading kitten" syndrome). The degree of thymic atrophy can be severe, amounting to virtual disappearance of the organ in some cases. Such kittens do not gain weight and often do not nurse vigorously. Many die from secondary bacterial or viral infections within the first few days or weeks of life. Those that survive are persistent carriers of FeLV and are thus capable

of transmitting the virus to other susceptible cats. The syndrome may also precede the development of an FeLV-induced malignancy.

Reproductive disorders. Queens infected with FeLV may experience one or more reproductive disorders, including fetal resorption, abortion, infertility, endometritis (uterine inflammation), and birth of "fading" kittens. Abortions characteristically occur late in gestation and are more frequent in high-density multiple-cat FeLV households than in solitary-cat households or multiple-cat households free of FeLV. It has been reported that nearly 75% of infertile queens are persistently viremic.

Chronic kidney disease. *Glomerulonephritis,* a type of kidney disease, has been described in cats in association with LSA, lymphocytic leukemia, and granulocytic leukemia. In addition, kidney disease in the absence of malignancy has been reported in FeLV-infected cats and may be the leading cause of feline death in an FeLV-infected household. *Immune-complex kidney disease,* ranging from subclinical microscopic lesions to the *nephrotic syndrome,* may be caused by formation of antigen-antibody complexes that accumulate in kidney glomeruli. The primary antigen against which the antibodies are directed appears to be the p27 core protein of FeLV.

A mild to moderately severe glomerulonephritis may occur in some cats suffering from *chronic progressive polyarthritis* (CPP), a symmetrical polyarthritis with similarities to rheumatoid arthritis of human beings. Although the cause is unknown, there is some evidence that dual infection of cats with FeLV and FeSFV may be associated with CPP in some cats.

Diseases secondary to immunosuppression. Secondary disease entities associated with FeLV-induced immunosuppression constitute one of the most important manifestations of FeLV infection. Up to 50% of all cats with severe bacterial infections or feline infectious anemia and 75% of cats with toxoplasmosis have an underlying FeLV infection. In addition to these disorders, FeLV-induced immunosuppression has been associated with chronic mouth and gum infections, poorly healing or recurrent abscesses, deep skin infections, chronic respiratory infections, acute colitis, severe ear infections, and feline infectious peritonitis. (All of these problems, of course, may also be seen in cats not infected with FeLV. Some of them—for example, the oral and respiratory infections—are commonly found in FIV-infected cats.) FeLV-induced immunosuppression probably contributes also to the development of FeLV-induced malignancies.

THE FESV-ASSOCIATED DISEASES

FeSV is the causative agent of some *fibrosarcomas* (tumors of connective tissue cells) and *malignant melanomas* (tumors of pigment-producing cells) in cats. Multiple fibrosarcomas arising in the skin of younger cats (generally less than five years of age) are usually associated with FeSV, whereas solitary fibrosarcomas found in older cats usually are not. FeSV-induced malignancies occur only rarely in cats, however, and thus are of relatively minor clinical significance when compared to the array of problems associated with persistent FeLV infection.

DIAGNOSTIC AIDS FOR FELV INFECTION

The FeLV p27 core protein provides the major antigenic basis for the detection of FeLV in both the fixed-cell *immuno-fluorescence assay* (IFA), also known as the slide test or Hardy test, and the *enzyme-linked immunosorbent assay* (ELISA). The IFA requires that drops of whole blood be smeared onto microscope slides and air-dried and that the slides be submitted to a diagnostic laboratory for testing. ELISA and other immunoassay tests use blood, serum, or body secretions such as saliva, and are manufactured in kit form for in-hospital use by veterinarians as well as in plate tests for use in diagnostic laboratories.

