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Feline Infectious Peritonitis

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Feline infectious peritonitis (FIP) is an important and complex disease of cats caused by a virus belonging to the family *Coronaviridae*. Coronaviruses are a large and widely distributed group of ribonucleic acid (RNA) viruses that infect several species of birds and mammals. They are important causes of upper respiratory and gastrointestinal disease, hepatitis, serositis (inflammation of the serous linings of body cavities, i.e., peritonitis, pleuritis), and encephalitis. Feline infectious peritonitis virus (FIPV), canine coronavirus (CCV), transmissible gastroenteritis virus (TGEV) of swine, and the human respiratory coronaviruses of the 229E group together comprise a cluster of closely related viruses within the Coronaviridae family. In fact, the major structural proteins of FIPV, TGEV, and CCV are so antigenically similar that some scientists regard these three viruses as host-range variants (i.e., variant forms of a single virus type, whose major dissimilarities are the animal species that each will infect and produce disease in) rather than as three individual viral species.

Feline Coronaviruses

Cats are susceptible to infection not only with FIPV but also with certain gastrointestinal coronaviruses (enteric coronaviruses), agents that may or may not be variants of FIPV (or vice versa). These feline enteric coronaviruses (FECVs) can produce a range of effects, from asymptomatic (inapparent) infection of the gastrointestinal tract to severe enteritis, in either kittens or adult cats.

Relationship of FECVs and FIPV. The nature of the relationship between FECVs and FIPV is perhaps illuminated by the observation that certain FIPV strains are capable of producing either FIP or enteritis or both. Enteritis can also be produced in newborn piglets by oral exposure to virulent FIPV. It is thus quite possible the FECVs and FIPV simply represent pathogenetic (rather than host-range) variants of a single coronavirus type—variants possessing, however, a relatively broad spectrum of virulence, from inapparent infection, to enteritis, to lethal, disseminated FIP. Spectra of such breadth and character are not without precedent in virology. For example, different strains of murine hepatitis coronavirus can produce different disease conditions in infected mice, including hepatitis, serositis, enteritis, encephalitis, and inapparent infection. In cats, variants of feline calicivirus produce a wide range of effects, from inapparent infection, to severe pneumonia and possibly enteritis. It is perhaps pertinent also to recall that the human gastrointestinal tract is the normal habitat for a number of viruses with pathogenic potential, including hepatitis A virus and poliovirus.

Host range. In nature, FIPV infections appear to be restricted to members of the cat family, including domestic breeds as well as certain exotic species—sand cats, caracals, lynx, cougars, cheetahs, jaguars, leopards, and lions. Additionally, there has been a single report of an FIP-like illness in Asian short-clawed otters, but to date no conclusive association of this disease with FIPV has been demonstrated.

Immunogenic Significance of FIPV Structural Components

Individual coronavirus particles are characterized morphologically by a fringe of radiating surface projections resembling the rays, or corona, of the sun. These projections, or *peplomers*, are responsible for attachment of the viruses to cells during infection and for the induction of virus-neutralizing antibody (VNA). The significance of VNA titers to coronavirus in cats—either healthy cats or those with FIP—has not yet been satisfactorily determined. The presence of this antibody is not necessarily an indication of protective immunity, since most cats with FIP are VNA-positive. Moreover, because of the especially close antigenic relationship between FIPV and TGEV, CCV, and FECVs—*all of which are infective for cats*—commonly used assays for VNA (or for other types of coronavirus antibody) cannot yet identify with certainty the exact coronavirus against which the antibody was raised (see the section entitled "Coronavirus Antibody Testing in Cats").

Cats with FIP also form antibody against the two other major structural components of FIPV: the inner *nucleocapsid*, which is closely associated with the viral RNA, and the outer *envelope*, in which the protruding peplomers are embedded. As in the case of VNA, there is as yet no clear consensus on the functional significance of the antibody response to these structural antigens. However, recent studies have demonstrated distinct structural differences among the envelopes of FIPV, TGEV, and CCV—differences that potentially could assist in serologic identification of the coronavirus that incites the antibody response in a given serum sample.

Immunopathogenesis of FIPV Infection

Scientific studies performed over the past several years have succeeded in identifying some of the major host-virus interactions of FIPV infection.

