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Pathogenesis of feline panleukopenia virus and canine parvovirus

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Feline panleukopenia virus (FPV) and canine parvovirus (CPV) and a number of closely related parvoviruses are widespread in nature, and they cause disease in many different carnivores. The viruses are all classified as members of the feline parvovirus subgroup of the family Parvoviridae (Siegl et al, 1985) and are named for the host from which they are isolated—hence CPV, FPV, raccoon parvovirus, mink enteritis virus (MEV), as well as blue fox parvovirus (BFPV) from Arctic foxes. The general properties of the autonomous parvoviruses have been reviewed by Cotmore and Tattersall (1987) and some previous reviews of canine and feline parvoviruses include Kurtzman (1993), Parrish (1990) and Pollock and Parrish (1985). The viruses contain a single-stranded DNA genome of about 5100 bases in length, and complete or partial DNA sequences of a number of different viruses have been determined (Reed et al, 1988; Martyn et al, 1990; Parrish 1991). The genomes contain two promoters which give rise to messages for either two nonstructural genes—NS1 (Carlson et al, 1987) and NS2, or for the structural protein genes VP1 and VP2. The VP1 and VP2 proteins are translated from overlapping open reading frames, and the complete sequence of VP2 is contained within the VP1 sequence (Reed et al, 1988).

The 25 nm diameter virus capsid is assembled from 60 copies of a combination of about 10% VP1 and 90% VP2 molecules. The atomic structures of FPV and CPV have both been determined (Tsao et al, 1991; Agbandje et al, 1993). Those show that the particle is a $T=1$ capsid, and that sequence differences between CPV and FPV are located in three different areas on or near the surface of the capsid. The virus is very stable in the environment, and can remain infectious in nature for days or weeks.

FPV has been known as the cause of diseases in cats, raccoons and some related carnivores for many years (Hindle and Findlay, 1932), but CPV is a new virus, probably derived from FPV or a close relative during the 1970s (reviewed by Parrish (1990)), and since has become established throughout the world. The virus capsid is the primary determinant of the host range of the viruses, and small differences (less than 10 amino acids) between CPV and FPV determine the ability of each virus to replicate in dogs or cats or their cultured cells (Parrish et al, 1988a; Chang et al, 1992; Truyen and Parrish, 1992; Truyen et al, 1994). Although CPV and FPC isolates are

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>98% identical in DNA sequence, the viruses can be readily distinguished by antigenic typing with monoclonal antibodies (Parrish and Carmichael, 1983), by their characteristic pH and temperature dependence of haemagglutination (Carmichael et al, 1980; Senda et al, 1988), and by host range in cultured cells or animals. The host range differences between the viruses are complex, and in experimental infection studies it was shown that CPV type-2 (see below) replicates in both canine and feline cells in culture, as well as in dogs, but it cannot replicate in cats after at least parenteral inoculation (Truyen and Parrish, 1992). In contrast, FPV replicates in feline but not canine cells in culture and in cats, and it also replicates in certain canine tissues after inoculation of animals, including thymus and bone marrow cells (Truyen and Parrish, 1992; Truyen et al, 1994). The natural animal host range of CPV includes dogs and close relatives such as wolves, coyotes, South American dogs, and Asiatic raccoon dogs. FPV and the FPV-like viruses infect both large and small cats, as well as mink, raccoons, and possibly foxes (reviewed by Parrish (1990)).

The emergence and evolution of CPV is interesting, as the virus appears to have been present initially in Europe, and then to have spread around the world during a period of about 6 months in 1978. The original strain of virus (called CPV type-2) was replaced between 1979 and 1981 by a genetically and antigenically distinct virus (CPV type-2a), which has itself subsequently also been largely replaced by a further antigenic variant, designated CPV type-2b (Parrish et al, 1985, 1988b, 1991). The origin of CPV is not known, although it most likely derived from FPV or from one of the closely related viruses of other carnivores—mink, raccoons, Asiatic raccoon dogs, or foxes. Derivation from an FPV vaccine strain in tissue culture has been suggested (Siegl, 1984), but there is currently no evidence to prove that hypothesis, and variation of a virus in nature is an equally likely source of CPV.

