Feline Leukemia and Related Viruses

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The role of viruses in causing some neoplasms (tumors) is well established. Certain viruses of both ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) types have been identified as causative agents for several kinds of tumors in a variety of animal species, including chickens, mice, cats, and monkeys. Some induce only benign growths such as papillomas, or warts; others cause malignant tumors (i.e., cancer) such as mammary carcinomas and leukemias. As a group these viruses are often called oncogenic, or tumor-forming, viruses, but evidence is accumulating that some also cause nontumorous forms of disease.

So far, only RNA oncogenic viruses have been isolated from cats. These closely resemble the RNA viruses of other species that cause leukemias (tumors of blood-forming cells) and sarcomas (tumors of other mesodermal tissue). On the basis of their structural and replication patterns, they have been referred to as C-type viruses. The somewhat similar A and B morphological types that cause mammary tumors in mice have not been observed in cats. All RNA tumor viruses are commonly called oncornaviruses (oncogenic RNA viruses).

Feline Oncornavirus Types and Characteristics

Feline leukemia virus (FeLV). The terms leukemia and the leukemia complex are commonly used to include all the neoplastic diseases of hematopoietic, or blood-forming, cells originating from either bone marrow or lymphoid tissue. Within this group there are many different tumor forms, all consisting of an uncontrolled proliferation of either white or red blood cells (leukocytes or erythrocytes). Oncornaviruses causing these kinds of malignant tumors are known as leukemia viruses.

In 1964 the first FeLV was demonstrated in Scotland by Dr. W. F. H. Jarrett and his associates, who were studying a cluster of leukemia cases in cats. Since that time this virus has been found in many other countries, including the United States. Experimental and epidemiological studies have shown that FeLV is contagious and causes leukemias and other diseases in cats. Different serotypes and strains of FeLV have been recognized, and there is some evidence that these may differ in their disease-producing potential.

Like other leukemia viruses, FeLV does not ordinarily destroy the cells that it infects. Instead, either it stimulates them to proliferate in a neoplastic manner or it has no observable pathogenic effect. By a budding process, infected cells produce new virus particles with a central RNA core surrounded by protein and a modified cell membrane envelope. Virus particles can be observed by electron microscopy (see figures), a method sometimes used for diagnosing infection. In addition to these formed virus particles, FeLV structural proteins and glycoproteins appear in the cytoplasm and on the surface of infected cells. Their presence can be observed by immunofluorescent techniques, which are the basis for diagnostic tests currently used to detect virus infection and immunity.

A unique characteristic of all oncornaviruses is the presence of a DNA polymerase enzyme, sometimes called reverse transcriptase. When the virus infects a cell, this enzyme is capable of transcribing the genetic information of the viral RNA into the chromosomal DNA of the cell that it infects. Thus virogenes and oncogenes carried by a virus may become permanently established as part of the genetic makeup of the infected cell. To eliminate an FeLV infection, it is therefore necessary to destroy all virus-infected cells.

Feline sarcoma virus (FeSV). Shortly after FeLV was discovered, S. P. Snyder and G. H. Thielen in California found a fibrosarcoma-inducing virus in a cat with multiple fibrosarcomas (malignant fibroblastic cell tumors), and J. E. Post and C. G. Rickard at Cornell University found, in a leukemic cat, a virus that induced liposarcomas (malignant fat cell tumors). Since then other FeSV's have been observed in other clinical cases of fibrosarcoma.

The physical, chemical, and antigenic properties of these sarcoma viruses are identical to those of FeLV, but their biological behavior is different. Unlike FeLV, they cause connective tissue sarcomas rather than leukemias, and in laboratory-cultured cells they cause a visible transformation that is not induced by FeLV.
Experimental transmission studies have shown that some strains of FeSV are highly pathogenic in young susceptible cats, causing nearly a 100 percent incidence of tumors after a short incubation period. In natural cat populations, however, sarcomas are not common, and compared with FeLV, FeSV appears to be an insignificant pathogen.

Feline endogenous virus. When fetuses and placentas of cats are examined by electron microscopy, a small number of C-type virus particles may be found that closely resemble FeLV and FeSV in appearance. In cat cells, where they originate, these viruses grow poorly, but they thrive in the cells of some other species, including man. The virus can be isolated by treating cultured cat cells with iodo­deoxyuridine or bromodeoxyuridine and then cultivating these cells with those of another species. In one interesting experiment human tumor cells were transplanted to a fetal cat, where, growing with living cat cells, they became infected with the feline endogenous virus. For some time this virus isolate, designated RD114, was suspected of being a human tumor virus. A similar virus was isolated from a cat kidney tissue culture cell line that has been extensively used for laboratory studies and vaccine production. It is suspected that all cats carry this virus in a latent, or hidden, form.