After infection of mononuclear white blood cells within lymphoid tissue at or near the site of initial virus penetration, a primary viremia involving the virus and/or virus-infected cells occurs within one week after exposure. In this way the virus is transported to other areas of the body, especially to organs such as the liver, spleen, and lymph nodes. These structures contain large populations of mononuclear white blood cells, such as *macrophages*, which appear to be primary target cells for FIPV infection. Hematogenous dissemination of the virus also results in infection of circulating mononuclear white blood cells *(monocytes)* and, importantly, in localization of the virus and virus-infected cells within the walls of small blood vessels (especially venules and small veins). A secondary cell-associated viremia may occur after initial infection of target tissues and result in further spread of the virus throughout the body. Deposition of the virus, virus-infected white blood cells, and virus-antibody complexes within blood vessel walls produces an intense, destructive inflammatory response (vascu-

litis), which damages vessels and allows fluid components of blood to escape into intercellular spaces and eventually to accumulate as characteristic fibrin-rich "FIP fluid" within body cavities.

Studies have also shown that some cats with serum coronavirus antibody experience a more rapid, fulminating disease course after FIPV exposure than do coronavirus antibody-negative cats receiving a similar exposure. Moreover, intravenous administration of immune serum containing anti-FIPV antibody to previously antibody-negative cats results in the more fulminating form of the disease after exposure to FIPV. A potential state of antibody-mediated hypersensitivity thus exists in FIP, in which coronavirus antibody perhaps (1) accelerates the uptake of FIPV (in the form of virus-antibody complexes) into receptive monocytes and macrophages, where production of additional infectious virus can be enhanced, and (2) promotes widespread destructive inflammatory reactions in blood vessel walls and tissues. It is thus the paradox of FIP that in those unfortunate animals that develop the lethal, disseminated disease, it is the immune system itself that helps to fuel the escalating inflammatory process—a process that reaches its inexorable conclusion only upon the death of the host.

The degree of hypersensitization by "coronavirus antibody" is dependent on the identity of the coronavirus(es) that originally incited the antibody response. Thus antibody resulting from exposure to FIPV or FECVs can hypersensitize, and antibody resulting from exposure to either CCV or coronavirus 229E usually cannot. It should be emphasized that the mere presence of coronavirus antibody in an animal's serum does not mean that FIP will ever develop in that animal in the future, even after repeated exposure to FIPV. *FIP is a relatively uncommon disease in nature, even in crowded cattery situations; the vast majority of coronavirus antibody-positive cats will never develop lethal FIP.* Many factors may determine whether FIP will develop after FIPV exposure: dose and virulence of infecting virus strain, route of exposure, age and immune status at the time of exposure, genetic makeup, concurrent viral infections (e.g., feline leukemia virus), and adverse environmental influences, such as stress and overcrowding.

Transmission of FIPV

The natural route by which FIPV is spread is still unknown; however, it is most likely that the initial infection results from ingestion or inhalation of the virus or both. Virus is probably excreted into the environment by a number of routes—in oral and respiratory secretions, in feces, and possibly in urine. Close contact between cats is usually required for effective transmission of FIPV, although the possibility of virus transmission in excreta and by other indirect methods (on clothing, bedding, feeding bowls, etc.) also exists. The potential for transmission by bloodsucking insects is unknown. Transmission of FIPV across the placenta to the developing fetus, although suggested by several reports, has not yet been definitely proven to occur.