A positive test for FeLV by IFA reflects the presence of FeLV-infected blood cells in a cat at the time the sample was taken. Additionally, a positive IFA test implies that a cat is shedding FeLV and is a health hazard to uninfected susceptible cats, especially kittens and cats on immunosuppressive drug therapy. *A positive test does not diagnose an FeLV-associated disease, only FeLV infection.* Approximately 97% of cats testing positive by IFA remain positive for life. A negative IFA test indicates that no detectable FeLV-infected blood cells are present. It does not exclude the possibility that a cat is incubating FeLV at the time of testing, nor does it imply that a cat has developed immunity to FeLV. In cats where LSAs and leukemias do not produce virus, representing about one-third of all feline lymphoid tumors, FeLV tests are negative.

A positive test by ELISA signifies the presence of circulating FeLV p27 in the blood fraction (plasma, serum, whole blood) tested. Most *but not all* cats positive by ELISA are actively shedding infectious FeLV. A negative ELISA test indicates that no detectable FeLV p27 is present, but, as in the IFA test, does not exclude the possibility of virus incubation and is not an indicator of immunity to FeLV.

Transiently viremic cats characteristically test positive and then revert to negative status within about twelve weeks. It is thus important that FeLV tests be repeated in twelve weeks to determine whether the viremia is transient or persistent. Virtually all cats positive by IFA are persistently viremic. *Both transiently and persistently viremic cats can shed infectious FeLV for the duration of the viremia.*

ELISA tests are also available to detect FeLV in saliva and tears. There is some small degree of variability in these tests, and some positive animals may be missed. Saliva and tear tests at present should be reserved for screening purposes and perhaps also for testing fractious cats that are difficult to bleed. All saliva and tear FeLV-positive tests should be confirmed by another test, preferably an IFA test.

In the last several years, comparative studies have identified some cats

that remain positive by ELISA but negative by IFA or by virus isolation (a procedure not commonly performed in the United States) for many months, even for years. As many as 30% of cats positive by ELISA may be negative by one or both of the other methods. Retests performed one to ten months after initial testing have shown that the FeLV status of most of these cats remains unchanged. The cellular source of the FeLV antigen causing the persistently positive ELISA results appears to lie in the bone marrow or lymph nodes. The most recent studies published indicate that persistently ELISA-positive/IFA-negative cats, unlike their persistently IFA-positive counterparts, do not give birth to infected kittens and that, in general, these animals do not appear to be shedding infectious FeLV into the environment. Importantly, studies thus far indicate that ELISA-positive/IFA-negative cats are not at great risk to develop one or more of the FeLV-associated diseases that can afflict persistently viremic (IFA-positive) cats.

TREATMENT OF SELECTED FELV-ASSOCIATED DISEASES

The therapeutic goals of the veterinarian in treating many of the FeLV-associated diseases are to provide palliative relief from clinical signs and to prolong life. However, therapy should be advocated only if there is the possibility of maintaining a good quality of life for the patient. In addition, ethical questions regarding prolonged treatment of persistently viremic animals shedding an oncogenic virus infectious for other, healthy cats must be addressed by both the veterinarian and cat owner. To date there is no consistent, effective way of reversing the FeLV-positive status of persistently viremic cats; several experimental therapies, however, are under investigation.

Lymphoid malignancies. For treating lymphoid malignancies, several therapeutic methods are available, including chemotherapy, surgery, and radiation therapy. In general, lymphoid malignancies are quite responsive to radiation, but their widespread anatomic distribution usually dictates other methods of treatment. Consequently, chemotherapy has become the treatment of choice for these tumors.

Combination chemotherapy involving simultaneous administration of several drugs generally will enhance chances for obtaining a clinical remission. Common therapeutic agents used in treating lymphoid malignancies include prednisolone, vincristine (Oncovin®), cyclophosphamide (Cytoxan®), and cytosine arabinoside (Cytosar®). Alternative drugs that can be used initially or substituted following a clinical relapse include vinblastine (Velban®), chlorambucil (Leukeran®), methotrexate (MTX®), and doxorubicin (Adriamycin®). *All of these agents have side effects* that must be taken into consideration when deciding on a therapeutic regimen.

In general, many lymphoid malignancies in cats will respond initially to combination chemotherapy. Unfortunately, malignant cells with resistance to the administered drugs often arise, and a second remission following a clinical relapse may be difficult to achieve. Lymphoid malignancies that respond best to treatment include the thymic and multicentric forms of LSA; those that respond the least include the alimentary form of LSA and lymphocytic leukemia.