Feline endogenous virus is inherited genetically. It is not infectious or pathogenic in cats. Since it can infect the cells of other species, however, studies are being made to determine whether the endogenous virus of one species can become the pathogenic virus of another. So far, inoculation of this feline virus into other species has not caused any disease.

Diseases Associated with FeSV and FeLV

FeSV has been associated only with fibrosarcomas and liposarcomas. As these tumors are rare in cats, this virus seems to have minor clinical significance.

FeLV, on the other hand, causes a variety of hematopoietic neoplasms, some anemias, and some immune deficiencies that predispose cats to certain other diseases. The various diseases associated with FeLV infection are briefly described below.

Lymphosarcoma. These tumors, making up the majority of malignancies caused by FeLV, consist of solid masses of proliferating lymphocytes. On the basis of organ involvement they are separated into various forms, including thymic, generalized (multicentric), alimentary, and renal. Combinations of these may occur.

Thymic lymphosarcoma typically occurs in cats one to two years old. Though this tumor may extend to other tissues, it primarily involves the thymus, which expands to form a large mass in the thorax. Its hidden location makes diagnosis difficult. When the tumor mass becomes large enough, lung compression by the tumor and accumulated fluid causes obvious respiratory difficulty. The clinical diagnosis may be confirmed by finding tumor cells in aspirated pleural fluid.

Generalized, or multicentric, lymphosarcoma is most likely to occur in middle-aged cats but is seen in a wide range of ages. Lymphoid tissue throughout the body is often involved. The lymph nodes, the spleen, and the liver may become markedly enlarged. These can be palpated, making recognition of this form of lymphosarcoma easier. A surgical biopsy may, however, be needed to distinguish this disease from others that also cause lymph node enlargement.

Alimentary lymphosarcoma often occurs in older cats. The major tumor masses arise from lymphoid tissue commonly present in the wall of the gastrointestinal tract. The associated mesenteric lymph node may also be involved. These tumors can cause partial intestinal obstruction, resulting in clinical signs such as vomiting, diarrhea, or inappetence.

Renal lymphosarcoma, which also usually affects older cats, may accompany the alimentary form. Nodular or diffuse infiltration of the kidney with neoplastic lymphoid cells causes gross enlargement that may be evident on palpation. Interference with normal renal function may cause clinical signs of renal insufficiency.

Lymphoid tumors involving only the skin, the eye, or areas of the nervous system occur infrequently in cats. Of these, only the ocular form has been induced experimentally by the inoculation of FeLV.

Lymphocytic leukemia. This is a true leukemia, where there is an abnormal proliferation of neoplastic lymphocytes in the circulating blood and the blood spaces such as the spleen and bone marrow. This condition may exist by itself or be associated with a lymphosarcoma form of disease. Examination of peripheral blood establishes the diagnosis.
**Myeloproliferative diseases.** Myeloid cells, those that form the bone marrow, consist mainly of developing red cells and white cells. Neoplastic proliferations of any of the variety of cells in this group are referred to as myeloproliferative diseases. Clinically these appear as true leukemias, involving the circulating blood and the blood spaces. Diagnosis is made by examining peripheral blood and bone marrow.

**Anemia.** Two forms of anemia have been associated with cats both naturally and experimentally infected with FeLV. One is a hypoplastic, or bone marrow depression, anemia and leukopenia in which a failure in the generation of both red cells and white cells results in low peripheral blood cell counts. The other kind of anemia induced by FeLV is a hemolytic form in which destruction of mature blood cells causes red cell depletion. It is suspected that both these kinds of anemia are caused by an immune mechanism initiated by an alteration of blood cell membranes infected by FeLV.

**Immune suppression.** Many kittens inoculated with FeLV develop thymic atrophy and become unusually susceptible to a variety of infections. Likewise, many adult cats persistently infected with FeLV have chronic or recurrent disease problems. Skin grafting and phytohemagglutinin lymphocyte stimulation tests have shown a deficiency of cell-mediated immunity in these infected cats. A similar deficiency of humoral immunity is suspected since many cats persistently infected with FeLV do not develop antibodies to this infecting virus. The immunosuppressive effects of leukemia viruses have also been observed in mice. The mechanism for these effects is not yet understood.

**Other diseases.** Cats with a variety of diseases have a high incidence of FeLV infection. Especially noteworthy among these diseases are feline infectious peritonitis, feline infectious anemia, toxoplasmosis, stomatitis, and respiratory diseases. There is no evidence that FeLV directly causes any of these, but there are indications that FeLV, by its immunosuppressive effect, lowers an infected cat's resistance to these conditions so that they become more serious disease problems. This fact may also explain why some sick cats respond poorly to treatment and some remain chronically ill or have repeated episodes of illness.