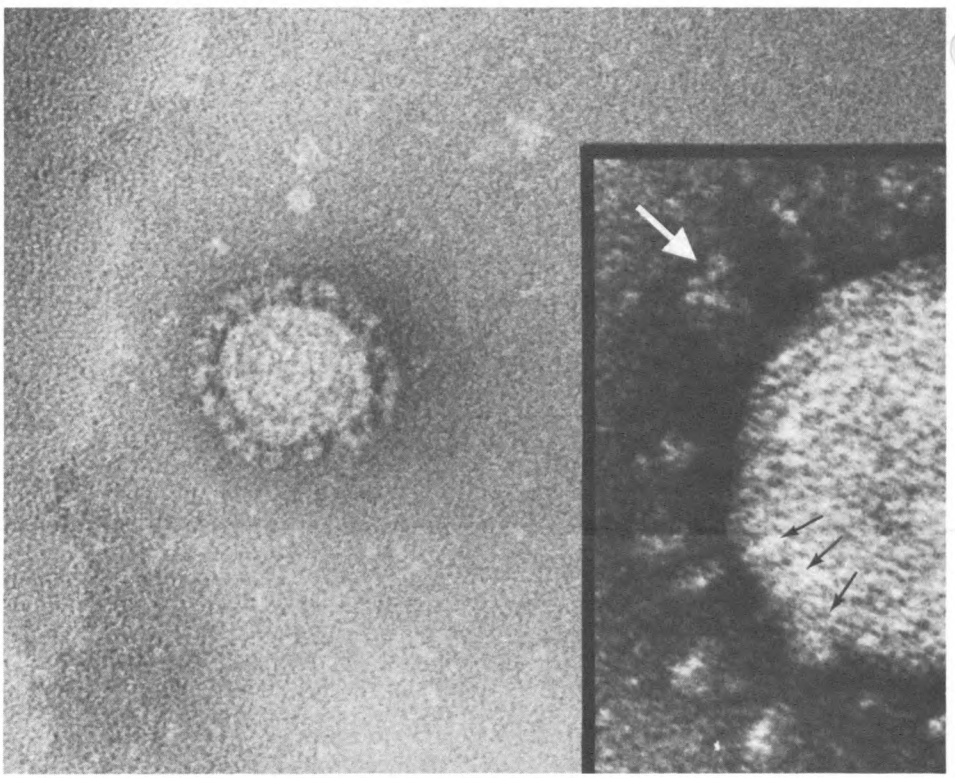

Figure 1. Electron photomicrograph of FIPV, demonstrating the thick fringe, or "corona," of peplomers characteristic of the Coronaviridae (x 261,000). Inset: Extreme magnification (x 348,000) of TGEV, illustrating the petal-shaped appearance of the peplomers (white arrow) and their attachments at the surface of the virus (black arrows).

In common with a number of other enveloped RNA viruses, FIPV is quite unstable once outside its host and is rapidly inactivated by most common household detergents and disinfectants. Household bleach (sodium hypochlorite, e.g., Clorox®) diluted 1:32 in water or in combination with A-33® to give a final concentration of 1:32 bleach and 1:64 A-33® has been recommended for rapid removal of FIPV from contaminated premises.

Clinical Signs of FIP

Primary vs. secondary FIP. There is evidence to suggest that in a certain percentage of cats, initial exposure to FIPV results in a localized upper respiratory disease that is usually mild and is characterized by sneezing, watery eyes, and watery nasal discharge. Although the vast majority of cats undergoing this "primary" form of FIP recover, some of them probably become healthy, but chronically infected, virus carriers (see the section entitled "The Question of Virus Carriers"). Only a very small number of exposed cats will proceed to develop the lethal, disseminated ("secondary") form of the disease weeks, months, or perhaps years after the primary infection.

Clinical signs of lethal, disseminated FIP. Most cases of lethal, disseminated FIP occur in cats less than three or four years old. The onset of clinical signs may be sudden (especially in kittens) or slow and insidious; the severity gradually increases over a period of weeks. Some signs may be quite nonspecific: intermittent inappetence, depression, weight loss, fever. In many cases, affected cats may continue to eat and remain alert and responsive for a considerable period of time; however, fever (which may fluctuate at different times of the day) is a constant finding and usually persists until the last few hours of life.

Three major clinical forms of disseminated FIP are recognized: (1) effusive ("wet") FIP; (2) noneffusive ("dry") FIP; and (3) combinations of the two.

Accumulation of fluid within the peritoneal cavity with progressive, painless enlargement of the abdomen is probably the most common clinical manifestation of effusive FIP. Respiratory distress may develop when abdominal fluid accumulation is excessive, or, more commonly, when accumulation of fluid occurs within the thorax, resulting in compression of the

lungs and exudation of fluid into airways. As outlined previously, this fluid is apparently the end product of the disseminated, immunologically mediated vasculitis that is characteristic of the disease. Other signs that are frequently seen include jaundice and a nonregenerative (depression) anemia. This anemia may be exacerbated by coinfection with feline leukemia virus or *Hemobartonella felis* (the parasite causing feline infectious anemia). Gastrointestinal, ocular, and neurologic signs may also occur in cases of effusive FIP. Rarely, the inflammatory process in the abdomen may damage the pancreas, resulting in clinical pancreatitis, pancreatic enzyme deficiency, or even diabetes mellitus. The course of the disease is quite variable, but the usual survival time after onset of clinical signs is about two or three months. Some young kittens may survive for no longer than a few days, and some adults may live for six to eight months with active clinical disease.

The onset of noneffusive FIP is often insidious; the clinical signs are reflective of involvement of specific organ systems in the FIP inflammatory process. Weight loss, depression, anemia, and fever are almost always present, but fluid accumulation is usually minimal. Clinical signs of kidney failure (increased water consumption and urination), liver failure (jaundice, neurologic signs), pancreatic disease (vomiting, diarrhea, voracious appetite, diabetes mellitus), neurologic disease (hind limb incoordination, loss of balance, tremors, behavioral changes, paralysis, seizures), or ocular disease (ocular inflammation, retinal disease, blindness) may be seen in various combinations in cats with severe organ impairment. The disease course is usually more chronic than in effusive FIP. Some cats, especially those with primary ocular involvement, may survive for as long as a year or more.

