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Development of Clinical Signs and Occurrence of Feline Corona Virus Antigen in Naturally Infected Barrier Reared Cats and Their Offspring

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Hök, K.: Development of clinical signs and occurrence of feline corona virus antigen in naturally infected barrier reared cats and their offspring. Acta vet. scand. 1993, 34, 345-356. – The onset and pattern of the clinical signs of feline corona virus (FCoV) infection in cats were studied in a setting behind an isolation barrier. Two FCoV-seropositive cats were the source of the infection, and 3 barrier reared cats – initially FCoV-seronegative – were the recipients. The first clinical sign in the recipients appeared 11 days after contact with the source of infection. After 2 years 1 male and 1 female of the recipients started to breed. Their offspring developed clinical signs of disease at an age of 4-5 weeks. A pattern of recurring upper respiratory tract signs and conjunctivitis at intervals of about 4 months was observed in both the recipients and their offspring, while CNS dependent signs and wasting remained or got worse, once developed. Once demonstrated, FCoV antigen persisted in *membrana nictitans* throughout the investigation, and was found in all cats but 4 (90%). The offspring died during 2 periods, around the first week of life (9/37), and at 3-5 months of age (5/25). For comparison 3 offspring were euthanised at an age of 1 day and 16 offspring at an age of 3-6 months. FCoV antigen was demonstrated in all organs investigated (100%) from offspring dying during the first period, and in 97% from those dying during the second period. For the offspring euthanised during the same 2 periods the corresponding findings were 95% and 85%. Offspring euthanized between 9 and 17 months (4 kittens) had antigen in 67% of all investigated organs. The incidence of FCoV antigen in almost every organ in the investigated newborn kittens suggests an intrauterine infection. The demonstration of FCoV antigen in all euthanised cats, suggests a persistant infection. Virus was cultivated from *membrana nictitans,* that was FCoV antigen positive in the M3 test.

feline infectious peritonitis; FIP; membrana nictitans; M3; test.

Introduction

Feline infectious peritonitis (FIP) is a disease in Felidae, in which it has not yet been clarified how transmission in nature takes place *(Gaskell* 1984, *Pedersen* 1976, 1987, 1988, *Weiss* 1989). Experimental exposure via nasal, oral, aerogenic, and parenteral routes have resulted in infections, though not always in disease *(Hayashi et al.* 1983, *Pedersen et al.* 1981, *Stoddart et al.* 1988, *Weiss & Scott* 1981a and b). Virus-excretion is possible via the salivary glands, the gastrointestinal, respiratory, and urogenital system *(Walter* 1987). A spread of virus via saliva would be favoured by the cat's

social behaviour to lick itself and others, and may result in an alimentary and/ or aerogenic infection. An intrauterine infection route has also been suggested *(Norsworthy* 1974, *Pastoret & Henroteaux* 1978, *Pedersen* 1987, Scott et al. 1979).

Recurrent respiratory tract infection and intermittent fever of unknown etiology have been observed in cats in multiple cat households, with FCoV-seropositive cats or with cats lost with clinical FIP *(Scott et al.* 1979). Furthermore, histopathological findings have indicated a relapsing or cyclic nature of FIP *(Walter* 1987).

The aim of this study was to study a cat to cat transmission of FIP – from asymptomatic, FCoV-seropositive cats to FCoV-seronegative cats – in a controlled barrier-maintained setting. The onset and pattern of clinical signs in the recipients as well as in their offspring was observed and the cats were screened for FCoV antigen.

Materials and methods

Animals

The study consisted of the following 4 groups of cats:

The Source of Infection (S) Group consisted of an asymptomatic, FCoV-seropositive, pedigree Persian breeding pair, with antibody titres against FCoV antigen above 1:300 (immunofluorescence (IF) performed at The European Veterinary Laboratory, Amsterdam, The Netherlands).

The Recipient (R) Group contained 3 FCoV-seronegative cats, 2 tomcats and 1 queen, 11 weeks old, of CIBA-GEIGY's Abyssinian type × European, barrier-bred at the National Veterinary Institute, Uppsala, Sweden. There they were additionally screened at the routine laboratory for calici, herpes, and feline leukemia virus and reported free, and were vaccinated twice with a killed parvovirus vaccine (Nordpan vet, NordVacc, Stockholm, Sweden.)

The Offspring (O) Group consisted of 37 kittens born in 7 litters within 3 years from the same couple in the R-Group.