Myeloproliferative disorders. The profound anemia that often accompanies myeloproliferative disorders is the most commanding concern of the veterinarian when contemplating treatment of affected cats. Thus the most important initial therapeutic procedure is the transfusion of fresh whole blood from a healthy donor cat. Chemotherapeutic regimens consist of many of the same drugs used in treating lymphoid malignancies, including prednisolone, cyclophosphamide, and cytosine arabinoside. The results of therapy for myeloproliferative disorders in cats, however, have been disappointing to date.

Aplastic anemia. Similarly, administration of fresh whole blood to cats with AA is imperative when red blood cell counts fall below acceptable levels. Transfusions also are often supplemented with corticosteroid therapy (prednisolone) and sometimes with additional agents such as cyclophosphamide. AA is generally a relentless, progressive condition, however, and repeated transfusions are frequently required to maintain adequate numbers of circulating red blood cells. Some success in treating AA has been reported by using interferon as an experimental therapeutic agent.

Antiviral therapy of FeLV-positive cats. At the present time there is no reliable, effective antiviral chemotherapy that will eliminate FeLV infection in persistently viremic cats. Zidovudine (also known as azidothymidine, or AZT) and 2', 3'-dideoxycytidine (also called DDC), which have been investigated for a number of years for the treatment of AIDS in people, may have some marginal efficacy against FeLV, but side effects and high cost have precluded more widespread study in cats. Drugs designed to modify or enhance the body's own immune response (which has the ultimate responsibility for clearing viral infections), such as the interferons and interleukins, may eventually prove of clinical value in treating FeLV and other retrovirus infections.

CONTROL OF FELV INFECTIONS

Elimination of FeLV from an infected household can be achieved by implementation of an FeLV test-and-removal program using the IFA test. This program has been highly effective in removing FeLV from infected multiple-cat households and catteries. In a survey of forty-five households and catteries from which 159 FeLV-positive cats were removed, 561 of 564 (99.5%) FeLV-negative cats remained negative on retesting. Multiple-cat households in which FeLV test-and-removal has not been implemented may experience infection rates over forty times greater than those experienced by households in which the

program has been successfully introduced.

FeLV-positive households. *All* cats in the household should be tested by IFA, regardless of age or condition. *All* cats found positive should be removed and the household premises cleaned with a commercial disinfectant or detergent. All litter boxes and food and water bowls should be thoroughly scrubbed and disinfected, or replaced. Cats that initially tested negative should be retested several times over a period of eight to twelve months, in case they were infected just before the first test (before the onset of detectable viremia) or are cycling in their level of detectable viremia. Because the time period between infection and viremia can be extremely variable, an infected cat that tested negative initially may be positive when tested again later. During the testing period no new cats should be allowed to enter the household. If any FeLV-positive cats are identified on subsequent testing, they should be removed and another period of quarantine and testing imposed. *All cats in the household should test negative for FeLV in two tests at least three months apart for the household to be considered "free" of infectious FeLV.*

FeLV-negative households. *All* new cats entering an FeLV-negative household should be tested before entry. Any positive cats should be excluded from entering the household. Cats testing negative should be quarantined in separate quarters for three to five months and retested negative one or two times before being allowed to mingle with the established FeLV-negative population. Ideally, new cats should be obtained only from other households or catteries practicing FeLV test-and-removal.

Because of the variable incubation period of infection, routine yearly or twice-yearly testing for FeLV is suggested for cats in catteries. Persistently viremic cats should never be used for breeding purposes, in part because infected queens will transmit the virus to their viable offspring.

If an FeLV-positive cat is removed from a single-cat household, a waiting period (suggested to be at least thirty days) should be observed before repopulating with one or more FeLV-negative cats. The litter box and food bowls should be thoroughly scrubbed and disinfected, or preferably replaced, and the premises decontaminated as thoroughly as possible with a commercial disinfectant.