**Glomerulonephritis,** a kind of kidney disease, has been observed in a number of FeLV-infected cats, both those with no tumors and those with leukemia. It is suspected that this disease is caused by the formation of FeLV antigen-antibody complexes that accumulate in kidney glomeruli.

Recently FeLV has been found in many cats with fetal resorption and abortion problems. FeLV is suspected of having a causative role in these conditions, but this has not been proven.

FeLV has been observed in the tissues of a number of feline mammary tumors. Here, also, it is uncertain whether it has anything to do with causing them. When experimentally inoculated into susceptible kittens, viruses isolated from these tumors have caused leukemia but not mammary tumors.

**Epidemiology of FeLV Infections**

**Incidence.** Less than 0.1 percent of all domestic cats develop leukemia each year. FeLV, found in 60 to 90 percent of these, is the obvious major cause for this kind of neoplasia, but not all leukemic cats have the virus. The incidence of FeLV-related diseases is not known but appears to be higher than the incidence of leukemia. Some clinically normal cats are also persistently infected with FeLV. The number of virus-infected cats at any given time, however, is estimated to be only about 2 percent of the cat population; this figure is much higher in certain confined populations.

**Transmission.** FeLV is transmitted from cat to cat by contact. Where contact between cats is high, as in cities and breeding colonies, the infection is widespread. Infected cats, whether they are sick or healthy virus carriers, can shed infectious virus particles in saliva, urine, and probably also milk, feces, and exhaled air. FeLV survives only a few hours to a few days in the environment, but during this time it can infect other cats. Genetic transmission from parent to offspring is also suspected since the virus is commonly present in the testes and ovaries of infected cats, and the offspring of such animals are often infected. Transmission by blood-sucking insects seems possible as well, but this has not been proven.

**Immunity.** Not all cats exposed to FeLV develop the disease or become persistent carriers. Many apparently develop some degree of immunity by means of a humoral immune response that suppresses virus infection. Two kinds of antibodies are produced: virus-neutralizing antibodies and antibodies directed against antigens on the surface of virus-infected cells (feline oncornavirus-associated cell membrane antigens, or FOCMA). The former protect against virus infection, and the latter, against tumor formation.
These kinds of antibodies can be transferred in colostrum from immune queens to their newborn kittens, providing temporary protection.

Laboratory tests have been developed for measuring the concentration levels (titers) of these antibodies. The level that constitutes a protective neutralizing titer has not been conclusively determined.

The distribution of nonimmune, immune, and infected cats varies in different populations. Some surveys have shown that anti-FOCMA antibodies are present in 50 percent of unconfined urban cats (in Boston, Detroit, and Glasgow) but in only 6 percent of rural cats (in Scotland). In the urban group only 6 percent of weaned kittens show evidence of immunity, but the percentage increases with age, presumably because opportunities for virus contact increase with age. The number of cats in the urban populations that develop leukemia and other FeLV-related diseases and show little or no immune response is low.

If FeLV is present among confined groups of cats in breeding colonies or multiscat households, however, the incidence of leukemia may be 25 percent or more, and the number of immune cats is low. If FeLV is absent, neither leukemia nor immunity develops.

Cats exposed to FeLV, then, respond in different ways. They may (1) not become infected at all, (2) become temporarily infected but develop immunity and overcome the infection, (3) become infected and continue to carry and shed virus particles indefinitely while remaining clinically normal, or (4) become infected and develop leukemia or one of the other FeLV-related diseases. Which of these will occur in any particular cat is related on the one hand to the ability of that cat to respond immunologically and on the other, to the immunosuppressive effects of the virus. The age of the cat and probably its genetic makeup, as well as the strain and the dosage of the infecting virus, influence these immune mechanisms.

How these factors balance out to cause either disease or immunity is not fully understood, but it is obvious that both immature age of the cat and group confinement favor disease rather than immunity. Immune responses are less successful in multicat households because exposure dosages are higher than in free-roaming cats.

Control and Management of FeLV Infections

Diagnosis—FeLV tests. Of the numerous techniques that have been developed for detecting FeLV and some of its components, the one that has been most practical for diagnosis is an indirect immunofluorescence technique developed by Dr. W. D. Hardy, of the Sloan-Kettering Institute in New York City, and now offered commercially by a number of laboratories. The test, performed on either blood or bone marrow smears, detects FeLV group specific antigen present in infected blood leukocytes. The validity of this test depends on the use of antisera specific only for the antigens associated with FeLV. If other activity is present, falsely positive results may be reported. At present there is no official control over the preparation of these test sera or the performance of the tests, and controversies have arisen because different laboratories have reported different results on samples from the same cat.

