Animal Virus Infections That Defy Vaccination: Equine Infectious Anemia, Caprine Arthritis-Encephalitis, Maedi-Visna, and Feline Infectious Peritonitis

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I. Ungulate Lentivirus Infections

A. INTRODUCTION

Lentiviruses are associated with persistent infection and chronic disease in three major species of livestock—horses, sheep, and goats. Another lentivirus named bovine immunodeficiency virus (BIV) recently has been described (Gonda *et al.*, 1987). It is a Visna-like virus

that was originally isolated over a decade ago from cattle with persistent lymphocytosis, lymphadenopathy, weakness, emaciation, and central nervous system (CNS) lesions (Van der Maaten *et al.*, 1972). There is very little information on the epidemiology, clinical manifestations, or importance of bovine lentivirus infections, so this section will concern itself mainly with the better characterized lentiviruses of horses, sheep, and goats. A phylogenetic tree showing the possible evolutionary relationship of various animal lentiviruses and human immunodeficiency virus (HIV) of man to each other and to types C and D retroviruses has been recently constructed (Gonda *et al.*, 1987) (Fig. 1). Just how far back in history that the various retroviruses diverged from each other has not been determined.

B. Course of Infection

1. Equine Infectious Anemia

Equine infectious anemia virus (EIAV) infects Equidae throughout the world. The disease is characterized by recurrent bouts of fever, anemia, thrombocytopenia, weight loss, and depression. Horses are infected by the transfer of blood between viremic and susceptible animals by biting flies (McGuire *et al.*, 1987), contaminated needles and surgical implements, *in utero* from mares in the clinical stages of illness, and neonatally by the ingestion of virus containing colostrum and milk (Issel and Foil, 1984; McGuire *et al.*, 1987; Stein *et al.*, 1942; Stein and Mott, 1942). Horses are most infectious when they are clinically ill. Horses in the later asymptomatic carrier stage of illness are minimally infectious by all of these routes.

The incubation period ranges from days to several months, depending mainly on the amount of virus that is transferred (McGuire *et al.*, 1987). The appearance of the initial fever corresponds to the primary viremic phase. Viremia declines rapidly as the fever subsides. Viremia and fever recur after periods as short as 2–8 weeks, however. Several recurrent episodes of disease are observed during the first several months of infection. A characteristic anemia begins to appear after the first febrile period. Although the hematocrit tends to improve after each febrile period, horses with frequent and severe febrile episodes usually get progressively more anemic. Clinical signs subside with time; the recurrent febrile episodes become milder and the anemia slowly resolves. Horses that survive this initial clinical phase of illness remain infected for life, but the level of virus in their blood and tissues is very low (Coggins, 1984).
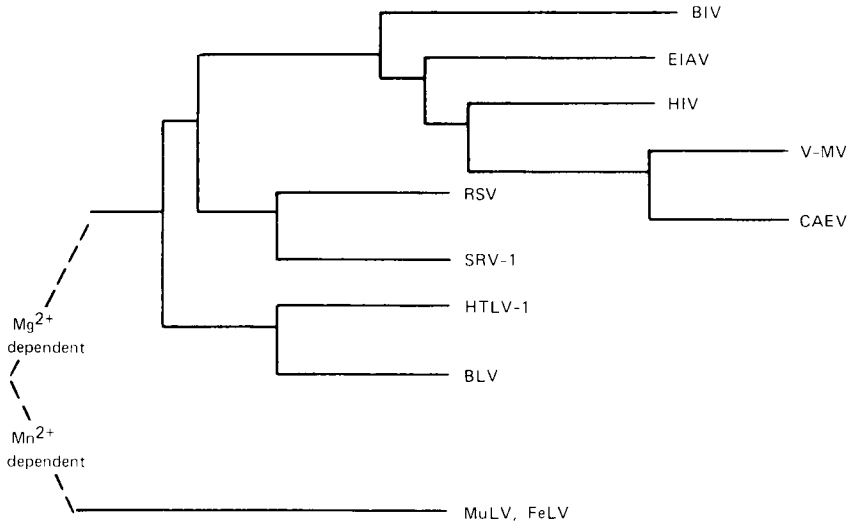
FIG. 1.   A phylogenetic tree for the evolution of type C, type D, and lentiviruses based on published amino acid sequences for the polymerase genes. The first major subdivision of retroviruses was based on the requirement of the polymerase enzyme for either Mg^{2+} or Mn^{2+}. BIV, bovine immunodeficiency virus; BLV, bovine leukemia virus; CAEV, caprine arthritis-encephalitis virus; EIAV, equine infectious anemia virus; FeLV, feline leukemia virus; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia virus-1; MuLV, murine leukemia virus; RSV, Rous sarcoma virus; SRV-1, simian retrovirus-1; V-MV, visna-maedi virus. [Redrawn from Gonda et al. (1987).]

