

# Feline infectious peritonitis: a coronavirus disease of cats

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## ABSTRACT

Infections of cats with the coronavirus causing feline infectious peritonitis (FIP) are mostly inapparent. In cases where a poly-serositis develops, it is a progressively debilitating, fatal disease with occasional neurological and ocular symptoms. Upon post-mortem examination, pyogranulomatous organ lesions are prominent; the body cavities may contain varying quantities of a viscid exudate. The agent, which is serologically related to TGE virus of swine, has a world wide distribution. It has been shown recently to replicate in laboratory rodents. Several observations indicate an immune pathogenesis of FIP.

## INTRODUCTION

Feline infectious peritonitis (FIP) is a variably progressive, usually fatal condition, affecting domestic and wild Felidae, which is characterized by fever, anorexia, depression and ascites. The most prominent features upon post-mortem examination are diffuse fibrinous peritonitis, mesothelial hyperplasia and focal necrosis in parenchymatous organs. The aetiological agent is a virus belonging to the Coronaviridae family, which is antigenically related to transmissible gastroenteritis (TGE) virus of swine. In the present article a short review is attempted of the clinical, pathological and epidemiological aspects of the disease; special attention is given to the characterization of FIP virus which has been subject to intensive study in the author's laboratory during the last 2 years.

### *Disease description*

(a) *Clinical Findings.* FIP is observed at about the same frequency in cats of all



ages (Robison, Holzworth & Gilmore, 1971), breeds (Hardy & Hurvirz, 1971; Ward & Pedersen, 1969) and in both sexes (Pedersen, 1976c; Ward & Pedersen, 1969). The clinical symptoms of the disease are not very characteristic: initially, the affected animal shows anorexia, elevated rectal temperature and general depression which may persist over a longer period of time; in classical cases these symptoms are accompanied by a gradual abdominal distension which, in combination with a progressive emaciation, often results in a dehydrated animal with an enlarged, undulating abdomen (Colby & Low, 1970; Ingram, 1971; Pedersen, 1976c; Robison *et al.*, 1971; Ward & Pedersen, 1969; Wolfe & Griesemer, 1966). Neurological signs (Slauson & Finn, 1972) (including posterior ataxia, incoordination, hyperaesthesia and convulsions), ocular lesions (Campbell & Reed, 1975; Carlton, Lavignette & Szech, 1973; Doherty, 1971; Gelatt, 1973; Slauson & Finn, 1972), icterus and scrotal swelling are encountered with varying frequency (Bland van den Berg & Botha, 1977; Holmberg & Gribble, 1973; Pedersen, 1976c; Ward & Pedersen, 1969). Haematological examination may show anemia, low haematocrit values, leucocytosis, mainly caused by neutrophilia with a mild left-shift accompanied by lymphopenia and eosinopenia (Bland van den Berg & Botha, 1977; Pedersen, 1976c). Terminal cases of the fulminating type may, however, show leucopenia (Pedersen, 1976c). Elevation of blood urea nitrogen and bilirubin, of the enzymes SGPT, SGOT, LDH and SAP on one hand, and proteinuria with increased levels of bilirubin and urobilinogen on the other hand, may be found as a reflection of liver damage and renal disease (Bland van den Berg & Botha, 1977). Due to a diffuse hypergammaglobulinaemia, the total plasma protein is elevated in most cases; also plasma fibrinogen levels are above normal (Pedersen, 1976c). Commonly the peritoneal (and the occasionally occurring pleural) exudates (specific gravity 1.017 to 1.047 g/ml) show high protein levels, which are mainly due to increased  $\gamma$ -globulin values (Gouffaux *et al.*, 1975). In the aqueous humour of affected eyes and cerebrospinal fluids from cats with extensive meningeal alterations, protein levels and white blood cell counts may be elevated, the neutrophils being the predominant cell type (Pedersen, 1976c).

(b) *Pathology*. Upon post-mortem examination, FIP can be found either in the classical fibronectrotic ('wet') form or in the granulomatous ('dry') form (Pedersen, 1976c) although a strict distinction cannot always be made. In classical 'wet' cases an inflammation of the parietal and visceral surfaces of the peritoneum and/or the pleura is most prominent; small necrotic lesions are observed and the body cavities are filled with variably extensive accumulations of a usually yellowish viscid and ropy exudate containing fibrin flakes. The masses of exudate adherent to the serosae are composed of fibrin, containing cells (mainly histiocytes) and necrotic material. Focal necrotic lesions may be present in parenchymatous organs (predominantly liver and kidneys); there, a histiocytic and lymphocytic reaction may form characteristic granulomatous lesions (Zook *et al.*, 1968). The 'dry' form of the disease is characterized macroscopically by disse-



