

Canine viral enteritis: Prevalence of parvo-, corona- and rotavirus infections in dogs in the Netherlands

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SUMMARY

After a brief review of the present knowledge about canine viral enteritis, the role played by parvoviral, coronaviral and rotaviral infections in contagious diarrhoea in dogs in the Netherlands is discussed.

For this purpose a serologic survey, pathologic findings in dogs, and the demonstration of parvoviral antigen with an immunofluorescence test and with a newly developed haemadsorption-elution-haemagglutination assay (HEHA) are presented.

It is concluded that infections with canine parvovirus, coronavirus and rotavirus appear widespread among dog populations in the Netherlands.

In the past year the general public, including the Dutch veterinary profession, has repeatedly been startled by reports of contagious diarrhoea in dogs. This article summarises present knowledge in the Netherlands concerning canine viral diarrhoea as well as measures to prevent viral enteritis in dogs. At the same time endeavours are being made, in cooperation with more research workers, to widen the insight into the epizootiology of contagious enteritis in dogs.

Editors-in-Chief.

Minor enzootics of contagious diarrhoea in the dog have regularly been recognized by veterinary practitioners in the Netherlands. However, widespread outbreaks of a highly contagious enteric disease, characterized by vomiting and an often haemorrhagic diarrhoea, seem to date only from the last three years. The first

reports of similar outbreaks came from the USA, where a canine coronavirus (CCV) was isolated from faecal and intestinal specimens (9). This or a similar virus had been isolated previously from dogs with diarrhoea (7). In a retrospective study it was shown that although not associated with enteric disease, CCV must have been present in dogs in the USA during the last few years (2). A second series of outbreaks of a more serious diarrhoeal disease in the USA was associated with a newly recognized parvovirus of the dog: canine parvovirus (CPV). In later studies CPV proved to be closely related to the virus which causes panleukopenia in the cat (3, 8, 21). From 1978 onwards CPV has been found in faeces of dogs involved in outbreaks of vomiting and diarrhoea all over the world. Also in our country parvovirus-

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like particles were observed in stools of dogs with diarrhoea and the virus was isolated in cell cultures (21). During the initial outbreaks in a breeding colony and boarding kennels in the Netherlands in 1978 mortality rates were high, especially among younger dogs (21). As in the outbreaks in other countries, the intestinal lesions were very similar to those of feline panleukopenia (13, 21). Apart from or in combination with gastrointestinal disease, infected young puppies also developed myocarditis of varying severity with large numbers of intranuclear virus particles present in the nuclei of myocardial cells (14). Recently also rotaviruses which are known to cause diarrhoea in many species, including man, have been associated with enteric disease in the dog (12). In the present paper the findings of our respective institutes on the subject of viral diarrhoea in dogs are compiled which might give an indication about the incidence of the different virus infections in the Netherlands. In addition the present knowledge about these infections is briefly reviewed.

CANINE PARVOVIRUS (CPV)

Viruses of the family parvoviridae are small (18 to 26 nm in diameter) unenveloped particles with an icosahedral symmetry and a genome consisting of a single molecule of single-stranded DNA. They are very resistant to physical and chemical influences. For their replication, viruses of the genus parvovirus depend on certain cell functions displayed during the late S-phase of cell mitosis. Consequently virus replication takes place especially in rapidly dividing cells as they are found, for example, in the intestinal epithelium and the foetus. Parvoviruses are encountered in a number of animal species in which at least some of them may cause disease symptoms (1, 25).

The first isolation of a parvovirus from dogs dates from 1970: the minute virus of canines (MVC). This infection does not seem to be associated with disease symptoms. No antigenic relationship with any of the known parvoviruses could be demonstrated (6, 25). CPV is another par-

vovirus of the dog, which was almost simultaneously isolated from dogs with diarrhoea in many countries all over the world. Just as the virus which causes mink virus enteritis, CPV is closely related to feline panleukopenia virus (FPV): two-way cross-reactivity was demonstrated in haemagglutination inhibition, immune electron microscopy, immunofluorescence, and virus neutralization tests (3, 8, 21). Serologic surveys in the USA, Australia, and in our country suggested that CPV was a new virus of the dog (8, 21, 28).

