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Feline Infectious Peritonitis

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One of the most poorly understood and enigmatic feline viruses is the feline coronavirus -the virus responsible for feline infectious peritonitis (FIP). In fact, the virus causing FIP, feline coronavirus (FCoV), is very common among cats, especially in multi-cat households, catteries, and shelters. Multi-cat situations of several years' duration will likely have a brush with FIP. It is no cause for either fear or ostracization. It is, however, a reason to make efforts to understand this disease and its means of control.

While the first description of feline infectious peritonitis was reported by Dr. Jean Holzworth in 1963, there are reports of clinical cases that are likely FIP going back to 1914. Even though we have known about this virus for a long time, we know frustratingly little about it. Research over the past 10 years is slowly shedding more light on this ever-present feline health problem. This article is designed to present some of the newer information and change some of the older ideas still found in print and other media.

Feline coronavirus operates differently from any other feline virus in several important ways:

a) Systemic antibodies have no protective function for the cat and may play a role in the disease FIP itself
b) Antibody titers are meaningless for diagnosis of FIP or prognosis; detection of the feline coronavirus is also not diagnostic, and currently no test exists that can distinguish the virus of FIP from the enteric form of FCoV
c) A vaccine is available, but there is no consensus on its efficacy or safety

First, some notes on terminology. ***FIP*** is the term for clinical disease associated with feline coronavirus infection. The common benign form of feline coronavirus is referred to as ***FECV*** (feline enteric coronavirus). When FECV has mutated into a disease-causing form, it is then referred to as ***FIPV*** (feline infectious peritonitis virus). Feline coronaviruses in general are referred to as ***FCoV***.

FECV is a very common, highly infectious feline virus. It belongs to the genus *Coronavirus*, which has members that infect other species (man, swine, cattle, birds, dogs). The majority of cats with FECV (about 90% or more) remain healthy. But in a small number of cases, FECV infection is the first step in a chain of events leading to FIP. This happens because coronaviruses are made of large numbers of nucleotides, the basic unit of genetic material, and they are very prone to mutations. As a virus reproduces itself, errors are made in copying these nucleotides. The more nucleotides, the more errors are possible. While most of these errors are harmless, some will have the effect of giving FECV the ability to cause disease. These mutant FECV strains are called FIPV. The precise mutation or mutations leading to disease development have not been clarified. Several possibilities exist, with

changes in several genes having been observed in FIPV, but consensus as to which specific mutations are responsible for causing the lethal disease has not been reached.

Recent research has shown that mutant FECVs arise within an individual cat. Thus, we now know that the vast majority of cats do not "catch" FIP, but they develop it themselves from their own mutant FECV. Non-pathogenic FECV lives and replicates within the cells of the intestinal tract and may be shed into the feces. But FIPV (the mutant form of FECV) has developed the ability to live and replicate within a type of white blood cell of the immune system that is called a monocyte (when in blood) and a macrophage (when in tissues). This ability of the virus to replicate to high levels in monocytes and macrophages is critical to the development of FIP. FIPV are able to spread throughout the cat's body, and are no longer localized in the intestinal tract and so are rarely shed into feces. Transmission of FIP from cat to cat is considered to be rare. This fact has caused leading FIP researchers to state that cats that are ill with FIP are unlikely to be a risk to other cats and thus do not need to be isolated.

A recent investigation identified mutations in FCoV found in tissues other than the intestines. These mutations, occurring in one gene (the 3c gene) were never identified in viruses found in the intestines. The investigators speculate that this gene may be required for efficient intestinal replication, and its mutation results in loss of this ability. Thus, this mutation may lead to increased virulence of the virus but prevent its replication in the gut, thereby preventing shedding in feces of the affected cat.

A kitten ill with the dry form of FIP.

It has been estimated that in multi-cat households where FECV has been introduced, 80%-90% of all the cats will be infected. In the general cat population, infection rates may reach 30%-40%. Multi-cat situations and catteries are especially likely to be FECV-positive since traffic of cats and kittens in and out of the establishment is common. However, the incidence of cases of FIP is quite low in comparison. Generally, most of these establishments experience far less than 10% losses to FIP over the years. Rare instances have been documented in which an apparent epidemic of FIP is associated with mortality rates of over 10% in a short period of time. One possible factor in these epidemics is the shedding of virulent virus, an uncommon situation. Usually, losses are sporadic and unpredictable. The peak ages for losses to FIP are from 6 months to 2 years old (with the highest incidence at 10 months of age). Age-associated immunity to FIP appears to be possible, although cases of FIP have been reported in elderly cats. Transmission of FIP from a queen to her unborn kittens has not been shown to occur, but transmission of FCoV from queen to kittens is common.

