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# FELINE health topics

for veterinarians



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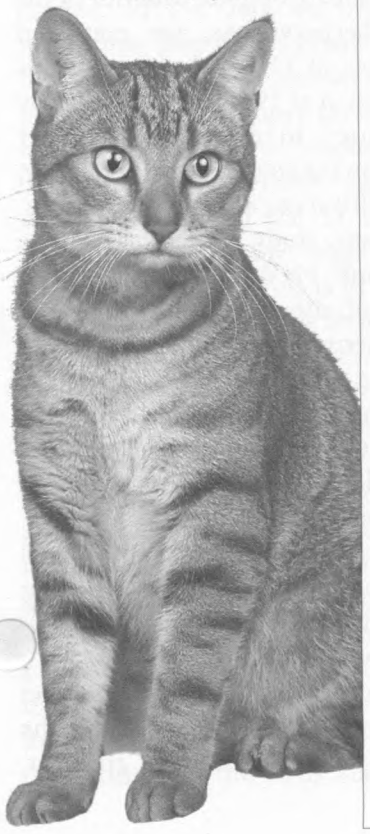

## Feline Herpesvirus: Clinical Syndromes and Diagnostic Testing

**David J. Maggs, BVSc(hons), Diplomate ACVO**
**Associate Professor, Comparative Ophthalmology**

University of California-Davis

Feline herpesvirus (FHV-1) is a ubiquitous virus that varies very little worldwide; i.e. strains do not vary greatly in their clinical virulence. And yet, we see a huge range of clinical signs in cats infected with this virus. There are probably a large number of reasons for this; however principle among these is likely the host's response to this virus. FHV-1-naïve kittens infected in the first few weeks of life against a backdrop of waning maternal immunity almost inevitably get severe upper respiratory and ocular disease with high morbidity but rare mortality. By contrast, adult cats can undergo viral reactivation with viral shedding and can infect in-contact cats; all without demonstrating clinical signs themselves. These two scenarios represent just the two extremes of infection; within your clinic you see cats with a huge diversity of clinical signs in between. For this reason, I like to consider clinical signs associated with FHV-1 under one of three broad categories: primary (first time) infection, recrudescent infections, and FHV-1-associated syndromes.

### Clinical Signs

**Primary herpetic disease**

Primary ocular FHV-1 infection is characterized by blepharospasm, conjunctival hyperemia, serous ocular discharge that becomes purulent by day 5-7 of infection, mild to moderate conjunctival swelling (chemosis), and often conjunctival ulcers. Corneal involvement is not reliable; however some cats develop corneal ulcers which are transiently dendritic at the very earliest phase only. These dendrites quickly coalesce to become geographic ulcers. The ocular signs are seen in association with typical signs of upper respiratory infection. The uncomplicated clinical course is typically 10-14 days; however it is critical to realize that almost all cats become latently infected within ganglia for life. Reactivation from latency is likely in at least 50 percent of cats, sometimes with viral shedding and clinical signs.

**Recrudescent FHV-1 syndromes**

Despite the frequency with which latently infected cats undergo viral reactivation at the ganglia and viral shedding at peripheral epithelial sites, recrudescent disease occurs in a minority of cases. Further, disease severity and tissue involvement can range very widely between individuals and even between episodes in the same cat. Recrudescent conjunctivitis is usually milder than in acute infections, but can become chronic and "smoldering". Although recrudescent conjunctivitis is usually nonulcerative, substantial conjunctival thickening and hyperemia can occur secondary to inflammatory cell infiltration. Corneal involvement is

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relatively frequent in recrudescent disease compared to primary infection and may involve the corneal epithelium or stroma. With epithelial involvement, dendritic and later geographic corneal ulceration may be seen just as in primary infections. Corneal stromal disease is typically immunopathological (i.e., immune-mediated, but not necessarily autoimmune) in origin and includes stromal neovascularization, edema, stromal cell infiltration, and ultimately fibrosis usually under an intact epithelium. Consensus has not been reached regarding the antigens responsible for the subepithelial immunological response within cornea and/or conjunctiva. Some believe the process is driven by viral antigens, while others are suspicious that altered self antigens are the focus of the immunological response.

## FHV-1-associated Disease Syndromes

The following diseases have been associated with detection of FHV-1 in affected tissues; however the causative role of the virus in each syndrome has been variably proven.

**Symblepharon.** There is little question that symblepharon can be a sequela to severe primary FHV-1 infection. It is commonly seen in young animals, and presumably occurs as a result of widespread ulceration with exposure of the conjunctival substantia propria and sometimes also the corneal stroma. FHV-1 is almost certainly the predominant cause of symblepharon formation in cats and other infectious agents are unlikely to cause symblepharon formation.

**Corneal sequestration.** Experimentally, FHV-1 inoculation (in cats receiving corticosteroids) can result in corneal sequestration. However, the prevalence of detectable FHV-1 in samples collected from cats with sequestra has varied widely in the clinical setting and the link between FHV-1 and sequestra has not been shown to be causative. It seems likely that sequestration is a non-specific response to stromal exposure or damage and that FHV-1 is just one possible cause of this disease. This is borne out in a study by Nasisse et al (1998) who reported identification of FHV-1 DNA in 86 of 156 (55 percent) of sequestra analyzed (compared with only six percent of clinically normal corneas). A lower prevalence of FHV-1 DNA was found in corneas of Persian and Himalayan cats with sequestration, suggesting that other non-viral causes of sequestration are more likely to be operative in these breeds.

**Eosinophilic keratitis.** Prior clinical studies have suggested a link between FHV-1 infection and eosinophilic keratitis (Nasisse et al 1998). PCR testing of corneal scrapings from cats with cytology-confirmed eosinophilic keratitis has revealed 76 percent (45/59) of cases to be FHV-1 positive. However, PCR performed on tears collected onto a STT was negative in 10 cats with cytologically proven eosinophilic keratitis (Allgoewer et al 2001). As with corneal sequestra, the role of the virus in the initiation or exacerbation of this disease has not been determined; however anecdotally some patients with this syndrome improve with antiviral therapy alone.

