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# A review of feline infectious peritonitis virus: molecular biology, immunopathogenesis, clinical aspects, and vaccination

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## ABSTRACT

Feline infectious peritonitis (FIP) has been an elusive and frustrating problem for veterinary practitioners and cat breeders for many years. Over the last several years, reports have begun to elucidate aspects of the molecular biology of the causal virus (FIPV). These papers complement a rapidly growing base of knowledge concerning the molecular organization and replication of coronaviruses in general. The fascinating immunopathogenesis of FIPV infection and the virus' interaction with macrophages has also been the subject of several recent papers. It is now clear that FIPV may be of interest to scientists other than veterinary virologists since its pathogenesis may provide a useful model system for other viruses whose infectivity is enhanced in the presence of virus-specific antibody. With these advances and the recent release of the first commercially-available FIPV vaccine, it is appropriate to review what is known about the organization and replication of coronaviruses and the pathogenesis of FIPV infection.

List of abbreviations: ADE=antibody-dependent enhancement; BCV=bovine coronavirus; C' = complement; C' -ADE=complement-mediated antibody-dependent enhancement; CCV=canine coronavirus; CNS=central nervous system; CR=complement receptor; CVLP=coronavirus-like particle; ds=double-stranded; DTH=delayed-type hypersensitivity; EAV=equine arteritis virus; FcR = Fc receptor; FECV=feline enteric coronavirus; FeLV=feline leukemia virus; FIP=feline infectious peritonitis; FIPV=feline infectious peritonitis virus; HCV-229E=human coronavirus 229E; HCV-OC43=human coronavirus OC43; HE=hemagglutinating esterase; HEV=hemagglutinating encephalomyelitis virus; HIV=human immunodeficiency virus; HRSV=human respiratory syncytial virus; IBV=infectious bronchitis virus; kB=kilobases; kDa=kilodaltons; LDHV=lactate dehydrogenase virus; M=membrane (protein); mAb=monoclonal antibody; MHC=major histocompatibility; MHV=mouse hepatitis virus; mRNA=messenger RNA; N=nucleocapsid (protein); N-linked=asparagine-linked (glycosylation); NS=nonstructural (protein); O-linked=serine- or threonine-linked (glycosylation); ORF=open reading frame; Pol=polymerase (protein); PRCV=porcine respiratory coronavirus; RCV=rat coronavirus; RECV=rabbit enteric coronavirus; RI=replicative intermediate; rHuIFN $\alpha$ =recombinant human interferon alpha; S=spike (protein); SDAV=sialodacryoadenitis virus; SIV=simian immunodeficiency virus; SPF=specific-pathogen-free; TCID<sub>50</sub>=tissue culture infectious dose 50%; TCV=turkey coronavirus; TGEV=transmissible gastroenteritis virus; ts=temperature-sensitive; VN=virus neutralization (-izing).

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## HISTORY

Feline infectious peritonitis was first described as a disease entity in the 1960s (Holzworth, 1963; Wolfe and Griesemer, 1966). The etiology of this disease was uncertain until 1970, when virus particles were described from 12 of 25 cats with FIP (Ward, 1970). This early paper by Ward is notable because it outlined several salient features regarding the viral etiology of FIP which have been confirmed by more recent studies. These include the tropism of the virus for macrophages, the presence of virions in vesicles and cysternae of the Golgi body, the lack of plasma membrane budding by the virus, and the presence of club-like projections from the surface of the virions. Ward and colleagues (Ward, 1970; Ward et al., 1974) suggested that the virus responsible for FIP might be a member of the Coronaviridae. Evidence for this characterization included structural similarities between mouse hepatitis virus (MHV) and the putative FIPV, disease similarities between FIP and MHV-related disease, and the possible association of a coronavirus with a retrovirus (feline leukemia virus (FeLV)/FIPV and murine leukemia virus/MHV, respectively) in the etiology of both diseases.

Confirmation of the viral etiology and elucidation of the pathogenesis of FIP was hampered for a number of years because of difficulties encountered in isolating FIPV from clinical cases and growing the virus *in vitro*. The first cultivation of the virus *in vitro* was accomplished using peritoneal exudate cell cultures (Pedersen, 1976a). In so doing, Pedersen confirmed the subcellular localizations, virion features, and macrophage tropism first described by Ward. The virus was subsequently grown in feline small intestinal organ cultures (Hoshino and Scott, 1978). Finally, the growth and serial passage, in a continuous cell line of feline origin, of a virus which produced FIP upon experimental inoculation of cats was demonstrated in 1979. This virus was also characterized as a coronavirus (O'Reilly et al., 1979).

## CORONAVIRIDAE

The family Coronaviridae includes pathogens of several mammalian and avian species. This family has been defined morphologically as a group of spherical to pleomorphic, large (60–220 nm), enveloped viruses with helical nucleocapsid cores (Wege, et al., 1982). Projecting from the envelope of coronavirus virions is a fringe of club- (Wege, et al., 1982) or petal-shaped (Holmes, 1985) spikes or peplomers. These spikes have given rise to the name coronavirus by analogy to either the corona of the sun or the crowns of thorns (corona spinarum) used in medieval artworks (Holmes, 1985).

Coronaviruses have historically been arranged antigenically into five groups (Wege, et al., 1982). One group includes FIPV and the related feline enteric coronavirus (FECV), canine coronavirus (CCV), transmissible gastroenter-

itis virus of swine (TGEV), and human coronavirus 229E (HCV-229E). A second group includes human coronavirus OC43 (HCV-OC43) and related isolates, MHV, rat coronavirus (RCV) and sialodacryoadenitis virus (SDAV), bovine coronavirus (BCV), and hemagglutinating encephalomyelitis virus of swine (HEV). The avian coronaviruses have been classified into two separate groups typified by infectious bronchitis virus (IBV) of chickens and turkey coronavirus (TCV). There are also several unclassified coronaviruses including an enteric coronavirus of rabbits (RECV) (Descoteaux and Lussier, 1990), a coronavirus which induces myocarditis after experimental inoculation of rabbits (Edwards, et al., 1992), and a coronavirus isolated from a horse (Mair et al., 1990).

Within this classification framework, recent work suggests that the barriers between antigenic groups are not absolute. TCV has been shown to be related antigenically to IBV as well as two mammalian coronaviruses, MHV and BCV (Dea, et al., 1990). Furthermore, an evolutionary relationship between TCV, BCV, MHV, and HCV-OC43 is supported by genetic sequence analysis of the 3' ends of these viruses (Verbeek and Tijssen, 1991). There is also evidence from a recent monoclonal antibody (mAb) analysis that HCV-229E should be moved out of the TGEV group (Sanchez, et al., 1990).

Beyond these changes within the coronavirus family, the Coronaviridae is now seen to represent a larger RNA virus superfamily. Toroviruses have been isolated from horses (Snijder, et al., 1990b), cattle (Koopmans, et al., 1991), cats (Muir, et al., 1990), and humans (Beards, et al., 1984). Though morphologically different (toroviruses have a tubular nucleocapsid), the genomic organization (Snijder, et al., 1990b; Snijder, et al., 1991) and protein structure (Snijder, et al., 1990a) of toroviruses and coronaviruses are very similar and there is evidence for recombination between toroviruses and coronaviruses during their co-evolution (Snijder, et al., 1991). Equine arteritis virus (EAV) contains an icosahedral-core and has been classified historically as a togavirus but is now included in the coronavirus superfamily because of its similar genetic organization (Den Boon, et al., 1991). Another traditional member of the Togaviridae, lactate dehydrogenase-elevating virus (LDHV), is also similar genetically to coronaviruses (Den Boon, et al., 1991; Kuo, et al., 1991).

### *Coronavirus infection of cells*

Coronaviruses appear to enter cells via plasma membrane fusion without significant involvement of phagocytic or endosomal pathways (Kooi, et al., 1991; Payne, et al., 1990; Stoddart, 1989; Sturman, et al., 1990; Weismiller, et al., 1990). Neither cytochalasin B (which disrupts cellular microfilaments and phagocytosis) nor lysosomotropic bases (which elevate endosomal pH) affected infection of macrophages by FIPV (Stoddart, 1989). BCV infection

of human rectal tumor cells was likewise unaffected by lysosomotropic bases and an electron microscopic analysis demonstrated BCV fusion only with the plasmalemma, not with intracellular membranes (Payne, et al., 1990). MHV infection of fibroblasts has also been found to be largely independent of endocytotic pathways (Kooi, et al., 1991).

