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# Persistent Viral Infection

## The Carrier State

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It is more than half a century since Goodpasture<sup>24</sup> summarized his studies on recurrent herpes simplex in humans with the conclusion, "It seems to me probable from experimental and clinical factors that herpetic virus does reside in a latent state within the human body and specifically in the nervous tissues, perhaps primarily within nerve cells of the ganglia; and that neural disturbances are frequently the basis of subsequent outbreaks." However, it was not until the 1970s that persistence of herpes simplex virus was documented as a masked infection in sensory nerve ganglia. The first such demonstration was in animals,<sup>54</sup> and then herpes virus persistence was shown in the trigeminal ganglion of man.<sup>5,6,53,73</sup>

Viral persistence in carrier animals has been demonstrated with the majority of herpes viruses and is one of the best studied of virus-host associations. The spectrum from acute fatal to chronic persistent disease is within the capacity of virtually every group of animal viruses.

The mechanisms that allow, or favor, the change from the predominantly cytopathic, virus-producing phase of the acute infection to a chronic, less cytotoxic and non-virus-producing or restricted replication phase are gradually being elucidated.

### DEFINITIONS

A *persistent virus infection* is one in which the virus in complete or partial form persists beyond the normal recovery and elimination period for that particular virus infection. The persistent virus may be either replicating (productive infection) or nonreplicating (nonproductive infection). The non-replicating phase may be re-activated to a replicating phase.

The host animal for a persistent virus infection is a *carrier*. A carrier may or may not shed virus in excretions or secretions, and shedding may occur continuously or intermittently.

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There is considerable confusion in the literature over the terms latent and latency. The dictionary definition of *latent* is "hidden or concealed, present or existing but not manifest." A *latent virus infection* is one in which infective virus is sometimes or always undetectable by conventional methods in secretions, excretions, or body fluids of the host animal. Conventional methods for infective virus detection would include cultivation in cell culture and demonstration of transmission to in-contact animals. Although the virus may be hidden using such conventional detection methods, the use of very sensitive techniques such as enzyme-linked immunosorbent assay (ELISA) for viral antigen detection or hybridization techniques to reveal viral nucleic acid sequences in host cell DNA are used to confirm the presence of virus or at least its genetic material.

The term *latent infection* is sometimes applied as a description of an infection that is asymptomatic (subclinical) and persists beyond the normal recovery period for that infection. This term causes confusion with virus latency and is best avoided.

*Slow virus infections* are a special form of persistent virus infections that are initially asymptomatic but after a prolonged period are likely to become clinical.

### ECOLOGICAL IMPORTANCE

Viruses are obligate intracellular parasites. In most cases, their ability to survive in the extracellular environment, particularly outside the host animal, is very limited compared with that of other microorganisms. Thus, the carrier state is a very important ecological mechanism that ensures survival of the virus in the interepidemic phase (Fig. 1). During this phase, opportunity for the virus to transfer to a new susceptible host is restricted, but the virus survives because of persistence. Sooner or later, contact with a new potential host will occur, and transmission may take place.

### DISEASE IMPORTANCE

Persistent virus infections may be associated with chronic or recurrent clinical signs of disease, such as with the recrudescing cold sores of herpes simplex. Alternatively, overt signs of disease may be absent because of the limited replication and limited cell damage. Viruses that are immunosuppressive contribute to their persistence by reducing the host's immune response, and continued immunodepression makes the host susceptible to other illnesses. An example is the association between persistent viremia with feline leukemia virus and diseases such as hemobartonellosis (infectious anemia) in cats.

Another potential consequence of persistent production of viral antigen is the formation of pathogenic immune complexes of antigen and antibody. Deposition of such complexes can cause vascular and basement membrane damage and lead, for instance, to glomerulonephritis.