What are the factors that predispose a small percentage of cats with FECV to the development of FIP? Research is currently trying to find more answers to this question, but some facts are becoming clear. Dr. Janet Foley and Dr. Niels Pedersen of the University of California at Davis have identified three key risk factors: genetic susceptibility, the presence of chronic FECV shedders, and cat-dense environments that favor the spread of FECV.

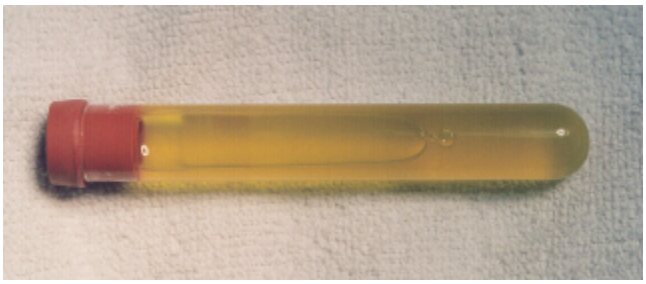
Drs. Foley and Pedersen identified a genetic predisposition to the development of FIP in 1996. They examined pedigree and health data from 10 generations of cats in several purebred catteries and found that the heritability of susceptibility to FIP could be very high (about 50%). It is likely a polygenetic trait rather than a simple dominant or recessive mode of inheritance. Inbreeding, by itself, is not a risk factor. Several breeds, including the Bengal, Birman, and Himalayan, are more likely to develop FIP. In addition, susceptibility along familial lines has also been documented. Selecting for overall disease resistance is a helpful tool for breeders.

The disease itself is primarily mediated by the immune response to the virus, rather than the virus itself. The mutant virus replicates efficiently in monocytes and macrophages throughout the body. In cats that develop FIP, the virus is not effectively cleared for reasons that remain unknown. These animals mount a good antibody response, but this is ineffective at clearing the virus – antibodies target mainly the viruses outside the infected cells. Effective viral clearance requires cell-mediated immunity, in which cells of the immune system target infected cells, thus eliminating these "virus factories." Why some cats mount this ineffective response is the subject of much investigation, and as suggested above, likely has a genetic component. The probable defect in immunity to FIP is in cell-mediated immunity. This type of immunity is important in defense against pathogens that replicate within a cell (as opposed to those that colonize extracellular spaces). Therefore cats that are susceptible to FIP are also likely susceptible to some other infections as well, especially fungal and viral infections. This finding gives breeders the ability to achieve success in reducing the risk of FIP by using pedigree analysis to select breeding cats from family backgrounds that have strong resistance to FIP and other infectious diseases.

Thus, to produce FIP, it takes not only the mutant virus, but a cat predisposed to mount an ineffective immune response to the virus – the "right" virus and the "right" cat. This is why **FIP is uncommon, though infection with FCoV is widespread among cats.**

The lesions of FIP arise from the immune response to the virus. Infected cells accumulate along the walls of blood vessels, and even migrate into the surrounding tissue. The inappropriate antibody-mediated response by the immune system leads to tissue damage at these sites through a variety of mechanisms. So-called "innocent bystanders" – uninfected cells – are often killed in the process. This leads to an intense inflammatory response that may be widespread along the blood vessels (effusive FIP) or it may be localized to specific tissues, such as the eye, or kidney (non-effusive FIP). Because this antibody response is ineffective at clearing the infection, the virus continues to replicate and accumulate, as does the inflammatory response. This progresses to multi-organ failure and inevitably death.

There are two forms of FIP. The effusive (or wet) form is characterized by accumulation of fluid in the chest or abdomen. This fluid is high in protein content and is often a yellow color.



The yellow fluid found in the abdomen of a kitten that died from wet FIP.

The non-effusive (or dry) form of FIP is characterized by inflammatory lesions called pyogranulomas that can be found in almost any organ of the body, including the nervous system. Signs of illness

common to both effusive and non-effusive forms of FIP include loss of appetite, weight loss, lethargy, and a fluctuating fever that is not responsive to antibiotics. Cats with the effusive form may develop a swollen abdomen or difficulty breathing because of fluid accumulation.