2. Caprine Arthritis-Encephalitis

Caprine arthritis-encephalitis virus (CAEV) infection is particularly common in milking goats (Narayan et al., 1987). Virtually all milking goat herds in the United States are affected, and an average of 80% of individual animals in these herds are virus carriers. The infection is much less common in nondairy or free-roaming goats (Adams et al., 1984). Kids are infected when they ingest colostrum from their chronically infected mothers (Kennedy-Stoskopf et al., 1985). The virus persists in high levels within macrophages in the synovium and mammary glands and is shed in the milk (Kennedy-Stoskopf et al., 1985). Horizontal transmission between infected and susceptible animals continues to occur throughout life (East et al., 1987). Contaminated teat cups may provide one mode of horizontal infection.

A primary phase of infection has not been recognized (Narayan et al., 1987). A proportion of infected goats develop a chronic rheumatoid-like

arthritis and fibrosis of the udder. Encephalitis is an uncommon manifestation of the infection in younger goats. The unrelenting arthritis gradually leads to joint enlargment, deformities, and lameness. As the animals become progressively more lame they are culled from the herd. This may take many years, however, and many infected animals remain in the milking string for a normal lifetime.

3. Ovine Visna-Maedi

Maedi is a chronic fibrosing interstitial pneumonia that was first recognized in Icelandic sheep following the introduction of infected rams from Europe in the 1930s (Sigurdsson, 1954). Visna is a chronic paralytic disorder of sheep (Sigurdsson, et al., 1957). Both diseases are forms of the same virus infection, i.e., visna-maedi virus (V-MV). The North American equivalent of maedi is a disease called ovine progressive pneumonia (OPP). The OPP virus (OPPV) is a variant of V-MV (Takemoto et al., 1971).

The V-MV is shed from body fluids, in particular sputum of animals with chronic pneumonia. Transmission is more efficient, therefore, when affected and susceptible animals are kept together in close confinement. Neonatal transmission through colostrum and milk may also occur, as well as in utero infections (Cutlip et al., 1981).

C. PATHOGENESIS

1. EIAV

EIAV replicates mainly in macrophages in the spleen, lymph nodes, and liver (McGuire et al., 1971). Infection of phagocytic elements is associated with hyperplasia of lymphoid cells and macrophages in the above organs, and interstitial mononuclear cell infiltrates in nonlymphoid tissues such as the kidney, adrenal glands, brain, and heart. Hyperplastic and infiltrative lesions tend to disappear as the horses enter the chronic carrier stage of illness.

The typical anemia of EIAV infection is caused both by a decreased production and increased destruction of red blood cells (reviewed by McGuire et al., 1987). There is a pronounced phagocytosis of red blood cells by macrophages. Immunosuppression does not occur to any extent in EIAV infection. There is a decrease in IgG(T) production in clinically affected horses, but its cause or significance are unknown (McGuire, 1976).

2. CAEV

CAEV replicates mainly in macrophages within the mammary gland and synovium (Narayan and Cork, 1985). Hyperplasia of lymphoid organs is not as prominent as in EIAV infection, but infiltrates in target tissues such as the synovial membrane may be quite pronounced. The clinical signs of arthritis and udder fibrosis result in part from host immune responses to virus-laden macrophages. Central nervous system signs in young goats are usually a result of demyelination with minimal inflammatory changes.

