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Cats, coronaviruses and coronavirus antibody tests

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ABSTRACT

Feline infectious peritonitis and other coronavirus infections of cats are briefly reviewed. Interpretation and applications of feline coronavirus antibody tests are described, and general recommendations are provided for practitioners. Some of the major unresolved questions regarding coronavirus infections of cats are delineated.

INTRODUCTION

The coronaviruses are a large and widely distributed family of single-stranded ribonucleic acid viruses, and are important causes of respiratory and enteric disease, vasculitis, serositis, hepatitis, and encephalomyelitis in several avian and mammalian species (Siddell *et al.*, 1983). Feline infectious peritonitis virus (FIPV), transmissible gastroenteritis virus (TGEV) of swine, canine coronavirus (CCV), and human respiratory-tract coronaviruses of the 229E group together comprise an antigenic cluster of closely-related viruses within the Coronaviridae family (Pedersen, Ward & Mengeling, 1978). In fact, the major structural polypeptides of FIPV, TGEV, and CCV are so similar antigenically that some regard these three agents as host–range mutants rather than as individual viral species (Horzinek, Lutz & Pedersen, 1982).

CORONAVIRUS INFECTIONS OF CATS

In domestic and exotic cats, FIPV is the aetiologic agent of a lethal disease—feline infectious peritonitis (FIP)—characterized by fibrinous serositis, vasculitis, and formation of disseminated pyogranulomas (Wolfe & Griesemer, 1966; Montali &

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Strandberg, 1972; Hayashi *et al.*, 1977). Serosal membranes, liver, kidneys, omentum, lungs, eyes, and central nervous system are commonly affected. The pathology is the result of complex immunologically mediated phenomena involving Arthus-like antigen–antibody-complement interactions across vessel walls (Jacobse-Geels, Daha & Horzinek, 1980, 1982; Pedersen & Boyle, 1980; Weiss, Dodds & Scott, 1980; Weiss & Scott, 1981a–c; Hayashi, Ishida & Fujiwara, 1982).

Recent studies have shown that some cats with either naturally or experimentally-acquired serum coronavirus antibody experience a more rapid, fulminating disease course following FIPV exposure than do coronavirus antibody-negative cats receiving the same challenge dose (Pedersen & Boyle, 1980; Weiss, Dodds & Scott, 1980; Weiss & Scott, 1981a–c). A potential state of antibody-mediated hypersensitivity thus exists in certain coronavirus antibody-positive cats challenged with FIPV, with this antibody perhaps (1) accelerating the uptake of FIPV (in the form of immune complexes) into reticuloendothelial and polymorphonuclear cells, and (2) promoting widespread destructive inflammatory reactions in blood vessel walls and tissues through immune complex deposition and complement activation (Jacobse-Geels, Daha & Horzinek, 1980, 1982; Pedersen & Boyle, 1980; Weiss, Dodds & Scott, 1980; Weiss & Scott, 1981a–c; Hayashi *et al.*, 1983a, 1984). Uptake of FIPV into macrophages appears to be enhanced by impaired T lymphocyte function (Hayashi *et al.*, 1983b).

In addition to FIPV, cats are susceptible to natural infection with certain enteric coronaviruses which may or may not be variants of FIPV (Pedersen *et al.*, 1981; McKiernan *et al.*, 1981; Dea, Roy & Elazhary, 1982). These feline enteric coronaviruses (FECVs) can produce a range of effects from asymptomatic infection of the gastrointestinal tract to severe enteritis in kittens and adult cats. 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 (Hayashi *et al.*, 1982, 1983a,b). Intestinal lesions can also be produced in newborn pigs by oral inoculation with virulent FIPV (Woods, Cheville & Gallagher, 1981). It is thus possible that FECVs and FIPV represent pathogenetic (rather than host-range) variants of a single coronavirus type—variants possessing, however, a relatively broad spectrum of virulence from asymptomatic infection to enteritis to lethal, disseminated FIP (Barlough, 1984b).

Reports indicate that at least two other coronaviruses in the FIPV antigenic cluster can infect cats under experimental conditions: TGEV, which produces an asymptomatic infection and is excreted in faeces for as long as three weeks post-exposure (Reynolds & Garwes, 1979), and CCV, which also produces an asymptomatic infection and is excreted from the oropharynx for at least one week (Barlough *et al.*, 1984b; Stoddart, Baldwin & Scott, 1984). At present the frequency of infection of cats in nature with these two coronaviruses is not known. Coronavirus 229E of human beings does not appear to replicate to any extent in experimentally-inoculated cats (Barlough, 1984a).