FIPV has also been incriminated as a cause of reproductive problems in breeding queens—infertility, fetal resorptions, abortions, stillbirths, birth of "fading" kittens, congenital malformations, and neonatal heart disease (acute congestive cardiomyopathy). *As of this writing there is no conclusive published evidence that the virus plays a role in any of these disease processes.* However, much additional research in this area will be required before the possibility of FIPV involvement in feline reproductive disorders can be entirely excluded.

Diagnosis of FIP

The clinical diagnosis of FIP is made by evaluating the history, presenting signs, and results of supportive laboratory tests. Clinicopathologic and serologic procedures important in diagnosis include analysis of thoracic or abdominal fluid (when present), hemogram, serum protein electrophoresis, clinical chemistry profiles, serum coronavirus antibody titer, and biopsy (when possible).

Biopsy is the only test procedure that can *definitively* diagnose FIP in the living animal. Exploratory laparotomy with an organ punch biopsy of affected tissues (especially the liver, spleen, omentum, and mesenteric lymph nodes) is the preferred method of obtaining FIP biopsy samples (percutaneous needle biopsy *cannot* be recommended, because of the friability of diseased organs and the potential for serious hemorrhage). Similarly, complete postmortem examination (necropsy) with microscopic evaluation of suitable tissues can provide a definitive diagnosis after death. *Any FIP diagnosis made in the absence of either biopsy or necropsy evaluation must be considered presumptive.* This is because of the large number of "FIP look-alike" diseases that can affect cats. These include lymphosarcoma and other tumors (especially those involving the liver, biliary tract, kidneys, and lungs), cardiomyopathy, nephrotic syndrome, septic peritonitis, diaphragmatic hernia, pyothorax, chylothorax, internal abscessation, pansteatitis, toxoplasmosis, cryptococcosis, and tuberculosis.

Thus, in individual cases clinicopathologic and serologic test procedures will assist in ruling out possible diagnoses, but only biopsy or necropsy evaluation will definitively identify the FIP disease process. It therefore follows that, as described in the following section, *the diagnosis of FIP must never be made simply on the basis of a coronavirus antibody titer determination.*

Coronavirus Antibody Testing in Cats

Laboratory test procedures for detection of coronavirus antibody in feline serum include virus neutralization (VN; for detection of virus-neutralizing antibody), indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), kinetics-based ELISA (KELA), agar gel immunodiffusion, and passive hemagglutination. Either FIPV itself or one of the other coronaviruses in the FIPV group (usually TGEV or CCV) can be used as the antibody "target" in most of these assays. The use of non-FIPV coronaviruses in antibody testing procedures has been popular in recent years because of the relative difficulty in routinely working with FIPV in the laboratory. In the United States the immunohistochemical tests (especially IFA) have gained the greatest popularity among veterinary diagnostic laboratories, in part because of their relative ease of performance and the widespread availability of the pertinent immunotechnologies.

It has been proposed on the basis of serologic survey data that most FIPV infections in nature result only in seroconversion (generation of serum antibody) without progression to inevitably fatal disease. This is because serum coronavirus antibody can be found not only in cats with lethal, disseminated FIP but also in many healthy cats and in many cats with diseases other than FIP, indicating that exposure of cats to coronavirus(es) is much more widespread than was once believed, especially in certain selected populations. In the general healthy feline population—excluding cats in catteries and multiple-cat households—about 10 to 40 percent of cats will have positive coronavirus antibody titers (*note:* "positive" refers only to the presence of antibody, *not* to the presence of the FIP disease process). A special situation is encountered when cats are clustered together in a cattery, in which case positive titers are either completely absent (i.e., there has been no coronavirus exposure) or are present in 80 to 90 percent of the cats within a cattery (indicating efficient spread of the virus once it has been introduced). The occurrence of coronavirus antibody does not necessarily correlate with the FIP history of a cattery; e.g., antibody has been detected in healthy cats in catteries that have experienced death losses to FIP as well as in catteries that have never lost a cat to FIP.