A kitten with the distended abdomen typical of the wet form of FIP.

As with so many aspects of FIP, testing remains problematic. To date, there is no way to screen healthy cats for the risk of developing FIP. Antibody titers are poorly correlated with risk of FIP and should not be used to screen healthy cats. As well as problems with interpretation of these antibody tests, there are problems with laboratory quality control. In addition, cats that have been vaccinated with some types of vaccines may test positive on coronavirus antibody tests due to cross-reaction between components of the cell culture used to produce the vaccine and test system components. **It remains true that a negative antibody titer does not rule out FIP. Neither does a positive antibody titer rule in FIP as a diagnosis, even if that titer is very high.**

Finding the virus itself in a cat is also not diagnostic for FIP. As stated above, the virus is common, and can be found in the blood of infected yet healthy cats. There are now DNA-based blood tests offered by a few labs that are purported to be FIP-specific. However, there are no published studies that have identified the genetic difference between FECV and FIPV, and most experts doubt the validity of these tests. A newer test from Auburn University, called the mRNA test for coronavirus, detects virus actively replicating outside the intestinal tract. This approach shows promise as an aid in the diagnosis of FIP, as efficient replication outside the gut occurs in FIP. But the fact remains that we have no screening test for FIP in well cats. Neither do we have a foolproof way to diagnose FIP in a sick cat. And always bear in mind that no current test can distinguish the FCoV that causes little or no disease from the FCoV that leads to FIP.

Dr. Andrew Sparkes and his colleagues at the University of Bristol, England, have suggested that combining several test results (e.g., globulin levels, lymphocyte counts) with clinical findings and antibody titer can help rule in or rule out FIP with some degree of certainty. In fact, combining test results that correlate with FIP (building the diagnostic “brick wall” for FIP, with each brick a separate test result), as well as ruling out other diseases, remains the only reliable means of antemortem diagnosis. The gold standard is still examination of affected tissue using a biopsy or findings at necropsy.

Unfortunately, there is no known effective treatment for cats with FIP. Treatments are aimed at palliative care and patient comfort. Drugs that suppress the immune system response to FIPV (such as prednisone) may temporarily stabilize patients. Newer therapies, such as recombinant feline interferon and pentoxifylline, have shown some limited success in a small number of patients but require more investigation before they can be recommended. Feline interferon is not available in all countries.

Recently, a new drug tested in three cats with the dry form of FIP demonstrated efficacy in prolonging life and alleviating signs. The drug, a polyprenyl immunostimulant, is an investigatory veterinary biologic and acts on the lymphocytes responsible for effective cell-mediated immunity. In this study, two cats with FIP were still alive two years after diagnosis, while one cat survived 14 months. Further studies are under way to assess its potential for FIP treatment.

Sadly, the majority of patients eventually deteriorate to the point where humane euthanasia is chosen.

So how can FIP be controlled? In addition to efforts in breeding resistant animals, preventing or reducing the incidence of FCoV infection is important. FECV is spread primarily by the fecal-oral route and, to a much lesser degree, through saliva or respiratory droplets. The virus can persist in the environment in dried feces on cat litter for 3 to 7 weeks, so scrupulous cleaning of cages and litter pans is important to reduce the amount of virus in the environment. Fortunately, FECV is susceptible to most common disinfectants and detergents. It is important to have adequate numbers of litter pans. Litter pans should be kept away from food bowls and spilled litter should be regularly vacuumed up from the floor.

Research has shown that there are two main patterns that occur with FECV infection. Most cats will become infected and recover, but will not be immune. They are susceptible to reinfection the next time they contact the virus. A small number of cats become infected but do not recover. They become persistent shedders of FECV in the cattery or shelter and are the source of reinfection for the other cats although they may never become ill. Therefore, the key to eliminating FECV (and thus the risk of FIP) in a cattery or other multi-cat establishment would be the identification and removal of chronic shedders. Currently, however, there is no easy way to determine which cats in a multi-cat environment are persistent shedders. The traditional antibody titer for FECV cannot reliably be used to determine which cats are chronic shedders. The most effective and practical tool is PCR analysis of feces for the presence of FECV, a test that is not yet widely available. Because shedding of the virus may be intermittent, testing of multiple samples over time is required. Dr. Hans Lutz at the University of Utrecht has shown that PCR on four fecal swabs taken at one-week intervals can determine the coronavirus-shedding status of a cat.