**Uveitis.** Herpes simplex virus type 1 (HSV-1) is a well-documented cause of uveitis in humans. Given the shared biological behavior of the alphaherpesviruses, we examined the role of FHV-1 in feline uveitis (Maggs et al 1999). The PCR assay was used to demonstrate FHV-1 DNA in the aqueous humor of 12/86 cats; all but one of which had uveitis. The same study also used ELISA to examine FHV-1-specific antibody concentrations in aqueous humor and serum. While seropositivity did not vary among cats, intraocular antibody production, as determined by a Goldman-Witmer coefficient (C-value) >1, was detected only in cats with uveitis. Additionally, a C-value >8, which is frequently quoted as a more clinically useful indicator of intraocular antibody production, was found only in cats with idiopathic uveitis. This information suggests that FHV-1 can infect the intraocular compartment and that,

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at least in some cats, it stimulates a specific and local antibody response. Because the trigeminal nerve supplies the uveal tract, it is possible that virus may reactivate spontaneously or via induction and arrive in the uvea (and aqueous humor) by the "round trip theory", as for surface ocular disease. Viral pathogenic mechanisms similar to those reported in surface disease are therefore plausible explanations for the uveal pathology seen. That is, virally-mediated cytolysis and immunopathological responses directed at auto or viral antigens are both possible. However, proving a casual association remains difficult.

**Dermatitis.** Periodically, FHV-1 has been identified as a cause of dermatological lesions, particularly those surrounding the eyes and involving nasal skin of domestic and wild felidae. This is not surprising when one considers the marked epithelial tropism of this virus and the reliability with which HSV-1 causes dermal lesions in humans. We have recently examined the diagnostic utility of FHV-1 PCR for this disease. FHV-1 DNA was detected in all nine biopsy specimens from five cats with herpetic dermatitis but in only one of 17 biopsy specimens from the 14 cats with nonherpetic dermatitis. FHV-1 DNA was not detected in any of the 21 biopsy specimens from the eight cats without dermatitis. This is in sharp contrast to the use of this technique in ocular tissues where the extent of viral shedding in normal animals dramatically reduces the sensitivity of a positive test in affected animals. When results of histologic examination were used as the gold standard in this study of cats with dermatitis, sensitivity and specificity of the PCR assay were 100 percent and 95 percent, respectively. We concluded that FHV-1 DNA can be detected in the skin of cats with herpetic dermatitis, that the virus may play a causative role in the disease, and that this PCR assay may be useful in confirming a diagnosis of herpetic dermatitis. (Holland et al 2006)

*Perhaps one of the best ways to diagnose FHV-1 is to maintain a strong clinical suspicion of its involvement in any cat with surface ocular disease and to be well aware of its classical clinical features, but to be questioning of its role in that disease process whenever it is detected using any currently available diagnostic assays.*

## Diagnosis of Herpetic Ocular Disease

A major paradox exists with respect to the diagnosis of FHV-1. Cats experiencing primary FHV-1 infection shed virus in sufficient quantities that viral detection is relatively easy. However, clinical signs during this phase of infection tend to be characteristic and self limiting, making definitive diagnosis less necessary. By contrast, during the more chronic FHV-1-associated syndromes, the diversity and ambiguity of clinical signs make viral identification more desirable, especially if specific antiviral therapy is being considered. However, the elusive nature of the virus in these chronic syndromes makes detection difficult. This is compounded by viral detection in normal animals. Indeed, the diagnosis of FHV-1 in individual cats represents one of the greatest challenges in the management of chronic herpetic diseases.

Although the extreme sensitivity (and specificity) of PCR has improved detection of virus, it has also confirmed that virus can be demonstrated in up to half of apparently normal cats. This must be considered when interpreting results of diagnostic assays in individual cats with disease. Additionally, we know that HSV-1 (and therefore possibly FHV-1) can be stimulated to reactivate by irritation of the peripheral sensory neurons. Therefore, it is possible that virus detected at a peripheral site in a diseased animal may be there as a result rather than a cause of the disease being investigated. Finally, no test in common usage can differentiate vaccine from wild-type virus. Therefore, there are at least 4 possible explanations when virus is detected in a cat with disease:

1. Its presence is *coincidental* (i.e., unrelated to the primary disease process)
2. Its presence is a *consequence* of the primary disease process
3. It is the *cause* of the primary disease process
4. It is *vaccine* virus

Even if virus is found, the clinician must consider whether specific antiviral treatment is warranted regardless of whether the virus is there as a cause or effect of the primary disease process. Currently, other than clinical acumen, there is no "test" that will answer that question!

For this reason, defining the "diagnostic" clinical signs is important. The only pathognomonic clinical sign of herpetic infection is the presence of dendritic corneal lesions. However, these are unreliably and transiently present, and although they may be fluorescein-positive, they are sometimes detect-

able only with rose bengal stain. Dendritic stromal scars that fail to retain fluorescein or rose bengal stains are also sometimes seen. Despite this, there are ways to create a high clinical suspicion of herpetic disease in cats. This starts by acknowledging that the vast majority of feline keratoconjunctivitis is due to FHV-1 or *Chlamydophila felis* (previously *Chlamydia psittaci*). Feline calicivirus is an unlikely and minor primary conjunctival pathogen and is not a recognized corneal pathogen. Data presented in the **Table 1** is intended to assist with the distinction of these two major differential diagnoses for any cat with keratoconjunctivitis. Differentiation of chronic or recurrent syndromes is more difficult than primary syndromes.

**Table 1: Summary of clinical signs produced in cats during primary infections by three common pathogens**

| Clinical Signs | FHV-1 | FCV | Chlamydia |
|---|---|---|---|
| Malaise/Anorexia | +++ | ++ | +/- |
| Sneezing | +++ | + | ++ |
| Nasal Discharge | +++ | ++ | ++ |
| Oral Ulceration | - | +++ | - |
| Ptyalism | + | +++ | +/- |
| Ocular Discharge | +++ | + | ++ |
| Conjunctivitis | +++ (Hyperemic) | - | +++ (Chemotic) |
| Keratitis | +++ | - | - |

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# Feline Herpesvirus: The Latest in Antiviral Therapy

**David J. Maggs BVSc(hons) Diplomate ACVO**
**Associate Professor, Comparative Ophthalmology**

University of California-Davis

I like to think of therapy for cats infected with feline herpesvirus-1 (FHV-1) as falling into one of four categories: supportive therapy, R&D antiviral therapy, therapies still undergoing investigation, and contraindicated therapies. For brevity, I have emphasized the latter three categories here.

## Antiviral Agents

FHV-1 is variably susceptible to inhibition by all commercially available antiviral ophthalmic medications studied thus far. However, the safety of these compounds is not readily predicted from their behavior in humans and their efficacy against FHV-1 often does not correlate with their activity against other viruses (even closely related viruses like herpes simplex virus (HSV) types 1 and 2.