minated grey lesions, ranging up to about 2 mm, which are most abundant in the kidneys, CNS, liver and mesenteric lymph nodes, although they may be encountered in other organs, too. They resemble the granulomatous organ lesions observed in the 'wet' form of the disease (Bland van den Berg & Botha, 1977; Hayashi *et al.*, 1977; Montali & Strandberg, 1972). The foci accumulate around smaller blood vessels where they are the expression of a vasculitis (Hayashi *et al.*, 1977). Ocular lesions are localized in the retina and meninges of the optical nerve, as well as in the nerve itself (Campbell & Reed, 1975; Doherty, 1971; Feldman, 1974; Gelatt, 1973; Holmberg & Gribble, 1973; Montali & Strandberg, 1972; Pedersen, Holliday & Cello, 1974; Slauson & Finn, 1972; White, 1972). Typical exudates (mutton-fat precipitates) may be found in the ocular chambers. CNS lesions are mainly located in the meninges, *pl. chorioideus* and ependyma and may also occur along the blood vessels in the parenchyma (Holmberg & Gribble, 1973; Montali & Strandberg, 1972; Pedersen *et al.*, 1974; Slauson & Finn, 1972; White, 1972).

### DIAGNOSIS

The diagnosis of FIP can easily be made in terminal classical cases where extensive accumulations of exudate are demonstrated in the abdomen and/or thorax. With less, or no exudate present, diagnosis constitutes a greater challenge, since most of the clinical alterations are rather uncharacteristic. In these cases demonstration of antiviral antibodies at high titers may give an indication, although these are also found in clinically healthy cats (Osterhaus, Horzinek & Reynolds, 1977; Pedersen, 1976b). Demonstration of viral antigen in sections through pathological lesions, using the direct immunofluorescence method would be the most straightforward method for aetiological diagnosis.

### GEOGRAPHICAL DISTRIBUTION

The condition was identified in the USA (*cf.* Pedersen, 1976c) in the early fifties and was diagnosed in Great Britain for the first time some ten years later (Ingram, 1970; Ishmael & Howell, 1968). Subsequently, it has been reported from Canada (Stevenson, Tilt & Purdy, 1971), Holland (Mieog & Richter, 1971), Japan (Konishi *et al.*, 1971), South Africa (Colly, 1970), Switzerland (Stünzi & Revel, 1973), Germany (Tuch, Witte & Wüller, 1974), Australia (Jones, & Hoog, 1974; Watson, Huxtable & Bennett, 1974), Belgium (Pastoret, Gouffaux & Henrotaux, 1974), Denmark (Flagstad, personal communication) and France (Aucclair-Semere & Groulade, 1975). From the reactions to a FIP questionnaire sent to some 50 Veterinary Schools it was learned that the disease had been diagnosed further in New Zealand, Sweden, Iran and Yugoslavia, whereas no cases were reported from Kenya, Portugal and Hungary. Since clinical FIP has been observed in all five continents it is safe to assume that the virus has a world-wide distribution.



## VIROLOGY AND SEROLOGY

The infectious nature of FIP was assumed from epidemiological observations. Reproduction of the disease with material passing through 200-nm pore filters constituted the first proof of its viral aetiology (Ward *et al.*, 1968; Zook *et al.*, 1968). In thin sections through macrophages, mesothelial cells and histiocytes from infected cats, double-shelled particles about 75 nm in diameter were shown electron-microscopically which matured by budding into the Golgi vesicles and the smooth surfaced cisternae of the endoplasmatic reticulum (Ward, 1970; Ward *et al.*, 1969). By experimental inoculation of kittens with peritoneal cell culture material from infected kittens the disease could be reproduced, indicating an aetiological role of the 75-nm particles for FIP (Pedersen, 1976a). Their resemblance to coronaviruses was noted by all these authors. From ascitic fluids and liver homogenates of natural and experimental cases of FIP, structures were purified, which appeared coronavirus-like on the basis of their morphology (round, non rigid, about 100 nm in diameter, surface projections), sedimentation behaviour (about 400 S) and buoyant density in sucrose (1.17–1.18 g/ml). Inoculation of kittens with gradient-purified virions resulted in fatal infection which was diagnosed as FIP upon post-mortem examination (Horzinek, Osterhaus & Ellens, 1977; Osterhaus, Horzinek & Ellens, 1976). Support for the coronavirus nature of FIP virus came from recent reports of an antigenic relationship to transmissible gastroenteritis (TGE) virus of swine. High titers of neutralizing activity against this porcine coronavirus were detected in sera and peritoneal fluids of FIP field cases (Reynolds, Garwes & Gaskell, 1977; Witte *et al.*, 1977). Using FITC-conjugated feline anti-FIP immunoglobulin preparations, TGE viral antigen could be demonstrated in infected porcine cells; on the other hand, FIP antigen could not be detected in cat organs using labelled anti-TGE immunoglobulins, which has been interpreted as a one-way antigenic relationship existing between the two viruses (Witte *et al.*, 1977). Using fluorescent anti-FIP and anti-TGE viral conjugates in parallel, the present authors have recently shown a complete correlation in the detection of field cases of TGE (Wirahadiredja, Anakotta & Osterhaus, 1978). In a sero-epidemiological study antibodies against TGE viral antigen could be detected by immunofluorescence in sera and ascites fluids from FIP infected cats, which showed no neutralizing activity against TGE virus. This is in contrast to the aforementioned results; as an explanation, the existence of FIP virus serotypes, with a more or less close antigenic relationship to TGE virus could be postulated (Osterhaus, Horzinek & Wirahadiredja, 1978a).