In addition to selecting disease-resistant breeding stock, breeders, shelter managers, and other multi-cat households can initiate husbandry practices that discourage the spread of FECV and development of FIP. Cat-dense environments favor the transmission of the highly contagious FECV. Dr. Diane Addie of the University of Glasgow, Scotland, recommends that the ideal way to house cats in catteries is individually. However, since this is not always possible, she recommends that they be kept in stable groups of no more than 3 or 4. Kittens should remain in groups of similar ages and not be mixed with adults in the cattery. Any measures that reduce environmental and social stress in the cattery population will have a beneficial effect.

Dr. Addie has also described a method for early weaning and isolation of kittens born to FECV-positive queens designed to prevent infection of the kittens. It involves rigorous barrier nursing techniques to prevent the spread of the highly contagious FECV, and so is not for every breeder or cattery. The procedure involves first isolating the pregnant queen in a separate area to have the kittens. When they are 5-6 weeks old (at the time when their maternal immunity to FECV is waning), the kittens are removed from the queen and isolated by themselves. Some of the difficulties with this method involve the strict infection control procedures needed and possible difficulties in socializing kittens. It also been reported by breeders that some early-weaned kittens may have behavioral problems, such as inappropriate suckling on littermates. When properly practiced, not only can FECV-negative kittens be produced, but the kittens are often less prone to respiratory diseases and other common kitten ailments.

Probably one of the most controversial areas in any discussion of FIP is Primucell FIP®, the vaccine made by Pfizer Animal Health, available since 1991. The vaccine is a modified-live temperature-sensitive viral mutant licensed for intranasal use in cats at least 16 weeks of age. The manufacturer recommends annual revaccination although no duration of immunity studies are available. The vaccine stimulates local immunity and may also produce an antibody titer. Evaluation of the risks and benefits associated with this vaccine is a difficult venture and has engendered much controversy.

Since FIP is a severe and fatal disease, the safety of any vaccine is a paramount consideration. Dr. Fred Scott of the Cornell Feline Health Center concluded in a recently published paper, that the risks associated with the Primucell FIP® vaccine are minimal in most situations. He notes that the vaccine has been in use for many years with no increase in the incidence of FIP. Troubling reports of a phenomenon called "antibody-dependent enhancement" (ADE) of infection arose from several labs, where cats vaccinated with FIP vaccines and challenged experimentally with virus developed accelerated disease instead of being protected. It is not known whether the phenomenon of ADE occurs in the real world and there is no easy way to find out. If it does occur, it is likely an uncommon event, but the possibility remains troubling.

On the other side of the issue, the benefits of the Primucell FIP® vaccine appear to be small. The best reported efficacy for the vaccine is seen when FCoV negative cats at least 16 weeks old were vaccinated twice (3 weeks apart), in a study by Dr. Nancy Reeves published in 1995. In this study, FCoV antibody-negative cats were vaccinated before entering a large cat shelter where FIP was endemic. The vaccinated cats experienced a significantly lower mortality rate than unvaccinated cats. The efficacy of the vaccination was calculated to be 75% (preventable fraction).

In catteries where FIP is endemic, studies have shown the vaccine had no effect on the incidence of disease. One reason may be that most kittens in catteries are infected between 6 and 10 weeks of age, long before the 16 weeks of age the vaccine is licensed for. Once a cat is infected with FCoV, the vaccine has no benefit. Some cattery owners have been using the vaccine at ages younger than 16 weeks to get around this problem. Dr. Johnny Hoskins has outlined a vaccination protocol for catteries experiencing FIP losses in kittens less than 16 weeks of age. He recommends giving the vaccine at 9, 13 and 17 weeks with annual revaccination afterward. Use of this protocol must be made with the knowledge that no controlled studies have been done on kittens under 16 weeks of age and that this is an off-label use. It would appear that the use of the vaccine according to the manufacturer's directions is limited to the vaccination of FCoV antibody-negative cats entering high-risk situations, such as catteries and shelters.

In conclusion, much has been discovered about FIP, but the picture is far from complete. As more is discovered, there will be improvement in our understanding of, our ability to diagnose, and our ability to treat and control this terrible disease.

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