**For these reasons, careful in vitro investigation of efficacy against FHV-1, followed by safety and pharmacokinetic trials, subsequent placebo-controlled efficacy studies in experimental animals, and finally judicious clinical trials in client-owned animals should always precede widespread clinical use and anecdotal reporting.**

Some important general concepts about antiviral agents assist with selection and expectations of this class of drugs:

- Because viruses reside intracellularly and utilize host cellular "machinery", antiviral agents tend to exhibit greater host toxicity than antibacterial drugs. This rarely limits topical application of these drugs but may severely limit their systemic use.
- Most antiviral agents in common use are virostatic, therefore they require relatively frequent dosing or topical application. In some cases, hourly application of ophthalmic preparations is recommended for at least the first 24 hours of therapy in humans.
- No antiviral drug is antibacterial.
- Antiviral drugs safe in humans are not necessarily safe in cats.
- Antiviral drugs effective against human herpesviruses are not necessarily effective against FHV-1.
- Antiviral prodrugs metabolized to their active form by humans are not predictably metabolized by cats.

The effect of some antiviral drugs on FHV-1 replication in vitro has been studied and their relative potency reported *(see Table below)*.

**Table 1: Relative in vitro efficacy against FHV-1 and HSV-1 of commercially available antiviral drugs (lower $IC_{50}$ = more effective)**

| | TFU | GCV | IDU | Cidofovir | PCV | Vidarabine | ACV | Foscarnet |
|---|---|---|---|---|---|---|---|---|
| $IC_{50}$ FHV-1 (μM) | 0.67 | 5.2 | 4.3-6.8 | 11.0 | 13.9 | 21.4 | 57.9-85.6 | 232.9 |
| $IC_{50}$ HSV-1 (μM) | 1.7 | 0.77 | 1.0 | 9.3 | 2.3 | 3.5 | 1.2 | 74.18 |

**Note: The "inhibitory concentration" ($IC_{50}$) is defined as the drug concentration at which plaque numbers were reduced by 50 percent relative to the number of plaques for nontreated control wells.**

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The following antiviral agents have been studied to varying degrees for their efficacy against FHV-1, their pharmacokinetics in cats, and/or their safety and efficacy in treating cats infected with FHV-1.

***Idoxuridine*** (IDU) is a nonspecific inhibitor of DNA synthesis, affecting any process requiring thymidine. Therefore, host cells and viruses are similarly affected, systemic therapy is not possible, and corneal toxicity

can occur. It has been used as an ophthalmic 0.1 percent solution or 0.5 percent ointment. This drug is reasonably well tolerated by most cats and seems efficacious in many. It is no longer commercially available in the USA but can be obtained from a compounding pharmacist. It should be applied to the affected eye five to six times daily.

***Vidarabine,*** like idoxuridine, is non-selective in its effect and so is associated with notable host toxicity if administered systemically. Because it affects a viral replication step different from that targeted by idoxuridine, vidarabine may be effective in patients whose disease seems resistant to idoxuridine. As a three percent ophthalmic ointment, vidarabine often appears to be better tolerated than many of the antiviral solutions. Where it is not available commercially, it can be obtained from a compounding pharmacist. Like idoxuridine, it should be applied to the affected eye five to six times daily.

***Trifluridine*** (TFU, Viroptic® or generic) is an analogue of thymidine whose specific mechanism of action against HSV-1 (for which it was developed) or FHV-1 is not completely understood. It is too toxic to be administered systemically but topically administered trifluridine is considered one of the most effective drugs for treating HSV-1 keratitis; in part due to its superior corneal epithelial penetration. It is also the most potent antiviral drug tested so far for FHV-1 (Table 1). It is commercially available in the USA as a one percent ophthalmic solution that should be applied to the affected eye five to six times daily. Its clinical efficacy is somewhat unpredictable, it is expensive, and frequently irritating.

***Acyclovir*** (ACV, Zovirax®) is the prototype of a group of antiviral drugs known as acyclic nucleoside analogues. Members of this group of antiviral agents all require three phosphorylation steps for activation. The first of these steps must be catalyzed by a viral enzyme, thymidine kinase. This fact increases their safety and permits them to be systemically administered to humans. However, the activity of this enzyme in FHV-1 has not been verified. This may explain why the $IC_{50}$ reported for acyclovir against FHV-1 is much higher than that reported for HSV-1. The second and third phosphorylation steps must be performed by host enzymes, which may not be present in cats or may not be as effective in cats as they are in humans. In addition to relatively low antiviral potency against FHV-1, acyclovir has poor bioavailability and is potentially toxic when systemically administered to cats. Oral administration of 50 mg/kg acyclovir to cats was associated with peak plasma levels of only 33 μM (approximately one third the $IC_{50}$ for this virus). Common signs of toxicity are referable to bone marrow suppression, therefore it appears wise to monitor a CBC in patients receiving acyclovir systemically.

***Valacyclovir*** (Valtrex®) is a prodrug of acyclovir that, in humans and cats, is more efficiently absorbed from the gastrointestinal tract compared with acyclovir and is converted to acyclovir by a hepatic hydrolase. Plasma concentrations of acyclovir that surpass the $IC_{50}$ for FHV-1 can be achieved after oral administration of this drug. However, in cats experimentally infected with FHV-1, valacyclovir induced fatal hepatic and renal necrosis, along with bone marrow suppression, and did not reduce viral shedding or clinical disease severity. Therefore, despite its superior pharmacokinetics, valacyclovir should **not** be used in FHV-1-infected cats.

***Penciclovir*** (PCV) is another acyclic nucleoside analogue and has potent antiviral activity against a number of human herpesviruses and FHV-1. It is available as a dermatologic cream for humans that should not be applied to the eye. Although there are some data regarding administration of famciclovir to cats (which is converted to penciclovir), in vivo studies of penciclovir's safety or efficacy in cats are lacking and at this time, its use in cats cannot be recommended.

***Famciclovir*** is a prodrug of penciclovir; however metabolism of famciclovir to penciclovir in humans is complex and requires dideacetylation, predominantly in the blood, and subsequent oxidation to penciclovir by aldehyde oxidase in the liver. Unfortunately, hepatic aldehyde oxidase activity is nearly absent in cats. This has necessitated cautious extrapolation to cats of data generated in humans. In a recent study of famciclovir pharmacokinetics in normal cats given nin to 18 mg/kg q eight to 12 hours, peak plasma penciclovir concentrations achieved were approximately one-fifth the concentration required for in vitro activity against FHV-1 (Thomasy et al 2007a). In a subsequent study cats given 90 mg/kg TID achieved plasma concentrations that were surprisingly low (approximately two-thirds of $IC_{50}$) (Thomasy et al 2007b). Taken together, data from these two studies suggest that the pharmacokinetics of famciclovir in cats are extremely complex and require more work. However, in a masked, prospective, placebo-controlled study of efficacy, experimentally infected cats receiving 90 mg/kg famciclovir TID had significantly reduced clinical signs and serum FHV-1 titers than did placebo-treated cats (Thomasy et al 2007b). No clinically importar adverse physical, hematologic o biochemical changes were associated with famciclovir administration. Despite this, there are anecdotal

reports that suggest famciclovir is effective in some cats with suspected herpetic disease at lower doses and dose frequency. Further studies of the pharmacokinetics, safety and efficacy of famciclovir and penciclovir are required before dose rates and frequency can be recommended for cats.