The Control Group consisted of 3, 2 months old, healthy, barrier reared, kittens (Ico:Fec Eur, Tif, IFFA-Credo, France), serologically and antigenically FCoV negative.

Containment

All 3 groups were kept together in the same room in a specially designed isolation unit of a modern animal facility. No other Felidae were kept in that isolation unit. A total change of clothes and shoes was required and operating facial mask, helmet and gloves had to be worn. The staff had no contact with other cats. The cats roamed freely in a room (12 m^2) with controlled light cycle (12/12), temperature (18°C±1) and humidity (55%±5). The animals were fed a commercial, canned, cat food (Mjau, Tre Kok, Solna, Sweden) and tap-water ad lib. The absorbent litter was sterilised sawdust which was replaced daily. The room was cleaned daily with detergent (604 Glasol, Euroclean, Åtvidaberg, Sweden).

Rectal temperature was measured with a mercury thermometer, the same thermometer (disinfected between each measurement) was used throughout the experiment. Body weights were registered using a lever balance (Stathmos, Lindell AB, Sweden).

The animals were screened annually for feline leukemia, calici and herpes virus by tests performed at the National Veterinary Institute, Uppsala, Sweden; the European Veterinary Laboratory, Amsterdam, The Netherlands; and the Feline Virus Unit, Glasgow, Scotland; and were found negative each time.

Screening for presence of FCoV antigen

The animals were screened on a monthly ba-

sis for FCoV antigen using indirect immunofluorescence assay (IIFA) on cells from the *membrana nictitans* (the M3 test) as described in detail elsewhere *(Hök* 1989). Briefly, the material was sampled by rolling a cotton topped stick over the outside of *membrana nictitans* and then pressing the cotton on 2 glass slides. The smears were air dried and stained using pre-immune serum and anti-FCoV-serum from a rabbit immunized with a FCoV-antigen, followed by an anti-rabbit-FITC-conjugated sera (Dacopatts A/S, Denmark). Fluoresceing cellcytoplasma in cells were considered positive.

Virus isolation

In live cats virus isolation was performed from the *membrana nictitans* using the following method. A cotton-tipped stick was swabbed over the outside of the *membrana nictitans* and placed in a Leighton tube (Nunclon) together with a cover slip and a newly trypsinated feline foetal lung (SVA-FL) tissue culture. After incubation for 3 days, an aliquot of O.2 ml was passaged to new Leighton tubes as above. Several passages were performed and judged to be positive when the following criteria were fullfilled:

a) characteristic cytopathogenic changes,
b) the presence of FCoV antigen in the cytoplasma as demonstrated by IIFA *(Hök* 1989),
c) a positive serum neutralisation test *(Hök* 1990). The serum used is described in detail elsewhere *(Hök* 1989).

Experimental design

The S-Group and R-Group arrived at the facility the same day and were placed together. The day of arrival was counted as the start of the experiment. Rectal temperature was taken daily from the start of the experiment till the end of the first period of clinical signs, and thereafter whenever the cats displayed clinical signs. Rectal temperature and body weight were also measured in kittens from the 2 last litters daily for more than 7 weeks, until termination. A temperature above 39.0°C was considered as fever. Virus isolation attempts were performed on asymptomatic cats in which FCoV antigen had been demonstrated in the *membrana nictitans* using the M3 test. Samples from *membrana nictitans* were taken for virus isolation from cats in the S-, R-, and O-Group – the tomcat in the S-Group, the breeding pair in the R-Group, and from 5 of their offspring (from litter 1, 3, 5, 6 and 7, at an age of 15, 7, 4, ½, and 3 months respectively) in the O-Group.

Euthanasia was performed on offspring at ages that correlated with those of the kittens that died, and at an age of about 1 year.

After death due to disease or euthanasia 7 organs: *membrana nictitans,* spleen, kidney, lung, liver, brain and thymus were screened for FCoV antigen using IIFA *(Hök* 1989, 1990).

Histopathology was performed on the 3 cats in the recipient group and on the 2 cats being the source of infection.

Calculations

A fluctuation index was calculated for rectal temperature using the following formula: the square root of the sum of the square of the difference between each measurement divided by the number of measurements

$$\left(\sqrt{\frac{\Sigma(X_n - X_{(n-1)})^2}{m}}\right).$$

The weight index was calculated as the sum of each body weight decrease from observation to observation divided by the sum of each body weight increase

$$\left(\frac{\Sigma-(X_n - X_{n-1})}{\Sigma+(X_n - X_{n-1})}\right).$$

The final body weight minus initial body weight, and maximum body weight minus minimum body weight were also calculated.