The disease

Clinical signs of CPV infections vary greatly with the age of the infected dog, its general condition, environmental circumstances, and secondary bacterial infections. From the observation that many adult dogs have developed antibodies against CPV during the last few years (Table 1) without developing overt clinical signs or without being vaccinated, one may conclude that many CPV infections take a subclinical course. In spontaneous cases with diarrhoea the incubation time is not exactly known: in experimentally induced infections it ranges from two to four days (17). It is most likely that natural infection usually takes place by the oral route, although experimentally other routes of infection proved to be successful (4). The first sign of infection in the dog is often a recurrent vomiting, followed by diarrhoea within one day. The consistency of the faeces may range from soft to fluid, with variable amounts of blood. At the onset of the disease the colour of the faeces is grayish in most cases. Apart from these gastrointestinal symptoms a general depression with anorexia is frequently present.

Especially young pups and small dogs may suffer from rapid dehydration and die suddenly. During the first four or five days the animals often develop severe leukopenia and in this period rectal temperature may be slightly elevated. In older dogs also normal temperatures are found during this period of leukopenia

Table 1. Percentages of dogs with antiviral antibodies.

Sera from	Year	Percentage of positive dogs (total number tested) for:		
		Parvovirus HAI \geq 8	Coronavirus IF \geq 20	Rotavirus CF \geq 5
Open population ²	1974	0 (100) ¹	12 (26)	12 (25)
Closed colony A	1974	0 (61)	0 (25)	4 (25)
	1976-			
Open population ²	1979	6 (50)	4 (19)	32 (17)
Closed colony A ³	1978	93 (46)	41 (29)	70 (30)
Closed colony B	1978	73 (22)	28 (18)	71 (14)
Closed colony C	1978	88 (32)	9 (32)	92 (26)
Dogs with diarrhoea	1978-	64 (33)	36 (33)	63 (8)
	1979			

¹ number of dogs tested

² submitted to Small Animal Clinic, Utrecht; no diarrhoea

³ with serious diarrhoeal problems

(2). In pups up to seven months of age, infection with CPV may lead also to cardiac insufficiency caused by a focal myocarditis.

These young animals, which may have suffered from gastrointestinal disease first, show an acute dyspnoea with vomiting and a general weakness. They may die suddenly or, if they survive, they may exhibit cardiac 'souffles' and insufficiencies. Changes in the ECG are manifest before clinical signs have developed (23). Experimental infection of dogs with CPV usually results in very mild disease symptoms (4, 18, 21).

Pathology and histopathology

In dogs with diarrhoea, morphological changes are usually confined to the intestinal tract. In typical cases the small intestine is locally dilated and turgid, with a peculiar hose-like stiffness, an irregular serosal surface, and often with obvious hyperaemia and pinpoint petechia visible through the serosa of dilated segments. The mucosa is red, with sometimes a scanty pseudomembranous inflammation present. In the lumen a watery or haemorrhagic fluid is found. Mesenteric lymph nodes are often swollen and haemorrhagic (10, 13).

Histologically a hyporegenerative villous atrophy with shortened or even without villi is found (Fig. 1). The crypts show a cystic enlargement and are filled with

mucous and with desquamated and degenerated epithelial and occasionally syncytial giant cells (Fig. 2). Also areas with total depletion of epithelial components and focal regenerative epithelial hyperplasia may be seen. Moreover, hyperaemia and small haemorrhages are seen in the lamina propria, the submucosa, the musculature, and the subserosa (Fig. 1). Basophilic nuclear inclusion bodies are occasionally found in epithelial cells of remaining crypts. In nuclear inclusions and in necrotic debris in crypts, parvovirus particles can be demonstrated by electron microscopy (5).

Pups which died suddenly by cardiac insufficiency show oedema of the lungs, clear yellow fluid in the body cavities, congestion of the liver, and a pale, often mottled appearance of the myocardium at autopsy. Histologically a mononuclear myocarditis of varying extent is present, with large nuclear basophilic and Feulgen positive inclusion bodies in myocardial muscle fibers (Fig. 3). Ultrastructurally these inclusions contain large numbers of parvovirus-like particles (5, 14).

Prevention

Sanitary measures, including the avoidance of direct contacts between dogs and of contact with a potentially contaminated environment, may reduce the spread of CPV. However, since the virus is extremely resistant to physical and

Fig. 1. Dog infected with CPV: Small intestine with hyperaemia, especially in the mucosa, and haemorrhages in the submucosa and muscular wall. Reduced thickness of the mucosa and villous atrophy (HE 32x).