The ability of a given coronavirus to infect specific hosts and/or tissues is thought to be dependent upon the presence of a specific cellular receptor (Lai, 1990). A receptor for MHV has recently been identified on murine enterocyte and hepatocyte membranes (Williams, et al., 1991) and cloned (Dvelsler, et al., 1991). The receptor is a 120 kilodalton (kDa) glycoprotein of the immunoglobulin superfamily, with amino acid sequence and antigenic homologies to members of the carcinoembryonic antigen family of proteins (Williams, et al., 1991). Transfection of fibroblasts with the putative MHV receptor gene conferred susceptibility to infection whereas mAb to the receptor blocked infection (Dvelsler, et al., 1991). In addition, the presence of a functional form of the receptor correlated with tissue and mouse strain susceptibility to infection with MHV (Williams, et al., 1991). To date, no work has been published concerning a receptor for FIPV.

### *Coronavirus genetics and replication*

A number of reviews have outlined the molecular biology of coronaviruses (Holmes, 1985; Lai, 1990; Spaan, et al., 1988; Sturman and Holmes, 1983). These will be drawn upon to create a model into which recent advances in the molecular biology of FIPV can be integrated.

Replication of coronaviruses is accomplished entirely in the cytoplasm of infected cells. The genome of coronaviruses is single-stranded RNA of positive polarity. Upon initial infection of a cell, the 5'-capped and 3'-polyadenylated genomic RNA can function as messenger RNA (mRNA). Coronaviruses are among the largest RNA viruses; the genome of IBV is over 27 kilobases (kB) (Boursnell, et al., 1987). Viral replication and transcription occur via the formation of double-stranded (ds) RNA replicative intermediates (RIs). A stretch of highly conserved nucleotides about 80 bases from the 3' end of the genome has been identified as a negative-strand initiation signal (Lai, 1990). Traditionally it was thought that new positive-sense, genomic-length RNA as well as positive-sense, subgenomic mRNAs were all transcribed off a genomic-length RI (Lai, et al., 1982). However, results from recent studies of TGEV (Sethna, et al., 1989; Sethna, et al., 1991), MHV (Sawicki and Sawicki, 1990), and BCV (Liu, et al., 1991) have demonstrated transcription via subgenomic RIs as well.

Coronavirus mRNAs form a 3'-nested set, i.e. all of the mRNAs share the same sequences at their 3' ends. The number of mRNAs varies among different coronaviruses. FIPV and IBV produce 6 mRNAs, TGEV produces 7

mRNAs, and BCV produces 8 mRNAs, including the genomic-length mRNA in each case. Despite this variation in number, there is a consensus coding pattern among all coronaviruses. From 5' to 3' the gene order is polymerase (Pol) polyprotein, spike (S) protein, membrane (M) protein, and nucleocapsid (N) protein, with nonstructural (NS) protein genes variably interspersed (Lai, 1990). The coding assignments (where known) and sizes of the FIPV (strain 79-1146) mRNAs are as follows: mRNA 1, 20 kB-genomic RNA (De Groot, et al., 1987d); mRNA 2, 9.6 kB- S protein (De Groot, et al., 1987c; De Groot, et al., 1987d); mRNA 3, 5.2 kB (De Groot, et al., 1987d); mRNA 4, 3.8 kB- M protein (De Groot, et al., 1987d; Vennema, et al., 1991); mRNA 5, 2.8 kB- N protein (De Groot, et al., 1987d; Vennema, et al., 1991); and, mRNA 6, 1.45 kB- open reading frames (ORFs) 1 and 2 (De Groot, et al., 1988). Each of the 6 FECV strain 1683 mRNAs has been found to be 0.3 kB shorter than the corresponding FIPV 79-1146 mRNAs, suggesting a deletion of 300 nucleotides at the 3' end of the FECV genome (Baines, 1988).

Although all but the smallest coronavirus mRNAs are structurally polycistronic, most are functionally monocistronic since only the unique 5'-most ORF of each mRNA is translated (Lai, 1990; Spaan, et al., 1988). Exceptions to this include the mRNAs which encode the polymerase proteins (see below), mRNAs 2 and 5 of MHV and mRNA 3 of TGEV (Shieh, et al., 1989; Spaan, et al., 1988), mRNAs 3 and 5 of IBV (Liu, et al., 1991), and mRNA 6 of FIPV (De Groot, et al., 1988). FIPV mRNA 6 encodes 2 polypeptides, an 11 kDa protein from ORF-1 and a 22 kDa protein from ORF-2. ORF-1 is homologous to ORF-X3 from TGEV, which is also encoded by the 3'-most mRNA of TGEV, mRNA 7. The 11 kDa protein from ORF-1 has structural similarity to membrane proteins (De Groot, et al., 1988). TGEV mRNA 7 lacks a homolog to ORF-2 (De Groot, et al., 1988). Thus, the deletion at the 3' end of the FECV genome compared to the FIPV genome (Baines, 1988) may be very interesting since both TGEV and FECV are largely restricted to replication in enterocytes, whereas FIPV infects macrophages in a variety of tissues systemically.

The genomic-length mRNAs of coronaviruses encode the RNA-dependent RNA polymerase proteins (Lai, 1990). Research with MHV has demonstrated two "temporally and enzymatically distinct...polymerase activities" in MHV transcription (Brayton, et al., 1984). In addition, *in vitro* translation of the genomic-length mRNA of MHV-A59 resulted in the detection of two predominant protein products, p220 and p28. The p28 product was shown to be the N-terminal portion of a larger precursor protein (p250) and could be detected by two-dimensional gel electrophoresis of MHV-infected cells only at late times (5-8 hours) after infection (Denison and Perlman, 1987). Cloning, sequencing, and *in vitro* translation of the IBV (Bournsnell, et al., 1987; Briery, et al., 1987; Briery, et al., 1989) and MHV (Lee, et al., 1991) Pol mRNAs has revealed that in both cases two ORFs are translated via a -1

frameshifting-pseudoknot to produce the Pol polyprotein. Nucleotide (Lee, et al., 1991) and protein (Denison, et al., 1991) sequence analysis of the MHV Pol region has also delineated a number of putative functional domains. These include membrane anchor, cysteine-rich, and protease domains in ORF-1a (Lee, et al., 1991), as well as polymerase, helicase, and zinc-finger domains and protease cleavage sites in ORF-1b (Denison, et al., 1991; Lee, et al., 1991). Similar domains have also been identified in the IBV (Gorbalenya, et al., 1989), torovirus, and EAV (DenBoon, et al., 1991) polymerases. But despite identification of these domains by sequence analysis, it is still unclear what the exact relationship is between the component proteins identified and the early and late polymerase activities which have been functionally defined. However, a group of temperature-sensitive (ts) mutants of MHV have been identified. These mutations fell into 5 complementation groups relative to positive- and negative-sense RNA transcription (Schaad, et al., 1990). Sequence analysis of such mutations may allow assignment of distinct polymerase functions to specific polymerase protein components.

For a given coronavirus, genomic-length and subgenomic mRNAs all contain an identical 5' leader sequence, the length of which varies among different coronaviruses (Spaan, et al., 1988). Lai and colleagues, working with MHV, have pioneered research into the role of leader RNA in coronavirus transcription. In 1984, the leader segments of several MHV A59 mRNA species were sequenced and found to be identical (Lai, et al., 1984). The same sequence was also found at the 5' end of the genomic-length RNA, suggesting that the 5'-genomic RNA coded for the mRNA leaders via the complementary 3' end of the negative-sense strand of the RI. Lai and colleagues reasoned that since coronavirus replication is an entirely cytoplasmic process, conventional eukaryotic splicing, a nuclear process, could not explain their findings. They also found a sequence complementary to a region near the 3' end of the leader at the initiation site for mRNA 7, suggesting a role for the leader in transcription initiation (Lai, et al., 1984). In 1986, Makino and colleagues demonstrated that during a mixed infection with two different MHV strains (B1 and CA21), the respective leader sequences could freely reassort (Makino, et al., 1986b). They have further demonstrated that such reassortment/recombination occurs at a high frequency (Makino, et al., 1986a; Makino et al., 1989b). It also appears that recombination occurs randomly with respect to the site of crossover (Banner and Lai, 1991). (A previous report had suggested that recombination crossover sites were clustered near a hypervariable region in the S gene (Banner et al., 1990).) The ability to study such recombinants may play a critical role in elucidating questions of coronavirus pathogenesis (Baines, 1988). Recombinants have already been used to localize functionally important epitopes on the S protein of MHV (Makino, et al., 1987).