The Chi square method was applied for statistical calculations.

Results

Source of Infection

Both cats were M3 test positive at arrival and remained so in all further M3 tests.

The queen in the S-Group had an FCoV antigen titre of 1:300. She developed 2 periods of clinical signs (such as fever, matted fur, conjunctivitis, diarrhea). Both periods coincided in time with the bouts of clinical signs in the recipients. The second time her condition continued to deteriorate and she died of non-effusive FIP, 5 months after the start of the study.

The tomcat in the S-Group kept his high serum titre >1000 in all screenings and remained asymptomatic, except for matted fur twice, and once matted fur plus eye lesions (corneal opacity and ulcers), each time when the other cats showed clinical signs. He was euthanised 6 days before litter no. 6 was born.

Both cats had histopathological changes suggesting FIP.

The Recipient Group

The first clinical signs in the 3 recipients started 11, 13 and 18 days after contact with the S-Group. The following clinical picture was observed: tufted fur, increased sleeping time, bilateral conjunctivitis (serous discharge), followed by rhinitis (serous discharge), fever spikes (up to 40°C), occasional vomiting and diarrhea and marked dorsal leanness. The initial signs lasted 2-3 weeks, except for the leanness which remained.

Relapses with similar signs appeared every 4-5 months and lasted about 1 week. For 3-5 days all 3 cats were ill, although the onset and termination of their signs could vary. At the first relapse, changed behaviour was observed in 2 cats. The third cat developped changed behaviour after 2 years of observation, at its fifth relapse and started wasting at its sixth relapse. The CNS dependant signs and wasting remained, unaltered or aggravated, once they developed in the recipients. Before breeding, 4 periods of intensified signs were recorded at approximately 4 month intervals, the second period in connection with the death of the S-queen. After breeding started, 8 relapses were registered in the cats present, 5 periods at 4 months intervals and then 3 periods at 6, 2, and 3½ months intervals. Except for 2 periods, they all occured 1 to 2 weeks after the appearance of the first clinical signs in kittens recently born.

A positive M3 test was seen 1 and 2 weeks respectively, after first contact in 2 of the recipients. These 2 remained positive ever after and the third cat remained negative.

Histopathological changes were in line with those seen in FIP.

Clinical signs in the Offspring Group

The first M3 test in the offspring was performed when they opened their eyes. All but 3 offsprings were positive at this first investigation, and they remained positive. The 3 negative offspring remained negative.

The earliest observed onset of clinical signs in surviving kittens was seen at an age of 25 days – though usually the onset occurred between 4 and 5 weeks. They started as a mild, bilateral, serous discharge of varying amount from the eyes. A rhinitis with serous discharge, sneezing and some fever spikes (up to 40°C) followed the first clinical signs in 19/25

Table 1. Survival time, and type of death in the offspring group.

Spontaneous death				Euthanised			
< 12 days		> 3 months		< 12 days		> 3 months	
Days	No.	Months	No.	Days	No.	Months	No.
1	4	3	2	1	3	3	5
2	2	4	1			5	8
5	1	5	2*			6	3
7	1					9	2
12	1					12	1
						17	1
	9		5		2		20

* One cat was euthanised as moribund.

kittens. These first periods of signs in the kittens lasted 2-4 weeks.

Relapses were observed in 20 kittens (in 4 kittens at an age of 3 months, and in 16 at an age of 5 months), 16 of them had only 1 relapse, 3 had 2 relapses and 1 had 4 relapses.

Balance disturbance was observed in 6 kittens and once developed it remained. In 4 of these 6 kittens it started in connection with the first period of signs, 2 died when 3 and 5 months old, and the other 2 were euthanised at an age of 5 months. In the last 2 kittens, euthanised at an age of 9 and 17 months, balance disturbance developed in connection with the first relapse.

The mewing changed into a hoarse croaking sound at the first relapse in 4/20 kittens.

Death occured at 2 age periods among the kittens born, the first period at 1-12 days of age (9/37), and the second period at 3-5 months (5/25) (Table 1).

FCoV-antigen was present in the area of perivascular cuffings and cellclusters – necrotic foci in the cryosections from all offspring.