3. V-MV

V-MV and OPP viruses also replicate mainly in macrophages (Narayan and Cork, 1985). The target organ for these viruses appears to be the lungs. Lung lesions are characterized by massive interstitial infiltrates of macrophages and hyperplasia of diffuse lymphoid aggregates (Sigurdsson, 1954). The resulting chronic interstitial pneumonia leads to a chronic cough, and in later stages, to fatigue, dyspnea, and cachexia. CNS lesions are of a demyelinating nature (Sigurdsson *et al.*, 1957).

D. IMMUNE RESPONSES

1. EIAV

Immunity to EIAV is the strongest of the various lentivirus infections of animals (McGuire *et al.*, 1987). The emergence of variant strains of the virus is associated with the rapid production of variant-specific virus-neutralizing antibodies. These antibodies are probably instrumental in eliminating each wave of viremia. Mutants of EIAV appear rapidly and randomly in the blood and not along a predestined mutagenic course (Hussain *et al.*, 1987; Salinovich *et al.*, 1986). Immunity appears to play a key role, however, in selecting for serologically distinct mutants. After the virus goes through a number of mutations, the virus-neutralizing antibodies in the blood also achieve a broad spectrum of specificity. The virus becomes relatively quiescent in macrophages after this time. Infectious virus is very difficult to find in the blood, and large amounts of tissues are required for transmission or virus recovery studies (Coggins, 1984; McGuire *et al.*, 1987). These observations suggest two things: (1) there is a finite number of major serological mutants of EIAV and these mutants arise during the first few months of infection, and (2) immunity, although

not completely effective, is nearly capable of eliminating the infection. EIAV infection represents, therefore, the single lentivirus infection of animals that comes closest to responding to host immunity in a conventional manner.

2. CAEV

Goats infected with CAEV develop weak or negligible titers of virus-neutralizing antibodies (Narayan *et al.*, 1987). There are tremendous amounts of anti-envelope antibodies as detectable by other types of assays, however (Johnson *et al.*, 1983; Narayan *et al.*, 1987). It appears, therefore, that either goats fail to respond immunologically to relevant antigens of the virus envelope or that the viral envelope lacks neutralizing epitopes. The former appears to be the case; some rabbits will develop complement-dependent virus-neutralizing antibodies when immunized with CAEV (Anderson *et al.*, 1983). A proportion of goats will produce virus-neutralizing antibodies if immunized with large amounts of viral antigen incorporated with high levels of inactivated *Mycobacterium tuberculosis* (Narayan *et al.*, 1984). The neutralizing activity of such artificially induced antibodies is extremely narrow, reacting only with the immunizing strain and not with other isolates.

Variant strains of CAEV appear in the blood of infected goats (Ellis *et al.*, 1987; Narayan *et al.*, 1987). The selection pressure for such variants is unknown; the lack of strong virus-neutralizing activity suggests that either it is not immunologic or that antibody-mediated selection is by mechanisms other than virus neutralization. Variant strains of the virus coexist in the body with parental strains (Ellis *et al.*, 1987; Narayan *et al.*, 1987).

3. V-MV

Host immunity to V-MV is intermediate between that of EIAV and CAEV. Virus-neutralizing antibodies to the infecting strain appear within a few weeks (Narayan *et al.*, 1987). Variants that fail to react to the initial neutralizing antibodies appear slowly with time (Lutley *et al.*, 1983; Narayan *et al.*, 1978, 1981), and at a lower frequency than with EIAV (Thormar *et al.*, 1983). The appearance of virus-neutralizing antibodies to new serotypes is relatively slow, often taking months or years. Antibody titers to variant viruses are not as high as to the parental infecting strain (Narayan *et al.*, 1987).

Unlike EIAV infection, virus-neutralizing antibodies have a limited effect on decreasing the burden of V-MV in infected sheep. One

possible explanation for this phenomena was described by Narayan and co-workers (1987). They found that virus-neutralizing antibodies from infected sheep required 15 min at body temperature to neutralize infectivity, whereas virus binding to infected cells took only 2 min. Theoretically, virus could spread from cell to cell faster than it could be neutralized.

Sheep infected with V-MV never reach a state like EIAV infection, where clinical signs are minimal and/or virus is not easily rescued from blood or tissues by animal inoculation or tissue culture isolation. Variant viruses, when present, appear to coexist with each other (reviewed by Narayan et al., 1987). Distinct serologic variants have been induced in vitro by treating cultures infected with early animal isolates with early immune sera. Viruses resistant to early antibodies appear within several week in vitro. Late isolates grown in the presence of late antisera showed much less tendency to undergo such rapid mutation (Narayan et al., 1987).