The continued presence of antigen in cells or tissues may provoke im-

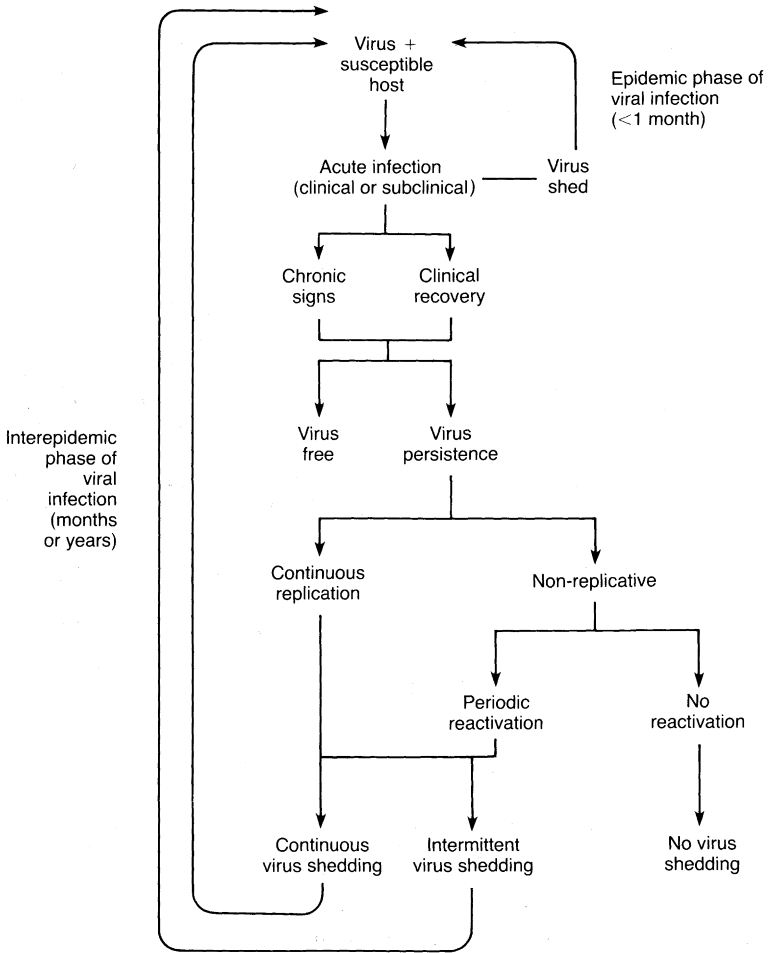


Figure 1. The interactions of virus and host and the importance of persistence in maintaining virus infections in a population during the epidemic phase and the interepidemic phase.

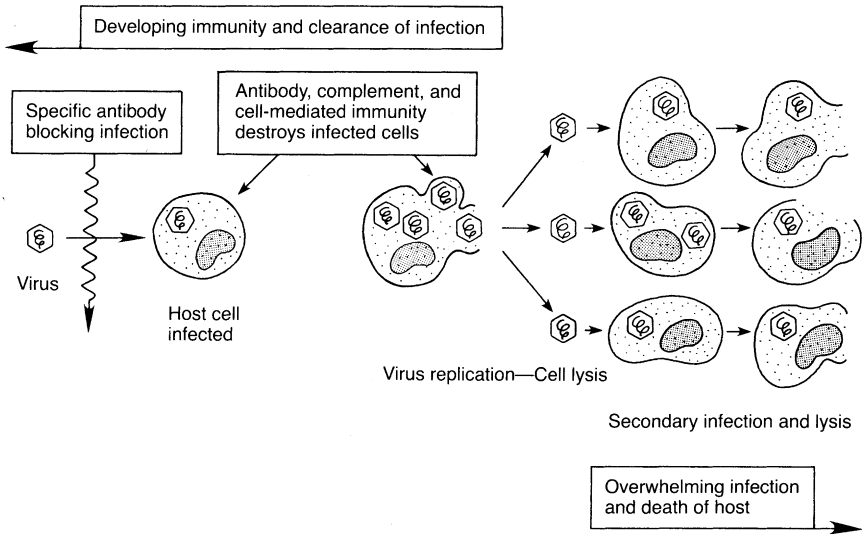


Figure 2. The two extreme consequences of acute viral infection are overwhelming infection with death of the host or development of immunity and elimination of infection.

immune responses against those infected cells or tissues. This may be a factor in the pathogenesis of demyelination in "old dog encephalitis" associated with persisting canine distemper antigen in brain tissue.

The presence of viral genetic material integrated in the host cell DNA potentially alters the DNA in such a way that the cell undergoes a transformation that may have malignant potential. Alternatively, the presence of the viral genetic material may make the host cell more susceptible to the effects of other mutagens or carcinogens.

### PATHOGENESIS OF PERSISTENCE

A frequent consequence of viral penetration of, and replication within, a host cell is death of that cell. Progeny virus will be released prior to cell death by budding from the cell membrane or during cell lysis. Uninhibited infection of contiguous susceptible cells allows the cycle to repeat until all susceptible cells are destroyed, and perhaps the host dies. Otherwise, host immunity will normally eliminate the virus (Fig. 2). The immune response is directed against the virus either when that virus is within the host cell (by direct cell-mediated cytotoxicity, or by antibody-mediated and complement-mediated cytotoxicity) or when it is outside the host cell (by antibody). In either case, the virus infection has a finite duration, typically 1 to 2 weeks. In most cases, a virus infection of more than 30 days can be regarded as persistent, and the host is designated a carrier.

A virus may persist in its host either in a dynamic replicative form or in a nonreplicative form subject to reactivation. Persistence with replication implies containment of the infection in a number of ways (Fig. 3):

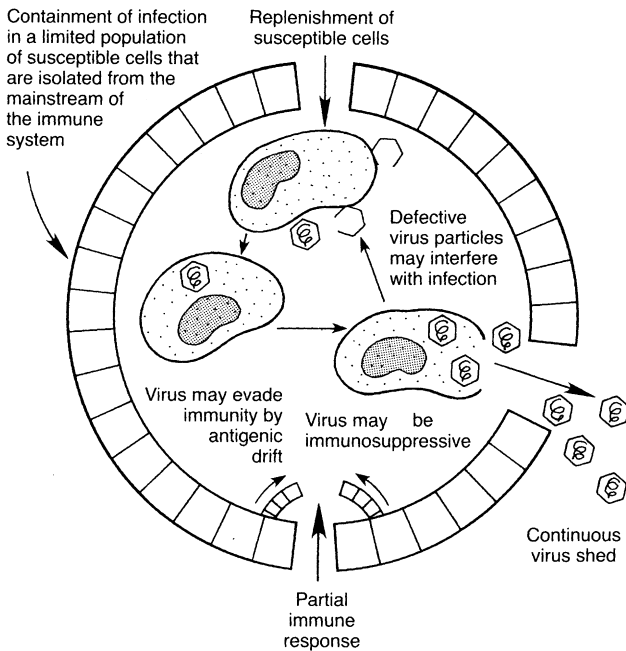


Figure 3. Virus persistence in a dynamic, replicative form, with continuous virus shed. There is a balance between virus replication with cell destruction and replenishment with susceptible cells. The extent of virus replication may be restricted by a limited population of susceptible cells, by defective virus particles that interfere with infection by complete particles, or by an immune response that is incomplete. Evasion of the immune response is enhanced by an isolated location, immunosuppression by the virus, or by antigenic drift of the virus.