This review considers the pathogenesis of FPV in cats, the very similar MEV in mink, and CPV in dogs. The pathogeneses of these infections are very similar, although small differences in the host species, its age, and the type of virus infecting it all affect the outcome of the infection.

DISEASES AND PATHOGENESIS

The pathogenesis of parvovirus infections is influenced primarily by the requirement of DNA replication of these autonomous parvoviruses for mitotic cells (Tennant et al, 1969), which determines many of the differences in the outcome of infections in fetal, neonatal or older animals. However, it is likely that not all the dividing cells in an animal are permissive for virus replication, and while the dividing lymphoid and intestinal epithelial cells are primary targets for virus replication by FPV, MEV and CPV (see below), developmentally regulated properties of some differentiated dividing cell populations may restrict parvovirus replication at the cellular level and determine the specific outcome of infection (reviewed by Cotmore and Tattersall, (1987)). The precise relationship between the presence of

dividing cells in tissues and their susceptibility to parvovirus infection in dogs, mink or cats has not been defined.

OLDER ANIMALS

The pathogenesis of infections by FPV in cats or CPV in dogs are very similar. Both viruses are considered together below, with differences between the infections being noted where those have been defined. The site of entry and initial virus infection has not been defined in detail, but it most likely occurs through cells of the nasopharynx, the tonsils or other lymphoid tissues (Reynolds, 1970; Csiza et al, 1971a; Appel et al, 1979; Carman and Povey, 1982; Pollock 1982; Macartney et al, 1984a). Animals also can be infected by most parenteral routes. Virus is isolated between 1 and 3 days after infection from the tonsil, retropharyngeal lymph nodes, thymus, and mesenteric lymph nodes, and after approximately 3 days virus is also recovered from the intestinal-associated lymphoid tissues and Peyer's patches (Csiza et al, 1971a; Carlson and Scott, 1977; Carlson et al, 1978; Macartney et al, 1984b; Carman and Povey, 1985a; Meunier et al, 1985a). Virus spreads systemically through a plasma viraemia, resulting in widespread infection of the lymphoid tissues including the thymus and all lymph nodes.

HAEMATAPOIESIS

The incidence of leukopenia or lymphopenia varies between the different viruses. Effects on erythrocyte levels are not seen after infection, possibly because of the long life span of the erythrocytes compared to the course of the disease.

FPV

Panleukopenia is a striking feature of many FPV infections of cats (Figure 1), where the total white cell counts may fall to 1000–2000 mm^{-3} or less, and neutrophil counts decrease to less than 200 mm^{-3}. Lymphocyte numbers decline, although to a lesser degree, but there is little effect on eosinophil, basophil, monocyte, or red cell numbers (Lawrence and Syverton, 1938; Hammon and Enders, 1939a,b; Lawrence et al, 1940; Rohovsky and Griesemer, 1967; Reynolds, 1969; Ichijo et al, 1976; Larsen et al, 1976; Carlson and Scott, 1977; Hosokawa et al, 1987).

CPV

Panleukopenia is very uncommon in CPV infections, although a relative lymphopenia is often observed (Figure 2). Dogs infected with CPV develop relative lymphopenia, and some animals develop neutropenia, but total leukocyte counts are generally not markedly affected (Robinson et al,

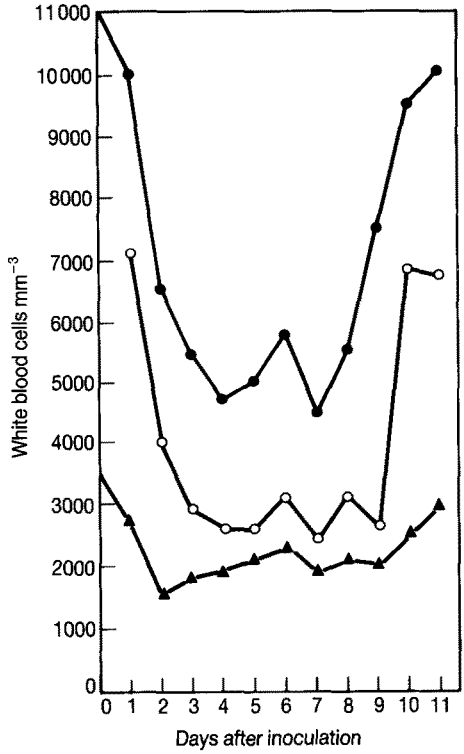

Figure 1. Total circulating (●) leukocyte, (○) lymphocytes and (▲) neutrophil counts of eight cats on various days after infection with FPV. Reproduced from Larsen et al (*Veterinary Pathology* **13:** 216–240, 1976) with permission.