Certain modifications of the test-and-removal program may be made for households in which both FeLV-negative and FeLV-positive cats are maintained. The positive cats in these households should be isolated from contact with *all* other cats. This will prevent not only the spread of FeLV to susceptible cats but also exposure of viremic cats to other infectious agents to which they may have a heightened susceptibility. No new cats should be introduced at any time, and the FeLV-positive cats should not be allowed to breed. Separate litter boxes and food bowls must be maintained for positive and negative cats. Cleanliness and personal hygiene should be observed at all times, and it has been suggested that separate clothing be kept for contact with FeLV-positive cats to minimize mechanical transmission of the virus. However, FeLV is relatively labile in the environment and the likelihood of virus transmission possible under these circumstances is uncertain, but probably minimal.

THE PROBLEM OF LATENCY

The persistence of the integrated provirus in infected cells and in their offspring (latent infection) is an important aspect of the replication cycle of retroviruses. Cells so infected frequently persist in the face of an active immune response. Evidence continues to accumulate that many cats that mount an effective immune response following FeLV infection nevertheless continue to harbor infections in bone marrow cells and lymph nodes. The implication of this finding is that many cats (from 30% to 60%) that have "recovered" from FeLV infection by developing an effective immune response and eliminating the virus from the bloodstream nevertheless are still infected; thus "FeLV-negative" cats are *not necessarily* free of FeLV. Pregnant queens that are latently infected may in some cases pass infectious FeLV through the colostrum or milk to their kittens; such infected kittens often become persistently viremic. In addition, some cats with FeLV-negative tumors have been shown to be harboring latent FeLV infections in the bone marrow. Definitive diagnosis of a latent infection requires culture of bone marrow cells in the laboratory; in a few cases, however, the latent infection localizes in lymphoid or other tissues without becoming established in the bone marrow.

Cats latently infected with FeLV are by definition not viremic and thus do not shed infectious FeLV into the environment. However, administration of corticosteroids (such as prednisolone) can reactivate some latent infections, resulting in re-emergence of FeLV into the bloodstream (i.e., reversion to FeLV-positive status). It is not known if this occurs following normal therapeutic dosing with steroids. Most latent infections are caused by FeLV-A and appear to dissipate within a relatively short period of time (less than a year), perhaps because the infected cells differentiate to extinction or are scavenged by immunological processes. Within three years of FeLV exposure, the majority of latent infections will have been extinguished.

Because corticosteroid release from the adrenal glands is a natural physiological response to stress, it seems reasonable to suspect that certain stressful life situations (in addition to pregnancy and lactation) in the day-to-day existence of cats—such as overcrowding, movement to new quarters, territorial conflicts, improper nutrition, and intercurrent disease—may serve to reactivate latent FeLV infections in nature. This could explain the occasionally observed instances in which a cat with a long history of negative FeLV tests in a closed cattery free of FeLV suddenly becomes FeLV-positive.

Although the majority of latently infected cats are not fated to develop FeLV-related disease in the future, a small percentage (estimated at less than 5%) will be affected in some way.

It is possible, for instance, that latent infections are responsible for many of the virus-negative LSAs, especially those of the intestinal type, seen in older cats. From an epizootiologic standpoint, however, the significance of latent infections is probably less than was once thought. If latently infected cats represented a truly important source of infection for susceptible cats, then FeLV test-and-removal programs based on the IFA test would not be so successful.

PUBLIC HEALTH ASPECTS OF FELV

The public health significance of FeLV, particularly the question of oncogenic potential for human beings, remains a largely unsettled issue. Surveys designed to determine the prevalence of circulating FeLV or antibody to FeLV in human beings have produced conflicting results over the years. Most recent surveys using highly specific testing methods have failed to find evidence of FeLV infection in human beings, including veterinarians and patients with lymphoid and other malignancies. Until a more complete understanding of the public health implications of FeLV is obtained, it seems prudent to restrict human exposure to persistently viremic (IFA-positive) cats when possible. *It must be emphasized, however, that as of this writing there is no conclusive evidence that any human illness (including cancer) has ever been caused by a feline retrovirus.*

IMMUNIZATION AGAINST FELV INFECTION

The proceedings of an international colloquium on immunization of cats against FeLV was published in the *Journal of the American Veterinary Medical Association,* November 15, 1991. The reader is referred to various manuscripts within that publication for additional details on immunization against FeLV.