1. The virus replicates in a limited population of cells or at a slowed rate so that there is a steady state between cell destruction and replacement of a susceptible population of cells.
2. The virus evades the immune response by replicating in relatively isolated sites (such as epithelial cells or nerve cells).
3. The virus evades the immune response by causing virus-induced immunosuppression.
4. The virus evades the immune response by continual mutation, effecting antigenic drift.
5. The virus is masked within cells as a defective infection.

Partial replication may occur, but the particles are incomplete or defective. Even if released from the cell, these defective particles are incapable of establishing productive infection in other cells, and they may interfere with and block infection of those cells by complete virus. Defective interfering (DI) particles are found with virtually all viruses studied. The proportion of DI particles in a population of virions is variable. Virus persistence in a static, nonreplicative form implies that viral RNA or DNA is present in cells but inhibited or repressed. There may be a block to translation from viral

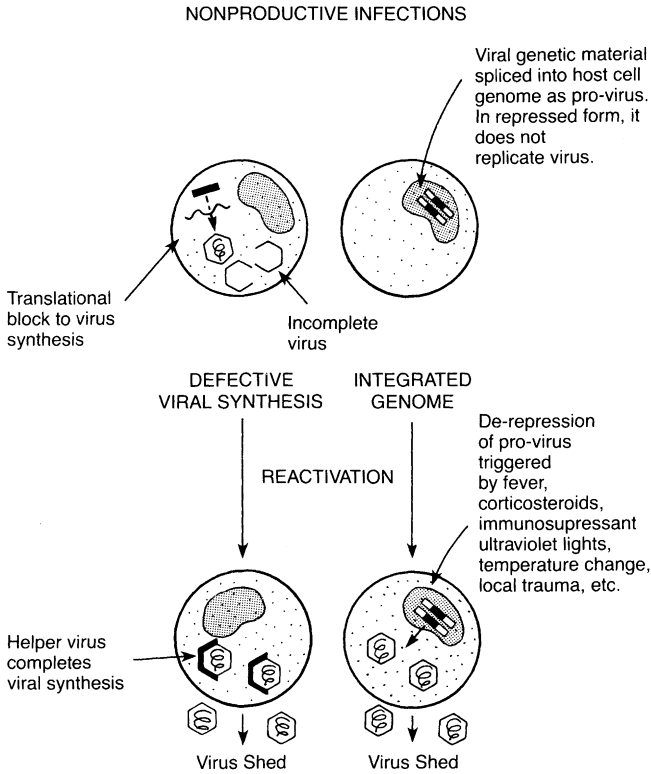


Figure 4. Static, nonreplicative viral persistence may be converted or reactivated to productive infection.

nucleic acid to viral protein synthesis or incomplete, defective virus may be produced. This defective synthesis might later be converted or assisted by another “helper” virus to become complete and productive. Alternatively, viral genetic material becomes integrated into the genetic material (DNA genome) of the host cell. The viral “blueprint” known as pro-virus can be passed to daughter cells *ad infinitum* or may be re-activated to produce virus (Fig. 4). DNA viruses such as herpesviruses have the best potential for such integration, but the RNA retroviruses such as feline leukemia virus are able to make a DNA copy of their genome via the enzyme reverse transcriptase. It has also been suggested that other RNA viruses might make use of leukemia virus reverse transcriptase to make copies of their nucleic acid, but this remains a hypothesis.

Host factors, including genetic susceptibility and specific or nonspecific immunodeficiency, can encourage viral persistence.

The different replication strategies of the various virus families can influence persistence, and strain variation can cause marked differences in the ability of that virus strain to persist. Thus, thymidine kinase-deficient mutants of herpes simplex cannot replicate normally in neurons and, therefore, do not induce a carrier state.

## REACTIVATION

In those persistent infections that involve a nonproducing phase, a "switch-on" mechanism is necessary to induce the host cell to commence virus replication. The end result is normally viral release with excretion shed from the host. Such "switch-on" factors include fever, corticosteroids, immunosuppressive drugs such as cyclophosphamide, ultraviolet light, temperature changes, local trauma, and so on. The mechanisms of reactivation at the cell level are largely unknown. One group of mediators may be prostaglandins. They have been shown to enhance herpes simplex virus replication probably by increasing intracellular levels of cyclic adenosine 3',5'-monophosphate (cAMP).

In other persistent infections in which there is continuous low-grade replication, similar triggers can increase replication, with consequential cell damage and virus shedding.

## EXAMPLES OF PERSISTENT VIRAL INFECTIONS IN DOGS AND CATS

As mentioned earlier, examples of persistence can be found in most virus families and carrier states occur in most animal species. Viral infections of dogs and cats in which persistence is known or suspected are listed in Table 1.

### FELINE VIRAL RHINOTRACHEITIS

This common herpesvirus infection of cats is characterized by acute upper respiratory signs such as ocular and nasal discharges, sneezing, hypersalivation, and dyspnea.