E. EXPERIMENTAL VACCINES

1. EIAV

EIA is the only lentivirus infection of animals where vaccination has some immunologic basis. Virus-neutralizing antibodies to various serotypes are strong, and infected horses usually reach a state where the virus is relatively well contained. The problem with variant serotypes, although formidable, is not impossible (Hussain et al., 1987). This optimism is supported by preliminary vaccine studies. Horses inoculated three to eight times with a virulence-attenuated, cloned isolate of the Wyoming strain of EIAV resisted challenge with an antigenically similar but virulent clone of the same strain (Kono et al., 1970). Immunity to other virulent isolates was not induced, however, and vaccinated animals immunized with different strains developed clinical signs of EIA.

2. CAEV

McGuire and co-workers (1986) attempted to immunize goats against CAEV using formalin-inactivated virus with Freund's complete adjuvant. Goats vaccinated several times with the preparation became infected following challenge-exposure with virulent virus. Moreover, vaccinated goats developed more severe arthritis than did unvaccinated control animals.

3. V-MV

Initial studies with inactivated V-MV vaccines have been unsuccessful. Cutlip and associates (1987) prepared heat-, formalin-, or ethyleneimine-inactivated whole virus vaccines and used them without adjuvants, or with alumnium hydroxide or Freund's complete adjuvant. The vaccinated sheep produced virus-precipitating antibodies but were not protected when challenge-exposed with live virus.

Nathanson and co-workers (1981) attempted a post-exposure vaccine experiment. Sheep were infected with V-MV and immediately began on a regimen of immunizations with either detergent-disrupted, gradient-purified virus in Freund's complete adjuvant or living V-MV-infected autochthonous testicular cells. Sheep injected with detergent-disrupted virus tended to have more severe lesions than infected control animals that were not given post-exposure vaccinations. The infected cell immunizations had no influence on the subsequent disease course.

F. DISCUSSION AND COMMENTARY

The prospects of developing effective vaccines against lentivirus infections of sheep and goats appears unlikely. There is some hope that vaccines may be developed against EIAV infection of horses, however. It is interesting to note that preliminary successes or failures to develop lentivirus vaccines have been predictable, given what is known about natural infections in each of these species. Horses respond reasonably well to their infection. After overcoming the initial phase of the illness, which is closely related to the rapid sequential appearance of random serotypic variants, horses are able to damp down the virus. Although they do not appear to be able to eliminate the virus completely from their bodies, the burden of infectious virus that remains is very low. Predictably, attenuated live-virus vaccines against EIAV were effective in preventing disease caused by serotypically similar virulent strains of the virus. Also predictably, this immunity was not strain specific. Attempts to immunize goats and sheep, which seem unable to substantially decrease their virus burden during the course of natural infection, have failed. This is also not surprising. Vaccines mimic the immunologic events that occur in natural infections, and all effective vaccines heretofore developed have been against diseases to which naturally infected individuals develop immunity. Conversely, no effective vaccines have ever been developed for infections against which the host cannot naturally and effectively respond.

There appears to be a great emphasis on the role of humoral immunity, in particular virus-neutralizing antibodies, in immunity to lentivirus infections (McGuire *et al.,* 1987; Narayan *et al.,* 1987). The inability to induce immunity is usually equated either to a failure to develop such antibodies or the emergence of antigenic variants. Such overemphasis on humoral immunity is unfortunate. Virus-neutralizing antibodies appear in the serum of humans infected with HIV and in sheep infected with V-MV. The disease course in these two infections is not substantially different from CAEV, which does not induce virus-neutralizing antibodies. Cellular immunity usually has proven to be the most effective entity in infections involving the cell-associated microorganisms. Why do lentiviruses persist, and even replicate, within infected cells in the face of host immunity (Narayan *et al.,* 1982; Peluso *et al.,* 1985)? Is there a primary failure of cell-mediated immunity to become specifically activated following lentivirus exposure, or do secondary inhibitory factors to cellular immunity arise as a result of infection? Vaccine development will be greatly impeded until these questions can be answered.