Most cats with clinical FIP have serum coronavirus antibody, often to high titer. Since many cats with diseases other than FIP can also have elevated titers (indicating previous coronavirus exposure), interpretation of their titers in the absence of a definitive diagnosis can be challenging. Now added complexity has been contributed to interpretation of coronavirus antibody titers in healthy cats and in cats with undiagnosed illnesses by recent reports that other coronaviruses that are serologically cross-reactive with FIPV can also infect cats *and generate coronavirus antibody in their serum.* These viruses include TGEV, which produces an inapparent infection and is shed in feces for as long as three weeks after exposure; CCV, which also produces an inapparent infection and is shed from the oropharynx for at least one week; and FECVs, which can produce either inapparent infection or enteritis of varying severity, in which the virus is excreted in feces. Because these viruses are all serologically cross-reactive with each other and with FIPV, and because several of them (FIPV, TGEV, CCV) are used relatively interchangeably in commercially available feline coronavirus antibody tests, the nonspecificity of these tests is readily apparent. The potential of these tests to identify FIPV-infected cats has been diminished not only by the widespread occurrence of serum coronavirus antibody in the general feline population but also by the possibility that non-FIPV coronaviruses may be responsible for some of the seroconversions they detect. The actual distribution in the general feline population of antibodies to each of these viruses is therefore unknown and will remain unknown until highly specific tests are developed that will be able to differentiate antibody against one coronavirus (e.g., FIPV) from antibody

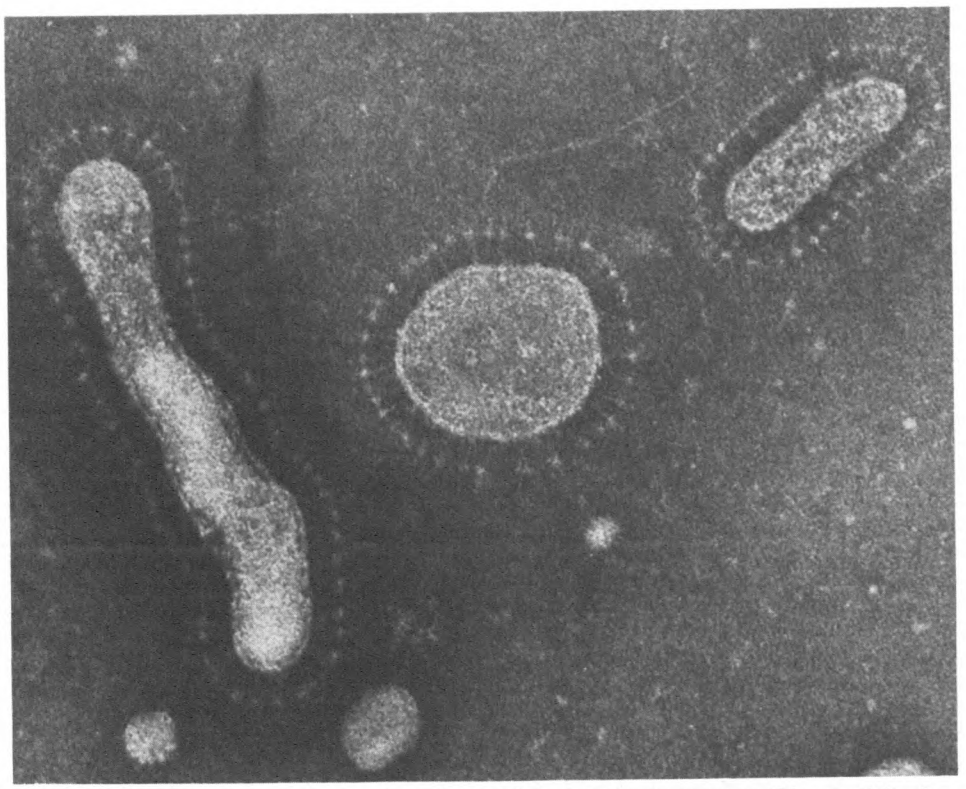

Figure 2. Electron photomicrograph of three feline enteric coronavirus-like particles in feces, demonstrating the characteristic knob-shaped peplomers attached by slender stalks (x 174,000).

against another coronavirus (e.g., CCV, TGEV).

These difficulties are further compounded by the plethora of test methodologies (IFA, VN, ELISA, KELA, etc.) employed by different laboratories, and by the complete absence of standardization of testing protocols. Conflicting titer results should therefore be *expected* when a serum sample is tested by different laboratories using different serologic techniques, or even by different laboratories using the *same* technique. *Titer results from a testing laboratory are best interpreted in light of specific information provided by that laboratory on the significance of titer levels generated by the individual test that it performs.*

Effect of recent vaccination. Research has revealed that antibody against *bovine* serum components can be found in the serum of certain cats—antibody capable of reacting with antigenically similar bovine serum components present in cell cultures used for growing target viruses for immunohistochemical assays such as IFA, ELISA, and KELA. Because these components adhere tightly to both cells and viruses, *reactivity against them can be mistaken for a coronavirus antibody response* unless feline serum samples are tested in parallel against cell culture preparations *without* coronavirus ("negative antigen" controls). In the IFA and conventional ELISA, which are frequently performed without benefit of negative antigen controls, antibody to bovine serum components is a potential source of false-positive coronavirus antibody test results. In the KELA, negative controls are routinely performed for each serum sample evaluated, and titer results are adjusted accordingly.