1980a; Carmichael et al, 1981; Pollock, 1982; Macartney et al, 1984a; Carman and Povey, 1985a).

Bone marrow

In FPV and CPV infections of cats and dogs the bone marrow may be severely affected, with a marked decrease in cellularity. Most animals show decreased numbers of myeloid, erythroid and megakaryocytic cells (Figure 3) (Hammon and Enders, 1939a,b; Lawrence et al, 1940; Robinson et al, 1980a; Boosinger et al, 1982; Macartney et al, 1984a; Carman and Povey, 1985a). Individual animals differ in both the extent of the depletion and the effects on individual cell types.

FPV

Many cells in feline bone marrow cell cultures were susceptible to infection by FPV. On average about 10–20% of the cells showed virus antigen or

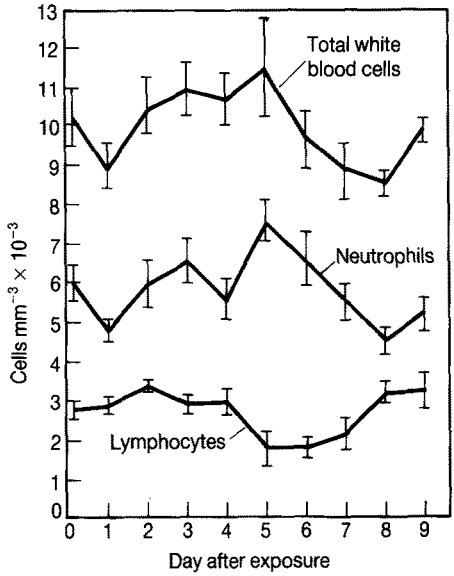

Figure 2. Mean counts and standard deviations of total circulating leukocytes, neutrophils and lymphocytes of dogs after infection with CPV. Reproduced from Carman and Povey (1985a, *Research in Veterinary Science* **38:** 141–150) with permission.

DNA by fluorescent antibody staining or by in situ hybridization (Kurtzman et al, 1989). At high doses of FPV there were reductions in both erythroid and myeloid colony formation, but at lower virus doses there was a greater suppression of the myeloid (CFU-GM) colony formation compared with the erythroid (BFU-E- and CFU-E-derived) colonies (Figure 4). The precise differentiated stages of the FPV-susceptible cell populations were not defined although they were presumed be early progenitors. They proposed that virus infection of the myeloid precursors would rapidly lead to reduced circulating neutrophil levels due to the rapid turnover of those cells (Kurtzman et al, 1989).

CPV

No effect of CPV on the regeneration of erythrocytes was observed when haemolytic anaemia was induced in dogs with phenylhydrazine before CPV infection, indicating that at least for CPV in dogs the virus does not greatly depress erythroid cell production (Brock et al, 1989). Although CPV infects canine bone marrow cells (Macartney et al, 1984b; O'Sullivan et al,1984; Meunier et al, 1985a; Truyen and Parrish, 1992) this does not result in a panleukopenia, suggesting that CPV and FPV infect different target cells in the bone marrow and probably other tissues of their respective hosts.