A more accurate but less practical method for demonstrating infection is to isolate the virus in a tissue culture. This method has not been offered by diagnostic laboratories, but some investigators have used it on a selected group of cases to substantiate the results of their immunofluorescent tests. Virus isolation is made from plasma, blood leukocytes, or bone marrow.

When choosing a laboratory to perform FeLV tests, it is wise to obtain some assurance of its credibility. Some official certification of reliable laboratories may be forthcoming in the future.

FeLV tests do not detect leukemia itself but rather reveal the virus infection that causes leukemia. Clinically normal virus carriers will give a positive test. Also, some clinically leukemic cats are virus-negative and would appear negative on these tests.

Treatment. Corticosteroids and other anticancer drugs such as cyclophosphamide and vincristine have been beneficial in producing remission of variable duration in cats, as in humans, with leukemia. Corticosteroids have also been helpful in treating FeLV-induced anemias. Generally, however, such treatments are only temporarily effective and do not eliminate the FeLV infection if it is present.

Methods of treatment to eliminate FeLV infections have not yet been developed, but immunotherapy and antiviral drug therapy are being studied and show some promise. This research is in the early stages of investigation.

Eradication of infection. One proven but sometimes drastic method of controlling disease is to identify the carriers of the causative agent and eradicate them. This method, being voluntarily applied against FeLV, is having favorable results, especially in those catteries where infection was causing many cases of leukemia and anemia.

In a procedure recommended by Dr. W. D. Hardy, all cats testing positive for FeLV are eliminated or isolated. Remaining virus-negative cats are tested at three-month intervals, and again, any cats testing positive are eliminated. After two negative tests, the cattery may be free of infection.

Experience has shown that most cats showing positive evidence of FeLV in their leukocytes remain positive indefinitely and have a high risk of eventually developing leukemia or anemia. A few such positive cats, however, have subsequently developed immunity and thrown off their infections. The latter would most likely occur, if ever, within three months, and therefore there is some rationale for holding positive cats in isolation for three months to see if they revert to a negative state.

Along with the eradication of infected animals, it is also important to
rid the premises of infection. Most common detergents and disinfectants can destroy FeLV.

**Vaccination.** Considerable effort is being directed toward developing vaccines that prevent FeLV infection and tumor growth. Experimental results have been favorable, but time is needed to prove their efficacy and safety before they can be offered for common use.

### The Human Hazard of FeLV

Considerable concern was aroused when it was shown that FeLV could infect and replicate in laboratory-cultured human cells. Also, it is possible to induce leukemia or sarcoma experimentally in dogs and monkeys by inoculating them before or on the day of their birth with FeLV or FeSV. Because these cross-species infections have occurred only in animals whose immune mechanisms were not functional, it is currently believed that normal humans would not become infected if naturally exposed to FeLV.

This belief is further substantiated by the fact that large numbers of humans have tested negative for FeLV, including many with leukemia and many who have had a great deal of contact with cats. Some humans may, however, be susceptible because they are not immunocompetent. These include fetal and newborn infants, people under immunosuppressive therapy, and those with genetic immunological defects.

Some human serums have shown virus-neutralizing and other antibody activity against FeLV or FeLV-infected cells. This activity has not been fully evaluated. It could represent previous exposure to FeLV resulting in a specific immune response, or it could just represent the presence of antibodies that coincidentally cross-react with FeLV antigens.

### Summary

1. There are three recognized feline oncornaviruses: FeLV, FeSV, and feline endogenous virus. Only FeLV appears to be clinically significant.
2. FeLV causes leukemia, anemias, and immunosuppression that predisposes cats to other diseases.
3. The outcome of FeLV infection is determined by multiple factors that cause either an effective immune response or immunosuppression in the infected host. The age of the host and the strain and the dosage of the infecting virus are most important among these factors.
4. Most adult pet cats naturally exposed to FeLV develop some immunity to the virus rather than disease, but similarly exposed young cats and groups of confined cats of various ages have a high incidence of disease and poor immune responses.
5. Virus carriers tend to remain so indefinitely and have a high risk of eventually developing fatal leukemia or anemia.
6. The fact that FeLV can be detected in blood smears can serve as the basis for a test and eradication system to control the spread of this infection.
7. When available, vaccines will probably be the best way to control FeLV infection.
8. FeLV is probably a health risk only to immunoincompetent humans, if to any humans.

### Further Information

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