Coronavirus transcription is thus proposed to occur via a discontinuous,

leader-primed mechanism (Lai, 1990). The leader is transcribed from the 3' end of the RI's negative-sense strand, dissociates from this template, then reassociates with the template at intergenic sites and primes downstream transcription. The sites of leader reassociation with the template are determined by homologous binding between sequences near the 3' end of the leader sequence and a consensus sequence in the intergenic regions. (Such a consensus intergenic sequence has been identified preceding the ORFs for the FIPV S (DeGroot, et al., 1987c), M, and N (Vennema, et al., 1991) proteins.) The 3' end of the MHV leader contains repeats of a UCUAA sequence which is also imperfectly repeated at intergenic sites (Lai, 1990). The number of repeats in the leader not only varies among strains of MHV but can also change during passage in vitro (Lai, 1990; Makino, et al., 1989a). These pentanucleotide repeats are thought to play an important role in the binding of leader to intergenic sequence RNA (Makino, et al., 1989a).

Coronavirus mRNAs are not all synthesized in equal amounts during transcription, but their individual, relative rates of synthesis are constant throughout transcription (Spaan, et al., 1988). The relative abundance of the mRNA species progressively increases from 5' to 3' along the genome (Konings, et al., 1988). Two factors may be responsible for governing this gradient in mRNA levels: the relative degree of homology, and thus binding efficiency, of leader RNA to the intergenic sequences (Lai, et al., 1984; Makino, et al., 1989a); or, the internal initiation events during leader-primed transcription, which may occur slowly enough to block the elongation of passing transcripts (Konings, et al., 1988). The later theory proposes that upstream transcripts are forced to pause at new sites of initiation and thus prematurely terminate and dissociate from the template. Such incomplete transcripts had previously been detected (Makino et al., 1986a). Ultimately, both mechanisms may be acting together to govern mRNA levels. In addition, with the recognition of subgenomic-mRNA replication (Hoffman, et al., 1990; Sawicki and Sawicki, 1990; Sethna, et al., 1989; Sethna, et al., 1991), it is possible that differing efficiencies of subgenomic-mRNA replication may also affect mRNA levels.

### *Coronavirus structural proteins*

#### *S protein*

All coronaviruses encode at least three structural proteins: S (formerly E2), M (formerly E1), and N (Holmes, 1985; Spaan, et al., 1988; Sturman and Holmes, 1977). The S protein forms the peplomers which project from the surface of virions and are responsible for receptor binding, induction of cell-to-cell fusion and fusion of the viral envelope with target cell membranes, induction of neutralizing Ab, and induction of cell-mediated immune (CMI) responses. In addition, alterations in the S protein have been shown to affect the virulence of MHV (Dalziel, et al., 1986) and BCV (Zhang, et al., 1991).



The MHV S protein also has Fc receptor-like activity (Oleszak, et al., 1992); binding of nonspecific Ab to cell surface-exposed S proteins may protect the infected cell from virus-specific Ab attachment and antibody-dependent cellular cytotoxicity (Oleszak, et al., 1992).

Coronavirus S proteins are 180–205 kDa glycoproteins with asparagine-linked (N-linked) oligosaccharide attachment. They contain an N-terminal signal sequence, a large domain exterior to the virus envelope, a transmembrane domain, and a C-terminal hydrophilic tail interior to the virus envelope (Spaan, et al., 1988). Each peplomer consists of 3 molecules of S protein arranged in a coiled-coil structure (De Groot, et al., 1987a; De Groot, et al., 1987b). The sequence of each S polypeptide can be divided into two regions, S1 and S2. S1 is the N-terminal portion and S2 is the region between S1 and the transmembrane domain (Spaan, et al., 1988). Studies of FIPV have confirmed that its S protein is also N-linked glycosylated (Olsen, et al., 1992c; Vennema, et al., 1990b), structurally similar to the generalized coronavirus S protein (De Groot, et al., 1987c), and responsible for mediating cell-to-cell fusion and neutralizing Ab induction (De Groot, et al., 1989).

There has been substantial interest in the extent to which S1/S2 proteolytic cleavage occurs among coronaviruses. Results appear to depend upon the virus in question as well as the cell type involved (Frana, et al., 1985; Spaan, et al., 1988). The S proteins of IBV and BCV appear to be cleaved consistently (Binns, et al., 1985; Cavanaugh, et al., 1986). Cleavage of the MHV S proteins varies among different MHV strains and the S proteins of FIPV, CCV, and TGEV were not thought to be cleaved at all (Spaan, et al., 1988). However, a trypsin-sensitive cleavage site has recently been demonstrated in the S protein of FIPV and FECV (Baines, 1988). Cleavage at this site did not occur during normal processing of the virus in cell culture and cleavage with exogenous trypsin did not increase virus infectivity for A72 or Crandell feline kidney cells (CrFKC). Cleavage did, however, increase the ability of attenuated strains of FIPV to infect feline macrophages (Baines, 1988). A latent cleavage site may also exist in the TGEV S protein (Rasschaert and Laude, 1987).

The degree of amino acid sequence homology among the S proteins of various coronaviruses differs for the S1 and S2 portions of the polypeptides. A comparison between FIPV, MHV, and IBV revealed 29–35% homology in S2, but little homology in S1 (DeGroot, et al., 1987b). Within the FIPV antigenic group of viruses, however, there is much greater homology throughout the S protein. A significant degree of antigenic homology has been noted among the S proteins of TGEV, porcine respiratory coronavirus (PRCV), FIPV, FECV, and CCV (Sanchez, et al., 1990). Comparison of the S gene sequences of TGEV and FIPV has revealed 39% homology over the first 274 amino acids and 93% homology for residues 275–1447 (Jacobs, et al., 1987).

Extensive efforts have gone into mapping the dominant antigenic sites on the S proteins of TGEV (Correa, et al., 1988; Correa, et al., 1990; Delmas, et

al., 1986; Delmas, et al., 1990; Garwas, et al., 1987; Gebauer, et al., 1991; Laviada, et al., 1990; Posthumus, et al., 1990), BCV (Yoo, et al., 1991), IBV (Koch, et al., 1990; Kusters, et al., 1989), MHV (Makino, et al., 1987; Routledge, et al., 1991; Stuhler, et al., 1991; Takese-Yoden, et al., 1990), and FIPV (Corapi, et al., 1992; Olsen, et al., 1992a). In all cases, multiple neutralizing domains have been delineated, with immunodominant domains generally located in the S1 portion of the protein. Neutralization domains have, however, been identified in S2 as well (Koch, et al., 1990; Kusters, et al., 1989; Makino, et al., 1987; Posthumus, et al., 1990; Routledge, et al., 1991). On the FIPV S protein, a number of epitopes have been defined which appear to mediate both virus neutralization and antibody-dependent enhancement (ADE) of FIPV infectivity (Corapi, et al., 1992; Olsen, et al., 1992a; Olsen, et al., 1992b).