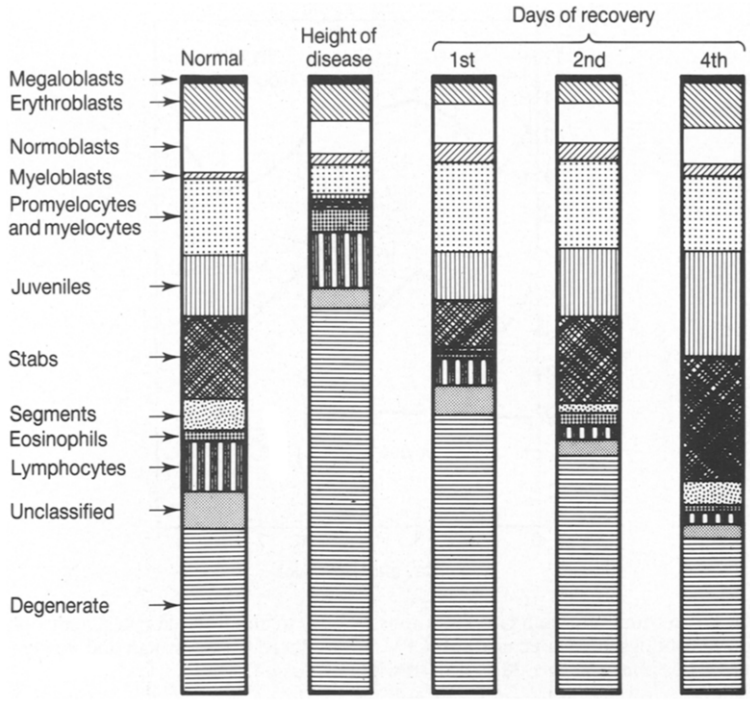

Figure 3. Differential bone marrow cell counts of cats at various stages of the infection with FPV. The data represents the counts from 13 normal marrows and a total of 31 marrows from infected cats. Reproduced from Lawrence et al (1940, *American Journal of Pathology* **16:** 333–354) with permission.

Lymphoid tissues

The infection of the lymphoid tissues results in lymphocytolysis, cellular depletion and, subsequently, tissue regeneration in surviving animals. Virus replication and cell destruction in lymphoid tissues occurs mostly in areas of dividing cells, including germinal centres of lymph nodes and in the thymus cortex (Figure 5) (Hammon and Enders, 1939a,b; Lawrence et al, 1940; Krunajevic, 1970; Reynolds, 1970; Carlson et al, 1977; Cooper et al, 1979; Robinson et al, 1980a; Macartney et al, 1984a,b; Carman and Povey, 1985a,b; Uttenthal et al, 1990). It is not known whether the loss of lymphocytes is due entirely to lysis of virus infected cells, but it is likely that at least some of the marked effects seen on cell numbers in the different lymphoid tissues are due to indirect effects such as binding to the cells by the high levels of virus in the infected tissues. The role(s) of cytokines in the pathogenesis of the infection have not been examined.

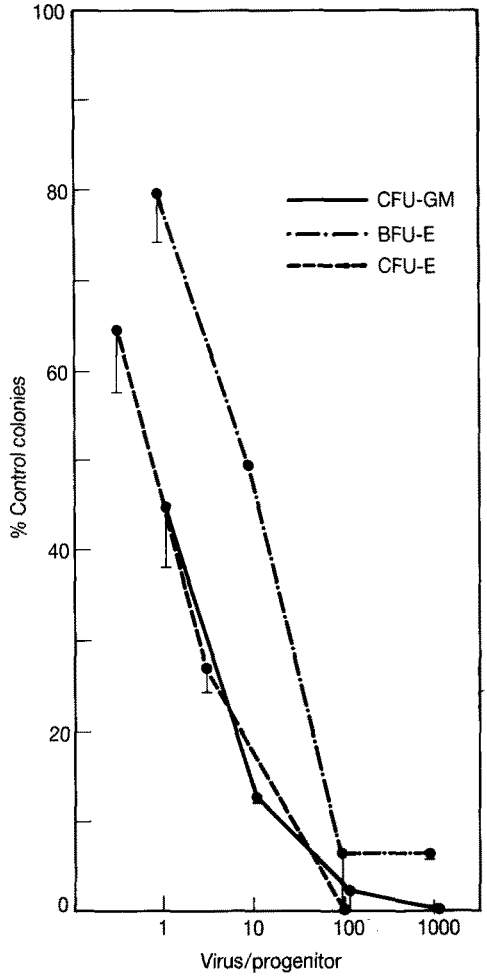

Figure 4. Inhibition of clonal haematopoietic colonies in culture by inoculation of various multiplicities of FPV, expressed as virus plaque forming units per cell. In this experiment the numbers of myeloid (CFU-GM) and early (BFU-E) and late (CFU-E) erythroid derived colonies after FPV infection. Values are the mean number of colonies in infected duplicate plates, compared to the uninfected control cultures. Reproduced from Kurtzman et al (1989, *Blood* **74:** 71–81) with permission.