There are several vaccines available to protect cats against FeLV infection. All current vaccines are inactivated whole-virus vaccines, subunit vaccines, or recombinant vaccines. Commercial companies continue to improve the efficacy of these vaccines. All vaccines rely on the same major principle for stimulation of protection against FeLV—that is, stimulation of neutralizing antibodies directed against the gp70 glycoprotein located within the peplomers or spikes on the surface of the virus particles. Two doses of vaccine are required for the initial immunization of cats, generally at nine and twelve weeks of age. Yearly booster vaccinations are then recommended for the life of the cat. Combination vaccines are appearing on the market containing an FeLV component in conjunction with one or more of the other immunogens routinely used in cats.

Considerable controversy has ensued over the years concerning the relative efficacy of one FeLV vaccine versus another vaccine. Various reports have supported the efficacy of one vaccine over another, although research in different laboratories using different techniques makes many of the comparative studies difficult to interpret. Veterinarians must familiarize themselves with the literature on these vaccines and then decide which vaccine will be used within their practice.

Considerable research is being directed at various novel FeLV vaccines, including virus-vector vaccines in which the gp70 gene is inserted into a carrier virus, such as vaccinia virus, other poxvirus, or feline herpesvirus. Another FeLV vaccine, the immune-stimulating complexes, or *ISCOM* vaccine, is under investigation in Europe and has shown promise in early clinical trials.

SELECTED GENERAL REFERENCES

August, J. R. 1991. Husbandry practices for cats infected with feline leukemia virus or feline immunodeficiency virus. *J. Am. Vet. Med. Assoc.* 199:1474–77.

Barlough, J. E. 1991. A special report to practitioners: Colloquium on feline leukemia virus and feline immunodeficiency virus. *Feline Pract.* 19(2):6–14.

Barr, M. C., P. P. Calle, M. E. Roelke, and F. W. Scott. 1989. Feline immunodeficiency virus infection in nondomestic felids. *J. Zoo Wildlife Med.* 20:265–72.

Charreyre, C., and N. C. Pedersen. 1991. Study of feline leukemia virus immunity. *J. Am. Vet. Med. Assoc.* 199:1316–24.

Clark, N., N. N. Kushner, C. B. Barrett, C. R. Kensil, D. Salsbury, and S. Cotter. 1991. Efficacy and safety field trials of a recombinant DNA vaccine against feline leukemia virus infection. *J. Am. Vet. Med. Assoc.* 199:1433–43.

Cotter, S. M. 1991. Management of healthy feline leukemia virus-positive cats. *J. Am. Vet. Med. Assoc.* 199:1470–73.

Cotter, S. M. 1990. Feline leukemia virus infection. In *Infectious Diseases of the Dog and Cat,* edited by C. E. Greene, pp. 316–33. Philadelphia: W. B. Saunders.

Hardy, W. D., Jr. 1991. General principles of retrovirus immunodetection tests. *J. Am. Vet. Med. Assoc.* 199:1282–87.

Hardy, W. D., Jr., and E. E. Zuckerman. 1991. Ten-year study comparing enzyme-linked immunosorbent assay with the immunofluorescent antibody test for detection of feline leukemia virus infection in cats. *J. Am. Vet. Med. Assoc.* 199:1365–73.

Hawkins, E. C. 1991. Saliva and tear tests for feline leukemia virus. *J. Am. Vet. Med. Assoc.* 199:1382–85.

Hawks, D. M., A. M. Legendre, and B. W. Rohrbach. 1991. Comparison of four test kits for feline leukemia virus antigen. *J. Am. Vet. Med. Assoc.* 199:1373–77.