Clinical signs in the 2 last litters

Rectal temperature and body weight were measured until death or termination in 11 cats, from Litter no. 6 Kittens 1-6 (L6K1-6) starting at an age of 3 months for 83 days, and from Litter no 7 Kittens 1-5 (L7K1-5) starting at an age of 2 months for 49 days. In litter no. 6 (L6) 3 kittens (L6K1-3) died of effusive FIP, and 3 kittens (L6K4-6) when euthanized displayed marked granulomatous lesions. L7K1-5 had the mildest clinical signs registered among the offspring and no gross lesions.

An absolute weight decrease (Fig.1) was observed in the kittens with effusive FIP (L6K1-3). A more pronounced fluctuation in the body weight was observed in the 3 kittens with the marked granulomatous lesions (L6K4-6) than in the clinically healthier kittens (L7K1-5) (Fig.1 and 2). A decrease in body weight was only observed once or twice in the Control Group. An increasing difference between maximum body weight minus minimum body weight and final body weight minus initial body weight (Fig.2) accompanied the severity of the infection in the 3 groups – from the clinically healthy (L7K1-5), via the granulomatous FIP (L6K4-6) to the effusive FIP (L6K1-3). The Control Group did not show this difference. The average body

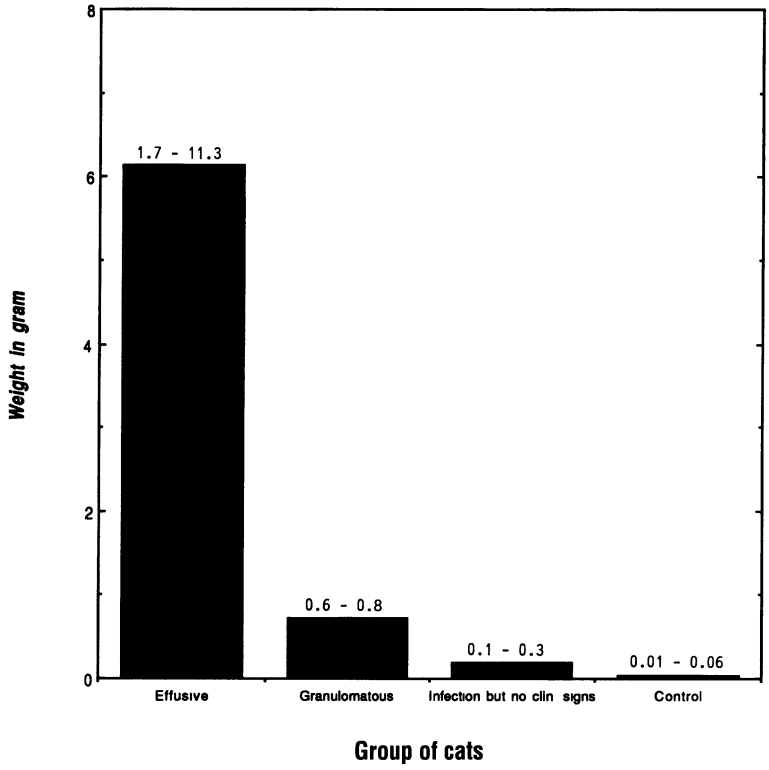

Figure 1. The sum of body weight decrease divided by the sum of body weight increase calculated for the offspring and the controls. The kittens in Litter no. 6 Kittens 1-6 (L6K1-6) were observed for 83 days, the observation period starting at an age of 3 months. The kittens in Litter no. 7 Kittens 1-5 (L7K1-5) were observed for 49 days starting at an age of 2 months, and the control kittens for 40 days starting at an age of 2 months. Range written above bars.

weight loss (Fig.1 and 2) was also related to the clinical severity of the disease, the fewer signs and lesions, the lesser weight loss.

Regarding the rectal temperature an increased temperature fluctuation and range accompanied the increasing severity of the disease (Fig.3).

The Control Group

The Control Group remained healthy and serologically negative for calici, herpes, feline leukemia and feline corona virus and had a negative section and histopathology post mortem.

Feline Corona Virus

Once FCoV antigen had been demonstrated in *membrana nictitans,* it persisted. FCoV antigen was demonstrated in *membrana nictitans* in all cats but 4 in the study (38/42), although FCoV-antigen was demonstrated in other organs investigated in these 4 cats.