II. Feline Infectious Peritonitis

A. INTRODUCTION

Feline infectious peritonitis (FIP) is a common viral disease entity of domestic cats. The FIP virus (FIPV) is antigenically similar to canine coronavirus (CCV), transmissible gastroenteritis virus (TGEV) of swine, human coronavirus 229E (HCV-229E), and feline enteric coronavirus (FeCV) (Pedersen, 1983a,b; Pedersen *et al.,* 1978).

FIPV has an interesting interrelationship with the common enteric coronavirus (FeCV) of cats (Pedersen, 1983a). The two viruses are closely related morphologically, antigenically, and genetically (Boyle *et al.,* 1984). In fact, coronaviruses of cats exist as a spectrum that ranges from highly virulent FIP inducers on one extreme to purely enteric pathogens (non-FIP inducers) on the other (Pedersen, 1987). Intermediate strains between these extremes exist in abudnance. Strains of coronaviruses that behave as enteric coronaviruses have even been cloned from stocks of FIPV-inducing viruses (Pedersen, 1987; Pederen and Black, 1983).

The primary difference between FeCV and FIPV isolates lies in their cell tropisms. FeCV isolates have a strong tropism for mature epithelial cells of the small intestine and are difficult to grow in culture

(Pedersen *et al.*, 1981b, 1984) and they can be found within macrophages in the regional mesenteric lymph nodes following infection, but there is no evidence that they actually replicate or persist in such cells (Pedersen *et al.*, 1984). They have very little systemic pathogenicity. Feline enteric coronaviruses cause mainly a localized infection of the gut; following recovery, the virus continues to be shed at some level in the feces of some cats (Pedersen *et al.*, 1981b, 1984). FIPV isolates are less tropic for the intestinal epithelium and have acquired a pronounced ability to replicate in macrophages (Pedersen, 1976). This ability to replicate in macrophages probably accounts for their disease-causing properties. Macrophages not only serve as an important site for replication, but also carry the virus to many other areas of the body (Weiss and Scott, 1981a).

B. COURSE OF INFECTION

FIP occurs mainly in cats between 6 months and 3 years of age. The disease is particularly prevalent among purebred kittens raised in catteries or among animals living in large multiple cat households. Outbreaks of disease tend to be sporadic, seldom involving more than one or two animals at a time. Mortality among clinically affected individuals is virtually 100%. The disease tends to appear, disappear, and reappear at unpredictable intervals among infected populations. many cofactors, including genetic susceptibility, stress, and other concurrent diseases (in particular feline leukemia virus infection) play important roles in the clinical expression of the infection (Pedersen, 1987).

The disease occurs in two basic forms: (1) the effusive or wet form of FIP, and (2) the noneffusive or dry form of FIP. The effusive form is about three to five times more prevalent than the noneffusive form in both natural and experimental infections (Pedersen, 1987). The effusive form of FIP is heralded by the appearance of a chronic fluctuating fever and abdominal and/or pleural fluid effusions. Effusions consist of a characteristic high protein exudate with a rather sticky or mucinous character. Affected individuals usually began to lose weight and become progressively more lethargic. Death ultimately ensues in from 1 to 12 weeks. A fluctuating and persistent fever is also seen in cats with noneffusive FIP. Instead of peritoneal or pleural effusions, cats with this form of the disease tend to develop a disseminated granulomatous disease with a predilection for the central nervous system, eyes, kidneys, mesenteric lymph nodes, and, less commonly, other parenchymatous organs. The clinical course is also one of progressive weight loss, anorexia, and death within 1–6 months.

C. PATHOGENESIS

The source of FIPV in nature is unknown. A chronic carrier state has been induced experimentally in cats (Pedersen, 1987). Carrier queens will pass the virus to their kittens in the prenatal or neonatal period of life (Pedersen, 1987). It is very difficult to induce FIP in susceptible cats by exposing them to cats that are clinically ill with the disease, however. Susceptible cats exposed to such animals are much more likely to develop an enteric coronavirus infection. This suggests that cats with FIP do not shed a great amount of FIPV; rather they shed FeCV. A second possible source of FIPV is FeCV carriers. FIPV may be a common mutation of the basic enteric coronavirus, and FIP-inducing mutants may be generated during initial FeCV infection or during the proceeding carrier state (Pedersen, 1987). FIPV migh⁺ be generated *de novo*, therefore, in any cat with acute or chronic FeCV infection. The mutant FIPV could infect the cat in which it originated, or might be shed in the excretions and infect other animals.