One possible explanation for the presence in feline serum of antibody that reacts with bovine serum components is routine vaccination. Cell culture vaccines prepared for use in cats (as well as vaccines for many other species) contain bovine serum components that could conceivably be the source of this noncoronavirus reactivity—reactivity that might be especially strong in serum samples drawn soon after parenteral vaccination. Both retrospective and prospective studies support this hypothesis. Using the KELA, a statistical association between recent vaccination and the presence of this noncoronavirus reactivity has been demonstrated. Importantly, production of this reactivity was found to be somewhat idiosyncratic; i.e., not all cats reacted to vaccination this way, nor did all vaccines always produce this reactivity. KELA studies have shown further that this reactivity dissipates with time, and that the probability of encountering it can be minimized if serum samples for KELA testing are drawn no sooner than three to four months after the most recent vaccination.

General recommendations. The presence of serum coronavirus antibody in any cat, whether healthy or diseased, is indicative *only* of exposure to a coronavirus in the FIPV group. A positive coronavirus antibody titer, although consistent with a clinical diagnosis of FIP (this type of FIP diagnosis is always presumptive), does not indicate that a cat actually has FIP, since many healthy cats and many cats with diseases other than FIP are also coronavirus antibody-positive. Neither does a positive titer indicate that a cat is protected against FIP, since most cats with FIP are also coronavirus antibody-positive. Considering that FIP occurs only sporadically in the general feline population, and that most cats in FIP-problem households are coronavirus antibody-positive and yet do not contract FIP, it would appear that many cats with coronavirus antibody are somehow protected against the disease. The question remains whether it is coronavirus antibody (of some type) that actually confers this protection or whether other unknown factors are involved. Lastly, present-day coronavirus antibody tests *have absolutely no predictive value;* i.e., a positive titer does not indicate that a cat is doomed to develop FIP at some future date.

Despite all the problems with current feline coronavirus antibody testing methods, there are still some select situations in which determination of antibody titers can be of use to the veterinarian and to the cat owner:

1. As a screening test, to determine the presence or absence of antibody in a previously untested household, and to detect *potential* virus carriers or shedders (see the section entitled "The Question of Virus Carriers") when introducing new cats into coronavirus antibody-negative households. *Based on the current understanding of feline coronavirus serology, screening would appear to be the major use for coronavirus antibody testing.* Screening of cats in a household experiencing undiagnosed disease problems may be especially useful. Only about 10 to 20 percent of the cats (a minimum number of three) in such a household need to be tested, because antibody will either be totally absent or present in 80 to 90 percent of the animals. Although the discovery of coronavirus antibody-positive cats in such households will not diagnose the problem, *knowledge that coronavirus antibody is absent may be helpful in ruling out an FIPV-group coronavirus as the culprit.*

2. As an *aid* (and nothing more than an aid) in the clinical diagnosis of a diseased cat with signs suggestive of FIP. A coronavirus antibody titer determination should be given no more weight than any of the other routine procedures (e.g., hemogram, clinical chemistry profiles, radiographs) used in arriving at a clinical diagnosis. A positive titer will not diagnose FIP, but a negative titer will usually rule it out, except under certain rare circumstances that are described in the following section.

Coronavirus antibody-negative FIP cases. A very small percentage of cats with FIP (usually diagnosed at necropsy) do not have *detectable* coronavirus antibody in their serum. Several explanations for this phenomenon are possible:

1. Detectable antibody may disappear from the circulation during the terminal stages of the disease. Submission of serum from some moribund cats thus may result in a negative titer determination in the presence of disseminated FIP.

2. Virus-antibody complexing is an important immunopathologic feature of FIP. In certain cases, if extensive complexing is present at the time of testing, there may be little unbound coronavirus antibody available to be detected. This may be the explanation, at least in part, for the absence of detectable antibody in the serum of some moribund cats.

3. The swiftness of the FIP disease process may be an important factor, especially in animals without previous coronavirus exposure. Cats experiencing a rapid disease course (such as some young kittens) may display a rather slowly rising antibody response that may be more difficult to detect in the early stages, especially if a non-FIPV coronavirus (TGEV, CCV) is used by the laboratory for antibody detection. Although serologically cross-reactive with FIPV, these viruses nevertheless *are different* from FIPV and thus are not as sensitive as FIPV in detecting low levels of anti-FIPV antibody.