During early studies with the disease, it was observed that infection could be transmitted to susceptible cats from cats that had apparently recovered from feline viral rhinotracheitis (FVR). The carrier state with FVR has now been well documented and is a sequel to infection in the majority of cats.<sup>9,36,58</sup>

Plummer and colleagues<sup>54</sup> were able, following adrenalin administration, to recover FVR virus from 1 of 6 cats 3 months after they had FVR infection. Gaskell and Povey<sup>21,22</sup> gave cats that had recovered from FVR intramuscular glucocorticoid (0.75 mg dexamethasone trimethylacetate with 2.25 mg prednisolone on days 0, 2, and 4) and were able to isolate FVR virus from oropharyngeal or nasal swabs. Of the cats studied, 82 per cent were chronic carriers. The interval between the known FVR infection and the re-isolation of virus was often many months. There was always some delay or lag period between the initiation of corticosteroid treatment and first recovery of virus. This was typically 1 week, but the range was from 4 to 21 days. It was also demonstrated that other "stressful" situations, such as re-housing or, less reliably, parturition, also stimulated shedding from carrier cats. For re-housing, the lag period was similar to that with corti-



**Table 1.** *Examples of Persistent Virus Infections of Cats and Dogs*

VIRUS	FAMILY OR GENUS	NATURE OF PERSISTENCE
Feline virus rhinotracheitis	Herpesviridae	Nonreplicative viral persistence in nerve cells (?); reactivation by corticosteroids; "stress" to give intermittent shedding.
Canine herpesvirus	Herpesviridae	Nonreplicative viral persistence probable; reactivation by corticosteroids; intermittent shedding.
Canine adenovirus-1	Adenoviridae	Replicative, persistent shed in urine.
Canine adenovirus-2	Adenoviridae	Replicative persistence in bronchial epithelium.
Rabies	Rhabdoviridae	Replicative in salivary gland of bats and some dogs in Africa and Middle East.
Feline panleukopenia	Parvoviridae	Replicative; may result from congenital infection.
Canine parvovirus	Parvoviridae	Replicative (?) Intermittent shed in feces.
Feline calicivirus	Caliciviridae	Replicative persistence in oropharyngeal epithelium; continuous shedding.
Canine parainfluenza	Paramyxovirus	Persistent infection in vivo not demonstrated.
Canine distemper	Morbillivirus	1. Replicative persistence in brain, uvea, foot pad. 2. Nonreplicative persistence in brain, bladder (?)
Canine coronavirus	Coronaviridae	Persistent infection not defined.
Feline infectious peritonitis	Coronaviridae	Persistent infection probable, not defined.
Feline enteric coronavirus	Coronaviridae	Persistent infection probable, not defined.
Coronavirus-like particles of cats	Coronaviridae	Persistent infection probable, not defined.
Feline leukemia	Retroviridae, Oncornavirus	1. Replicative with persistent viremia. 2. Nonreplicative, proviral DNA in host cell genome, potential for reactivation.
Feline syncytial-forming virus	Retroviridae, Spumavirus	Replicative.

costeroid administration (mean 7.2 days), but following parturition, the delay was as long as 52 days. It was hypothesized that the stress of late lactation, as kittens approached weaning, precipitated virus re-excretion. In these studies, there were many instances of "spontaneous" virus re-excretion not associated with an identified trigger factor.

Regardless of the precipitating factor, the duration of an episode of FVR re-excretion is on average 1 week, with a range of 1 to 13 days. Following this period, virus replication ceases and cats are refractory to further triggering of re-excretion. The refractory period varies from a few days to several months.

### **Mechanisms and Sites of Persistence of FVR**

Despite several studies, the tissue or cell location of FVR virus persistence remains uncertain. In other herpesvirus carrier states, neurons, particularly of the trigeminal or other ganglia, lymphoid cells,<sup>39</sup> or epithelial cells<sup>67</sup> have been identified as locations of virus persistence. There is evidence that the persistent form is viral DNA, which is blocked in its transcription so that virus synthesis cannot occur.<sup>20,61</sup>

Plummer<sup>53</sup> used co-culture of trigeminal ganglia explants and cell monolayers and successfully isolated herpesviruses from monkeys and humans but not from the ganglia of 20 cats, over half of which had been infected previously with FVR, based on serologic evidence. Ellis<sup>11</sup> failed to isolate FVR from trigeminal ganglion, maxillary nerve, olfactory lobe and nerve endings, submandibular lymph node, spleen, and parotid salivary gland of 16 FVR carriers, even though most cats were shedding FVR into the oropharynx at the time of euthanasia. However, Gaskell and Povey<sup>23</sup> recovered virus from 1 of 17 trigeminal ganglion co-cultures or explants and from 1 of 6 olfactory bulb co-cultures or explants of 37 FVR-recovered cats. Eight of these cats, including those from which the positive trigeminal ganglion and olfactory bulb preparations were derived, were shedding virus at the time of euthanasia.

### **Diagnosis of FVR Carriers**

FVR-carrier cats may be suspected on the basis of circumstantial evidence. For example, a queen cat whose litters regularly develop upper respiratory signs just before or at weaning is a candidate carrier. Suspicion is enhanced if it is noticed that she develops an ocular or nasal discharge, maybe unilateral and often mild, a few days before the kittens develop symptoms. Chronic rhinitis (snuffler) cats are not always carriers; in fact, most attempts to culture virus from such cats are negative. Recurrent keratoconjunctivitis, however, is an indication of an FVR carrier, but chronic chlamydial infection would need to be considered.

FVR-carrier cats have virus-neutralizing antibody, and the titer is usually high ( $\geq 1:96$ ) and persisting. A negative or rapidly declining titer indicates the cat is a non-carrier or has very infrequent episodes of viral reactivation.

The best method of detecting carriers is to require owners to keep daily health records that emphasize ocular or nasal discharge and sneezing and, in particular, identify these signs in mature cats as preceding signs of rhino-

tracheitis in kittens. Suspect adult cats with ocular and nasal discharge should be swabbed from the eye, nose, and throat, and samples should be submitted in virus-transport medium on ice to the testing laboratory.