Hawks, D. M., A. M. Legendre, B. W. Rohrbach, R. Sebring, L. Chavez, H.-J. Chu, and W. M. Acree. 1991. Antibody response of kittens after vaccination followed by exposure to feline leukemia virus-infected cats. *J. Am. Vet. Med. Assoc.* 199:1463–69.

Hoover, E. A., and J. I. Mullins. 1991. Feline leukemia virus infection and diseases. *J. Am. Vet. Med. Assoc.* 199:1470–73.

Hoover, E. A., N. A. Perigo, S. L. Quackenbush, C. K. Mathiason-DuBard, J. M. Overbaugh, W. S. Kloetzer, J. H. Elder, and J. I. Mullins. 1991. Protection against feline leukemia virus infection by use of an inactivated virus vaccine. *J. Am. Vet. Med. Assoc.* 199:1392–1401.

Jacobson, R. H. 1991. How well do serodiagnostic tests predict the infection or disease status of cats? *J. Am. Vet. Med. Assoc.* 199:1343–47.

Jacobson, R. H., and N. A. Lopez. 1991. Comparative study of diagnostic testing for feline leukemia virus infection. *J. Am. Vet. Med. Assoc.* 199:1389–91.

Jarrett, O., A. M. Pacitti, M. J. Hosie, and G. Reid. 1991. Comparison of diagnostic methods for feline leukemia virus and feline immunodeficiency virus. *J. Am. Vet. Med. Assoc.* 199:1362–64.

Kensil, C. R., C. Barrett, N. Kushner, G. Beltz, J. Storey, U. Patel, J. Recchia, A. Aubert, and D. Marciani. 1991. Development of a genetically engineered vaccine against feline leukemia virus infection. *J. Am. Vet. Med. Assoc.* 199:1423–27.

Legendre, A. M., D. M. Hawks, R. Sebring, B. Rohrbach, L. Chavez, H.-J. Chu, and W. M. Acree. 1991. Comparison of the efficacy of three commercial feline leukemia virus vaccines in a natural challenge exposure. *J. Am. Vet. Med. Assoc.* 199:1456–62.

Loar, A. S. 1991. Feline leukemia virus tests: evaluation and interpretation. In *Consultations in Feline Internal Medicine*, edited by J. R. August, pp. 535–41. Philadelphia: W. B. Saunders.

Lopez, N. A., R. H. Jacobson, J. M. Scarlett, S. A. Center, J. F. Randolph, and F. W. Scott. 1989. Sensitivity and specificity of blood test kits for feline leukemia virus antigen. *J. Am. Vet. Med. Assoc.* 195:747–51.

Macy, D. W. 1989. Management of the FeLV-positive patient. In *Current Veterinary Therapy X*, edited by R. W. Kirk, pp. 1069–76. Philadelphia: W. B. Saunders.

Mullins, J. I., E. A. Hoover, J. Overbaugh, S. L. Quackenbush, P. R. Donahue, and M. L. Poss. 1989. FeLV-FAIDS-induced immunodeficiency syndrome in cats. *Vet. Immunol. Immunopathol.* 21:25–37.

O'Connor, T. P., Jr., Q. J. Tonelli, and J. M. Scarlett. 1991. Report of the National FeLV/FIV Awareness Project. *J. Am. Vet. Med. Assoc.* 199:1348–53.

Osterhaus, A. D. M. E., K. Weijer, K. H. J. Siebelink, G. F. Rimmelzwaan, and M. L. Bosch. 1991. Toward vaccination against feline leukemia virus and feline immunodeficiency virus infections. *J. Am. Vet. Med. Assoc.* 199:1443–46.

Pedersen, N. C. 1991. Feline leukemia virus infection. In *Feline Husbandry: Diseases and Management in the Multiple-Cat Environment*, edited by N. C. Pedersen, pp. 210–22. Goleta, Calif.: American Veterinary Publications.

Pedersen, N. C., and J. E. Barlough. 1991. Clinical overview of feline immunodeficiency virus. *J. Am. Vet. Med. Assoc.* 199:1298–1305.