Intestinal infection

Intestinal infections appear very similar for all the carnivore parvoviruses. FPV or CPV infect the rapidly dividing epithelial cells in the crypts of the intestinal villi of the ileum and jejunum between 3 and 5 days after inoculation, and virus is found throughout the epithelium of those portions of the intestine 4–8 days after infection (Figure 6) (Carlson and Scott, 1977; Carlson et al, 1977; Carman and Povey, 1985a; Meunier et al, 1985a;

Uttenthal et al, 1990). The degree and the severity of the infection are in part determined by the rate of turnover of the intestinal epithelial cells. Germ-free cats showed reduced FPV replication in the small intestine (Rohovsky and Griesemer, 1967; Carlson and Scott, 1977), while treating cats with mild HCl enemas resulted in increased cell replication and virus infection of the colonic epithelium (Schindel et al, 1978).

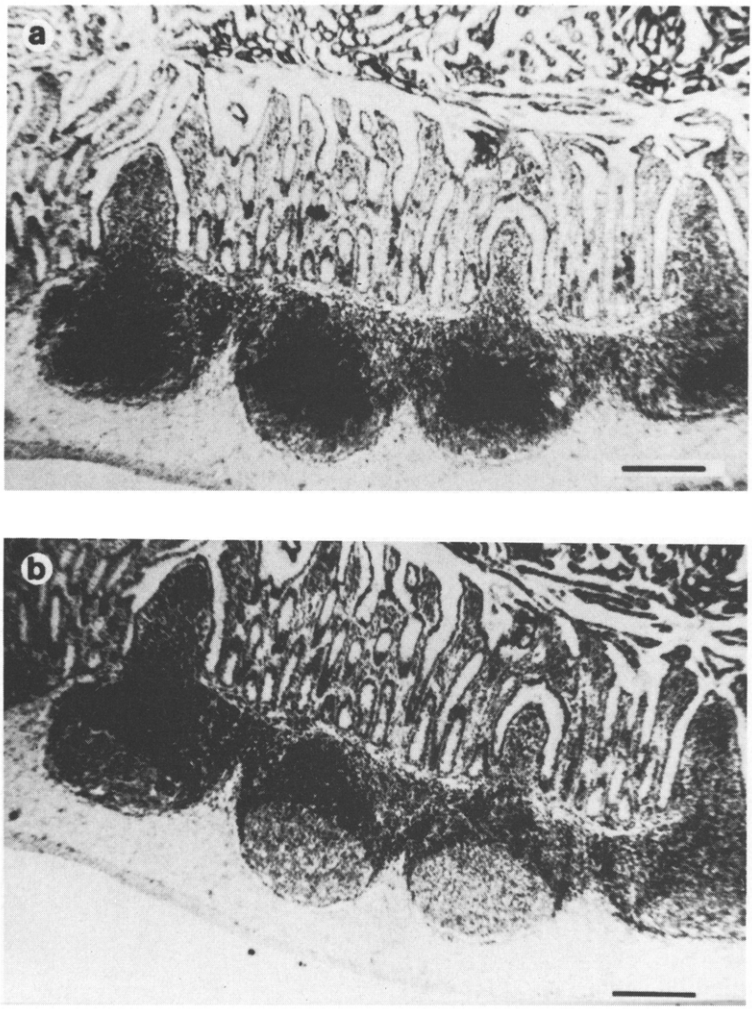

Figure 5. Ileum sections of mink 8 days after infection with MEV, probed with either (a) a plus-sense RNA probe that detects viral DNA present in virions as well as replicative form DNA, or (b) a minus-sense probe that would detect only replicative forms of viral DNA. The hybridization is evident with the plus-sense probe over the gut-associated lymphoid tissues. Bar—230 μm. Reproduced from Uttenthal et al (1990, *Journal of Virology* **64:** 2768–2779) with permission.

The virus infection and loss of epithelial cells results in a flattened and attenuated epithelium with shortened intestinal villi leading to loss of osmotic regulation, with a resulting diarrhea often containing blood and mucus (Rohovsky and Griesemer, 1967; Larsen et al, 1976; Okaniwa et al, 1976; Landsverk and Nordstoga, 1978; Cooper et al, 1979; Yasoshima et al, 1982; Macartney et al, 1984c). Animals may become dehydrated and pyretic, possibly because of endotoxin uptake from the gut. Intestinal parasites or coinfection with other agents such as coronavirus or bacteria are suggested to increase the severity of the disease.