In FIP, hypersensitization by coronavirus antibody is dependent upon the identity of the coronavirus(es) that originally incited the antibody response. Thus, antibody arising from exposure to FIPV or FECVs can hypersensitize (Weiss, Dodds & Scott, 1980; Pedersen & Boyle, 1980; Pedersen *et al.*, 1981; Weiss & Scott, 1981a–c), while antibody resulting from exposure to TGEV, CCV, or coronavirus 229E usually does not (Witte *et al.*, 1977; Woods & Pedersen, 1979; Barlough, 1984a; Barlough *et al.*, 1984b; Stoddart, Baldwin & Scott, 1984). However, some sensitization due to a TGEV strain apparently occurred in one report (Toma *et al.*, 1979).

It should be emphasized at this point 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 FIPV exposure. FIP is a relatively uncommon disease in nature, even in crowded cattery situations; the vast majority of coronavirus antibody-positive cats will never develop it. The factors that determine whether FIP *does* develop following FIPV exposure are multiple, probably including: dose and virulence of infecting virus strain; route of exposure; age and immune status at time of exposure; possibly genetic predisposition; concurrent viral infections (e.g., feline leukaemia virus); and adverse environmental influences, such as stress and overcrowding (Scott, Weiss & Hoshino, 1979; Barlough & Weiss, 1983).

The route by which FIPV is spread in nature is still unknown. However, it is most likely that initial infection results from ingestion and/or inhalation of the virus. Virus is probably excreted into the environment by a number of routes: in oral and respiratory secretions, faeces, and possibly urine. Close contact between cats usually is 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 haematophagous arthropods is unknown. Transmission across the placenta to the developing foetus, although suggested in the past (Flagstad & Larsen, 1976; Pastoret & Henroteaux, 1978), has not yet been conclusively proven to occur.

In common with many other enveloped viruses, FIPV is quite unstable once outside its host, and is rapidly inactivated by many common detergents and disinfecting agents, such as sodium hypochlorite (bleach) (Pedersen, 1976; Barlough & Weiss, 1983).

DIAGNOSIS OF FIP

The clinical diagnosis of FIP is made by evaluation of history and presenting signs and the results of supportive laboratory procedures (Weiss & Scott, 1980). Clinicopathologic and serologic procedures important in diagnosis include: analysis of thoracic and abdominal effusion (viscous, opaque, straw-coloured to yellow, specific gravity 1·017 to 1·047, protein 5 to 10 g/dl, variable cell numbers, high fibrin content), haemogram, clinical chemistry profile, serum protein

electrophoresis (hypergammaglobulinaemia), serum coronavirus antibody titre, and biopsy (when possible).

It is important to remember that a biopsy is the only test procedure that can be used to *definitively* diagnosis FIP in the living animal. Explortory laparotomy with organ punch biopsy of affected tissues (especially liver, spleen, omentum, and mesenteric lymph node) is the preferred technique for collection of biopsy samples (percutaneous needle biopsy *cannot* be recommended owing to the friability of diseased organs and the potential for serious haemorrhage). Similarly, complete necropsy examination with histologic evaluation of suitable tissues will provide a reliable diagnosis after death. *Any diagnosis of FIP made in the absence of biopsy or necropsy examination must be considered presumptive.* This is because of the large number of potential 'FIP look-alike' diseases that can affect cats. These can include: lymphosarcoma and other tumours (especially those involving the liver, biliary tract, kidneys, or lungs), cardiomyopathy, pyothorax, chylothorax, septic peritonitis, hepatitis, internal abscessation, diaphragmatic hernia, pansteatitis, toxoplasmosis, cryptococcosis, and tuberculosis (Barlough & Weiss, 1983).

Thus, in individual cases, clinicopathologic and serologic procedures will assist in ruling out possible diagnoses, but only biopsy or necropsy examination will definitively identify the FIP disease process.