### **Treatment and Control of FVR Carriers**

Most carriers remain symptomless or have only mild signs during episodes of virus shedding. Therefore, clinical therapy is not required. Attempts to eradicate the carrier state by immune-stimulation and booster vaccination have not been generally successful. Studies should be done with the potent immunopotentiating drugs, but if the FVR genome is integrated in the host cell, elimination is difficult or impossible.

In the absence of a therapeutic or immunologic mechanism for clearing the carrier of FVR virus, control means separating carriers from susceptible animals. Young kittens are most susceptible in the time between losing protective maternal antibody (usually from 5 weeks on) and responding to vaccination (response rate is low before 9 weeks). One approach is to enhance maternal antibody by booster vaccination of queens with killed vaccine between 1 month and 1 week before kittening. This will help protect the kitten for longer and allow for age resistance. If the mother is a suspected carrier, the kittens are weaned early and moved to an isolated room at 5 weeks of age. They remain in isolation until they have had doses of vaccine at 9 and 12 weeks. Three days after the second dose of vaccine, they can be reintroduced to the cattery, unless they are to be sold immediately. Because FVR does not spread far in air and is relatively fragile on clothing, isolation is not difficult. Attendants' hands are a problem because surface moisture does preserve FVR and other viruses. Therefore, scrupulous handwashing before handling kittens is a priority. FVR carriers are not a threat to well-vaccinated (annually boosted) adult cats.

## **CANINE HERPESVIRUS**

Canine herpesvirus (CHV) causes a fatal hemorrhagic enteritis in puppies less than 2 weeks of age. In older dogs, the infection is often subclinical, but upper respiratory disease signs and vesicular lesions of the external genitalia have been described. The infection is only sporadically recognized, but antibody prevalence rates of 6 per cent<sup>13</sup> and 12.8 per cent<sup>44</sup> suggest that infection is more common. Carrier dogs have been demonstrated by the recovery of CHV from dog kidney cell cultures that spontaneously degenerated,<sup>72</sup> from fetal and neonatal pups obtained by cesarian section from healthy bitches,<sup>74</sup> and by recovery of virus in nasal secretions of healthy dogs treated with corticosteroids or antilymphocyte serum.<sup>7</sup>

A manifestation of recrudescent CHV in carrier bitches may be the occurrence of papulovesicular lesions on the vaginal mucosa and mucodermal junction of the vulva.<sup>31,57</sup> Recrudescent canine herpes with virus shedding from the genital or respiratory tract may be stimulated by the stress of parturition and lactation and be an important source of infection for the neonatal pup. Successive litters of pups may be affected, but maternal an-

tibody usually makes the infection subclinical in litters born by carrier bitches.

### CANINE ADENOVIRUSES

In humans, adenoviruses can be recovered from the tonsils and adenoids of healthy carriers. Adenoviruses were isolated from 61 (62 per cent) of 98 tonsil and adenoid specimens by tissue fragment cultivation.<sup>80</sup> The cat, surprisingly, is not host to a recognized adenovirus, but the dog is host to two. These are canine adenovirus-1 (CAV-1, infectious canine hepatitis virus) and canine adenovirus-2 (CAV-2 associated with kennel cough). Persistent shedding of CAV-1 in the urine has been documented for at least 6 to 9 months following infection.<sup>55</sup> The virus persists in renal tubular epithelium.<sup>85</sup> Persistence of CAV-2 has been noted in bronchial epithelial cells.<sup>3</sup>

### RABIES

Rabies in dogs and cats is most often an acute, fatal infection. However, in some cases, subclinical persistent infection occurs. This is most likely in dogs in parts of Africa, such as Ethiopia. These dogs have usually recovered from mild disease and intermittently excrete virus in saliva for many months.<sup>17</sup> This appears to be a feature of infection with unusual strains of rabies virus of restricted distribution, because no evidence of such incidents has been reported in North America. Asymptomatic salivary gland infection in bats also results in a prolonged period of rabies virus shedding.

### PARVOVIRUS IN CATS AND DOGS

Parvovirus infections of cats (panleukopenia) and dogs (canine parvoviruses, particularly CPV-2, the cause of an acute gastroenteritis) are capable of establishing persistent infections. With panleukopenia, virus has been recovered from kidneys and lung of congenitally infected kittens at 1 year of age,<sup>10</sup> and there are unconfirmed reports of CPV-2 being shed intermittently in the feces of isolated carrier dogs over a 6-month period. The mechanism of the persistence is unknown. The carrier state is less significant with parvovirus than in most other virus infections because the extraordinary survivability of the virus in the environment for up to a year or longer ensures the perpetuation of infection cycles.

### FELINE CALICIVIRUS

Members of the family Caliciviridae are recognized in many different animal hosts including pigs (vesicular exanthema), sea mammals such as seals and sea-lions, calves, human beings, and chickens. The best known infection is feline calicivirus (FCV), which is very widespread in the cat population.