Coronavirus S proteins are co-translationally glycosylated, with the majority of S protein incorporated into budding virions and a smaller portion transported to the plasma membrane (Sturman and Holmes, 1975). S protein which was incorporated into virions was transported substantially faster than recombinant-expressed S protein (DeGroot, et al., 1989; Vennema, et al., 1990b), suggesting the existence of a retention signal in the cytoplasmic tail of S (Vennema, et al., 1990b). A second study, however, would appear to refute the presence of such a retention signal since C-terminally-truncated S protein expressed by a recombinant vaccinia virus was completely retained in the endoplasmic reticulum (ER) of infected cells (Pulford and Britton, 1991). Trimerization of the TGEV S protein has been shown to occur primarily at a stage when the carbohydrate moieties are only partially trimmed, with terminal glycosylation occurring mainly on trimeric S protein (Delmas and Luade, 1990). In addition, oligomerization appears to be the rate-limiting step in transport of TGEV S protein from the ER to the Golgi body (Delmas and Luade, 1990). Antigenic sites on the TGEV S protein may be structurally dependent upon or independent of trimerization (Delmas and Luade, 1990). However, the majority of antigenic sites on both the S and M proteins of TGEV appear to require at least core-glycosylation (Delmas and Luade, 1991). This appears not to be the case for the S protein of FIPV (Olsen et al., 1992c), despite the high degree of antigenic homology between the S proteins of FIPV and TGEV (Jacobs, et al., 1987).

### *M protein*

The M or membrane proteins of coronaviruses are smaller surface glycoproteins, approximately 25–30 kDa in size (Spaan, et al., 1988). As opposed to the substantial external portion of coronavirus S proteins, only about 10% of the N-terminal portion of the M proteins protrudes from the viral envelope (Spaan, et al., 1988). The form of glycosylation (N-linked or O-linked) and the presence or absence of a signal peptide on the M protein varies among

different coronaviruses (Spaan, et al., 1988). The M proteins of TGEV (Pulford and Britton, 1990), IBV (Lai, 1990), and FIPV and FECV (Baines, 1988) are N-linked glycoproteins, whereas glycosylation of the M protein of MHV is O-linked (Lai, 1990). For those coronaviruses lacking an N-terminal signal sequence on the M protein, one of the three alpha helices which span the developing virus membrane may function as a signal sequence (Spaan, et al., 1988). The first membrane spanning domain may also be responsible for targetting M proteins to the Golgi (Machamer, et al., 1990). M protein is necessary for virus maturation and its insertion into Golgi membranes determines, via interaction with the N protein, the sites of virus assembly and budding (Holmes, 1985; Lai, 1990; Spaan, et al., 1988). Though the S proteins have traditionally been associated with the induction of protective immune responses to coronaviruses, mAb to the M protein of MHV has been shown to protect mice against acute encephalitis (Fleming, et al., 1989). In addition, a recombinant vaccinia virus expressing the M protein of FIPV 79-1146 induced protection against challenge with virulent FIPV for 3 of 8 vaccinated cats (Vennema, et al., 1991).

### *N protein*

The third structural protein common to all coronaviruses is the N protein. The N proteins are highly basic proteins of 43–50 kDa which are phosphorylated on serine residues (Spaan, et al. 1988). Like many viral nucleocapsid proteins, the coronavirus N proteins encase the genomic RNA and play an integral part in formation of the helical nucleocapsids (Spaan, et al. 1988). In addition, N protein appears to be critical for viral transcription. In vitro studies have demonstrated that antibody to N protein inhibited transcription of MHV (Baric, et al., 1988). Subsequent studies confirmed a specific interaction of N protein with MHV leader RNA at bases 56 to 65 (from the 5' end of the leader) and ruled out direct binding of N protein to negative-sense RNA in RIs (Baric, et al., 1988; Stohlman, et al., 1988). These authors suggested that N protein may be an integral part of the transcription complex, possibly functioning to open secondary structure constraints known to occur at the region of N binding, targeting the transcription complex of protein and leader RNA during the discontinuous transcription process, or serving to prevent RNA-RNA base pairing after transcription. A sequence comparison of the N genes from 5 strains of MHV has demonstrated that each N protein contains 3 highly homologous domains separated by 2 more variable "spacer regions". The central domain appears to be responsible for RNA binding (Parker and Masters, 1990). The level of N protein may also act as the switch between transcription/mRNA synthesis and replication/genomic RNA synthesis for coronaviruses (Lai, 1990). Involvement of N proteins in the transcription of helical RNA viruses is by no means limited to coronaviruses. N

protein functions similarly during the transcription and replication of rhabdoviruses (Banerjee, 1987).

### *HE protein*

A fourth structural protein, HE, is present in certain strains of MHV as well as BCV and HCV-0C43. It is a glycoprotein of approximately 65kDa which functionally exists as a dimer (Hogue, et al., 1989; Spaan, et al., 1988). This protein from BCV has been shown to have hemagglutinating activity and to be a "receptor-destroying enzyme with acetylerase activity" (Hogue, et al., 1989; Spaan, et al., 1988; Storz, et al., 1991; Vlasak, et al., 1988). Recent work, however, indicates that the S protein of BCV is actually a more efficient hemagglutinin than the HE protein (Schultze, et al., 1991). No such HE protein has been identified for FIPV.

Completion of the coronavirus replication cycle requires encapsidation of viral RNA and release of virions from infected cells. Recent studies with MHV have demonstrated a 347-nucleotide encapsidation sequence at the 3' end of ORF-1b (Makino, et al., 1990; Van Der Most, et al., 1991). This location would explain the fact that only genomic-length MHV RNA is packaged (Van Der Most, et al., 1991). However, BCV (Hoffman, et al., 1990) and TGEV (Sethna, et al., 1991) subgenomic RNAs are also packaged, suggesting that this encapsidation sequence site may not be consistent among all coronaviruses. Subsequent to passage through the Golgi, mature virions may be released from post-Golgi vesicles by either fusion with the plasma membrane or cell lysis (Holmes, 1985).

### *Clinical aspects of coronavirus infections*

Coronaviruses produce a broad range of disease manifestations in their respective hosts (McIntosh, 1985; Wege, et al., 1982). Many coronaviruses induce diseases limited to a single organ system. For instance, TCV, BCV, CCV, RECV, FECV, and TGEV produce primarily enteric disease while IBV, RCV, and the HCVs are mainly respiratory tract pathogens. A respiratory coronavirus has also been identified recently in swine. It was initially sought out because of a high incidence of TGEV Ab in populations of pigs without evidence of TGEV-related enteric disease (Pensaert, et al., 1986; Van Nieuwstadt and Pol, 1989). Experimentally, the severity of clinical disease associated with porcine respiratory coronavirus (PRCV) infection has varied from mild (O'Toole, et al., 1989) to fatal (Van Nieuwstadt and Pol, 1989) and may depend upon the strain and dose of PRCV and the age of piglets at challenge. Though PRCV primarily infects epithelial cells and macrophages in the respiratory tract, it is also capable of limited replication in the gastrointestinal tract (Cox, et al., 1990a; Cox, et al., 1990b; O'Toole, et al., 1989). Like FIPV

and FECV, TGEV and PRCV are very similar antigenically across the S, M, and N proteins, though mAb analysis of their S proteins appears to offer a method for differentiating these two viruses (Callebaut, et al., 1988; Callebaut, et al., 1989). Genetic comparisons of PRCV and TGEV have revealed deletions in the PRCV S gene and the first NS gene downstream of S (Page, et al., 1991; Rasschaert, et al., 1990; Wesley, et al., 1991). Interestingly, analysis of a small plaque variant of TGEV also revealed alterations in the NS genes downstream of S (Wesley, et al., 1990). This variant virus also exhibited a different cell tropism within the small intestine. As previously noted, the FECV genome also appears to be deleted in comparison to FIPV.

As opposed to these coronaviruses which induce disease of primarily a single organ system, disease manifestations of MHV and FIPV infections involve a variety of organs (Wege, et al., 1982). In MHV infections, the exact nature of the disease produced (hepatic, neurologic, or enteric) depends upon the strain of virus and the route and dose of inoculation, as well as host factors such as age and genetic make-up (Levy, et al., 1984; Wege, et al., 1982). The pathogenicity of MHV-3 for different strains of mice has also been correlated with the ability of the virus to either replicate in or lyse macrophages or lymphocytes or mediate T cell-induced expression of a procoagulant monokine (Chung, et al., 1991; Lamontagne, et al., 1989a; Lamontagne, et al., 1989b; Lamontagne and Jolicoeur, 1991; Levy and Abecassis, 1989). Similar correlations between host resistance to virus infection *in vivo* and intrinsic resistance (Morahan, et al., 1985) of macrophages to infection *in vitro* have been documented for several other virus families (Mogensen, 1985). As will be seen, the nature of FIP is also multifactorial with regard to virus strain, host parameters, and virus-immune cell interactions.

