

THE BIOLOGY OF TWO HERPESVIRUS INFECTIONS OF DOMESTIC ANIMALS.

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ABSTRACT.

One of the major features of herpesvirus infections of animals is latency. From time to time detectable episodes of virus shedding may occur, both apparently spontaneously and as a result of certain endogenous and exogenous stimuli. A number of experimental systems have been investigated to study the phenomenon of latency and recrudescence, mainly using herpes simplex virus infection in the mouse model. However, there are a number of other animal species that can be studied where the herpesvirus is in its own natural host-virus system. Two such examples, the cat and pigeon herpesviruses, are described here. Both of these produce a latent infection in their hosts, and can be reactivated under well-defined conditions either as a result of natural, physiological stresses, or from more artificial stimuli. As a result of these observations, some conclusions are drawn about the biological role of latency.

INTRODUCTION.

One of the major features of herpesvirus infections of animals is the phenomenon of latency. Latency may be defined as the masked persistence of virus in the host, so that it cannot be detected by conventional virological techniques. From time to time, however, detectable episodes of virus shedding (re-excretion) may occur, both apparently spontaneously and as a result of certain endogenous or exogenous stimuli, and which may or may not be accompanied by clinical signs (recrudescence). Thus in people, herpes simplex virus (HSV) recrudescence tends to occur after physiological stresses such as menstruation or pyrexia (Roizman, 1965), and in animal herpesvirus infections stresses such as a change of housing or the reproductive period may induce virus re-excretion (Gaskell and Povey, 1977, 1982; McFerran et al., 1984; Vindevogel et al., 1985). Re-excretion may also be stimulated in many species by means of corticosteroid or other immuno-suppressive treatment (Sheffy and Davies, 1972; Gaskell and Povey, 1973; Vindevogel et al., 1980b; Wittmann et al., 1982), though the exact mechanism of this is unknown.

A number of experimental systems have been investigated in order to study the phenomenon of latency and recrudescence. The majority have concentrated on human HSV infection in the mouse model, the mouse being chosen not only because of convenience and our immunological knowledge of the host, but also because of its low background level of spontaneous reactivation compared to some other laboratory species (Sekizawa et al., 1980; Openshaw, 1984). A variety of methods have been used in

the mouse to induce re-excretion, including corticosteroid treatment (Underwood and Weed, 1974), cyclophosphamide (Kurata et al., 1978), skin trauma (Hill et al., 1978) and ultraviolet light (Blyth et al., 1976). Possible mechanisms for the establishment, maintenance and control of HSV latency, particularly with respect to experimental findings on the mouse model, have been discussed by Blyth and Hill (1984).

However, there are a number of other animal species that may be studied where the herpesvirus is in its own natural host-virus system. Studying latency in the proper animal species reduces errors that may arise as a result of experimental contrivance, for the same herpesvirus infection may give different results both within and between species. In veterinary medicine compared to human medicine however, virus re-excretion or shedding ("reactivation" in the mouse model) is considered more important than recrudescence, for it is the epidemiological implications of the re-excreting animal in a herd or group that are important, rather than recrudescence in the individual.

This paper describes two herpesvirus infections of animals; Felid herpesvirus 1 (FHV 1) and Pigeon herpesvirus 1 (PHV 1). Both of these produce a latent infection in their hosts, and can be reactivated under well-defined conditions either as a result of natural, physiological stresses, or from more artificial stimuli. As a result of these observations, some conclusions are drawn about the biological role of latency.

FELID HERPESVIRUS 1 (FHV 1).

FHV 1 is an alphaherpesvirus of cats. It is a respiratory pathogen producing a disease known as feline viral rhinotracheitis. In contrast to the broader host range of some other herpesviruses such as ADV or HSV, the virus only affects domestic cats and other Felidae (Povey, 1979). All isolates so far examined from many parts of the world show antigenic homogeneity on the basis of conventional serological cross-neutralisation tests (Crandell et al., 1960; Bittle et al., 1960; Johnson and Thomas, 1966), although more refined serological techniques have not been used. Recent work using restriction enzyme analysis of the viral DNA has confirmed this high degree of similarity between strains which in general is reflected in the relatively uniform biological behaviour of isolates (Hermann et al., 1984). However strains of modified virulence do exist, having been produced in recent years for vaccines (Slater and York, 1976; Davies and Beckenhauer, 1976; Bittle and Rubic, 1975).