Treatment and Control

Although it is possible that "mild" cases of FIP may occasionally occur, in which clinical signs are minimal and will spontaneously resolve, the vast majority of cats that develop disseminated FIP will die, usually within a few weeks or months of onset.

Present-day treatment of cats with FIP is palliative because no curative therapy yet exists. There are no effective antiviral drugs or prophylactic vaccines for FIP, nor is there any way to eliminate the virus from infected animals. However, some treatment regimens may induce short-term (usually weeks) remissions in a small percentage of carefully chosen patients. The best candidates for treatment are cats that are still in good physical condition; are still eating; do not show severe anemia, neurologic signs, or other significant organ dysfunction; and are not also infected with feline leukemia virus. *The feline leukemia virus status of all suspect FIP cases should be determined before beginning treatment, because the prognosis for cats infected with both viruses is extremely poor.*

The basic aim of palliative therapy in FIP is to alleviate the self-destroying inflammatory response of disseminated FIP, which represents the immune system's unsuccessful attempt to eliminate the virus from the patient's body. The most effective treatment protocols combine corticosteroids (prednisone or prednisolone), cytotoxic drugs (melphalan [Alkeran®] or cyclophosphamide [Cytoxan®]), and broad-spectrum antibiotics with maintenance of nutrient intake and fluid and electrolyte balance. Cats receiving cytotoxic drugs should be routinely monitored for evidence of bone marrow suppression and kidney dysfunction. If the patient shows a positive response to therapy over the first few weeks, treatment should be continued for at least three months. If the patient is in complete remission at that time (unfortunately, an infrequent occurrence), corticosteroids and cytotoxic drugs may be *slowly* withdrawn. Treatment should be reinstated, however, if signs of FIP recur. Progressive physical deterioration of the patient during treatment is generally a poor prognostic sign. *There is no documented evidence that supplemental multivitamin therapy is of any benefit in FIP.*

In light of current scientific information, a test-and-removal program for coronavirus antibody-positive cats similar to that used for feline leukemia virus infection *cannot be recommended.* Because there is no available serodiagnostic test that can specifically identify antibody-positive cats with FIP, antibody-positive cats with diseases other than FIP, or "FIP-immune"antibody-positive cats, or that can specifically identify antibody-positive cats that are shedding FIPV into the environment, or even that can identify the exact coronavirus(es) against which the antibodies in these cats were raised, *there is no known medical reason for destroying these animals.*

Immunization against FIP

A safe and efficacious FIP vaccine has not yet been developed. Experiments thus far reported with various FIPV, TGEV, FECV, CCV, and coronavirus 229E preparations have been unsuccessful in uniformly conferring protective immunity. Paradoxically, because of the immunopathologic nature of the disease, vaccination using sensitizing coronaviruses (FIPV, FECV) predisposes cats to lethal, disseminated FIP. Vaccination with TGEV, CCV, or coronavirus 229E neither sensitizes nor protects. Future investigations into the immunogenicity of individual viral proteins of cell culture-adapted FIPV isolates may however yield information that will lead ultimately to development of a safe and effective subunit vaccine.

The Question of Virus Carriers

A second important area of ongoing FIP research involves the identification and characterization of the FIPV carrier state. There is no recognized environmental reservoir of FIPV; the natural reservoir is assumed to be infected cats. How, then, does the virus maintain itself in these animals? For how long do infected cats harbor the virus? For how long do they shed the virus, and by what route(s)? What route is most important for effective virus transmission to other cats? Is shedding continuous or only intermittent? Is it possibly stress related? What percentage of cats infected with FIPV actually become chronic carriers? To what extent is a coronavirus antibody-positive cat a potential disease threat to other cats (especially kittens) with which it may come into contact? Can an infected queen infect her kittens *in utero?* If so, does *in utero* infection result in disease?

Clearly, much research will be required before these questions and others can be satisfactorily answered. A serologic test for detecting carrier animals that are shedding FIPV, similar to the Hardy test for feline leukemia virus infection, is urgently needed. Until such a test is developed, control must be based on isolation of cats with suspected FIP, and maintenance of coronavirus antibody-negative catteries when possible. *Euthanasia of coronavirus antibody-positive cats to achieve the latter purpose, however, cannot be justified.*

Public-Health Aspects of FIPV

As of this writing, FIPV does not appear to be a health hazard for human beings.