#### FELINE CORONAVIRUSES

FIPV is only one of the coronaviruses which can infect cats. Most notably, a distinction must be drawn between FIPV and FECV (Pedersen, 1983a; Pedersen, et al., 1981b; Pedersen, et al., 1984; Stoddart and Gaskell, 1985; Tupper, et al., 1987). FECV infections are generally inapparent or induce only mild enteritis, though more severe enteric disease has been seen in young, specific-pathogen-free (SPF) kittens (Pedersen, 1983a; Pedersen, et al., 1981b). Clinical signs may include a low-grade fever, mucoid diarrhea, sometimes with hematochezia, occasional vomiting, anorexia, and lethargy. A transient leukopenia may accompany the onset of diarrhea. FECV targets the epithelium of the small intestine. Histologically, villous atrophy may develop (most prominently in the jejunum and ileum) in severe cases. Serum antibodies appear 10–14 days after infection (Pedersen, 1983a).

FECVs must also be differentiated from “coronavirus-like particles” (CVLPs). CVLPs have been detected in the feces of a variety of species of

animals, both with and without diarrhea. These include rodents, dogs, cats, pigs, cows, poultry species, man, and non-human primates (Hoshino and Scott, 1980). CVLPs detected in the feces of clinically normal cats were morphologically similar to CVLPs from other species (Hoshino and Scott, 1980). CVLPs can be distinguished from enteric coronaviruses based upon the ultrastructural characteristics of their surface projections. Coronavirus peplomers are typically petal-shaped with a short stalk whereas the projections from the surface of CVLPs are spherical or teardrop-shaped and attached via a long stalk (Hoshino and Scott, 1980). (Based upon this distinction, one report (Dea, et al., 1982) of feline CVLPs may have been describing a true enteric coronavirus.) The role of CVLPs as pathogenic agents or their identity as viruses is yet to be conclusively determined (McIntosh, 1985).

It is vitally important to realize that there are multiple strains of both FIPV and FECV which vary substantially in pathogenicity (Fiscus, et al., 1987; Fiscus and Teramoto, 1987b; Pedersen and Floyd, 1985; Stoddart, 1989; Stoddart and Scott, 1989). Among FIPV strains, for instance, UCD2 is relatively avirulent, UCD3 and 4 are intermediate in virulence, and UCD1 and 79-1146 are extremely virulent (Pedersen and Floyd, 1985). Feline coronaviruses have also been separated into two groups based upon reactivity with S protein-specific mAbs. Group I viruses are typified by FIPV strains UCD2 and 3 and NW1, while group II consistently includes 79-1146, DF2/Nor15, and FECV 1683 (Fiscus and Teramoto, 1987a; Fiscus and Teramoto, 1987b; Hohdatsu, et al., 1991b). The classification of FIPV strains UCD1 and 4 and TN406/Black varies between studies. This type of antigenic classification may also reflect biological characteristics such as rate of internalization and cell-to-cell spread (Fiscus and Teramoto, 1987b).

Certain strains of feline coronaviruses (e.g., the Yayoi strain) can apparently produce both enteritis with diarrhea as well as fatal FIP (Hayashi, et al., 1982). The existence of such intermediate strains and the antigenic similarity among FIPV and FECV isolates may indicate that all feline coronaviruses are simply different biotypes of a single prototypical virus (Scott, 1989). It has even been suggested that that FIPV strains are directly derived from FECVs by mutation or recombination in the gastrointestinal tract of an infected cat (Evermann, et al., 1991; Pedersen, et al., 1981b).

Finally, cats can also be infected with heterologous coronaviruses from other species. Cats which were infected experimentally with TGEV shed the virus in their feces and mounted homologous and heterologous humoral immune responses (Reynolds and Garwes, 1979). Conversely, pigs infected orally with virulent FIPV demonstrated clinical signs, histologic lesions, and coronaviral antigen localization typical of TGEV infection (Woods, et al., 1981). Cats infected with CCV remained clinically normal and demonstrated homologous as well as heterologous humoral immune responses, but virus was not detectable in their stools (Barlough, et al., 1984). Infection of cats with HCV-

229E resulted in only an homologous antibody response, with "little or no replication of the virus in inoculated animals" (Barlough, et al., 1985). Given this potential for cross-species infection and the close antigenic relationship between FIPV, FECV, TGEV, and CCV (Horzinek, et al., 1982; Pedersen, et al., 1978; Sanchez, et al., 1990), all of these viruses may be host-range mutants of one another (Horzinek, et al., 1982).

#### CLINICAL ASPECTS OF FIP

The clinical characteristics of FIP in domestic cats have been well outlined (Barlough and Scott, 1988; Hoskins, 1991; Pedersen, 1983b; Pedersen and Floyd, 1985; Scott, 1989; Stoddart and Gaskell, 1985). Although a cat of any age may be affected, disease occurs most often in cats from 6 months to 5 years of age, with the majority of cases occurring in cats  $\leq 1$  year of age (Addie and Jarrett, 1992; Scott, 1991). It has been suggested that the incidence of FIP is greater among purebred cats (Pedersen, 1983b), though it is unclear whether this reflects an actual genetic predisposition to infection or only increased FIPV exposure and transmission in cattery situations (Scott, 1991). Although the attack rate for FIP is greater in catteries and multi-cat households, it is still a disease which usually occurs only sporadically (Pedersen, 1983b).

##### *Transmission and shedding of FIPV*

Transmission of FIPV is thought to occur via ingestion or inhalation subsequent to cat-to-cat contact. FIPV is shed from infected cats in their feces and oronasal secretions. Virus shedding has only been documented to occur for 14–15 days after experimental infection. Thus, most cats are probably not shedding the virus at the time of clinical illness (Scott, 1991; Stoddart, et al., 1988a,b,c). There have been reports of transplacental transmission and reproductive tract disease manifestations (Scott, 1991), but this route of transmission and form of disease are yet to be conclusively proven experimentally. Anecdotal reports, however, indicate that queens, both seropositive and possibly seronegative, may repeatedly give birth to kittens which develop FIP over the first few months of life (Scott, 1991).

Survival of FIPV in the environment has traditionally been assumed to be quite limited, given the enveloped nature of coronaviruses. A recent report, however, suggests that after drying onto a surface, infectious virus may persist for up to 7 weeks (Scott, 1991). Nonetheless, FIPV is readily inactivated by commonly used disinfectants (Scott, 1991).

The incubation period for FIP varies greatly. It may be as short as two weeks or clinical disease may not be evident for months to years following infection (Scott, 1989). The existence of an FIPV latent carrier state remains an assumption, but is supported by such circumstantial evidence as the prolonged

incubation periods and the apparent activation of clinical disease upon subsequent infection with FeLV (Pedersen, 1983b) or corticosteroid treatment (Pedersen and Floyd, 1985). In addition, a recent study of multicat households in the UK also supports the existence of asymptomatic carrier cats, their importance in FIPV transmission, and the potential for FIPV shedding subsequent to the first 15 days after infection (Addie and Jarrett, 1992).

### *Clinical signs*

There are two major forms of FIP, the effusive or “wet” form and the non-effusive or “dry” form. In addition, there may be a combination of these forms with multiple granulomas but only limited, localized fluid accumulation. In the effusive form of the disease, fibrin-rich fluid accumulates in the peritoneal, pleural, pericardial, and/or renal subcapsular spaces. The specific signs exhibited by each cat depend upon the site of the effusion. The abdominal enlargement seen with peritoneal fluid accumulation is generally non-painful. Dyspnea may accompany significant pleural effusion and signs of cor pulmonale may accompany pericardial effusion. Renal subcapsular fluid accumulation is sometimes palpable upon physical examination. Regardless of the site(s) of fluid extravasation, there are certain general signs which are typically present in all cases: anorexia, weight loss, listlessness, dehydration, and fever. The fever may fluctuate over a diurnal or longer pattern. Other specific signs may occur with extension of the inflammatory process in the peritoneum to specific organs, e.g., jaundice with hepatic involvement. Likewise, exocrine or endocrine pancreatic insufficiency may become evident with pancreatic involvement, but this is rare.