No serological relationship has been demonstrated between FHV 1 and a second feline herpesvirus associated with urolithiasis (Fabricant and Gillespie, 1971), nor with several other alphaherpesviruses of other species (Povey, 1979).

FHV 1 is highly infectious to susceptible cats, infection occurring via the intranasal, oral or conjunctival routes. In the acute phase of the disease, the major sites of virus replication are in the nasal septum, turbinates, nasopharynx and tonsils; conjunctivae, mandibular lymph nodes and trachea are also often involved (Crandell et al., 1961; Gaskell and

Povey, 1979a). A viraemia has only rarely been reported. A possible genital tropism has been investigated experimentally, but is not thought to be of significance under natural conditions (Bittle and Peckham, 1971; Hoover and Griesemer, 1971).

The virus is a comparatively labile virus, surviving under typical external environment conditions for less than a day (Povey and Johnson, 1970) and susceptible to all common disinfectants (Scott, 1980). As an aerosol, it is relatively unstable at midrange and higher relative humidities (Donaldson and Ferris, 1976).

Incidence and clinical signs.

FHV 1 is a highly successful virus in cats. It is widespread throughout the world (Crandell, 1973) and together with feline calicivirus, accounts for the majority of cases of feline respiratory disease (Kahn and Hoover, 1976; Gaskell and Wardley, 1978). Clinically it is the most significant of the feline respiratory pathogens. Serological surveys prior to vaccination demonstrated FHV 1 serum neutralising antibody titres in 26-70% of cats, depending on the nature of the sample population (Studdert and Martin, 1970; Povey and Johnson, 1971; Ellis, 1981). In general infection is less common in isolated household pets than in colony animals. However, the household pet is artificially separated from other cats by man; an open colony situation being a truer reflection of how virus and host evolved together. Once the virus has gained access to a susceptible colony, often by means of a clinically normal carrier, the disease rapidly becomes endemic, its presence being noted by the existence of chronically affected animals with recurrent or persistent signs. Outbreaks of acute disease may also occur, particularly in young kittens when they lose their passive immunity.

Acute infection with FHV 1 is characterised by depression, sneezing and ocular and nasal discharges (Crandell et al., 1961; Gaskell and Povey, 1979a). There is usually a fever and loss of appetite. Conjunctivitis, hypersalivation, and sometimes dyspnoea and coughing may develop and there may be a recurrence of the pyrexia. A leucocytosis with a left shift is present throughout the course of the disease. Other, rarer manifestations have been reviewed by Gaskell and Wardley (1978) and Povey (1979). Mortality may be high in young or debilitated cats and virus generalisation may occasionally occur. The majority of clinical signs have usually resolved in 10-20 days, but some animals may be left with chronic sequelae such as conjunctivitis, rhinitis, or sinusitis. These are probably mainly due to severe mucosal damage and secondary bacterial infection, but may also occur as a result of viral recrudescence.

Experimental infection and induction of re-excretion.

The most common route of infection used experimentally is intranasal, although several other routes have been investigated (Povey, 1979). The incubation period is 2-7 days, though it may be longer and has been shown to be dose-related (Gaskell and Povey, 1979a). Virus is shed in oropharyngeal, nasal and conjunctival secretions for a period of one to three

weeks, titres of up to $10^{4.5}$ (mean 10^4) TCID₅₀ per ml. of secretion being reached (Gaskell, 1975).

Experimentally it has been shown that the majority of FHV 1 recovered animals are latently infected virus carriers (Gaskell and Povey, 1973, 1977). Re-excretion may occur spontaneously, but is most likely to occur following stress. Under experimental conditions it has been shown that a change of housing may induce virus shedding in 18% of 22 FHV 1 recovered cats on 15% occasions, and corticosteroid in 69% of 32 cats on 54% occasions (Gaskell and Povey, 1973, 1977). Climatic stress appeared to be ineffective in inducing re-excretion. The apparently spontaneous shedding rate was 0.9% on any one day. In these studies, a total of 82% of FHV 1 recovered cats shed endogenous virus on at least one occasion and 45% shed virus spontaneously or under "natural" stress conditions and thus could be considered epidemiologically important. Similar findings have been reported by Ellis (1981) and Goddard (1984).