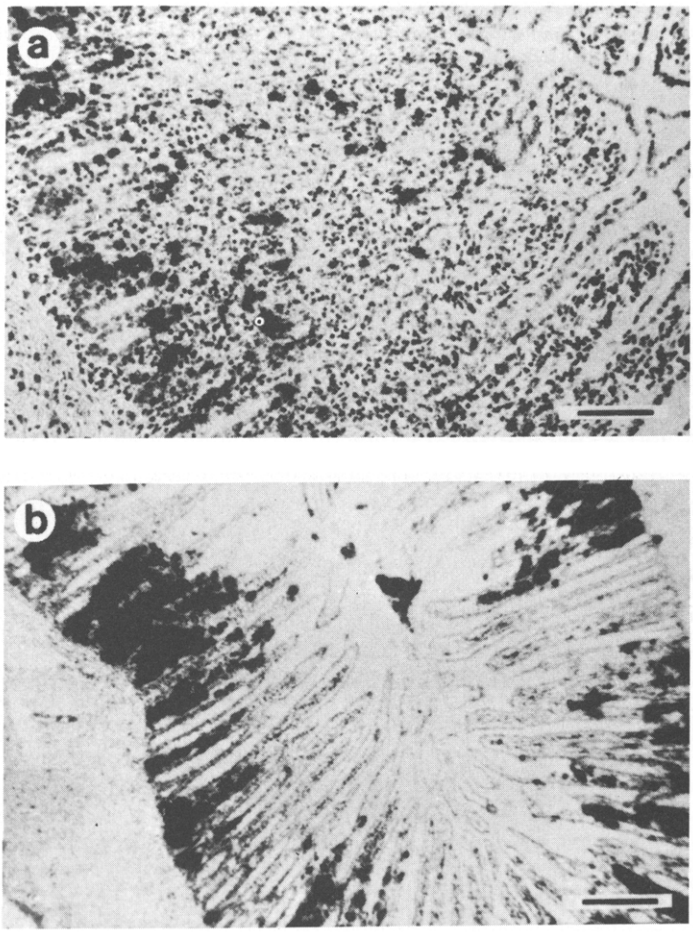

Figure 6. (a) Ileum section of mink infected for days with MEV, probed with a minus-sense RNA probe which would detect replicating forms of viral DNA. Grains are observed over epithelial cells in the crypts and on the villi. Bar—80 μm. (b) Ileum section of mink infected for 6 days with MEV. Heavy grain production is observed in the lumen of the intestine and over areas of the crypts and the villi. Bar—230 μm. Reproduced from Uttenthal et al (1990, *Journal of Virology* **64:** 2768–2779) with permission.

During the intestinal phase of the infection virus is excreted in large amounts in the faeces—with up to 10^7 and 10^9 infectious units being shed per gram (Carmichael et al, 1981; Carman and Povey, 1985b; Meunier et al, 1985a,b).

Disease severity

The clinical disease probably results from the extent of damage by virus caused to the small intestine. There is variation in the response of individual animals to virus infection, and serological studies indicate that infections by CPV in dogs (and probably by FPV in cats) are often mild or subclinical (Meunier et al, 1980; Parrish et al, 1982). A correlation was observed between the viral titres in serum and faeces and the severity of the disease observed in dogs inoculated with CPV (Meunier et al, 1985b).

A number of attenuated strains of CPV and FPV have been isolated by repeated passage of the viruses in cells in tissue culture (Carmichael et al, 1981; Bass et al, 1982; Burtonboy et al, 1991). The attenuating mutations in those viruses were not known, but the viruses were shed at lower titres in the faeces, suggesting that decreased replication in the intestine resulted in decreased enteritis.

FETAL OR NEONATAL INFECTIONS

Infection of neonates results in different disease from that seen in older animals, and is characterized by infection of the developing cerebellum in kittens or of the heart in puppies. Enteritis is not observed in very young animals.