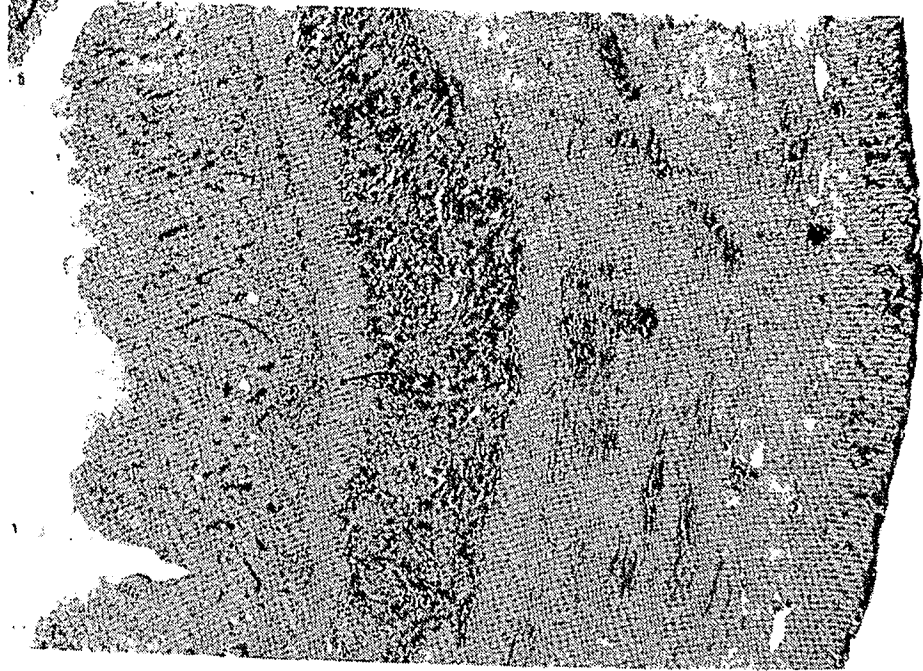


Fig. 2. Dog infected with CPV; Small intestine: mucosa with remnants of crypts filled with desquamated and degenerated epithelial cells and some syncytial giant cells (HE 32x).

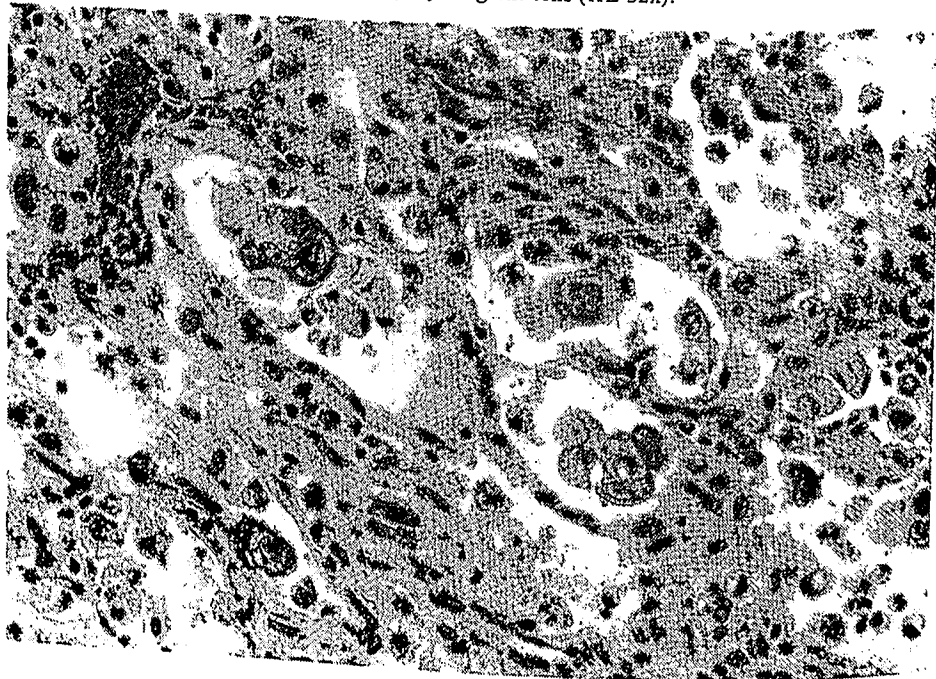
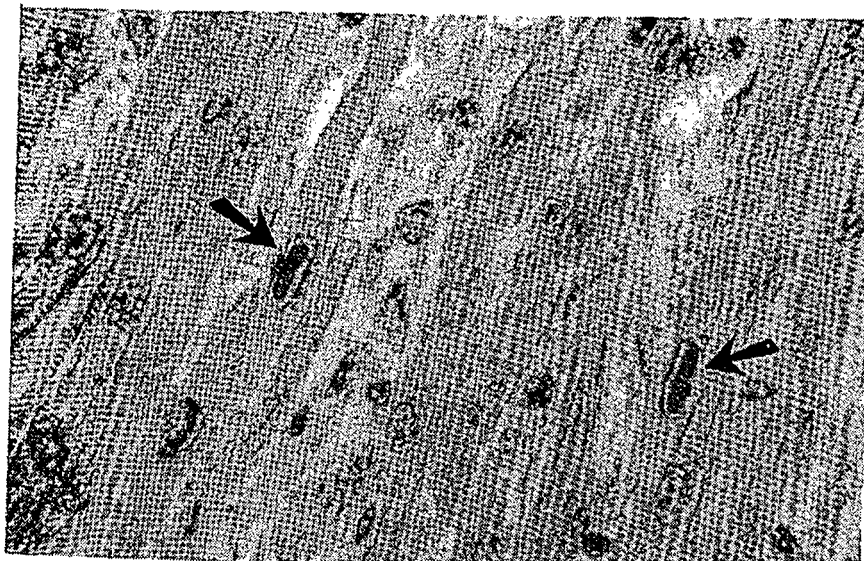