A lag period occurred before onset of virus shedding of from 4-11 days (mean 7.2) after corticosteroid treatment, and from 4-10 days (mean 7.2) after re-housing (Gaskell and Povey, 1973, 1977). The duration of virus shedding ranged from 1-13 days (mean 6.5) after corticosteroid and 4-7 days (mean 7.2) after re-housing. Titres of virus shed were generally lower (p less than 0.01) than in the acute stage of the disease, although amounts of up to $10^{3.5}$ (mean $10^{3.1}$) TCID₅₀ per ml. of secretion were recorded (Gaskell, 1975). In some cases (72% following corticosteroid stress, 30% following re-housing) shedding was accompanied by recrudescence of mild clinical signs, though occasionally signs were seen in carriers unassociated with detectable episodes of re-excretion.

It appeared that there was a refractory period following an episode of corticosteroid induced re-excretion during which further administration of corticosteroid was less effective (Gaskell and Povey, 1977). Cats which did re-excrete as a result of treatment had last shed virus on an average of 16 weeks before, whereas cats which did not re-excrete had experienced their last episode of virus shedding on an average of only eight weeks before (p less than 0.01). Considerable variation was apparent however, both within and between individuals.

The site or sites of latency have not been completely elucidated for FHV 1. Despite several unsuccessful attempts in the past to isolate virus from the trigeminal ganglia and a number of other tissues of latently infected cats (Plummer et al., 1973; Gaskell and Povey, 1979b; Ellis, 1982), recently virus has been isolated using a tissue fragment culture technique from the trigeminal ganglia of a small proportion, 3 (18%) of 17 recovered animals (Gaskell and Goddard, 1984; Gaskell et al., 1985). However, it remains to be seen if this is the major or only site of viral persistence in this species.

Natural transmission of the disease.

The major method of spread of FHV 1 is by direct cat-to-cat contact, either from animals in the acute stage of the disease, or from shedding carriers. There is no evidence of vertical transmission. Indirect transmission may also occur,

but probably less frequently, and only within the close confines of a cattery. Carrier cats are of considerable epidemiological significance: they are widespread in the population, and in an endemic cattery, constitute the majority of recovered animals. In the field situation, surveys of clinical normal cats have shown an apparently spontaneous shedding rate of 1-2% (Wardley et al., 1974; Ellis, 1981), and Gaskell (1975) recorded FHV 1 re-excretion in 3 of 75 cats 9-12 days after entering a boarding cattery. It seems probable, therefore, extrapolating from the experimental studies, that other stresses, such as going to stud, to a cat show, or entering a new cat colony, may also induce similar episodes of re-excretion.

Although carriers are undoubtedly a source of infectious virus and can initiate outbreaks of disease, it seems that cross-infection is less easily achieved from a shedding carrier than from an acutely infected animal (Gaskell and Povey, 1982). Thus under experimental conditions, fairly intimate contact of several days' duration is necessary before successful transmission may occur. This is presumably because discharges are usually more copious and in slightly higher titre in acutely infected animals than in carriers.

Under more natural conditions, however, it is likely that the greatest importance of the carrier lies in its ability to transmit the virus within the close contact of family groups, thus enabling it to perpetuate the host-virus relationship into the next generation. In studies on the possible transmission of FHV 1 from carrier queens to their kittens, the shedding rate from queens in the 10 week post-partum period did appear to be marginally increased above the spontaneous rate: four of ten queens re-excreted virus and four kittens from three litters developed a contact infection (Gaskell and Povey, 1982). None showed clinical signs and were presumably infected under cover of passive immunity. Two shed virus for one day only and did not become carriers, and two shed virus for two to three weeks and were subsequently shown to have become carriers: their SN antibody titres rising from less than 1 in 4 and 1 in 8 prior to re-excretion, to 1 in 96 and 1 in 128 after. The establishment of a latent carrier state under cover of passive immunity in animals which then became sero-negative, has also been shown for HSV infection in mice (Sekizawa et al., 1980).