The route of infection in nature is unknown. It is either intrinsic as suggested above, or it is extrinsic. Experimental studies mimicking both possibilities have been reported. Following oral or intratracheal infection (extrinsic exposure), the virus infects the mature epithelial cells (Hayashi *et al.*, 1982; Pedersen *et al.*, 1981a). Following intraperitoneal or other parenteral routes (intrinsic exposure), the virus replicates initially in phagocytic cells. Regardless of the initial site of replication, replication within macrophages appears to be central to the disease. Once the virus enters phagocytic cells (directly, or via the gut or respiratory epithelium), virus replication begins in earnest. Macrophages also carry the virus to the various target tissues (Weiss and Scott, 1981a). The main targets are the serosal membranes lining the abdominal and pleural cavities and organs, meninges, and ependyma of brain and spinal cord, and the uveal tract (Pedersen, 1983b). The type of disease that develops is dependent on the type and strength of the immune response resulting during primary infection (Pedersen, 1987).

D. IMMUNE RESPONSE

The bulk of experimental evidence supports the notion that FIPV immunity is entirely cellular (Pedersen, 1987). The passive transfer of sera, even from FIPV-immune individuals, makes the recipient more susceptible rather than immune to disease (Pedersen and Boyle, 1980; Weiss and Scott, 1981b). Following infection and spread of the virus to phagocytic cells, both humoral and cellular immunity are triggered. If

the cat makes humoral immunity, but fails to develop cellular immunity, the effusive form of FIP ensues (Pedersen, 1987). If the animal makes good cellular immunity, regardless of the humoral immune response, the infection is rapidly contained within macrophages and no clinical signs are observed. If, however, cellular immunity is only partial, the noneffusive form of FIP develops. The noneffusive form of FIP represents, therefore, an intermediate state between complete and minimal immunity. Strong macrophage and T-lymphocyte activation presumably are essential for containment of virus. In contrast, partial cellular immunity will be only partially effective in slowing down the spread and replication of the virus, and thus granulomas develop. The effusive form of FIP is characterized by masses of virus-laden proliferating macrophages around blood vessels in the omentum and serosal surfaces and no cellular immunity. In contrast, the lesions of noneffusive FIP have fewer macrophages, less of the macrophages are infected with virus, and the level of antigen in infected macrophages is lower. Evidence from experimental infection suggests that the effusive form is almost always preceded by a brief episode of effusive disease (Pedersen, 1987). This further supports the importance of stepwise immunity in the pathogenesis of FIP.

Naturally and experimentally infected cats occasionally have recovered spontaneously from the infection. Recovery is either very rapid, with no clinical illness seen following initial infection, or it progresses at a slower pace from the noneffusive form of illness (Pedersen and Black, 1983; Pedersen, 1987).

There is an interesting immunologic relationship between FeCV and FIPV infections. Cats that have previously recovered from FeCV infection, and have cross-reacting antibodies to FIPV, will develop an accelerated form of effusive FIP upon challenge-exposure with FIPV (Pedersen and Boyle, 1980; Pedersen et al., 1981b; Weiss and Scott, 1981b). Effusive FIP in coronavirus antibody-free cats usually occurs from 7 to 14 days following infection with FIPV, which is at the same time that serum antibodies are detectable in the blood (Pedersen et al., 1981a). These cats usually die after a period of 2–4 weeks of illness. If the cats are preinfected with FeCV, however, they will develop effusive FIP within 24–48 hr and die from a more fulminating form of the disease within a week or so (Pedersen et al., 1981b). The accelerated form of the disease can be recreated by passively administering FeCV immune sera to susceptible cats prior to infection with FIPV (Pedersen and Boyle, 1980). It can also be recreated by administering serum from cats with active FIP, or cats that are immune to FIP (Pedersen and Black, 1983). The failure of immune sera to protect cats from FIPV

infection, and the acceleration of disease associated with antibodies, is supportive of the idea that humoral immunity is nonprotective and, indeed, harmful.