Feline ataxia

Infection of kittens either in utero or shortly after birth can result in viral replication in the cells of the external germinal epithelium of the cerebellum, resulting in cerebella hypoplasia (Csiza et al, 1971a; Kilham et al, 1971). Most viable kittens subsequently suffered from ataxia (Kilham et al, 1967; Csiza et al, 1971a,b).

Canine myocarditis

CPV infection of neonatal puppies can result in death from myocarditis, generally between 3 and 8 weeks of age, but sometimes up to 16 weeks of age at death (Jesyk et al, 1979; Robinson et al, 1979, 1980b). Mortality in litters varied between 20 and 100%, and disease onset was rapid, and characterized by cardiac arrhythmia, dyspnoea and pulmonary oedema, followed by death (Jesyk et al, 1979; Robinson et al, 1979, 1980b; Parrish et al, 1982; Meunier et al, 1984). Affected pups suffer a variety of subclinical abnormalities with progressive multifocal necrosis of the myocardium, often with a mononuclear cell infiltrate. Myocardial cells often contained intranuclear inclu-

sion bodies. Lungs may be oedematous, most likely secondary to the heart failure (Jesyk et al, 1979; Robinson et al, 1980b). The age dependence of the myocardial infection is probably due to the active cell division of the myocardial cells in pups only under 15 days of age (Bishop, 1972).

More rarely, neonatal infections can give a generalized infection with lesions in many different tissues (Lenghaus and Studdert, 1982; Johnson and Castro, 1984). In utero infections of cats by FPV or Arctic foxes by BFPV may result in fetal death and resorption, abortion or neonatal death (Kilham et al, 1967, 1971; Veijalainen and Smeds, 1988).

Immunity

The course of infection is rapid, with little virus being recovered from tissues or faeces by 10–14 days post-infection (Csiza et al, 1971a; Macartney et al, 1984b). The functional immunity against these viruses which acts both for recovery and to protect against infection appears to be mediated through serum antibody. T-cell epitopes in the CPV sequences recognized by dog lymphocytes have been defined within the capsid protein gene (Rimmelzwaan et al, 1990). Colostrum-derived maternal immunity protects against parvovirus infection until serum antibody titres decline to very low levels (Parrish et al, 1982; Pollock and Carmichael, 1982; Ishibashi et al, 1983; Macartney et al, 1988). The role of local immunity in the gut is not known, although levels and classes of antibody in the jejunum collected by cannulation after CPV infection or vaccination suggested that the antibody was being specifically secreted (Nara et al, 1983). However, parenteral administration of anti-CPV antibodies both protect dogs against oral challenge and prevent virus replication in the intestine (Ishibashi et al, 1983; Meunier et al, 1985a).

CONCLUSION

These virus infections are interesting models where the emergence of new viruses apparently occurred through the acquisition of host range differences in the capsid protein gene, leading to infection of a new host family. The pathogenesis of CPV and FPV infection has been well defined, and is largely dependent on the requirement of the virus for dividing cells for replication, making the diseases age dependent. However, poorly defined differences in the susceptibility of cell populations in the bone marrow, the heart or the cerebellum of the cat and dog also give rise to distinct outcomes of various virus and host combinations.

SUMMARY

Feline panleukopenia virus (FPV) and canine parvovirus (CPV) are autonomous parvoviruses which infect cats or dogs, respectively. Both viruses cause an acute disease, with virus replicating for less than seven days before

being cleared by the developing immune responses. The viruses have a broad tropism for mitotically active cells. In neonatal animals the viruses replicate in a large number of tissues, and FPV infection of the germinal epithelium of the cerebellum leads to cerebellar hypoplasia, while CPV may infect the hearts of neonatal pups, causing myocarditis. In older animals the virus replicates systemically, primarily in the primary and secondary lymphoid tissues, and also in the rapidly replicating cells of the small intestinal epithelial crypts. A transient panleukopenia or relative lymphopenia is often observed after FPV or CPV infection, respectively. Whether the reduction in cell numbers in vivo is due to virus replicating in and killing cells, or due to other indirect effects, is not known. However, FPV kills both erythroid and myeloid colony progenitors in in vitro bone marow cultures, and it has been suggested that virus replication in the myeloid cells in vivo could lead to the reduced neutrophil levels seen after FPV infection of cats.

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