Signs associated with non-effusive FIP are more unpredictable because of the more discrete nature of organ involvement by the pyogranulomatous lesions. Fever, however, is particularly consistent with this form of FIP and may be the only initially-evident clinical sign. Consequently, FIP should be a prominent rule-out for cats which present with a fever-of-unknown-origin. Central nervous system (CNS) and ocular involvement are more common with the non-effusive form of FIP. CNS signs may reflect spinal cord involvement with upper-motor neuron paresis and ataxia, or cerebral or cerebello-medullary lesions with ataxia, nystagmus, behavioral changes, or seizures. Signs of ocular disease may accompany other manifestations of FIP or may be the only clinically apparent evidence of FIP. Most commonly the uveal tract is involved, resulting in iritis, uveitis, or chorioretinitis. Retinal hemorrhage and detachment or panophthalmitis may also occur.

The course of disease tends to be different for the various forms of FIP. Cats with effusive disease generally progress along a more fulminant course, with death in weeks to several months. Young kittens tend to survive for the shortest periods of time. The non-effusive form of the disease may wax and



wane over a period of many months, particularly in cases with only ocular involvement.

#### PATHOGENESIS OF FIP

Our understanding of the pathogenesis of FIP is still incomplete and evolving. It is clear that exposure to FIPV does not consistently correlate with the development of clinical disease (Pedersen, 1983b). Other disease determinants may include the strain of FIPV involved (Pedersen and Floyd, 1985), the dose and route of infection (Pedersen, et al., 1981a), nonspecific stress factors, and the age (Stoddart and Gaskell, 1985), immune status/FeLV status (Pedersen, 1983b), and genetic makeup of the cat (Pedersen, 1983b).

Support for the role of genetic factors comes from the possible increased incidence of FIP in purebred cats and from the nature of FIP in cheetahs. FIPV has been documented to cause clinical disease in a variety of exotic felid species including cheetahs, sand cats, caracals, lynx, cougars, jaguars, leopards, pallas cats, and lions (Barlough and Scott, 1988; Pedersen, 1983b). Cheetahs, however, appear to be exceptionally sensitive to FIPV infection. FIPV infection in a captive breeding colony of cheetahs in Oregon in 1983 produced a "disease storm" with high morbidity and mortality. Investigations of this epizootic (Evermann, et al., 1988; O'Brien, et al., 1985) demonstrated that cheetahs are genetically homogeneous at their major histocompatibility (MHC) loci. It has been hypothesized that because of a lack of MHC variability, cheetahs may be deficient in their ability to present FIPV antigen and mount protective immune responses (O'Brien, et al., 1985). The recent characterization of the domestic cat MHC (Winkler, et al., 1989) should allow further investigation into the possible genetic basis for any increased incidence of FIP in purebred domestic cats.

Following oronasal infection, FIPV first replicates in pharyngeal, respiratory (Hayashi, et al., 1983b; Scott, 1989), or intestinal epithelial cells (Pedersen, 1983b). A primarily cell-associated viremia subsequently occurs in which monocytes are the predominant cell type infected (Weiss and Scott, 1981b). Monocytes likely serve to distribute FIPV to target organs throughout the body. The virus localizes in macrophages in the reticuloendothelial organs and perivascularly in many organs (Weiss and Scott, 1981c). The histologic lesions of FIP are characterized as necrotizing pyogranulomas with phlebitis and thrombosis (Weiss and Scott, 1981c).

One of the most perplexing aspects of the pathogenesis of FIP is the frequent occurrence of accelerated, more fulminant disease upon FIPV challenge of seropositive as compared with seronegative cats. Accelerated FIP was first documented when it was shown that the onset of clinical disease among experimentally infected kittens correlated with the appearance of serum antibodies (Pedersen and Boyle, 1980). Confirmation of these results came with

the demonstration that the onset of viremia, clinical signs, thrombocytopenia, lymphopenia, and the appearance of viral antigen and necrotizing lesions in affected tissues all occurred earlier in seropositive kittens than in seronegative kittens (Weiss and Scott, 1981b; Weiss and Scott, 1981c). Survival times were also significantly shorter for seropositive kittens (Pedersen and Boyle, 1980; Weiss and Scott, 1981b). In addition, seronegative kittens given immune serum (Pedersen and Boyle, 1980; Weiss and Scott, 1981a) or anti-FIPV IgG (Pedersen and Boyle, 1980) before challenge developed clinical disease in the same manner and over the same time course as seropositive kittens. Jacobse-Geels and colleagues (Jacobse-Geels, et al., 1980; 1982) demonstrated immune complex and complement (C') deposition in FIP. Both host proteins as well as FIPV proteins have been demonstrated in the immune complexes purified from sera and ascites fluid of cats with FIP (Horzinek, et al., 1986), though the potential significance of an autoimmune component in the pathogenesis of FIP is yet to be evaluated. With activation of C', other inflammatory mediator cascades as well as the blood coagulation cascade may be initiated. Subclinical disseminated intravascular coagulation (DIC) has been demonstrated during experimental FIP (Weiss, et al., 1980). Other inflammatory mediators which have been implicated in the pathogenesis of FIP include IL1 (Goitsuka, et al., 1987), IL6 (Goitsuka, et al., 1990), and leukotriene B4 and prostaglandin E2 (Weiss and Vaughn, 1987).

The demonstration of immune complex deposition in FIP initially seemed to explain both the pathologic changes of FIP and the phenomenon of accelerated FIP. However, a new consideration has been introduced with the demonstration of antibody-dependent enhancement (ADE) of FIPV infection of macrophages *in vitro* (Corapi, et al., 1992; Hohdatsu, et al., 1991a; Olsen, et al., 1992b, 1993; Stoddart, 1989).

#### *Antibody-dependent enhancement of virus infectivity*

Antibody-dependent enhancement of virus infection occurs when monocytes or macrophages are more efficiently infected by complexes of virus plus Ab, via receptor-mediated endocytosis, than by virus alone (Porterfield, 1986). Since ADE of virus infection *in vitro* was first documented in 1964 (Hawkes, 1964), it has been demonstrated for a wide range of viruses. A partial list includes flaviviruses such as West Nile virus and Murray Valley encephalitis virus (Cardosa, et al., 1986; Pieris and Porterfield, 1981), alphaviruses such as Semliki Forest virus, Sindbis virus, and Western equine encephalitis virus (Chanas, et al., 1982; Pieris and Porterfield, 1981), bunyaviruses (Lewis, et al., 1989; Pieris and Porterfield, 1981), human respiratory syncytial virus (HRSV) (Gimenez, et al., 1989; Krilov, et al., 1989), influenza A virus (Ochiai, et al., 1988; 1990; 1992), LDHV (Inada and Mims, 1985), rabies virus (King, et al., 1984), murine cytomegalovirus (Inada, et

al., 1985), reoviruses (Burstin, et al., 1983), and arenaviruses (Lewis, et al., 1988). However, the most informative work regarding ADE of virus infection has come from studies of dengue virus (DV), human immunodeficiency virus (HIV), and most recently FIPV (see below).

Despite all of the descriptions of ADE of virus infectivity, numerous questions remain regarding the actual basis of the enhancement. For instance, which receptors mediate ADE of virus infectivity? Traditionally the process has been attributed to Fc receptors (FcRs) for IgG, both FcRI and FcRII (Littaua, et al., 1990; Porterfield, 1986). Work with HIV and simian immunodeficiency virus (SIV) has, however, demonstrated enhancement of virus infectivity via FcRs alone (Homsy, et al., 1989; Takeda, et al., 1988); via C' receptors (CRs) and CD4 in the presence of both C' and Ab (C'-ADE) (Montefiori, et al., 1990a,b; Robinson, et al., 1988a, 1990b,c) or in the presence of C' alone (Robinson, et al., 1989b); via FcR and CD4 (Connor, et al., 1991; Takeda, et al., 1990); and, in the presence of soluble CD4 (Allan, et al., 1990; Werner, et al., 1990) or synthetic peptides to HIV (DeRossi, et al., 1991) in the absence of serum and C'. CRs have been implicated in ADE of flaviviruses as well (Cardosa, et al., 1983). To date, reports of ADE of FIPV infectivity (Corapi, et al., 1992; Hohdatsu, et al., 1991a; Olsen, et al., 1992b; Stoddart, 1989) have reported only FcR-mediated enhancement in the absence of C'. Given the involvement of C' activation in the pathogenesis of FIP (Jacobse-Geels, et al., 1980; Jacobse-Geels, et al., 1982), the potential for C'-ADE of FIPV needs to be addressed as well.