CORONAVIRUS ANTIBODY TESTS

Laboratory test procedures for detection of coronavirus antibody in feline sera include biological assays such as virus neutralization (VN); non-biological, immunochemical techniques such as indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), and kinetics-based ELISA (KELA); and other methods such as agar gel immunodiffusion and passive haemagglutination (Barlough, Jacobson & Scott, 1983), though the availability of such tests varies worldwide. Either FIPV itself or one of the other coronaviruses in the FIPV antigenic cluster (usually TGEV or CCV) can be used as the target antigen in most of these assays. The use of non-FIPV coronaviruses in antibody-testing procedures has become popular in recent years because of long-standing difficulties in routinely propagating FIPV in the laboratory. In general, the immunochemical tests (especially the IFA) have gained the greatest popularity among veterinary diagnostic laboratories, in part because of their relative ease of performance and widespread availability of the pertinent immunotechnologies.

It has been proposed on the basis of serosurvey data that most FIPV infections in nature result only in seroconversion without progression to lethal, disseminated FIP (Barlough, Jacobson & Scott, 1983). This is because serum coronavirus antibody can be found not only in cats with FIP but also in many healthy cats and in many cats with other diseases, indicating that exposure of cats to coronavirus(es) is much more widespread than was once believed. In the general healthy

feline population—excluding cats in catteries and multiple-cat households—approximately 10 to 40 per cent of cats will have positive coronavirus antibody titres (*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 catteries, in which case positive titres are either completely absent (i.e., there has been no coronavirus exposure), or are present in 80 to 90 per cent of the cats within a household (indicating efficient spread of virus once it has been introduced). The occurrence of coronavirus antibody in a cattery does not necessarily correlate with its FIP history; e.g., antibody has been found 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 histopathologically confirmed FIP have serum coronavirus antibody, often of high titre (Weiss & Scott, 1980; Barlough, Jacobson & Scott, 1983). Because many cats with undiagnosed illnesses also have elevated titres (indicating previous coronavirus exposure), interpretation of their titres may be difficult. Added complexity has been contributed to interpretation of coronavirus antibody titres in healthy cats and in cats with undiagnosed illnesses by the finding that other coronaviruses (e.g., FECV, and experimentally TEGV and CCV) can also infect cats *and generate coronavirus antibody in their sera.* Because these viruses are all serologically cross-reactive with each other and with FIPV, and because several of them are used relatively interchangeably in commercially available coronavirus antibody tests, the non-specificity of these tests is readily apparent. The serodiagnostic potential of these assays (i.e., their ability to identify cats with active FIP and/or potential virus carriers/excretors) is thus limited not only by the widespread distribution of serum coronavirus antibody in the feline population, but also by the possibility that non-FIPV coronaviruses may be responsible for some of the seroconversions that they detect. The actual distribution of antibodies in the general feline population to each of these coronaviruses is therefore unknown, and will remain unknown until highly specific assays capable of differentiating antibody against one coronavirus (e.g. FIPV) from antibody against another (e.g., TGEV) are developed.

These difficulties are compounded further by the plethora of test procedures (i.e., IFA, VN, ELISA, KELA) employed by different laboratories, and by the absence of standardization of testing protocols. Results are therefore best interpreted in the light of specific information provided by the testing laboratory utilized, on the significance of titre levels generated by the individual test that it performs.

Effect of recent vaccination. Recent research has shown 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 to propagate target viruses for immunochemical assays such as the IFA, ELISA, and KELA (Barlough *et al.*, 1983, 1984a). Because such serum components can adhere tightly to both cells and virus (Johansson, Bergquist & Grandien, 1976; Kraaijeveld, Madge & Macnaughton, 1980; Barlough *et al.*,

1983), reactivity against them can be mistaken for a coronavirus antibody response unless feline serum samples are tested in parallel against uninfected cell culture control preparations (Barlough *et al.*, 1983, 1984a). One possible explanation for the presence of this reactivity is routine vaccination. Owing to the frequent presence of extraneous cell culture material in many partially purified commercial biologicals, routine parenteral vaccination would seem to provide an ideal opportunity for vaccinees to respond immunologically not only to vaccine virus but also to immunogenic elements of cell culture medium, such as bovine serum proteins (Bonin, Schmidt & Schmidt, 1973; Johansson, Bergquist & Grandien, 1976; Tizard, 1982; Barlough *et al.*, 1983, 1984a, 1985; Snyder, Eernisse & Erickson, 1983). KELA studies have shown that this reactivity dissipates with time, and that the probability of encountering it can be minimized if serum samples for elective serotesting are drawn no sooner than three to four months following the most recent parenteral vaccination (Barlough *et al.*, 1984a).