Numerous attempts to propagate FIP virus in primary feline cell cultures (Low *et al.*, 1971; Parker & Collins, 1971; Pedersen, 1976a) and continuous lines (Pedersen, 1976a) have failed. So far, *in vitro* growth of the virus has only been demonstrated in cultures derived from peritoneal exudates of kittens after experimental infection with FIP virus (Pedersen, 1976a). Successful propagation of the



virus in suckling mice, as has been shown for other Coronaviridae members (McIntosh, 1974), was described recently; with infectious mouse brain material, the disease could be reproduced in the cat (Osterhaus *et al.*, 1978a). In brain sections of infected mice, particles with a typical coronavirus morphology have been demonstrated by electron microscopy (Horzinek *et al.*, 1978). Also suckling rats and hamsters supported FIP virus replication after intracerebral inoculation, whereas the rabbit appeared refractory to infection (Osterhaus *et al.*, 1978b).

### EPIZOOTIOLOGY

Originally, FIP virus was considered an agent which occurred only in cats, and infections were believed always to be fatal. Since this constitutes an epidemiological paradox, either an extra-feline reservoir exists, or the fatal disease history is not the only course a FIP virus infection can take. Although the authors' recent demonstration of virus replication in the mouse, rat and hamster does not prove their significance for FIP epidemiology, rodents should be further studied in this respect. The experimental intracerebral infection of suckling laboratory mice is abortive (Horzinek *et al.*, 1978) which virtually excludes this species as a reservoir host candidate. Similar studies with the rat are in progress.

Also with respect to the second assumption, a correction must be made. Large scale serological studies using either a homologous immunofluorescence test with liver sections of infected cats serving as antigen (Pedersen, 1976b) or the above-mentioned heterologous reaction (Osterhaus *et al.*, 1977) have demonstrated that antibodies to FIP virus may be widespread among cats. About 20% of clinically healthy randomized animals and about 90% of the cats from catteries with a FIP history were found serologically positive. This indicates that only a small percentage of infected cats actually develop clinical signs of FIP. The epizootiological role of subclinically, or inapparently infected animals—cats but also wild rodents—certainly needs further investigation.

### OPEN QUESTIONS

It is felt that two technical achievements have been made in 1977 both of which will certainly accelerate research on FIP and its virus. Firstly, determination of FIP viral antibodies, using feline serum/TGE viral antigen combinations has become a standardized routine technique (Osterhaus *et al.*, 1977) since the demonstration of heterologous immunofluorescence by Witte *et al.*, (1977). Secondly, the mouse as an easily available laboratory animal now offers the possibility for quantitative work with FIP virus using current titration techniques. Questions of practical importance can now be tackled, e.g. stability of the virus to environmental conditions, neutralizing antibody in feline sera and their protective capacity, virus attenuation for vaccination purposes and so forth.

It has been mentioned that clinically healthy cats may possess FIP viral



antibodies; infected and diseased animals, however, also show antibodies in sera and ascitic fluids which even reach significantly higher titers as compared with those in healthy cats. Based on these observations it is the authors' hypothesis that FIP symptoms are the consequence of the host's immune reaction rather than of viral cytopathogenicity. This hypothesis is further supported by the following observations:

(1) FIP occurs at higher frequency in cats showing evidence of infection with feline leukemia virus which is known to cause T-cell dependent immunosuppression (Cotter, Gilmore & Rollins, 1973).

(2) Antibody-complement lesions have been demonstrated by electron microscopy on virus particles prepared from diseased cats (Horzinek, Osterhaus & Ellens, 1977).

(3) In the feline host FIP virus replicates predominantly in macrophage-like cells (Pedersen, 1976a). This cell species is known to have a key function in immune response.

Apart from the necessary insight into the (immuno)pathogenesis of FIP with its far-reaching prophylactic consequences, the mode of virus transmission (portals of entry, excretion) certainly requires further study.

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