***Cidofovir*** is a cytosine analogue that requires two host-mediated phosphorylation steps, but does not require virally-mediated phosphorylation. Its safety arises from its relatively high affinity for viral DNA polymerase compared with human DNA polymerase. Its metabolites also appear to have a particularly long tissue half-life, suggesting less frequent application may be possible. It is available in injectable form in the United States but has been compounded for topical application as a 0.5 percent solution. In a recent study (Fontenelle et al 2008), twice daily topical application to cats experimentally infected with FHV-1 was associated with reduced viral shedding and clinical disease. There are occasional reports of its experimental topical use being associated with stenosis of the nasolacrimal drainage system components and, as yet, it is not commercially available as an ophthalmic agent in humans. Therefore, although its in vitro and short-term in vivo efficacy against FHV-1 are proven, at this stage there are insufficient data to support its long term safety as a topical agent in cats.

## Agents with Potential Antiviral Activity

***Lysine:*** Interest in the potential suppressive effects of orally administered lysine on FHV-1 replication in cats arises from several in vitro and clinical trials suggesting that arginine is an essential amino acid for viral replication, and that lysine may antagonize arginine availability or utilization by the virus at numerous levels. We have recently shown that, in the presence of diminished arginine concentrations, in vitro replication of FHV-1 was suppressed by approximately 80 percent when the lysine concentration in the culture medium was doubled. (Maggs et al 2000) This effect was negated at higher arginine concentrations, which suggests a similar mechanism of arginine antagonism to that described for HSV-1. The requirement for a high lysine-to-arginine ratio for in vitro efficacy, along with the fact that humans involved in clinical trials were required to limit their arginine intake, raised some concern regarding application of this treatment to cats, since they are exquisitely sensitive to arginine deficiency. However, the safety and efficacy of 500 mg lysine PO BID to cats (beginning six hours prior to experimental inoculation with FHV-1) was associated with less severe conjunctivitis than cats receiving placebo. However, viral shedding, as determined by VI, did not differ between groups. (Stiles et al 2002) Subsequently, we demonstrated that oral lysine supplementation helps to prevent viral reactivation and/or shedding in latently infected cats (Maggs et al 2003). Despite significant elevations in plasma lysine concentration, no change in plasma arginine concentration or any ill effects attributable to lysine administration were observed in either study.

Once or twice daily bolus administration of lysine is often impractical, especially long term. Therefore, we studied the safety and efficacy of incorporating lysine into cat food. Results of an initial safety trial were encouraging (Fascetti et al 2004). Cats fed a diet supplemented with up to 8.6 percent (dry matter) lysine showed no signs of toxicity, had normal plasma arginine concentrations, and had normal food intake. Mean plasma lysine concentration of these cats was increased to levels similar to that achieved with bolus administration. In a subsequent study (Maggs et al 2007), 25 cats with enzootic upper respiratory tract disease were fed a diet supplemented to 5.1 percent lysine while 25 cats remained on a basal ration for 52 days following rehousing intended to cause viral reactivation. Ironically, food (and therefore lysine) intake decreased coincident with peak disease and viral presence. As a result, cats did not receive lysine at the very time they needed it most. Perhaps because of this, disease in cats fed the supplemented ration was more severe than that in cats fed the basal diet. In addition, viral shedding was more frequent in cats receiving the supplemented diet. On the basis of these data, dietary lysine supplementation cannot be recommended at this stage. Based on all of these studies, I currently recommend cats receive 500 mg L-lysine PO q 12 hours.

***λ-carrageenan*** is a red seaweed extract containing sulfated polysaccharides with demonstrated antiviral activity against numerous enveloped viruses including FHV-1 but only when used prior to viral adsorption. It was well tolerated when applied topically four times per day in normal cats (Stiles J et al 2008). However, it was ineffective in experimentally infected cats when one drop of a 250 μg/mL solution of λ-carrageenan was applied before and after infection (n = 6 cats) or after infection only (n = 6 cats).

***Leflunomide*** is an immunosuppressive agent that appears to have some in vitro antiviral effects against many herpesviruses including FHV-1. The proposed method of action is through alteration in outer tegument formation. In vivo studies are required.

***Lactoferrin*** is a mammalian iron-binding glycoprotein that has

antibacterial, antifungal, antiprotozoal, and antiviral properties. It is produced by mucosal epithelial cells of many mammalian species and is present in secretions such as tears. Lactoferrin has a very potent antiviral effect against FHV-1 replication in vitro apparently through inhibition of FHV-1 adsorption to the cell surface and/or penetration of the virus into the cell (Beaumont SL et al 2003).

***The interferons*** (IFN) are a group of cytokines that have diverse immunological and antiviral functions. Interferons are divided into four groups; α, β, γ, and ω interferons, and numerous subtypes. Viral infection stimulates cells to secrete IFN into the extracellular space. Interferon then binds to specific receptors on neighboring cells, and through mechanisms not fully understood, prevents or limits the cell-to-cell spread of infection.

Although interferons may play important physiological roles in the control of viral infections, in vitro and clinical trials attempting to elucidate potential therapeutic applications have produced conflicting results. In vitro application of recombinant human IFNα or recombinant feline IFNω significantly reduced FHV-1 titer and/or cytopathic effect while not producing any detectable cytotoxic changes in the host cell lines. (Siebeck et al 2006) At higher concentrations, the effect the recombinant feline IFNω was greater than that of IFNα. In a separate in vitro study (Weiss 1989), acyclovir combined with human recombinant IFNα was associated with a nearly eightfold reduction in the dose of acyclovir required to achieve maximal inhibition of FHV-1 without increased cytotoxicity. Significant synergistic interactions resulted when the IFNα was given before or after infection at the lower doses of acyclovir; however IFNα pretreatment was more effective.

There are relatively few peer-reviewed, placebo-controlled, prospective clinical trials of IFN administration in cats. One study (Haid et al 2008) utilized 10,000 IU recombinant feline IFNω administered OU q 12 hours and 20,000 IU administered PO q 24 hours. IFN administration was initiated two days prior to viral inoculation but was not continued after inoculation. No beneficial effects were shown. In a separate study, systemic administration of IFNα ($10^8$ IU/kg subcutaneously BID beginning 1 day prior to inoculation) did not prevent disease, but cumulative clinical scores were lower for cats treated with IFNα (Cocker et al 1987). An abstract has also been presented detailing preliminary low-dose data comparing one, five or 25 IU IFNω administered PO q 24 hrs to cats undergoing primary experimental FHV-1 infection. In this study IFN was given after viral challenge only; 24 and 48 hours post inoculation. Scores for disease severity were significantly lower in cats receiving five or 25 units than in control cats. Given the relative lack of controlled studies and the variability in methodology and outcome in the few studies to date, further research is necessary to determine dosage, timing, and efficacy (if any) of this group of compounds, especially in the more chronic or recrudescent infections seen most commonly by ophthalmologists.