The accelerated form of effusive FIP occurring in previously FeCV-sensitized cats has strong clinical and immunopathologic similarities to the dengue hemorrhagic shock syndrome of man (Horzinek and Osterhaus, 1979; Pedersen and Boyle, 1980; Weiss and Scott, 1981b). This occurs in people that are primarily sensitized to one serotype of dengue fever virus and subsequently infected with a closely related but different serotype.

E. Experimental Vaccines

Cats immunized with closely related coronaviruses, such as FeCV, CCV, TGEV, or HCV-229E are not protected against FIPV challenge-exposure (Barlough et al., 1984, 1985; Pedersen et al., 1981b; Stoddart et al., 1988; Toma et al., 1979; Woods and Pedersen, 1979). Cats preimmunized with virulence-attenuated live or inactivated FIPV are also hypersensitive to virulent FIPV exposure (Jacobse-Geels et al., 1980; Pedersen and Black, 1983).

Immunity to FIPV has been induced with some difficulty in cats using virulent strains of FIPV. A proportion of cats infected with sublethal doses of highly virulent FIPV will seroconvert and be resistant to subsequent challenge-exposure with massive levels of the same virulent virus (Pedersen and Black, 1983). A similar phenomena has been observed with cats that are infected experimentally with FIPV strains of low virulence (Pedersen, 1987). Cats infected with low-virulence strains will either develop FIP, or seroconvert without illness. If this latter group of animals is challenged with a more virulent strain of FIPV, some will be immune and some will develop accelerated effusive FIP (Pedersen, 1987).

Kittens born to queens that have been immunized with virulent FIPV will pass on maternal antibodies to their young (Pedersen, 1987). These antibodies will last for only 4 weeks or so. After this time, the kittens undergo an active asymptomatic coronavirus infection, as evidenced by a rise in antibody titers starting at around 4–6 weeks of age (Pedersen, 1987). The queen is the source of this infection. If these kittens are challenge-exposed to a large dose of virulent FIPV between 8 and 10 weeks of age, they will be immune (Pedersen, 1987). If they are not infected until 22 weeks of age, however, some will be immune and others will develop the accelerated form of the disease (Pedersen, 1987).

When FIPV recovered cats are infected with feline leukemia virus (FeLV) between 0 and 4 months after FIPV challenge, they will almost always develop FIP and die within several weeks (Pedersen, 1987). It is apparent, therefore, that FIPV recovered cats still carry the virus for a period of time after initial exposure. If FIPV immune cats are not infected with FeLV until 7–9 months after initial FIPV challenge, FIP cannot be induced (Pedersen, 1987). This suggests either that the FIPV is lost with time from the body, or that the overlying FIPV immunity has gained sufficient strength during the ensuing months to withstand perturbations caused by the FeLV infection. Experiments with the immunity of kittens born to FIPV carrier queens suggests that the former situation is correct. If so, immunity to FIPV involves premunition (infection immunity), and immunity is only maintained for as long as the virus persists in the body.

F. DISCUSSION AND COMMENTARY

The likelihood of developing an effective FIPV vaccine given the immunologic vicissitudes of FIPV infection appear slim. Based on what is known about immunity to this virus, the ideal vaccine would be an attenuated live agent that would persist in macrophages for long periods of time without inducing disease. Persistence of the virus would also have to induce protective cellular immunity. Attempts have been made to find just such FIPV isolates (Pedersen, 1987). If they are too attenuated, they will not persist long enough in macrophages to induce immunity. If they are partially attenuated in virulence, they will persist in macrophages and induce immunity in a portion of cats, but will either cause FIP or hypersensitization to FIPV in others.

An ideal killed vaccine would induce strong cellular immunity by mimicking the way virulent FIPV is presented to macrophages. It would also have to induce immunity that would persist for a long epriod of time. At the present time, all killed and avirulent FIPV vaccines have failed to induce protective cellular immunity and have actually sensitized vaccinates to disease. Because virus persistence appears to be essential for immunity, it is unlikely that such an idealized killed virus vaccine could be developed. The same misgivings that apply to inactivated whole virus vaccines could also be echoed for subunit vaccines made up of the viral proteins.

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