One serotype is recognized in cats, but it is antigenically variable. The most likely clinical signs associated with FCV are tongue ulcers, other buccal cavity erosions, and an early interstitial pneumonia that later becomes proliferative. Persistently infected cats are found frequently. Such carriers may shed virus for weeks, months, and sometimes years.<sup>59,60,82,83</sup> The shedding appears more or less continuous as virus is consistently recoverable, particularly from the oropharynx of these carrier cats. The tonsil is the tissue from which FCV is most regularly recovered; unfortunately, however, tonsillectomy is not successful as a means to eradicate the persistent infection.<sup>84</sup> Although there is no direct evidence, it seems that the virus replicates continuously in a variety of epithelial or subepithelial cells in the oropharyngeal region. Carrier cats have anticalicivirus antibody in their serum, but it is either incompletely neutralizing or unable to effectively reach virus in the epithelial locations. The recovery of FCV from the throat of a symptomless cat may indicate that the cat is a carrier or that it is a subclinical infection or reinfection. In an extensive series of surveys, FCV was isolated from 8 per cent of household pets, 24.02 per cent of cats attending cat shows, and 41.5 per cent of cats in two large research cat colonies.<sup>84</sup>

Feline calicivirus carriers usually cease shedding virus at some stage, and cessation is sudden. This suggests some rapid change in the immune response of that cat, but the nature of the alteration has yet to be discovered.

Detection of calicivirus carriers is achieved by recovering virus from oropharyngeal swabs. These are collected by vigorous rotation of cotton-tipped swabs in the tonsillar regions. The swabs are submitted in virus-transport medium to a suitable laboratory. Any positive cats should be segregated as far as possible from other cats and re-swabbed twice at 2-week intervals. If the cat remains a virus shedder throughout the period, it can be regarded as a carrier. The disease risk by transmission from carriers to other cats depends on the virulence of the FCV strain involved. Young kittens that lose their maternal antibody between 3 and 9 weeks of age are most susceptible. This age group should not be allowed to have contact with carriers. Kittens born by carrier mothers will regularly become infected with FCV between 3 and 9 weeks; most will show some clinical signs, but these are usually not severe.<sup>37</sup> Protection of kittens may be enhanced by booster-vaccinating queens with a killed FCV-containing vaccine between 1 month and 1 week before kitting. This provides kittens with optimal levels of maternal antibody. Kittens should be weaned early to an area separate from adult cats at 5 weeks of age and kept separate until they are sold or attain 3 months of age. At this time, they will have received vaccine (at 9 and 12 weeks) and can be returned to the main colony.

## CANINE PARAINFLUENZA

Canine parainfluenza (CPI) virus is primarily a respiratory pathogen associated with tracheobronchitis. Most infections involve virus shedding for up to 9 days; persistent infections have not been documented. Recently, however, Evermann and colleagues<sup>15</sup> described a case of posterior paresis in a 7-month-old Basset Hound. CPI virus was isolated from the cerebro-

spinal fluid of this dog. The isolate had the ability to establish a persistent infection in vero cell cultures *in vitro*. This *in vitro* persistence may be of significance in the pathogenesis of the nervous disease.<sup>19</sup>

## CANINE DISTEMPER

Dogs with canine distemper shed virus in all excretions and secretions during the acute phase of infection. Virus is present in urine for up to 22 days and in saliva for up to 41 days after infection.<sup>69</sup> In a pathogenesis study,<sup>2</sup> distemper virus antigen was detected by fluorescent antibody labeling in neurons of the cerebrum, brain stem, and Purkinje cells of the cerebellum of two dogs that developed convulsions 41 days and 60 days after infection. Distemper virus antigen was also detected in the sebaceous glands and epidermis of the foot pads of both dogs. In another study, persistence of CDV was demonstrated in the uvea up to 56 days after infection.<sup>76</sup>

Two neurologic diseases of adult dogs, the diffuse demyelinating pan-encephalitis of old dog encephalitis (ODE) and a chronic multifocal encephalitis, are associated with CDV. These syndromes may occur weeks, months, or years after initial systemic CDV, or they may develop without any preceding clinical illness. Lincoln and colleagues<sup>43</sup> demonstrated CDV antigen by immunofluorescence in neurons and glial cells of the cerebral cortex in two cases of ODE. However, those authors could not recover virus nor transmit infection. Subsequently, successful isolation of CDV was accomplished from two of six dogs diagnosed as ODE and two of six dogs with chronic distemper encephalitis.<sup>35</sup> Three isolations were made by explant culture of brain tissues, and the fourth isolation was made in bladder epithelial cell culture. The presence of IgG rather than IgM antibody in serum and cerebrospinal fluid of these dogs suggested persistent rather than recent virus infection. Vandeveld and colleagues also isolated CDV from two of three cases of multifocal encephalitis but not from three cases of ODE, although all ODE cases and two of the three multifocal encephalitis cases were positive for CDV antigen by immunofluorescence. It is not clear that the mechanisms of persistence of CDV are different for ODE and multifocal encephalitis, nor is it clear that they involve chronic low-grade productive infection by virus in selected cells, or that there is a stage of incomplete virus replication. Although it is difficult to extrapolate from *in vitro* studies, the persistence of a laboratory strain of CDV in cell culture was associated with classical defective interfering (DI) particles released into the supernatant of the culture. However, persistence with a strain of CDV from ODE involved large numbers of nucleocapsids in the cytoplasm of infected cells that might have been defective but were not released and remained cell-associated.<sup>78</sup>

In addition to the finding of anti-CDV IgG antibody in the CSF of dogs with chronic CDV neurologic disease, the continuing presence of interferon in the cerebrospinal fluid also facilitated CDV entry and persistence.<sup>79</sup>

The factors determining persistence of CDV and the pathogenesis for chronic neurologic disease in dogs remain unclarified, but virus strain is probably of considerable importance.<sup>68,77</sup>

### **Measles, Multiple Sclerosis, and Subacute Sclerosing Panencephalitis**

Multiple sclerosis (MS) and subacute sclerosing panencephalitis (SSPE) are two chronic neurologic diseases that have some similarities pathologically to the chronic forms of canine distemper. Although both of these diseases are linked with measles virus, the association is only strong in the case of SSPE. Measles virus has been occasionally recovered from brain tissue of SSPE patients by co-cultivation.<sup>34,49</sup> Measles virus nucleic acid sequences have been detected in MS brain tissues. Although measles vaccine virus only rarely leads to persistent infection and neurologic disease in man, it should be used with caution. In view of this and the relatively poor protection conferred by measles vaccine against distemper,<sup>4</sup> there is little to recommend the use of measles vaccine in distemper prophylaxis in puppies.