## Contraindicated Therapy

Anti-inflammatory therapy carries with it relative or, in some circumstances, absolute contraindications in cats with herpetic disease, especially those undergoing primary infection and use of such agents remains controversial in the management of FHV-1 infections. However, a return to basic virology and a review of the literature makes some general comments possible. FHV-1 produces disease by at least two very different mechanisms that require markedly different (in fact, almost opposite) therapeutic approaches. Cytolytic infection represents active viral replication and is often ulcerative. Immunomodulation at this point is almost certainly contraindicated. By contrast, immunopathological (or immune-mediated) injury is mediated by host inflammatory responses and driven by persistent viral antigen and/or autoimmunity.

Systemic administration of **corticosteroids** is a well-established and reliable means of inducing viral reactivation from latency. This must be considered whenever these drugs are considered in the clinical management of FHV-1-infected cats. The ability of locally-administered corticosteroids to exacerbate self-limiting primary conjunctival infection and to sometimes induce chronic herpetic keratitis has also been well established. Complications seen in corticosteroid treated eyes included deeper and more persistent corneal ulcers, corneal edema, corneal vascularization, sequestrum or band keratopathy formation, and protracted viral shedding (Nasisse MP et al 1989). Topical corticosteroids are therefore contraindicated in primary ocular FHV-1 infection.

The potential complications from using corticosteroids have prompted interest in the use of **non-steroidal anti-inflammatory drugs (NSAIDs)** for managing the inflammatory effects of ocular FHV-1 infection. Although there are no studies of their effects in cats infected with FHV-1, they are known to have similar negative effects to corticosteroids in humans and experimental studies investigating HSV-1. **Cyclosporine** is capable of suppressing inflammatory events operative in viral stromal keratitis, but also impairs viral clearance from the eye and suppresses

some beneficial immune responses. In vitro, cyclosporine exerts a dose dependent effect on HSV-1 replication. In some experimental model systems, however, cyclosporine therapy resulted in more severe and persistent keratitis. In a recent clinical trial, cyclosporine and trifluridine were used in combination to treat herpetic stromal keratitis in humans with good results. Use of cyclosporine in chronic feline herpetic disease has been inadequately studied and I am unaware of any studies examining the effects of **tacrolimus** on ocular herpetic infections in any species. This suggests that use of these agents should, as a minimum, be restricted by the same principles that govern the use of corticosteroids in herpetic stromal keratitis.

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# Cornell Feline Health Center Research Grants Program

The primary intent of the Cornell Feline Health Center (CFHC) Research Grants Program is to provide research monies to Cornell University faculty of the College of Veterinary Medicine to encourage and support investigations of feline health issues. An annual Request for Proposals (RFP) is issued by the Office of the Associate Dean for Research and Graduate Studies. The proposals are peer reviewed by the College Research Council, and the best scoring proposals pertaining to feline research are eligible to receive funding from the CFHC according to the amount of research funds that are available that year.

A total of nine proposals were submitted for the 2008-2009 fiscal year, and the following four research proposals were funded by the CFHC Research Grants Program.

1. *The Role of Feline Junction Adhesion Molecule A in Feline Calicivirus Infection*—John Parker, Assistant Professor, Baker Institute
2. *Detection of Pathogenic Role of Amoeba in Feline Corneal Disease*—Eric Ledbetter, Assistant Professor, Department of Clinical Sciences
3. *Elucidating the Role of Mucosal Bacteria in Inflammatory Bowel Disease in Cats*— Kenneth Simpson, Professor, Department of Clinical Sciences
4. *Comparison of Glomerular Filtration Rate Determination by Single-Slice Dynamic CT and Renal Scintigraphy in Cats*—Peter Scrivani, Assistant Professor, Department of Clinical Sciences

Because it receives no direct support from the State, College, or University, the CFHC is dependent upon financial contributions from cat owners and veterinarians, and fees from services rendered and materials provided. With increased funding, additional worthy research projects could be funded. Bequests, like the recent Dr. Jean Holzworth bequest to establish the Holzworth Fund to support clinical feline research, can provide long-term research support.

## CFHC Sponsored Research—Publications Report

The following summaries are abstracts of recent publications that resulted from research supported by the CFHC.

1. Ossiboff RJ, Sheh A, Shotton J, Pesavento PA, Parker JL. *Feline caliciviruses (FCVs) isolated from cats with virulent systemic disease possess in vitro phenotypes distinct from those of other FCV isolates.* J Gen Virol. 88:506-517, 2007.

**Abstract:** "During the past decade, several outbreaks of severe systemic disease associated with feline calicivirus (FCV) have occurred in the USA and the UK. This new disease has caused high mortality in the affected animals and has been termed virulent systemic (VS)-FCV disease. Currently, there are no genetic or in vitro diagnostic methods to distinguish viruses isolated from cases of VS-FCV disease from other isolates. Here, five in vitro properties, as well as the capsid and proteinase-polymerase (pro-pol) sequences, of a set of FCV isolates that included seven isolates from five distinct FC-FCV outbreaks ('VS isolates') were investigated. Although all of the FCV isolates investigated had similar kinetics of growth under single-cycle conditions, VS isolates infected tissue-culture cells more efficiently under multiple-cycle growth conditions. Moreover, it was found that cells infected with VS isolates showed cytopathic effects earlier than cells infected with non-VS isolates, although no difference in relative ATP levels were noted at times when morphological changes were first seen. Both VS and other (non-VS) isolates of FCV demonstrated similar temperature stabilities. Phylogenetic analyses and alignments of the capsid and pro-pol regions of the genome did not reveal any conserved changes that correlated with virulence, and the VS isolates did not segregate into a unique clade. These results suggest that VS isolates have arisen independently several times since first being described and can spread

more efficiently in tissue culture than other isolates when infected at low multiplicity."