A second question is what are the specific viral components which mediate ADE of infectivity for each virus? mAbs have been used to delineate viral proteins and specific epitopes involved in ADE of DV (Morens, et al., 1987), HIV (Robinson, et al., 1990a,b; 1991), and FIPV (Corapi, et al., 1992; Hohdatsu, et al., 1991a; Olsen, et al., 1992b). For FIPV, studies (Corapi, et al., 1992; Olsen, et al., 1992b) indicate that enhancement is strictly mediated by epitopes on the S protein, while a third paper found that M protein-specific mAbs could also mediate ADE of FIPV infectivity (Hohdatsu, et al., 1991a).

An associated fact is that individual epitopes are capable of mediating both virus neutralization (VN) and ADE of virus infectivity. This has been clearly shown for DV (Halstead, et al., 1984; Morens and Halstead, 1990) and HIV (Robinson, et al., 1991), as well as for FIPV (Corapi, et al., 1992; Hohdatsu, et al., 1991a; Olsen, et al., 1992b). Does the subclass of a given Ab determine whether it is able to mediate both neutralization and ADE of virus infectivity? Results with FIPV suggest that IgG2a mAbs can mediate both processes while IgG1 mAbs can only mediate VN (Corapi, et al., 1992). A report of ADE of HIV infectivity (Robinson, et al., 1990b) found no dependence upon Ig subclass, but since this was a report of C'-ADE, the results don't refute the conclusions from the FIPV report (Corapi et al., 1992).

Work with ADE of FIPV infectivity has demonstrated a bell-shaped distri-

bution of enhancement relative to Ab concentration, with maximal enhancement occurring at subneutralizing concentrations of Ab (Olsen, et al., 1992b). Similar results have been obtained with DV (Morens and Halstead, 1990). Mechanistically, how does the binding of enhancing Ab to a particular epitope on a virus induce an increase in virus infectivity? It has been suggested that enhancing Abs increase the binding of virus to cell surfaces, thereby potentiating a productive interaction between virus and its normal cell surface receptor (Connor, et al., 1991; Mady, et al., 1991; Porterfield, 1986). In support of this, bispecific Abs to DV or HIV and a variety of cell surface molecules in addition to FcRs were found to enhance virus infectivity (Connor, et al., 1991; Mady, et al., 1991). However, results of an *in situ* hybridization analysis of ADE of FIPV infectivity found no difference in the initial uptake of virus by macrophages infected in the presence or absence of enhancing Ab (Olsen and Scott, 1992). In other virus systems it has also been suggested that enhancing Ab may facilitate uncoating (Jolly, 1989; Porterfield, 1986; Robinson, et al., 1989a).

The ultimate question is what bearing ADE of virus infection, as described *in vitro*, has upon the pathogenesis of disease *in vivo* and the development of virus vaccines. This question has fueled an ongoing debate among researchers of DV (Halstead, 1989; Morens and Halstead, 1990; Rosen, 1989) and HIV (Bolognesi, 1989; Homsy, et al., 1990; Robinson, et al., 1988b). There is a substantial body of epidemiological information to suggest that ADE of DV infection of macrophages underlies the development of a more severe form of dengue called dengue hemorrhagic fever or dengue shock syndrome. Experimental data has, however, been largely restricted to measurements of viremia levels or clinical pathology parameters in nonhuman primates (Halstead, 1979; Halstead, et al., 1973; Morens and Halstead, 1987; 1990). An attempt has been made to correlate the presence of enhancing Abs in the serum of HIV-infected patients to the progression of acquired immunodeficiency syndrome. However, the *in vitro* enhancement levels demonstrated were fairly low and the number of patients was limited (Homsy, et al., 1990). With HRSV, Ab may not only function to enhance infectivity, but also to enhance leukotriene production in infected cells (Ananaba and Anderson, 1991).

Recent results of FIPV candidate vaccine testing seem to provide the strongest support to date for a direct relationship between enhanced infectivity *in vitro* and enhanced disease *in vivo*. Inoculation of cats with a recombinant vaccinia virus expressing the S protein of FIPV 79-1146 sensitized the cats and led to accelerated disease after FIPV challenge (Vennema, et al., 1990a). Inoculation with recombinant vaccinia viruses expressing the M or N proteins of FIPV 79-1146 did not predispose the cats to accelerated disease (Vennema, et al., 1991). (These results *in vivo* also support the *in vitro*-defined localization of enhancing epitopes to the S protein of FIPV (Corapi, et al., 1992; Olsen, et al., 1992b)). In addition, recent experiments among groups

of cats used to study the efficacy of a candidate FIP vaccine demonstrated a statistically significant association (under certain challenge conditions) between the ability of a cat's serum to mediate enhancement of FIPV infectivity *in vitro* and the development of accelerated FIP *in vivo* (Olsen and Scott, 1992).

#### DIAGNOSIS OF FIP

It is very difficult to make a definitive diagnosis of FIP. Biopsy and subsequent histopathologic examination is the only absolutely conclusive method for antemortem diagnosis (Barlough and Scott, 1988). Short of this, a variety of factors must be taken together to support a diagnosis of FIP (Barlough and Scott, 1988; Pedersen, 1983b; Scott, 1989; Stoddart and Gaskell, 1985; Sparkes, et al., 1991). Clinicopathologically, patients may demonstrate any of the following, depending upon the particular organ system affected: elevated serum liver enzyme and bilirubin levels, elevated serum urea nitrogen and creatinine levels, elevated fibrinogen levels, decreased packed cell volumes, neutrophilia, lymphopenia, or proteinuria. Analysis of blood protein levels may be very helpful. While albumin levels may be normal or decreased, globulin levels are often increased. Serum protein electrophoresis commonly demonstrates a polyclonal gammopathy. In cases of effusive FIP, analysis of fluid obtained by abdomino- or thoracocentesis may be helpful. The fluid is generally yellow (though there may be various degrees of blood-tinging) and viscous with visible strands of fibrin. Fluid analysis should reveal a high specific gravity and elevated protein level, with variable numbers of inflammatory cells. The fluid may clot upon standing. Cerebrospinal fluid may reveal elevated protein levels and increased cellularity when FIP affects the CNS.

The ability to utilize serologic testing in the diagnosis of FIPV infection and clinical FIP is limited. An early serologic study revealed that 20% of a local general cat population and 87% of cats in FIP "problem catteries" were seropositive, but very few of the cats developed clinical disease (Pedersen, 1976b). These results suggested that there was a mild primary form of the disease (Pedersen, 1976b) and that more severe, classical FIP was an uncommon secondary sequela (Pedersen, 1983b). Subsequent to the discovery of the antigenically-related FECVs, it has been suggested that the vast majority of seropositive test results may indicate exposure to FECVs rather than FIPVs (Pedersen, 1983b). At this point, "the presence of serum coronavirus antibody in any cat, whether healthy or diseased, is indicative only of prior exposure to a coronavirus in the FIPV antigenic group" (Barlough and Scott, 1988), and has "little predictive or diagnostic value" (Scott, 1989). In addition, not all cats with FIP will have elevated coronavirus Ab titers. In a recent study, 10 of 39 cats with FIP had coronavirus titers of  $\leq 80$ , and 2 of the 10 cats tested negative for coronavirus Ab (Sparkes, et al., 1991). Early

attempts to serologically discriminate between cats infected with FIPV versus FECV were uniformly unsuccessful (Ingersoll and Wylie, 1988a,b). However, mAbs which distinguish FIPV 79-1146 and FECV 1683 have recently been identified (Corapi, et al., 1992; Hohdatsu, et al., 1991c). Such mAbs may provide the basis for a competitive enzyme-linked immunosorbent assay to differentiate between a cat's exposure to FIPV and FECV (Fiscus and Teramoto, 1987a).