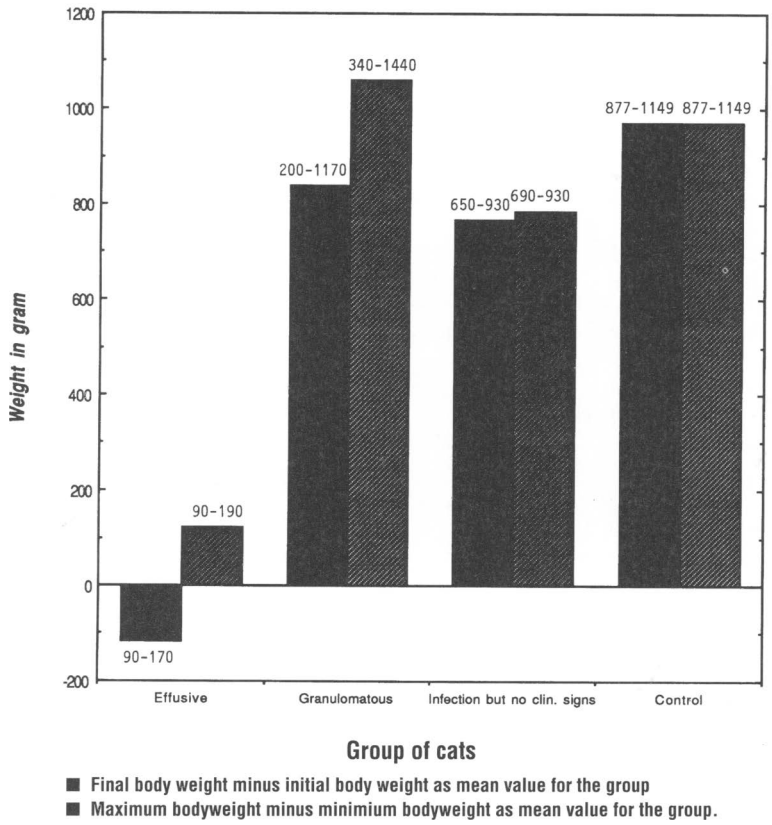

Figure 2. The mean value of final body weight minus initial body weight and for maximum body weight minus minimum body weight calculated for 4 groups of kittens – effusive FIP in Litter no. 6 Kittens 1-3 (L6K1-3), granulomatous FIP in L6K4-6, clinically healthy with no gross lesions L7K1-5, and controls.
L6K1-6 were observed from an age of 3 months for 83 days, L7K1-5 from an age of 2 months for 49 days, and the control kittens from an age of 2 months for 40 days. Range written above staples.

FCoV was isolated from *membrana nictitans,* where FCoV-antigen had been demonstrated, and was grown in cell cultures from all 8 animals sampled.

Table 2 and 3 shows the results from IIFA performed on 7 organs *(membrana nictitans,* spleen, kidney, lung, liver, brain and thymus). With increasing age in the offspring there were fewer organs with demonstrable FCoV antigen. For comparison the adult cats in the study (the S- and R-Group) were included in the table. In a comparison between euthanised cats younger than 6 months and those older than 9 months there was a statistically significant ($p<0,05$) difference in the number of organs with demonstrable FCoV antigen.

Discussion

The time for the onset of clinical signs in the Recipient Group was in line with other observations *(Hök* 1993, *Ward et al.* 1974). The same source of infection was used as in an-

Table 2. FCoV antigen demonstrated in organs from cats divided in groups according to age and type of death. Organs investigated are membrana nictitans, spleen, kidney, lung, liver, brain, and thymus.

	Age of offspring					Adults
	< 12 days		3-6 months		9-17 months	>3 years
No of cats	Died 9	Euth 3	Died 5°	Euth. 16	Euth 4	Euth. 5#
Organs						
Pos/total	62/62	20/21	32/33	94/111	15/23*	23/30*
Pos.in %	100	95	97	85	65	77

* Three cats in each of these groups had an involuted thymus and thymus was therefore omitted from these 2 groups.
# One of these cats died.
° One of these cats was euthanised moribund.
Euth. = euthanised.

other study *(Hök* 1993). The first sign observed was 3 days earlier in the present study than in the previous study. The time from the first clinical sign observed until all cats demonstrated signs was of approximately the same length (6 and 7 days). The difference in time for onset may therefore depend upon individual resistance to the infection.