The hypothesis that MS might be directly related to human exposure to CDV continues to be explored by epidemiologists. Findings have been somewhat contradictory and inconclusive,<sup>1</sup> and a definitive study is still required.

### **CANINE CORONAVIRUS**

Canine coronavirus (CCV) can cause a diarrhea in dogs that is generally milder than clinical canine parvovirus disease, and the diarrhea is often mucoid, infrequently bloody, sometimes orange with a strong odor, and there is usually not leukopenia. Experimentally infected dogs shed the virus for nearly 2 weeks,<sup>40</sup> but they may be contagious for longer periods.<sup>8</sup>

### **FELINE CORONAVIRUSES**

A coronavirus capable of experimentally inducing vasculitis and granulomatous disease is designated feline infectious peritonitis virus (FIPV). A morphologically and serologically indistinguishable coronavirus is not capable of inducing the infectious peritonitis syndrome and is essentially confined to the enteric tract of cats. This virus is known as feline enteric coronavirus (FECV). In addition, particles morphologically and antigenically distinct from FIPV and FECV and designated coronavirus-like particles (CVLPs) have also been recognized in cat stool specimens. The feline coronaviruses have been reviewed by Pedersen.<sup>50</sup>

Feline enteric coronavirus is most often associated with subclinical infection, but it is capable of producing mild pyrexia, leukopenia, and enteritis in young kittens.<sup>51</sup> The CVLPs may also cause mild enteric disease but most usually are involved in asymptomatic infections.<sup>75</sup> The patterns of FECV and CVLP infection within cat colonies suggest that carrier cats infect kittens and induce virus shedding with or without antibody production.<sup>42,75</sup> Most of these infections coincide with waning of maternally derived antibody at 5 to 7 weeks of age.<sup>42</sup>

The pathogenesis of FIP is uncertain, although there is evidence that the natural disease is the end result of immune-complex formation involving

FIPV antigen and the abundant antibody that usually characterizes the advancement of the disease. The immune complexes may result from a delayed triggering of the immune response to a persistent FIPV infection in carrier cats. It could also occur in a presensitized cat following re-exposure to virus. There may be carrier cats that do not themselves develop FIP disease but they are capable of shedding the virus either continuously or sporadically. Such carrier cats may be those with persisting high ( $\geq 1:400$ ) serum antibody levels to FIPV and that do not develop clinical signs. However, this is purely speculative because such carriers have not been identified.

### FELINE LEUKEMIA VIRUS

Feline leukemia virus (FeLV), an oncornavirus of the family Retroviridae, is responsible directly or indirectly for a broad range of clinicopathologic conditions in cats. These include lymphosarcoma, leukemias, anemias, enterocolitis, reproductive failure, thymic atrophy in kittens, glomerulonephritis, and immunodepression with its various consequences such as chronic infections.

The Retroviridae are RNA viruses that possess the enzyme reverse transcriptase. This allows synthesis of a DNA replicate of the viral genome. The DNA replicate is inserted as pro-virus into the DNA of the host cell. Here it may induce synthesis of new virus components or it may lie dormant for a considerable time. If the pro-virus insertion into the host DNA is at the site of an oncogene or adjacent to it (proto-oncogene), the recombination may de-repress the oncogene directly or promote the de-repression of the oncogene sometime later. This leads to cell neoplastic transformation and development of tumors. If the cell divides, the viral genetic material is passed to daughter cells. This is viral persistence at its most advanced evolutionary state.

When cats are exposed to FeLV, the consequences are variable. The determining factors include age of cat, duration of exposure, dose of virus, and strain virulence of virus. Brief exposure of adult cats to FeLV is unlikely to result in virus infection. Prolonged exposure of adult cats to high doses or lesser exposure of neonatal kittens may well allow virus to establish. In one study, 100 per cent of neonatal kittens became viremic after exposure to FeLV, whereas only 85 per cent of 8-week-old genetically related kittens became viremic with an equal dose of the same virus strain.<sup>32</sup> Following successful infection, initial virus multiplication occurs in a variety of lymphoreticular cells, particularly those in the tonsil, blood germinal centers of lymphoid tissues, thymic medulla of kittens, and bone marrow. Many of these infected cells will contribute to a viremia, but the release of infected neutrophils and platelets from the bone marrow is the main source for viremia. This viremia of bone marrow origin commences up to 6 weeks following initial infection, and it may be prevented by early and adequate immune response. The most important component of this response is virus-neutralizing (VN) antibody directed against the FeLV envelope glycoprotein, gp70. The other important part of the immune response is antibody against the feline oncornavirus-associated cell membrane antigen (FOCMA). This



is a viral-induced antigen that is present on the cell membrane of FeLV-infected and transformed cells. Antibody to FOCMA can aid in the immune destruction of such potentially malignant cells.