From other studies it appears that there are many cases where carrier queens shed virus either when their own or other kittens in close contact are unprotected by maternal antibody, and cases of acute disease result (Povey and Johnson, 1967; Crandell, 1971). Although such cases will aid viral dissemination in the short term, in many ways it is not a good method for the virus to perpetuate itself in its host as mortality and also chronic sequelae in young kittens can be high. The findings outlined above, however, show that on some occasions at least, the cat has an ideal method of perpetuating a balanced virus-host relationship which does not depend on the development of clinical disease. This then leads to the establishment in the next generation of the latent carrier state, so the cycle is complete.

Immune control of re-excretion.

Immunity to re-infection following primary infection with FHV 1 is not very complete or persistent; an animal may be re-infected within six months of a primary infection, although such cats show only mild clinical signs and a reduced period of virus shedding (Walton and Gillespie, 1970). A number of vaccines have been developed for use in controlling the disease, including live attenuated vaccines given intranasally or systemically, and inactivated vaccines given systemically. These have been reviewed elsewhere (Gaskell, 1981). All vaccines protect to a large extent against clinical signs following challenge, though the intranasal route may be marginally more effective. However it has been shown that following systemic vaccination, cats generally replicate virus for several days after challenge and may subsequently become latent field virus carriers (Orr et al., 1978). Following intranasal vaccination, however, with a cold-adapted strain of FHV 1, virus replication after challenge appeared to be minimal, and in the short term at least, no animals appeared to have become carriers (Orr et al., 1980; Cocker et al., 1984). Thus some vaccinated animals, whilst themselves protected from clinical disease, may still be a source to others of infectious field virus.

Whether or not repeated vaccination helps control viral re-excretion episodes is not known. There appears to be a natural refractory period after an episode of re-excretion (see earlier) and so it seems possible that externally administered antigen may also help control re-excretion.

PIGEON HERPESVIRUS 1 (PHV 1).

PHV 1 is predominantly a respiratory pathogen of pigeons, although it also occurs in budgerigars and is antigenically indistinguishable from falcon or owl herpesviruses (Mare and Graham, 1973; Purchase et al., 1972). However it is probable that pigeons are the predominant natural host of PHV 1, and that infection in budgerigars, and possibly other species, is an epidemiological dead-end. Thus, although a spectrum of clinical signs may be seen in infected pigeons, in budgerigars, PHV 1 provokes, both naturally and experimentally, a fatal hepatitis (Vindevogel and Duchatel, 1977; Vindevogel et al., 1978, 1980c).

A similar situation exists with Aujeszky's disease virus (ADV) (Suid herpesvirus 1) where pigs are the main host, and infection in other species, such as cattle, dogs and cats, is of no epidemiological significance (Aguilar-Setién et al., 1979a, 1979b).

Incidence and clinical signs.

PHV 1 infection is widespread in domestic pigeon populations. In Belgium, specific antibodies have been detected in the sera of 84% of clinically normal pigeons and 63% of pigeons affected with acute respiratory illness. PHV 1 has been isolated in 60% of dove-cots permanently affected with respiratory disease and from 82% of pigeons affected with acute

respiratory troubles (Vindevogel et al., 1981; Vindevogel and Duchatel, 1978). A similar situation has been described in Germany and France (Heffels et al., 1981; Landre et al., 1982). Virus has also been isolated from pigeons coming from dove-cots where all birds are devoid of detectable specific antibodies (Landre et al., 1982).

Under natural conditions, clinical disease is predominantly seen in primary infection of young pigeons derived from parents free of the infection, or in carriers of the virus with the help of debilitating factors (Vindevogel et al., 1980a, 1981). Experimental disease may be reliably produced in squabs born from virus-free parents (Vindevogel and Pastoret, 1981).

Classical signs of PHV 1 infection in pigeons are conjunctivitis, rhinitis, and focal necrosis, in the mouth, pharynx and larynx. In some cases, particularly in pigeons weakened by debilitating factors such as parasitic disorders or secondary bacterial invaders, viral dissemination may also occur and lesions may be observed in liver, spleen, kidney and pancreas (Cornwell and Wright, 1970; Boyle and Binnington, 1973; Vindevogel et al., 1975; Vindevogel and Pastoret, 1981).