The first clinical sign in the offspring was at an age of 4-5 weeks, which may coincide with a drop of maternal antibodies as described by *Pedersen & Floyd* (1985). They registered the lowest titre of antibodies at an age of 5 weeks in kittens born to infected mothers.

Table 3. Number of organs from 25 cats older than 3 months, in which FCoV antigen was detected by indirect immunofluorescence.

Organs	% positive
Membrana nictitans	88
Spleen	88
Kidney	88
Lung	96
Liver	80
CNS	54

The first clinical signs observed in this study were similar to the first signs observed in other studies *(Hök* 1993, *Maess* 1985, *Neu & Pfeifer* 1985, *Ward et al.* 1974). The relapsing signs were similar to those reported by *Hök* (1993), and to recurrent signs observed in catteries with FIP problem *(Scott et al.* 1979). However, the longer intervals between signs in this study compared to previous study may require further clarification. All relapses were not purely spontaneously recurrent as 2 bouts of clinical signs started when an animal was moribund (relapse no. 1 before breeding, and relapse no. 7 after breeding) and 6 bouts after the first clinical signs had developped in a newborn litter (in all but litter No. 2). In these cases it is possible a reinfection occured.

The time for the second period of deaths in the offspring at an age of 3-5 months, coincided with the highest incidence of deaths registered at an age of 4-6 months in a necropsy material survey *(Walter & Rudolph* 1988).

The positive M3 test – the demonstration of FCoV antigen in cells from *membrana nictitans* – in 90% of the cats (38/42) was of the same magnitude as in other investigations *(Hök* 1989, 1990, 1991). The cultivation of

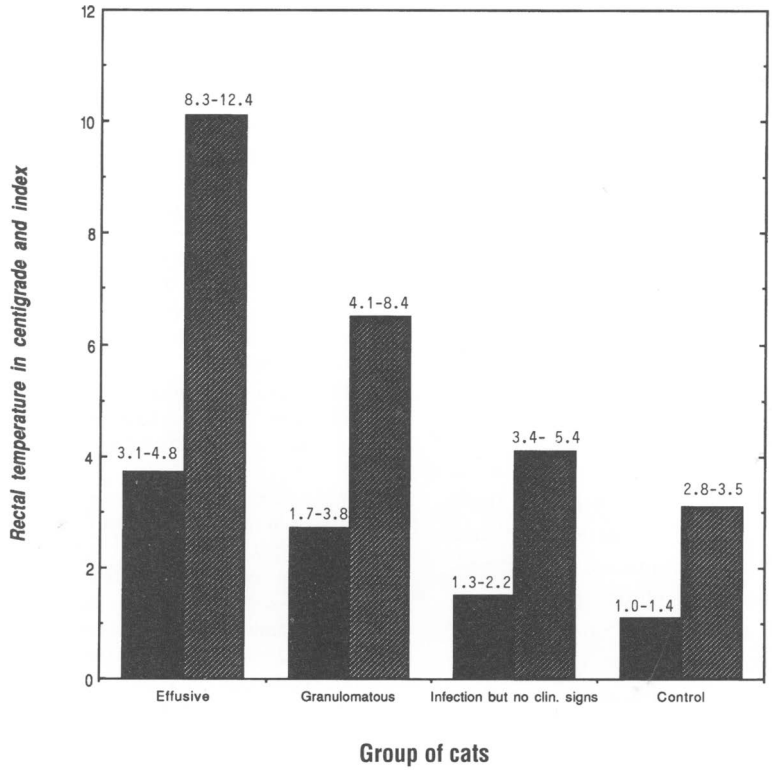

Figure 3. The mean value was calculated for a fluctuation index for rectal temperatures $\sqrt{\Sigma(xn - x(n-1))2}/m$), and for the range between the maximum and minimum rectal temperature in 4 groups – effusive FIP in Litter no. 6 Kittens 1-3 (L6K1-3); granulomatous FIP in L6K4-6; clinically healthy with no gross lesions L7K1-5, and the control group.
L6K1-6 were observed from an age of 3 months for 83 days, L7K1-5 from an age of 2 months for 49 days, and the control kittens from an age of 2 months for 40 days. Range written above bars.