Fig. 3. Pup infected with CPV: Myocarditis wit basophilic intranuclear inclusion bodies (arrows) (HE 100x).



chemical influences and is excreted with faeces and probably also with urine and other secretions and excretions, prevention of CPV disease should preferably be based upon prophylactic vaccinations of susceptible animals. The close antigenic relationship demonstrated between CPV and FPV in serologic tests raised the expectation that vaccines developed for the prevention of feline panleukopenia could also be used for the prevention of CPV disease in the dog. Of both live and inactivated FPV vaccines it has been demonstrated that under certain conditions they may protect dogs against challenge with virulent CPV. With inactivated vaccines better protection was obtained when they were administered twice (3). However, live FPV vaccines that have not been examined for their pathogenicity to dogs should preferably not be used at present. Vaccination of young puppies and of pregnant bitches with live FPV vaccines not licensed for use in dogs should certainly not be advised. Incorporation of specific CPV vaccines in routine vaccination programs for dogs will probably be needed in the near future.

CANINE CORONAVIRUS (CCV)

Viruses of the family Coronaviridae are pleomorphic particles with a diameter

ranging from 60 to 180 nm. They contain a single-stranded RNA genome and an envelope covered with widely spaced projections which measure about 20 nm and cause the corona-like aspect of the particle (corona, L. = crown). Viruses of this family are more sensitive to physical and chemical influences than parvoviruses. Coronaviruses infect different animal species, including man, in which respiratory, gastrointestinal or other symptoms may be caused.

A canine coronavirus which proved to be closely related to transmissible gastroenteritis (TGE) virus of swine was first isolated in Germany in 1971 from dogs with gastro-enteritis (7).

The presence of the virus in dogs in the USA was demonstrated by virus isolation in 1976 (2) and in Australia in 1978 (24). In the Netherlands, only serological evidence has so far indicated the presence of coronavirus in dogs (Table 1).

Experimental infection experiments have shown that TGE virus can replicate in epithelial cells of the canine intestinal tract, without causing morphological or functional alterations (16).

The disease

Clinically the disease caused by CCV is difficult to differentiate from gastrointestinal disease caused by CPV. As in the

latter, symptoms seem to vary greatly with the age of the animal, its general condition, environmental circumstances, and secondary bacterial infections. High percentages of seropositive dogs (Table 1) which apparently have not shown any clinical symptoms indicate that many dogs must have been infected subclinically with this or a related virus.