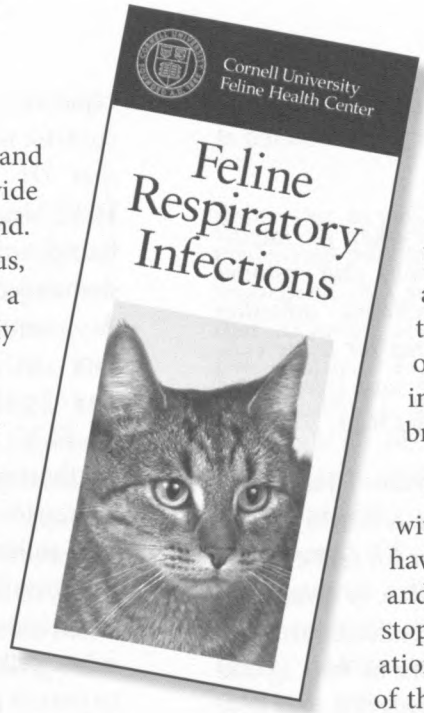
2. Ossiboff RJ, Parker JS. *Identification of regions and residues in feline junctional adhesion molecule required for feline calicivirus binding and infection.* J Virol. 81:13608-13621, 2007.

Abstract: "The feline junctional adhesion molecule A (fJAM-A) is a functional receptor for feline calicivirus (FCV). fJAM-A is a member of the immunoglobulin superfamily (IgSF) and consists of two Ig-like extracellular domains (D1 and D2), a membrane-spanning domain, and a short cytoplasmic tail. To identify regions of fJAM-A that interact with FCV, we purified recombinant fJAM-A ectodomain and D1 and D2 domains. We found that preincubation of FCV with the ectodomain or D1 was sufficient to inhibit FCV infection in plaque reduction assays. In enzyme-linked immunosorbent assays, FCV binding to fJAM-A ectodomain was concentration dependent and saturable; however, FCV bound D1 alone weakly and was unable to bind D2. To characterize FCV binding to surface-expressed fJAM-A, we transfected truncated and chimeric forms of fJAM-A into a nonpermissive cell line and assayed binding by flow cytometry. Only D1 was necessary for FCV binding to cells; all other domains could be replaced. Using a structure-guided mutational approach, we identified three mutants of fJAM-A within D1 (D42N, K43N, and S97A) that exhibited significantly decreased capacities to bind FCV. In contrast to our finding that D1 mediated FCV binding, we found that all domains of fJAM-A were necessary to confer susceptibility to FCV infection. Furthermore, surface expression of fJAM-A was not sufficient to permit FCV infection by all of the isolates we investigated. This indicates that (i) other cellular factors are required to permit productive FCV infection and (ii) individual FCV isolates differ in the factors they require."

3. Sekis I, Ramstead K, Rishniw M, Schwark WS, McDonough SP, Goldstein RE, Papich M, Simpson KW. *Single-dose pharmacokinetics and genotoxicity of metronidazole in cats.* J Feline Med Surg. 11(2):60-68, 2009.

Abstract: "Single-dose pharmacokinetics and genotoxicity of metronidazole in cats were evaluated. Cats received either 5mg/kg metronidazole intravenously, or 20mg/kg metronidazole benzoate (12.4mg/kg metronidazole base) orally in a single dose. Serial plasma samples were collected and assayed for metronidazole using high pressure liquid chromatography (HPLC). Genotoxicity was assessed in vitro in feline peripheral blood mononuclear cells (PBMC) and a feline T-cell lymphoma line incubated with metronidazole, and in vivo in PBMC collected before, during and seven days after oral metronidazole, by use of the COMET assay. Systemic absorption of metronidazole was variable (mean=65+/-28%) with a peak of 8.84+/-5.4 mug/ml at 3.6+/-2.9h. The terminal half-life was 5.34h from the intravenous dose and 5.16h from the oral dose. Systemic clearance was low (mean=91.57ml/h/kg [1.53 ml/kg/min]), and the apparent volume of distribution (steady state) was 0.650+/-0.254l/kg. Genotoxicity was detected at all concentrations of metronidazole in feline PBMC and the T-cell lymphoma line in vitro. Genotoxicity was also observed in PBMC collected from cats after seven days of oral metronidazole but resolved within six days of discontinuing metronidazole."

# Feline Respiratory Infections




## Client Information Brochure*

Respiratory infections of cats are common and produce important diseases, especially for cats in animal shelters, breeding catteries, farms, and feral populations. While vaccines have greatly reduced the incidence of serious respiratory disease, these vaccines have not eliminated the respiratory pathogens from the cat population.

The causes of feline respiratory infections include viruses, bacteria, fungi, and protozoal organisms -- truly a respiratory disease complex. The two most important viruses are feline herpesvirus type 1 (FHV-1), and feline calicivirus (FCV). Bacteria are not as important as FHV-1 and FCV as causes of respiratory disease; however, *Chlamydophila felis* is the third most important respiratory agent in cats, causing feline chlamydiosis (feline pneumonitis).

## Feline Herpesvirus Infection

Feline viral rhinotracheitis (FVR, "rhino", coryza) is a common, acute herpesvirus disease of domestic and exotic cats characterized by upper respiratory disease (sneezing, nasal discharge, eye infection), ulcers of the cornea of the eye, and fever.

The cause or etiology of FVR is feline herpesvirus-1 (FHV-1), which has physical and chemical properties like herpesviruses of other species. There is only one strain of FHV-1 worldwide. It is a rather labile virus that is readily inactivated by disinfectants, and probably will only survive in the environment a few days at most.

All domestic and exotic cats are susceptible to FHV-1, and the virus is found worldwide wherever cats are found. FHV-1 is very contagious, infecting all cats within a group of cats, but it rarely results in a fatal disease.

The virus is transmitted from an infected to a susceptible cat by direct contact and by aerosols generated by sneezing, like the human cold viruses. The initial site of viral infection is usually the mucous membranes of the mouth, nose and eye. After an incubation period of four to five days, a mild to severe upper respiratory disease occurs, which may last for one to ten days. Some cats will develop secondary bacterial infections of the nose and sinuses resulting a chronic upper respiratory disease and sinusitis.

Like most herpesviruses, FHV-1 infection usually results in a latent infection for the life of the cat whereby the virus is "stored" within the nerve ganglia of the head and spine. Periodically, there is a recrudescence of virus replication following stress such as mothering of kittens, introduction of a new cat, or treatment with corticosteroids. Virus replication and shed of infectious virus again occur, but usually clinical disease does not occur.

Sneezing is usually the first **clinical sign** observed, and this may be explosive or paroxysmal. Bilateral watery discharge from the eyes and nose follows quickly after the sneezing starts, and the conjunctiva of the eyes become swollen and red. As the disease progresses, this discharge often becomes thicker and more purulent. In some cases, especially in very young kittens, the eyelids may be pasted shut, and plugging of the nostrils may occur resulting in open mouth breathing.