FCoV from *membrana nictitans* from asymptomatic cats, that were M3 positive, indicates that the ocular discharge is potentially infectious from M3 positive cats. FCoV antigen was found in all cats, thus supporting the suggestion that FCoV is an ubiquitous, persistent cell-associated infection *(Weiss & Scott* 1981a, *Hök* 1993). The antigen in these organs was distributed in a similar fashion as described in other reports *(Hayashi et al.* 1982, *Stoddart et al.* 1988, *Walter* 1987, *Weiss & Scott* 1981 a and b). Antigen was demonstrated in almost all organs (Table 2) in kittens that died (100%) or were euthanised (97%) the first week of their life, thus supporting the suggestion that FIP can be intrauterine transmitted *(McKeirnan et al.* 1981, *Norsworthy* 1974, *Pedersen* 1987, *Scott et al.* 1979). A further support for an intrauterine infection is the high mortality among the newborn kittens (24%). This cor-

relates with the findings of *Scott et al.* (1979).

The incidence of demonstrable FCoV antigen in 5 organs from the 25 offspring alive older than 3 months (Table 3), was compared with the incidence of demonstrable FCoV antigen in the corresponding 5 organs from a selected material of 113 autopsied cats in a field study *(Hök* 1990) and showed similar results.

Taken together the pattern of recurrent signs in all cats investigated, the persistance of FCoV antigen in *membrana nictitans* once demonstrated, the cultivation of FCoV from *membrana nictitans* from asymptomatic M3 positive animals, and the fact that virus could be demonstrated in the colony during the 4 years the study lasted, indicate that FIP, like many coronaviruses (i.e. murine hepatitis virus, avian infectious bronchitis virus), is a persistent infection *(Wege* 1982, *Siddell* 1983) of recurrent nature. Essentially these results agree with earlier observations of a recurrent nature of FIP made both clinically *(Carlton et al.* 1973, *Hök* 1993, *McKeirnan* 1981, *Norsworthy* 1979, *Scott et al.* 1979, *Stoddart et al.* 1984, *Tuch et al.* 1974) and histopathologically *(Walter* 1987).

Conclusion

The results from this study indicate that FIP is a persistent, recurrent infection, that can be vertically transmitted, and has a minimum incubation time of 11 days. The results further shows that the ocular discharge from M3 positive cats may be potentially contagious.

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Sammanfattning

Utveckling av kliniska symptom och forekomst av felint coronavirusantigen hos naturligt infekterade barriaruppfodda katter och deras avkomma.

De kliniska symptomens uppträdande hos katt vid FCoV-smitta och symptomens fortsatta mönster studerades i ett forsök bakom barriar. Smittokällan var två FCoV-seropositiva katter och tre barriaruppfödda, vid ankomsten FCoV-seronegativa, katter utsattes för smittan. Det forsta sjukdomstecknet uppträdde hos de barriaruppfödda katterna 11 dagar efter kontakt. Två år senare parade sig två av de barriaruppfodda katterna. Hos deras avkomma upptradde forsta sjukdomstecknet vid en ålder av 4-5 veckor. Ett monster av återkommande förstärkta symptom från ogonslemhinnorna och övre luftvägarna i intervaller på ca 4 månader kunde iakttagas både hos de barriäruppfodda katterna samt hos ovannamnda pars avkomma. CNS-relaterade symptom samt avmagring kvarstod eller förvärrades när de en gång först hade upptratt. FCoV-antigen påvisades hos alla katter utom fyra (90%), och kunde fortsatt påvisas under resten av forsoket nar det en gång hade påvisats. Ungar fódda av ovannamnda par dog vid två olika åldrar under första levnadsveckan (9/37 kattungar) och mellan 3-5 månaders ålder (5/25 kattungar). FCoV-antigen återfanns i samtliga undersokta organ (100%) från ungar som dog under den första levnadsveckan och i 97% hos ungar som dog under den andra tidsperioden. For ungar som avlivades vid motsvarande åldrar påvisades FCoV-antigen i 95% (3 kattungar) respektive 85% (16 kattungar) av alla undersokta organ. I organ från ungar avlivade mellan 9 och 17 månader

(4 kattungar) påvisades FCoV-antigen i 67% av alla undersökta organ. Förekomsten av FCoV-antigen i nästan samtliga undersökta organ från nyfödda ungar talar for en intrauterin smitta, medan forekomsten av FCoV-antigen hos samtliga avlivade katter talar for en kvarstående infektion. Virus kunde odlas från en FCoV-antigen-positiv membrana nictitans.

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