An inadequate immune response at this stage will lead to persistence of the virus either as a productive, persistent viremia or as a regressive, nonviremic state. A major factor in determining that the immune response will be inadequate is an immunosuppressive polypeptide, p15e, which is an integral part of the FeLV particle. The immunosuppressive mechanisms involved are complex and are well reviewed by Rojko and Olsen.<sup>65</sup> The degree of immunodepression is proportional to the quantity of p15e that is dependent on the scale of initial virus replication. This in turn relates to the previously mentioned factors of age of cat, duration of exposure, and dose and strain of virus.

Viremia with FeLV is detectable by an indirect fluorescent antibody technique on peripheral blood smears or by an enzyme-linked immunosorbent assay (ELISA) test on plasma. Viremic cats will usually be shedding FeLV in saliva and also in feces and urine.<sup>33</sup>

It has been estimated that in the overall cat population, assuming a 50 per cent infection rate, 1.8 per cent of FeLV-infected cats become persistently viremic.<sup>18</sup> The rate may be much higher (up to 30 per cent) in FeLV-endemic catteries.<sup>28</sup> When persistent viremia occurs, it is highly likely to lead at some subsequent time to development of neoplastic or non-neoplastic FeLV-related diseases such as non-regenerative anemia.<sup>27,33</sup> Thus, it is estimated that 0.5 per cent of FeLV-infected cats or, rather, less than one third of persistently viremic cats will die of virus-positive lymphosarcoma or leukemia, with a median induction period of 17.6 months. The estimates for non-neoplastic FeLV-related deaths are 1.3 per cent of FeLV-infected cats, or just over two thirds of persistently viremic animals, with a median induction period of 24.6 months.<sup>18</sup> Only rarely will persistently viremic cats subsequently become nonviremic.

Persistently viremic cats are important as sources of FeLV infection. The identification and removal of these animals are an important and successful control measure in clearing FeLV from endemically infected catteries.<sup>29</sup>

Usually VN antibody and other antibodies cannot be demonstrated in persistently viremic cats, but some of these cats do have antibody to gp70, FOCMA, p15e, and other viral proteins.<sup>45,47</sup> These carriers may remain healthy for years and maintain antibody titers. They will probably eventually succumb to FeLV-related disease, particularly those associated with excess antibody that forms immune complexes with antigen resulting in glomerulonephritis and hypocomplementemia.<sup>38,41,71</sup>

An alternative to persistent viremia following FeLV infection with a delayed or inadequate immune response is a nonproductive (masked) virus persistence. As a retrovirus, FeLV has the property of inserting pro-viral DNA in the DNA of host cat cells. Evidence suggests that marrow myelomonocytic precursor cells and certain nodal T lymphocytes are predilection cells for such integrated persistence.<sup>64</sup> The masked FeLV may be reactivated from these cells by *in vitro* propagation of marrow cells, stimulation of nodal lymphocytes by the T-cell mitogen staphylococcal protein A, and by adrenal

corticosteroid hormones.<sup>46,56,63,64</sup> Viral recrudescence *in vivo* may occur in response to hormonal changes, immunologic changes, and aging.<sup>64</sup>

Reactivation may be detected as relapsing viremias.<sup>56</sup> It could be responsible for maintaining high levels of anti-viral and anti-FOCMA antibodies.<sup>14</sup> Partial viral expression may be detected by the presence in serum of p27 antigen (ELISA test positive), but without viremia (indirect fluorescent antibody test negative).<sup>45,66</sup>

It is likely that a high proportion (more than 70 per cent) of cats infected with FeLV but that do not develop persistent productive infection are non-productively but persistently infected. Of these, a small number will reactivate under natural circumstances. After protracted incubation periods of months or years, some will develop FeLV-related disease. These animals account for those lymphosarcomas that are FeLV-negative but FOCMA-positive.<sup>30</sup>

Kittens can be born with nonproductive FeLV infection that can be reactivated by *in vitro* culture of marrow and thymus cells. It has been suggested that maternally derived VN antibody may be responsible for maintaining the congenital infection in an apparently nonproductive form.<sup>64</sup>

There is no evidence that the recently introduced feline leukemia vaccine (Leukocell\*) has any effect on either persistent viremia or nonproductive persistent infections once these have occurred; further study is needed, however.

## FELINE SYNCYTIAL-FORMING VIRUS

Feline syncytial-forming virus (FeSFV) is also a retrovirus (subfamily Spumavirinae). FeSFV is found as a persistent infection in many cats.<sup>62</sup> The virus is frequently isolated in primary cell cultures prepared from various tissues of healthy cats and fetuses.<sup>26</sup> It may sometimes be isolated from throat swabs, or buffy coat.<sup>12,70</sup> Isolates have been made from cats with urolithiasis,<sup>16</sup> infectious peritonitis,<sup>43a</sup> and polyarthritis,<sup>52</sup> but there is no clear association between disease and infection with this virus.

## CONCLUSIONS

All the viral infections of the dog and cat probably have viral persistence as an important aspect of their epidemiology. In some cases, such as feline viral rhinotracheitis or feline calicivirus, the carrier state is very common and well documented. In others, such as infectious peritonitis, carriers are hypothesized but not proven. As we prevent the acute aspects of many of these diseases by vaccination, the persistent infection becomes an important restriction to achieving complete control or eradication of the problem. This article has described a variety of ways in which virus persistence can occur. Better understanding of these mechanisms of persistence and the interaction with immune factors is a prerequisite to the logical use of immunoregulatory,

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immunostimulant, or antiviral drugs to eliminate such persistent infections. Meanwhile, the veterinarian dealing with the prevention and control of viral diseases in dogs and cats can apply some logical management principles to reduce the impact of carrier animals in a group or colony.

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