Experimental infection and induction of re-excretion.

After inoculation with PHV 1 by pharyngeal painting, susceptible squabs excrete virus for a minimum of 7 to 10 days (Vindevogel et al., 1980b). The typical lesions appear 1 to 3 days after infection when the viral excretion reaches its highest titre. Virus usually remains confined near the site of inoculation, although viraemia may occur.

Mild episodes of recurrence, without clinical signs, occur spontaneously (Vindevogel et al., 1980b). High titres of specific antibodies do not prevent these recurrences, and conversely, recurrent episodes do not occur more frequently when the animals are nearly devoid of specific antibodies.

PHV 1 re-excretion can be provoked experimentally by cyclophosphamide (Cy) treatment, and this period of re-excretion may be accompanied by lesions of varying severity and some birds may die (Vindevogel et al., 1980b; Vindevogel and Pastoret, 1981). In one group, all birds re-excreted infectious virus starting 2 to 5 days after the first injection of Cy for between 1 to 10 days: amounts of virus shed were similar to those seen in the acute phase of the disease. The mechanism by which Cy initiates viral re-excretion is not known. It may be due to a direct cytotoxic effect on latently infected cells or indirectly through the effects of Cy on B and T lymphocytes (Coignoul and Vindevogel, 1980). This effect of Cy on the immune system may account for the more severe clinical syndrome and higher mortality seen in Cy treated birds (Vindevogel et al., 1980b; Vindevogel and Pastoret, 1981).

Natural transmission of the disease.

As far as is known, egg transmission of the disease does not occur. No genital form of the disease has been detected and neither virus nor its antigen could be demonstrated in cell cultures derived from embryos from infected parents (Vindevogel and Pastoret, 1980, 1981).

Although virus may be spread horizontally from acutely

infected birds, infection is mainly perpetuated by means of carriers. Thus in a flock of pigeons infected with PHV 1, virtually all the mature birds are asymptomatic carriers of the virus and are thus a potential source of infection to their offspring, and to any susceptible in-coming birds. Apparently spontaneous episodes of re-excretion may occur, and since significant amounts of virus are shed, such birds presumably may transmit the infection (Vindevogel et al., 1980b). However there is some evidence that these spontaneous episodes are not as long-lasting as Cy-induced or natural stress-induced episodes of re-excretion, and thus they may not be of such epidemiological significance.

Studies have shown however, that virtually all pigeons will experience an asymptomatic re-excretion episode of reasonable duration during the reproductive period. Most of them re-excrete virus soon after the hatching period, when they regurgitate "milk" for their squabs (Vindevogel et al., 1985). After weaning (12th week after hatching) all parents cease shedding virus. The squabs become infected but are protected from the disease by passive immunity of parental origin, conferred to the squabs through the egg yolk. Most of the squabs themselves then become asymptomatic carriers after this initial infection, though they are very soon devoid of detectable antibodies. However, infection may be unmasked by Cy treatment, and presumably such squabs may themselves be capable subsequently of transmitting the virus to the next generation.

Under natural conditions therefore, there is a sophisticated equilibrium between the virus and its host that prevents the occurrence of disease. Nearly all the birds are infected and the infection can be perpetuated with a small number of infected birds, without exogenous introduction of wild virus.

Immune control of re-excretion.

Primary infection of pigeons with a pathogenic strain of PHV 1 (Vindevogel et al., 1982) prevents recurrence of the disease after re-infection. The protection is sufficient to inhibit viral multiplication in some birds. Both attenuated and oil-adjuvanted inactivated vaccines have been developed and are effective in reducing primary viral excretion and symptoms after challenge (Vindevogel et al., 1982a and b). Nevertheless neither vaccine was able to prevent the appearance of carriers since most of the pigeons subsequently re-excreted virus after Cy treatment. However vaccination helps to prevent spontaneous viral re-excretion and therefore helps to control viral dissemination. If animals are vaccinated with an inactivated vaccine after challenge with a virulent strain, experimental re-excretion is also reduced.