Rojko, J. L., and W. D. Hardy, Jr. 1989. Feline leukemia virus and other retroviruses. In *The Cat: Diseases and Clinical Management*, edited by R. G. Sherding, pp. 229–332. New York: Churchill Livingstone.

Rojko, J. L., and G. J. Kociba. 1991. Pathogenesis of infection by the feline leukemia virus. *J. Am. Vet. Med. Assoc.* 199:1305–10.

Scarlett, J. M., and R. V. H. Pollock. 1991. Year two of follow-up evaluation of a randomized, blind field trial of a commercial feline leukemia virus vaccine. *J. Am. Vet. Med. Assoc.* 199:1431–32.

Scott, F. W., B. Hancock, W. D. Hardy, Jr., E. A. Hoover, M. C. Horzinek, R. H. Jacobson, N. C. Pedersen, and J. E. Saidla. 1991. Panel report on the Colloquium on Feline Leukemia Virus/Feline Immunodeficiency Virus: Tests and Vaccination. *J. Am. Vet. Med. Assoc.* 199:1273–78.

Sebring, R. W., H.-J. Chu, L. G. Chavez, D. S. Sandblom, D. R. Hustead, B. Dale, D. Wolf, and W. M. Acree. 1991. Feline leukemia virus vaccine development. *J. Am. Vet. Med. Assoc.* 199:1413–19.

Tizard, I. 1991. Use of immunomodulators as an aid to clinical management of feline leukemia virus-infected cats. *J. Am. Vet. Med. Assoc.* 199:1482–85.

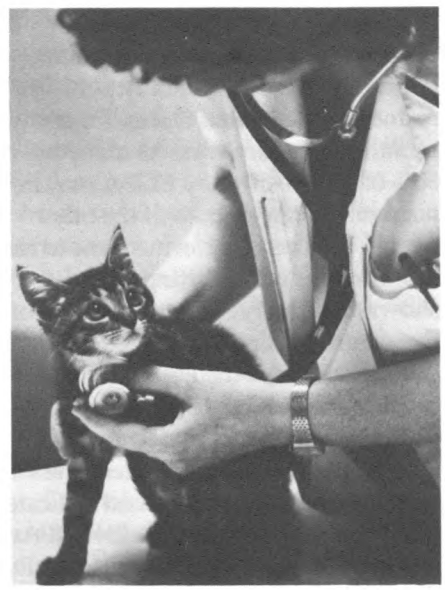
Tizard, I., and E. P. Bass. 1991. Evaluation of a killed, whole virion feline leukemia virus vaccine. *J. Am. Vet. Med. Assoc.* 199:1410–13.

Tompkins, M. B., P. D. Nelson, R. V. English, and C. Novotney. 1991. Early events in the immunopathogenesis of feline retrovirus infections. *J. Am. Vet. Med. Assoc.* 199:1311–15.

Tonelli, Q. J. 1991. Enzyme-linked immunosorbent assay methods for detection of feline leukemia virus and feline immunodeficiency virus. *J. Am. Vet. Med. Assoc.* 199:1336–39.

Weiss, R. C., J. M. Cummins, and A. B. Richards. 1991. Low-dose orally administered alpha interferon treatment for feline leukemia virus infection. *J. Am. Vet. Med. Assoc.* 199:1477–81.

York, S. M., and C. J. York. 1991. Development of a whole killed feline leukemia virus vaccine. *J. Am. Vet. Med. Assoc.* 199:1419–22.



About the Cornell Feline Health Center

The ultimate purpose of the Cornell Feline Health Center is to improve the health of cats by developing methods to prevent or cure feline diseases and by providing continuing education to veterinarians and cat owners. The Cornell Feline Health Center is a nonprofit organization supported primarily by private contributions. Correspondence may be directed to:

Cornell Feline Health Center
Cornell University
College of Veterinary Medicine
Ithaca, NY 14853-6401

Printed on recycled paper.

Cornell University is an equal-opportunity, affirmative-action educator and employer.

Office of Publications Services
293 30M U