GENERAL RECOMMENDATIONS

The presence of serum coronavirus antibody in any cat, whether healthy or diseased, is indicative of only one thing: previous exposure to a coronavirus in the FIPV antigenic group. A positive coronavirus antibody titre, while consistent with a clinical diagnosis of FIP, does not indicate that a cat actually has FIP, because many healthy cats and many cats with other diseases are also coronavirus antibody-positive. Neither, however, does a positive titre indicate that a cat is protected against FIP, because most cats with FIP also are 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 (perhaps most cats) with coronavirus antibody are protected against the natural disease. The question remains whether it is coronavirus antibody that actually confers this protection or whether unrecognized cellular immunologic factors are involved. It is especially important to realize that present-day coronavirus antibody tests have absolutely no predictive value; i.e., a positive titre in no way indicates that a cat is doomed to develop FIP at some uncertain future date.

Despite all the problems with current feline coronavirus antibody testing methods, there are still some select situations in which determination of antibody titres can be of benefit to the veterinary surgeon and to the cat owner (Barlough, Jacobson & Scott, 1983):

(1) As a screening test, to determine the presence or absence of antibody in a previously untested household, and to detect potential virus carriers/excretors when introducing new cats into coronavirus antibody-negative households. Based on our current understanding of feline coronaviral serology, screening would appear to be the major use for coronavirus antibody testing today. Screening of cats in a household experiencing undiagnosed disease problems may be especially useful. Only about 10 to 20 per cent of the cats (a minimum of three) in such a household

need to be tested, because antibody will be either totally absent or present in 80 to 90 per cent of the animals (Scott, Weiss & Hoshino, 1979). While 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 aetiologic 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 titre determination should be given no more weight than any of the other routine procedures used in arriving at a clinical diagnosis. A positive titre will not diagnose FIP, but a negative titre will usually rule it out.

Coronavirus antibody-negative FIP cases. A very small percentage of cats with FIP do not have *detectable* coronavirus antibody in their sera. Several explanations for this phenomenon are possible:

(1) Detectable antibody may sometimes disappear from the circulation during the terminal stages of the disease. Submission of serum from some moribund cats thus may result in a negative titre determination despite the presence of disseminated FIP (Barlough, 1983).

(2) Immune-complexing is an important immunopathologic feature of FIP. In certain cases, if extensive immune complexing is present at the time of testing, it is conceivable that there may be little free, unbound coronavirus antibody available to be detected. This 'cloaking effect' may in fact 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 is an important factor, especially in animals without previous coronavirus exposure. Cats experiencing a peracute disease course (such as some young kittens) may display a rather sluggish antibody response that can be more difficult to detect in the earlier stages, especially if a non-FIPV coronavirus (TGEV, CCV) is used by the laboratory for antibody detected. Although serologically cross-reactive with FIPV, these viruses nevertheless are different from FIPV and thus are not as sensitive as FIPV at detecting lower levels of specific anti-FIPV antibody.

A test-and-removal programme for coronavirus antibody-positive cats similar to that utilized for feline leukaemia virus-positive cats, based upon current scientific information, cannot be recommended (Scott, 1979; Barlough & Weiss, 1983). Because there is no available serodiagnostic test that can differentiate between antibody-positive cats with FIP, antibody-positive cats with diseases other than FIP, or 'FIP-immune' seropositive cats, that can specifically identify antibody-positive cats that are excreting FIPV, or that can even identify the exact coronavirus(es) against which the antibodies in seropositive cats were raised, there is no known medical reason for destroying these animals.

UNRESOLVED QUESTIONS

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 harbour the virus? For how long do they excrete the virus, and by what route(s)? What route is most important for effective virus transmission to other cats? Is excretion continuous or 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 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, further research will be required before these questions and others can be satisfactorily resolved. Importantly, an antigen detection test for identifying carrier animals that are excreting FIPV, similar to those currently available for feline leukaemia virus infection, is urgently needed so that rational FIPV control procedures can be devised. Until then, 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 this latter purpose, however, cannot be justified.*

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