Clinical symptoms develop after an incubation period of one to five days (9). The virus probably enters the body via the orale route and first replicates in the epithelium of the small intestine. The first symptoms are a sudden decrease in appetite and loose stools. These signs may be preceded or accompanied by vomiting, although this is supposed to occur less frequently than in cases of parvoviral diarrhoea. Faeces contain variable amounts of mucus and blood, tend to have a yellowish colour, and may vary considerably in consistency. Body temperature is increased in some cases. Leukopenia is less pronounced than in cases of CPV infections and is usually not recognized. Although most dogs recover within two weeks, persistent diarrhoea for three to four weeks has been reported (2). Especially young pups may suffer from rapid dehydration and lethality may be high in these animals. Experimental CCV infection of dogs was mild without exception: not all dogs developed diarrhoea (2).

Pathology and histopathology

In experimentally infected pups intestinal loops are dilated and filled with a thin, watery material (15). In naturally occurring disease lesions may be more severe, with moderate congestion to frank haemorrhages of the intestinal mucosa (2). Histologically in both experimental and natural disease a hyperregenerative villous atrophy is seen which is characterized by atrophy and fusion of the intestinal villi, a decreased number of goblet cells, deepening of the crypts which have an intact epithelial lining, and by an increased cellularity of the lamina propria (15). Coronavirus particles can be demonstrated electron-microscopical-

ly in the cytoplasm of the epithelial cells covering the villi but are absent in those lining the crypts (15, 26).

Prevention

At present, with no CCV vaccine available, prevention of CCV disease in dogs should be based mainly upon sanitary measures. Special attention should be paid to removal and decontamination of faeces and isolation of potentially infected animals. However, similar measures proved largely unsuccessful in stopping the spread of the virus: in breeding colonies in the Netherlands, which we screened serologically, the infection was or had become endemic during the last few years, in spite of the usual hygienic regimens (Table 1).

ROTAVIRUS

Rotaviruses should probably be included as a new genus in the family Reoviridae. Intact particles measure approx. 70 nm, are unenveloped, and have been described as double-shelled: the capsid consists of a double layer of capsomeres, the inner of which has an icosahedral symmetry. The appearance is suggestive of a wheel, hence the name rotavirus (rota, L. = wheel). The viral genome is a double stranded and segmented RNA.

Rotavirus infections are very common in young individuals, including man. In many instances these infections have been associated with enteritis and diarrhoea, although symptomless infections do occur, especially in colostrum-fed and adult animals (18).

A rotavirus has not been isolated from dogs in cell culture, which may be due to the extreme difficulties to adapt these viruses to passage in cell culture. Rotavirus particles have been demonstrated in diarrhoeic faeces of a dog (12) and experimental infection of dogs with rotavirus of human origin resulted in virus replication and even spontaneous infection of a contact dog (27). Similarly we succeeded in demonstrating the replication of rotavirus of porcine origin in very young puppies after experimental oral infection (unpublished observations). In both

cases, however, no diarrhoea or other illness was observed. Also antibody surveys in dogs indicated that these animals were naturally infected with rotavirus (19, Table 1). Whether under field conditions inter-species infections, or infections with a specific rotavirus occur, is not clear and the significance of young dogs for the epizootiology of rotavirus infections in other species cannot be evaluated at this moment. As in other animal species (18), caution should be exercised in ascribing etiological significance to the detection of rotavirus in diarrhoeic faeces of the dog. Prevention of rotavirus infections in other animal species is mainly achieved by a combination of hygienic measures, ingestion of adequate amounts of colostrum antibody, and vaccination of either the young animals or their mothers (18). Whether the development of a vaccine for rotavirus infections in dogs is desirable is questionable at the moment.

PRÉVALENCE IN DOGS IN THE NETHERLANDS

Serologic survey

Sera collected from Dutch dogs of different origins (at different times) were tested for the presence of antiviral antibodies. Antibodies against CPV were demonstrated in a haemagglutination inhibition (HAI) test (21). In a heterologous indirect immunofluorescence (IF) test with TGE virus infected cells as antigen (21, 23) sera were tested for the presence of antibodies against coronavirus. Of course they may be caused by an infection with CCV but also by TGE virus infections. Antibodies against rotavirus were demonstrated in a complement fixation (CF) test with bovine rotavirus as antigen (18). Titers lower than respectively 8, 20, and 5 were not considered specific. The results of this survey are shown in Table 1. In sera collected in 1974 from the open population and from breeding colony A no antibodies against CPV were demonstrated. In some of the sera, antibodies against coronavirus and rotavirus were found. In sera of dogs in the open population collected in the periode from 1976 to 1979

antibodies against all three viruses were found. The first serum with antibodies against CPV dates from November 1977, the others from 1979. In sera collected from the closed colonies in 1978 after the outbreaks of diarrhoeal disease had started, antibodies were found against all three viruses: in sera from colony A with serious problems of diarrhoea, but also from colonies B and C where no problems had been recognized. Also in sera of dogs from all over the country with serious diarrhoeal problems antibodies against all three viruses were found. However, no paired serum samples of these dogs were tested and at least a number of them may not have been ill long enough to develop antibodies.