Nevertheless, vaccination is not the complete answer for the control of PHV infection, since young pigeons are often infected shortly after hatching and vaccination does not prevent the development of a carrier state or subsequent episodes of re-excretion.

DISCUSSION.

These animal-herpesvirus systems demonstrate the phenomenon of latency in the natural host. In each system, well-defined re-excretion episodes may be provoked by means of artificial stimuli such as corticosteroid or cyclophosphamide. In addition, re-excretion episodes may also be stimulated by means of natural stresses such as reproduction or a change of housing.

There are several advantages to using natural host-virus systems to study the phenomenon of herpesvirus latency. Firstly, since virus and host probably evolved together over a considerable period, the biological and epidemiological significance of spontaneous and natural shedding episodes may be assessed. In addition, observations on the mechanism of establishing, maintaining, reactivating, and controlling latency are probably more valid since they also relate to a naturally evolved relationship. In contrast, laboratory models such as the mouse-HSV system are easier and cheaper to maintain and are better defined genetically and immunologically.

To be a successful parasite, a virus needs to be able to ensure its transmission to as many animals as possible in each generation. Herpesviruses are in general relatively fragile outside their host, and therefore they cannot rely on external survival for their long-term persistence. In general, they have no reservoir or alternative hosts. Transmission by direct contact spread from acutely infected to susceptible animals certainly occurs, but requires a sufficient number of susceptible animals in the population and sufficient opportunities for contact between them or the virus will die out. Herpesviruses have therefore evolved the highly successful method of perpetuating themselves in a population by means of latently-infected carriers. Such carriers are only of biological significance, however, if shedding episodes coincide with the presence of susceptible individuals in close enough contact for transmission to occur.

In a population where the disease is endemic, the time when this is most likely to occur is just before or during weaning when the parent and young are still in very close contact but the young have become susceptible to the virus due to the waning of passive antibody.

Studies on the cat and pigeons have shown however that the timing of the shedding episode during this post-partum period is crucial. If it is too soon, only transient infection will occur and the offspring might not themselves become carriers. If it is too late, i.e. when maternal antibody has completely waned, then the clinical disease may be too severe and the host's survival compromised. Ideally the shedding episode should occur whilst the offspring are still protected from clinical disease, but not from virus shedding and the subsequent development of a latent carrier state. In the pigeon particularly, but to a lesser extent also in the cat, such a balanced virus-host relationship does occur, ensuring survival of the virus in as many animals as possible in the next generation, so that the cycle is complete. Indeed it may be that even in the cat, under more natural conditions, shedding

may occur in more animals during the post-partum period than was apparent from these studies: the cats used in this work had previously been induced to shed artificially on a number of occasions, and this may have induced a relative "refractory period", making them less likely to shed after parturition.

In a herd or family group, where the young are of similar age and are in reasonably close contact, not all the parents need to re-excrete to ensure virus transmission to all the offspring. Once one clinical case has occurred, virus dissemination will be greatly increased. Nevertheless, such a system, which tends to be seen particularly in cat colonies, is not ideal, since the timing of shedding in relation to the presence or absence of maternal antibody may be less than perfect. Severe clinical disease may then ensue and mortality and chronic sequelae may be significant, thus jeopardizing the host's and therefore the virus's survival into the next generation.

Another useful tool for the virus epidemiologically is the increased likelihood of shedding after a change in living conditions, a situation which has been demonstrated particularly in cats. Thus if an animal is driven from its territory or family group, then it is likely to re-excrete virus in its new surroundings and may therefore infect another population. By this means the virus has a mechanism for increasing its chances of horizontal spread.

In conclusion, observations on natural host-virus systems may tell us more about the biological significance of latency, and indeed, more about the host-virus relationship in general. Perhaps if most natural infections occur in young animals when they are losing their passive immunity, this should be the age at which both the mechanisms for establishing and controlling latency should be examined. It should be interesting to compare the frequency of recrudescence in people or animals that have experienced asymptomatic primary infection at an early age under cover of passive immunity, with those who experienced later symptomatic infections. Finally perhaps hormone influences on re-excretion rates and recrudescence disease should be examined in more detail.

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