Feline Enteric Coronavirus-like Particles

The electron microscope (EM) has enabled diagnosticians and researchers to visualize virus particles, and it has proved a powerful tool in the discovery of viruses and "virus-like" agents that cannot be grown in tissue culture (the traditional method of isolating and identifying viruses). Most of these previously undescribed particles have been observed in fecal samples from persons and animals with enteric disorders. Because the prevalence of the particles in the feces of healthy individuals is unknown, it has been difficult to determine whether they in fact cause gastrointestinal disease.

Particles that have been characterized as "coronavirus-like" on the basis of their appearance under the EM have been identified in the feces of a number of animal species, including cats. These coronavirus-like particles (CVLPs) vary widely in size and shape and possess radiating surface projections reminiscent of coronaviral peplomers (see figure 2). Closer examination, however, has revealed that individual CVLP projections consist of a delicate, round or oval knob-shaped structure anchored to the particle by a slender stalk; thus they are distinguishable from the more petal-shaped projections of "typical" coronaviruses (compare the CVLPs in figure 2 with the "typical" coronaviruses in figure 1). *CVLPs have not been positively identified as the cause of disease in any species to date.* However, they have most frequently been identified in diarrheic feces, and human enteric CVLPs have been implicated as a cause of gastroin-

testinal disease in infants, older children, and adults.

Enteric CVLPs were first detected by electron microscopy in cat feces in 1979 and were subsequently found in 10.8 percent of the fecal samples collected in a survey of 185 privately owned cats hospitalized at the Small Animal Clinic of the Veterinary Medical Teaching Hospital at Cornell. Laboratory cats have been infected with feline enteric CVLPs by inoculation with purified CVLP-containing fecal material by various routes, and by natural exposure to CVLP-excreting cats. Cats infected in this manner subsequently excreted CVLPs in feces, *yet showed no clinical signs of disease* and remained coronavirus antibody-negative by KELA. In addition, kittens raised in the Cornell University feline breeding colony routinely become infected soon after birth with enteric CVLPs excreted by their dams, yet remain clinically healthy.

Feline enteric CVLPs appear to be quite different from FIPV and from the recently described FECVs. Recent studies strongly suggest that feline enteric CVLPs are indeed infectious agents, but further research is required before the distribution and importance of CVLPs in the feline population, and their relationship (if any) to feline coronaviruses, can be determined. Although they are interesting from the virologist's point of view, *feline enteric CVLPs have not yet been determined to be the cause of any disease in cats.*

Summary

1. Cats are susceptible to infection with at least four serologically cross-reactive coronaviruses: FIPV, FECVs, TGEV, and CCV. Of these, only FIPV and FECVs appear to be of great clinical significance.

2. In domestic and exotic cats, FIPV is the causative agent of a lethal, immunologically mediated disease characterized variably by serositis, hepatitis, encephalitis, and enteritis. FECVs, on the other hand, have been associated primarily with enteritis. It is possible that FIPV and FECVs represent pathogenetic variants of a single coronavirus type—variants possessing, however, a relatively broad spectrum of virulence, from inapparent infection, to enteritis, to lethal, disseminated FIP. Neither TGEV nor CCV has been shown to produce recognizable signs of disease in cats.

3. The natural route by which FIPV is spread from cat to cat is unknown; however, it is most likely that the initial infection results from either ingestion or inhalation of the virus or both. Virus is probably excreted into the environment by a number of routes—in oral and respiratory secretions, in feces, and possibly in urine. There is no known environmental reservoir for FIPV; the natural reservoir is assumed to be infected cats. FIPV is quite unstable once outside its host and is rapidly inactivated by most common household detergents and disinfectants.

4. The clinical diagnosis of FIP is made by evaluating the history, presenting signs, and results of supportive laboratory tests. In the living animal, biopsy is the only test procedure that can definitively diagnose FIP; similarly, necropsy can provide a definitive diagnosis after death. Any FIP diagnosis made in the absence of either biopsy or necropsy evaluation must be considered presumptive.

5. Based on the current understanding of feline coronavirus serology, screening would appear to be the major use for coronavirus antibody testing. Titer results from a testing laboratory are best interpreted in light of specific information provided by that laboratory on the significance of titer levels generated by the individual test that it performs. The presence of serum coronavirus antibody in any cat, whether healthy or diseased, is indicative only of exposure to a coronavirus in the FIPV group. A positive antibody titer does not diagnose FIP, nor does it indicate that a cat is doomed to develop FIP at some future date.

6. Treatment methods for FIP are palliative, and a safe and efficacious vaccine has not yet been developed.

Selected General References

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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 largely by private tax-deductible contributions. Correspondence may be directed to:

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