Cats infected with FHV-1 usually have a high fever, and they usually will stop eating. Ulcerations of the cornea of the eye may follow in a few days. These ulcers start as shallow erosions, but rarely may move to deep ulcers and a severe inflammation of the entire eye globe with loss of the eye.

If the infection with FHV-1 occurs in very young or newborn kittens, the disease is often severe and generalize with a high mortality.

**Diagnosis** of FHV-1 infection is both easy and very difficult. Upper respiratory infection, like the common cold, is obvious. If the clinical signs include an acute onset, paroxysmal sneezing, bilateral mucopurulent to purulent ocular and nasal discharge, and the development of ulcerative keratitis, the clinical diagnosis is FHV-1 infection. However, laboratory tests may be required to confirm the diagnosis if the clinical signs are less dramatic.

**Treatment** for FHV-1 infection usually involves your veterinarian treating the cat as an outpatient because of the extreme contagiousness of the infection. Broad spectrum antibiotics for secondary infection are often given, and good nursing care is vital. Eye ointment

or drops may be required to ease the inflammation in the eyes. Chronic sinusitis and chronic ocular/nasal discharge are frequent sequelae of FHV-1 infection, and these are difficult to treat.

**Prevention and control:** Vaccination against FHV-1 is imperative for all cats – the FHV vaccine is a core vaccine to be given to all cats. The American Association of Feline Practitioners vaccine guidelines recommend the initial kitten series of two or more vaccinations when kittens are six to 16 weeks of age, a single booster vaccine one year later, then revaccination every three years thereafter. The FHV vaccines do not produce 100 percent protection, but they do provide protection against serious systemic disease.

Acutely infected cats shed large quantities of infectious virus, so non-vaccinated cats must be kept away from infected cats. Cats that have recovered from infection are latently infected with FHV-1, and many will periodically shed virus for the rest of their lives, usually without showing any clinical signs.

At normal room temperature, FHV-1 may survive a few days at most on contaminated surfaces. It is not a stable virus, and routine disinfection of contaminated surfaces, food dishes, and litter pans with most any commercial disinfectant will inactivate the virus.

## Feline Calicivirus

Feline calicivirus (FCV) infection is a common, acute viral infection of cats characterized by a short incubation period and one or more of the following syndromes: upper respiratory infection; pneumonia; ulcerations of the mouth, nose or feet; arthritis; or rarely enteritis. A relatively rare but deadly strain of the virus, virulent systemic feline calicivirus (VS-FCV), causes a severe systemic hemorrhagic disease with a high mortality.

All cats, both domestic and exotic, are susceptible to FCV. The virus is found world-wide and is a very common infection. While the frequency of infection is high in most cat populations, the mortality is usually very low, unless the severe pneumonia or the virulent systemic forms of the disease occurs, then the mortality may be significant. The virus can be transmitted between cats by direct contact, or by obtaining the virus from contaminated objects or people. Recovered cats will continue to shed small quantities of infectious virus from their mouths for many months.

Following exposure to FCV, there is local infection of oral and nasal tissue, then topical spread of virus throughout the respiratory system, followed by spread of the virus throughout the body. The incubation period from exposure to clinical disease is usually three to five days, and the duration of illness can be as short as one day or as long as 10 days. Recovery is usually complete without serious sequelae.

**Clinical disease** may appear in one or more of the following six forms.

1. **Upper respiratory** disease is usually mild, with minimal sneezing, and only slight watery ocular and nasal discharge.

2. **Ulcerative stomatitis** may occur with ulcers on the tongue, palate, lips, gums, or external nares. These start as vesicles or blisters which then rupture to form shallow ulcers. These ulcers heal in several days without complications. Rarely, ulcers can also appear on the paws.

3. **Pneumonia** may occur as a primary viral pneumonia without bacterial complications, but with severe consolidation of the lung. This results in difficult breathing, and may lead to death if there is extensive lung involvement.

4. **Enteritis,** if present, is usually mild and not of serious concern.

5. **Arthritis** or "limping kitten syndrome" is an acute disease that may appear with or without signs of other forms of FCV infection. This may occur during a natural infection, or rarely after FCV vaccination. Affected cats have a severe, shifting lameness, with painful joints. This form of FCV disease is usually short and self-limiting with rapid recovery without complications.

6. **Severe systemic hemorrhagic disease** is a very severe form of FCV disease with hemorrhages in various tissues throughout the body, and often edema or swelling of tissues of the head and limbs. This may occur in adults as well as in kittens, even cats that have been previously vaccinated against FCV.

**Clinical diagnosis** of upper respiratory infection is easy, but a definitive diagnosis of FCV may require laboratory tests. If there is fever with mild upper respiratory signs without excessive sneezing, ulcers in the mouth, pneumonia, or acute arthritis, a presumptive diagnosis of FCV is warranted.

Cats that have recovered from FCV infection are immune against serious disease, but these cats are persistently infected and will shed small quantities of virus from the mouth for many months.

All cats should be vaccinated against FCV with the same schedule as listed above for FHV.

FCV vaccines are core vaccines, and usually are given as a combination FVR-FCV vaccine. These

vaccines protect against serious disease, but they do not prevent reinfection and shed of virus.

## Feline Chlamydiosis

Feline chlamydiosis, also known as pneumonitis, is a not-infrequent respiratory disease of cats characterized by a relatively long incubation period (6-10 days), conjunctivitis, often unilateral, and an inflammation of the lungs (pneumonitis). The causative agent is an intracellular bacterial organism called *Chlamydophila felis* (*C. felis*, formerly called *Chlamydia psittaci* var. *felis*). This organism can infect both domestic and exotic cats, and very rarely can produce a mild infection of the eyes of humans.

*C. felis* is transmitted between cats primarily by direct contact between acutely infected or carrier cats and susceptible cats. After an incubation of six to 10 days, conjunctivitis develops and often will persist for weeks or months. Inflammation of the lungs may also occur, but mortality is rare. Infected cats can be successfully treated with specific antibiotics.

Vaccines available to aid in protection against chlamydiosis are listed as "non core," that is they may be used in specific situations where risk of infection is high, but are not necessarily recommended for all cats.

## Other Respiratory Infectious Diseases of Cats

**Feline leukemia virus (FeLV)** and **feline immunodeficiency virus (FIV),** two common viruses in cats, do not produce respiratory disease directly, but both viruses cause a serious decline in the immune system which predisposes to secondary respiratory disease from a variety of organisms.

**Avian H5N1** influenza is a viral disease of domestic and wild birds that also may infect domestic and exotic cats. It is caused by the highly virulent H5N1 strain of avian flu virus, and infection in cats is characterized by fever, lethargy, conjunctivitis, pneumonia with severe respiratory distress, and possibly death. Infection has been reported in Asia and Europe in cats that have ingested infected birds. This virus has not been reported in the United States.