Pathologic findings

In the Netherlands pathologic findings similar to those of CPV infections were first recognized at the end of 1977. Both the intestinal and the cardiac form were seen at that time. Since then the disease showed an increasing incidence. Whereas in the beginning the enteric form was seen in both young and older dogs, the scene has changed and now mainly young dogs up to one year of age seem to be affected. The cardiac form has been seen in pups of 3-10 weeks old with sudden and unexpected death.

Recently, however, also chronic cardiac insufficiency due to CPV infection has been observed in older pups. From January 1979 up to May 1980 in autopsy material of at least 26 submitted dogs from all over the country 'typical' CPV lesions were encountered in intestines and less frequently in hearts.

Demonstration of viral antigen

Frozen sections of small intestines and kidneys of dogs from all over the country which had died with symptoms of contagious diarrhoea and which had shown intestinal lesions were tested in an indirect IFT with a feline anti-CPV serum (21). A serum of an SPF cat was used as a negative control serum. Intestinal sections of 16 out of 47 dogs were positive in

the IFT (Fig. 4). In four of these dogs antigen was also demonstrated in the kidneys with this method (Fig. 5). In none of the dogs could coronavirus antigen be demonstrated in a similar IFT with a porcine anti-TGE virus serum.

In addition we developed a rapid method to demonstrate parvoviral antigen directly in the faeces of the dog: a haemadsorption - elution - haemagglutination assay (HEHA) which had originally been developed for the demonstration of coronavirus antigen in bovine faeces (11). Briefly, the assay is performed as follows: parvoviral antigen present in a faecal suspension is adsorbed to feline erythrocytes for one hour at 4° C. The antigen is then eluted from the cells for one hour at 37° C and subsequently used in a haemagglutination (HA) test, again with feline erythrocytes (21). Positive samples are assayed in a HAI test with a feline anti-CPV serum (21) and a control (SPF) feline serum, to demonstrate the specificity of the HA for the presence of parvoviral antigen. With this test we screened faecal samples of 50 dogs with acute diarrhoea from all over the country during the last few months. Samples of 31 of these

animals gave a positive HA with feline erythrocytes, which could be inhibited with the specific anti-CPV serum and not with the control serum in 20 cases. Consequently only in these cases was HA activity considered indicative for the presence of parvoviral antigen. So far we have no data about the sensitivity of this HEHA as compared to other assays, such as IEM and IF tests. Further studies will be needed to evaluate its value for rapid diagnosis of CPV infections in the dog and possibly also of FPV infections of the cat.

Conclusions

From the serologic data presented it can be concluded that infections with CPV, and rotaviruses are widespread among dog populations in the Netherlands at this moment. We may also conclude that many of these infections, run a subclinical course in dogs and that only in certain conditions is infection with these viruses associated with clinical symptoms. Results of pathological and histopathological examination of a limited number of dogs suggested that CPV infections occur regularly in the Netherlands in associa-

Fig. 4. Indirect immunofluorescence of jejunal section of a dog with diarrhoeal disease, with a feline anti-CPV serum. Note immunofluorescence in crypt (100x).



Fig. 5. Indirect immunofluorescence of kidney section of a dog with diarrhoeal disease, with a teline anti-CPV-serum. Note immunofluorescence in glomerulus (100x).



tion with enteric and also with myocardial disease in young dogs. This is confirmed by the demonstration of parvoviral antigen in intestines and kidneys of dogs with similar case histories by means of indirect IFT and, on the other hand, by the demonstration of parvoviral antigen directly in faeces of dogs with diarrhoea by means of the newly developed HEHA. The role played by infections with CCV and rotavirus in outbreaks of contagious

diarrhoea in the Netherlands is not clear at this moment. Further studies are required to evaluate the conditions which determine the pathogenicity of these viruses, infecting the dog either simultaneously or alone.

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