One final complication in feline coronavirus serologic testing is that cats may produce Ab directed against bovine serum components, possibly as a result of their presence in routine vaccine preparations (Barlough and Scott, 1988). These Abs can produce false positive coronavirus titers if bovine serum is also used to propagate the target viruses used for coronavirus Ab testing. Such cross-reacting Abs decrease over a period of 3-4 months after vaccination (Barlough and Scott, 1988).

#### TREATMENT OF FIP

Treatment of cats suffering from FIP is largely symptomatic, e.g. fluid replacement and nutritional support. Due to the immunologic nature of the disease, immunosuppressive doses of corticosteroids (2-4 mg of prednisolone per kg per day) are often prescribed, along with broad spectrum antibiotics (Barlough and Scott, 1988). Less commonly, immunosuppressive drugs such as cyclophosphamide or melphalan are used (Barlough and Scott, 1988).

Ribavirin, human recombinant alpha interferon (rHuIFN $\alpha$ ), and feline fibroblastic beta IFN have been shown to inhibit FIPV replication in vitro (Weiss and Oostrom-Ram, 1989; Weiss and Toivio-Kinnucan, 1988). In vivo, high-dose therapy with rHuIFN $\alpha$   $\pm$  an immunomodulating drug derived from *Propionibacterium acnes* was successful in suppressing clinical signs of disease and prolonging survival times in cats, but was unable to significantly protect against fatal disease (Weiss, et al., 1990).

#### CATTERY CONTROL OF FIPV

With the potentially long and unpredictable incubation period for FIP, the difficulty inherent in identifying cats which are shedding the virus and distinguishing FIPV from FECV serologic responses, and the survivability of FIPV in the environment, it is not surprising that feline coronaviruses have been notoriously difficult to control in multicat environments. It is becoming increasingly clear that controlling contact between kittens and adult carrier cats may be the critical factor in controlling enzootic FIP in catteries. Addie and Jarret have shown that isolation of kittens and their queen from the rest of the cattery population reduced seroconversion among the kittens, and that

isolation of kittens from their queens as well (from 2 to 6 weeks of age) completely eliminated seroconversion among the kittens (Addie and Jarrett, 1990, 1992). However, the role of queens is more complicated. A special form of immunity may be conferred by infected queens to their offspring. Pedersen and Floyd demonstrated that kittens born to FIPV-infected queens could resist challenge with virulent FIPV. They suggested that "natural" transmission of FIPV from queens to kittens at an early age may provide a form of pre-natation immunity (Pedersen and Floyd, 1985).

#### IMMUNITY TO FIPV

Given the immune-mediated pathogenesis of FIP, what is the basis for protective immunity to FIPV infection? Clearly, humoral immunity is not protective (Pedersen, 1983b). Some form of immunity would seem to exist, however, since there are reports (though rare) of spontaneous remissions, and the rate of seropositivity in cats far exceeds the incidence of clinical disease (Pedersen, 1983b). It has been suggested that CMI responses may be important in immunity (Pedersen and Floyd, 1985; Scott, 1989). Weiss and Cox evaluated delayed-type hypersensitivity (DTH) skin reactions to FIPV antigen in cats. They initially found a strong DTH response in an FIP-resistant cat, but only "minimal" response in a susceptible cat (Weiss and Cox, 1988). Subsequent work with more subjects documented similar results; after lethal challenge with FIPV, 5 of 9 cats with positive DTH responses to FIPV antigen had increased survival times compared to DTH(-) cats (Weiss and Cox, 1989). Further support for the importance of CMI responses to FIPV resistance comes from work in nude mice. Following intracerebral challenge with FIPV, mortality rates were significantly higher for homozygous (nu/nu) than heterozygous (nu/+) nude mice (Takenouchi, et al., 1985). More severe intestinal lesions have also been noted after FIPV challenge in thymectomized kittens as opposed to normal kittens (Hayashi, et al., 1983a). However, CMI responses may also contribute to the granulomatous lesions seen in non-effusive FIP when CMI responses are only partially protective (Pedersen, 1983b; Weiss and Cox, 1989).

#### VACCINATION AGAINST FIPV INFECTION

Considering the lack of understanding as to what constitutes protective immunity to FIPV infection and the problem of ADE of infection and disease, the development of a safe and effective vaccine against FIPV has been very problematic. A variety of approaches has been unsuccessful (Olsen and Scott, 1991) including the administration of inactivated FIPV (Scott, 1992), avirulent FIPV (FIPV UCD2, 3, and 4) or sublethal doses of virulent FIPV (Pedersen, 1988; Pedersen and Black, 1983), heterologous (CCV, HCV-229E,

TGEV) live virus vaccines (Barlough, et al., 1984, 1985; Woods and Pederesen, 1979), and a recombinant vaccinia virus expressing FIPV S protein (Vennema, et al., 1990a).

Most recently, a temperature-sensitive mutant of FIPV DF2 has been developed as an FIPV vaccine (Christianson, et al., 1989). This vaccine strain was derived after 99 passages of parental FIPV DF2 in cell culture (passages 61–99 at 31 °C) followed by ultraviolet irradiation. Intranasal vaccination of cats induces strong mucosal IgA and lymphocyte blastogenesis responses (Gerber, 1991; Gerber, et al., 1990). The vaccine's safety has been demonstrated after parenteral administration, administration to corticosteroid- and FeLV-immunosuppressed cats, and administration to cats previously exposed to FECV (Gerber, 1991; Gerber, et al., 1990). The mean vaccine efficacy (calculated by the author from published data as preventable fraction) for 11 experimental challenge studies conducted by the manufacturer (Gerber, 1991) was 78%. However, independent testing of this vaccine which has just been completed (Scott, et al., 1992) partially refutes these initially reported (Gerber, 1991) efficacy and safety results. The data presented by Scott et al. indicate that the ability of the vaccine to protect cats against experimental challenge is dependent upon the strain and particularly the dose of challenge virus. Low dose exposure ( $10^3$  TCID<sub>50</sub>) resulted in protection of  $\geq 50\%$  of vaccinated cats, while higher dose exposure ( $\geq 10^5$  TCID<sub>50</sub>) resulted in virtually no protection and even induced accelerated FIP in many cases. To date, accelerated FIP has not been reported under field conditions. However, field studies conducted by the manufacturer in 11 multicat facilities also failed to demonstrate a significant difference in the incidence of FIP or kitten mortality between vaccinated and unvaccinated cats (Fanton, 1991).

#### SUMMARY

Coronaviruses are now seen as representative of a larger RNA virus superfamily whose viruses employ a unique and interesting replication scheme. In addition, traditional antigenically-defined boundaries within the Coronaviridae are falling and the emerging relationships between PRCV and TGEV and FIPV and FECV should provide for a fruitful area of viral pathogenesis research. While our knowledge of the molecular biology of feline coronaviruses is limited compared to that of MHV and IBV, the cloning and characterization of the FIPV S, M, N, and 3' ORFs has provided very useful information. The recent characterization of the MHV receptor should provide an impetus for the identification of an FIPV receptor.

Development of the ts DF2 vaccine also represents a significant achievement. But while this vaccine has provided encouragement for the control of FIPV infections, there are still questions concerning its safety under experimental conditions and its efficacy under field conditions. In this regard, the



immunopathogenesis of FIP has become even more complex with recent advances in our understanding of ADE of FIPV infectivity. The identification of discrete epitopes which mediate ADE may allow for the development of a recombinant-engineered FIPV vaccine from which enhancing epitopes have been deleted. In addition, the work of Vennema and colleagues (1991) with a recombinant vaccinia virus expressing the M protein of FIPV deserves further consideration.

As regards the treatment of FIP, Weiss and colleagues' work (1988–1990) with specific antiviral drugs will hopefully be expanded, perhaps evaluating the combination of ribavirin and interferon *in vivo*. In addition, Addie and Jarrett's (1990, 1992) data regarding control of enzootic FIP in catteries is very encouraging. However, the lack of a diagnostic test which is specific for FIPV exposure remains as a significant hurdle to the routine control of FIPV infections.

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