***Bordetella bronchiseptica*** is a bacterium that usually causes a subclinical infection of cats, but it may contribute to the overall severity of a disease caused by other respiratory pathogens. In rare cases, it may produce a fatal pneumonia in young kittens. A feline bordetella vaccine is available that may be given to cats entering or residing in multiple-cat environments where *B. bronchiseptica* infections associated with clinical disease have been documented.

**Cat plague,** caused by the bacterium *Yersinia pestis,* is an important disease in southwestern United States. Cats get infected by flea bites from fleas that have been infected from rodents, or by ingestion of infected rodents. Infected cats usually have fever and painful lymph nodes (bubonic plague), but they may have a severe respiratory disease (pneumonic plague). *Y. pestis* can be transmitted from infected cats to people, resulting in a severe and possibly fatal disease. This is the same organism that caused the death of millions of people in Europe during the "black plague."

***Pasteurella multocida,*** a bacterium commonly found in the cat's mouth and respiratory system, by itself generally does not produce respiratory disease, but does contribute as a secondary pathogen. Its most important role is producing cat bite abscesses in both cats and humans.

**Streptococcal infections** may contribute to respiratory disease in cats as secondary bacterial pathogens and cause inflammation of the pharynx and sinuses.

***Bartonella henselae,*** the cause of cat-scratch disease in humans, generally produces only subclinical infection in cats.

***Mycoplasma*** are commonly found in the respiratory system of cats and may contribute to disease as secondary pathogens.

***Toxoplasma gondii*** is a common protozoal infection of cats that is usually subclinical, but rarely can produce pneumonia.

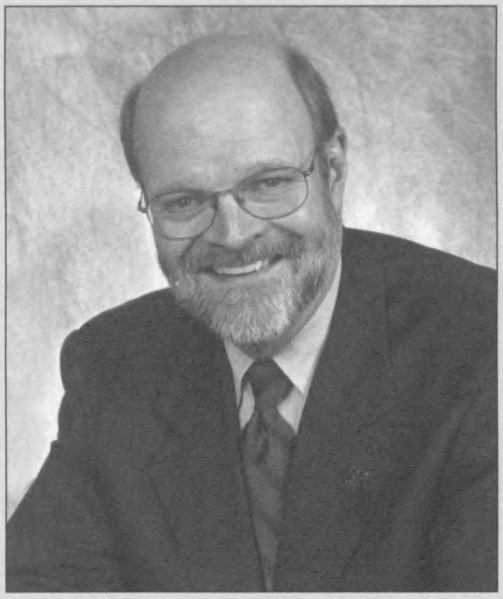
**Fungi** can cause serious chronic respiratory disease in cats, including the organisms that cause blastomycosis *(Blastomyces dermatitidis)*, aspergillosis *(Aspergillus fumigatus)*, histoplasmosis *(Histoplasma capsulatum)*, and cryptococcosis *(Cryptococcus neoformans)*. The first three organisms may cause pneumonia, while cryptococcosis is usually an infection of the upper respiratory area, especially the nose.

* *The Cornell Feline Health Center's client education brochures address the most commonly asked questions on feline disorders and are a valuable resource to help you in educating clients on feline health issues. To place an order for Feline Respiratory Infections or any of the other brochures in this series, please call Pam Sackett at 607-253-3443. To download an order form from our website, please visit:* **www.vet.cornell.edu/fhc/brochures/orderBrochure.pdf**

# Announcing the James R. Richards, Jr. Memorial Feline Lectures

The James R. Richards, Jr. Memorial Feline Lectures were established to honor the outstanding contributions that the late Dr. James R. Richards, Jr., made to the field of feline medicine to improve the health and well being of cats everywhere. A series of state-of-the-art lectures on various areas of feline medicine will be held (1) periodically at the College of Veterinary Medicine, (2) at the annual New York State Veterinary Conference, and (3) at the annual Fred Scott Feline Symposium. The first of these lectures will be given by Dr. Michael Lappin of Colorado State University during the 21st Fred Scott Feline Symposium at Cornell University on July 24-26, 2009. The second lecture will be given by Dr. John August of Texas A&M University during the annual New York State Veterinary Conference at Cornell University on October 1-4, 2009.

Dr. Richards was Director of the Cornell Feline Health Center (1997-2007), and was Past President of the American Association of Feline Practitioners. Funds contributed to the James R. Richards, Jr. Memorial Fund for Feline Health by his many friends and colleagues are being placed in an endowment fund at Cornell University, and the income from this fund will support these memorial lectures in perpetuity.



*The Late Dr. James R. Richards, Jr.*

We can think of no finer way to support Dr. Richards' passion for cats and for education than by making it possible, through these memorial lectures, for the leaders in feline medicine to share their newest and most pertinent knowledge directly with those veterinarians (and future veterinarians) working each day to improve the lives of cats everywhere.

**If you would like to make a tax-deductible contribution to the Dr. James R. Richards, Jr. Memorial Fund for Feline Health or to any of the purposes listed below, please complete the following form – making sure to check the appropriate designation box – and return it with your preferred method of payment. Gifts without a designation will be applied where needed most. To make your gift online, please visit: http://www.vet.cornell.edu/fhc/oppsupp.htm**

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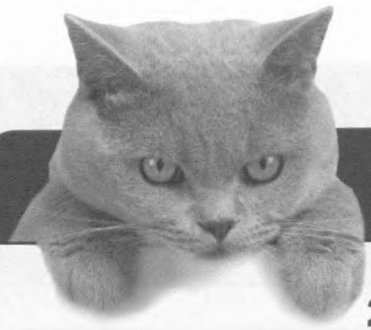

# SAVE THE DATE!

## 21st Fred Scott Feline Symposium

## July 24-26, 2009

### Cornell Feline Health Center and the Office of Continuing Education
### College of Veterinary Medicine, Cornell University, Ithaca, NY

The 21st Feline Symposium will feature two outstanding speakers: Dr. Michael Lappin of Colorado State University, and Dr. Jacquie Rand of the University of Queensland, Australia. Additional speakers will include faculty from the College of Veterinary Medicine at Cornell. Topics will include: feline diabetes, feline obesity, feline vaccine controversies, update on feline gastrointestinal diseases, pet ownership for immune-suppressed individuals, and feline diagnostic medicine: use of molecular assays in feline infectious diseases. During the symposium, Dr. Lappin will give the first James R. Richards, Jr. Memorial Feline Lecture.

Mark your calendars now and plan to attend this exciting program! For more information, or to register, please contact Amanda Mott at amm36@cornell.edu or by telephone at: (607) 253-3200.

CORNELL FELINE HEALTH CENTER

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