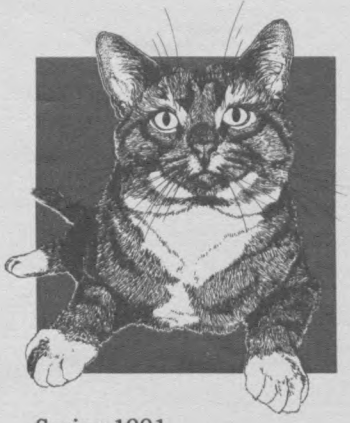

Feline Health Topics

for veterinarians

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Feline Infectious Peritonitis Vaccination— Past and Present

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In the 25 years since feline infectious peritonitis (FIP) was first described as a disease entity, a great deal has been learned about the viral etiology and pathogenesis of this devastating disease. But despite these advances, FIP continues to instill fear and frustration among cat owners and veterinarians. While FIP only occurs sporadically in the general pet cat population, it is a much more frequently occurring and serious problem in catteries, multiple cat households, and shelters. The reasons for this dichotomy include factors such as the stress inherent in multicat housing and the increased potential for exposure and transmission in such circumstances. The prolonged and variable incubation period of FIP also makes it difficult to trace back and identify possible source cats. Perhaps the two biggest impediments to control of FIP are the lack of a specific test for and vaccine against the causative agent, feline infectious peritonitis virus (FIPV). Notably, the first commercially offered vaccine has just been marketed, *Primucell FIP®* by SmithKline Beecham Animal Health (formerly Norden Laboratories). Because of this, we'd like to review the history of FIPV vaccination attempts and what is currently known about Primucell FIP®.

Inside this issue ...

Coronaviruses

Feline infectious peritonitis virus is only one of several coronaviruses that can infect cats. These include canine coronavirus (CCV), transmissible gastroenteritis virus of swine (TGEV), and most importantly, feline enteric coronavirus (FECV). FIPV and FECV are antigenically very closely related viruses. The major difference is that FIPV can induce a fatal, systemic disease, whereas FECV most often produces subclinical or self-limiting enteritis. This is because FECV replication is primarily restricted to the intestinal epithelial cells, whereas FIPV can pass the mucosal border of the intestinal tract to infect monocytes/macrophages and spread systemically. Because of their close antigenic relationship, but dramatically different disease potential, we now consider FIPV and FECV to be simply altered biotypes of the same virus.

FIP Pathogenesis

Why has it historically been so difficult to produce a vaccine against FIPV infection? The answer lies in the pathogenesis of FIP. After infection through the mucosal surfaces of the upper respiratory or intestinal

tracts, a primary viremia takes FIPV to its many target organs. The basic pathologic lesion in these target organs is an Arthus-type vasculitis caused by the deposition of virus and viral specific antibody, followed by complement activation and an intense inflammatory response. This leads to the classic pyogranulomas and/or fluid accumulation of FIP. Thus antibodies formed in response to FIPV infection are the basis for the pathogenesis of FIP rather than being protective. We also know that FIPV-specific antibodies are deleterious at a second level—antibodies can increase the infectivity of FIPV for macrophages, the target cell for FIPV replication. This occurs through a Fc-receptor-mediated process called antibody-dependent enhancement (ADE) of infection, a well documented phenomenon with viruses such as dengue virus and human immunodeficiency virus. A final problem to overcome for vaccination is that once in macrophages, FIPV is largely protected from any effective immune response.

Past Vaccine Failures

To date, numerous attempts to produce a safe and effective vaccine against FIPV have been largely unsuccessful. We will review these by vaccine type.

Inactivated or killed vaccines have justifiably received the least attention. For an infection like FIPV, where cell-mediated immune (CMI) responses are so important to protection, a killed vaccine is unlikely to produce satisfactory results. Inactivated vaccines generally induce a somewhat poor CMI response as compared to modified live virus vaccines. Several early attempts to produce inactivated vaccines by traditional means resulted in sensitization or enhanced disease instead of protection against virulent FIPV.

Approaches to FIPV vaccination using live or modified live viruses have been more thoroughly evaluated. Dr. Barlough and colleagues at Cornell University tried using heterologous live coronaviruses as FIPV vaccines. Inoculation of cats with either canine coronavirus or human coronavirus 229E did not protect the cats against subsequent challenge with FIPV. Similarly unsuccessful results were obtained using transmissible gastroenteritis virus, a coronavirus that is very closely related to FIPV.

There are at least nine different strains of FIPV, which vary in virulence from being almost 100% fatal to almost 0%. Therefore, it made sense to see if a somewhat avirulent but fully "live" strains could serve as a vaccine strain. Drs. Pedersen and Floyd evaluated strains UCD2, UCD3, and UCD4 and found that only UCD3 demonstrated any ability to protect cats against virulent FIPV (strain UCD1) challenge. However, UCD3 could still cause too much disease to be considered as a viable vaccine candidate. The FECV's evaluated to date induce substantial antibody-dependent acceleration of disease without protection, and are currently unacceptable as vaccine viruses.

Feline Health Topics

A publication for veterinary professionals

The ultimate purpose of the Cornell Feline Health Center is to improve the health of cats everywhere, by developing methods to prevent or cure feline diseases, and by providing continuing education to veterinarians and cat owners. All contributions are tax-deductible.

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Virulent FIPV strains have been experimentally rendered less virulent and evaluated as "modified" live virus vaccines. Use of a modified TN-406/Black strain again led to antibody-dependent acceleration of disease instead of protection.

Researchers at the Cornell Feline Health Center have also developed a modified live strain of FIPV for use as an intranasal vaccine, and have assessed its potential to protect cats against lethal FIPV challenge. The results, first reported at the Eastern States Veterinary Conference in January 1988, have been better than those of many other reported studies, but frustrating because of their inconsistency. Protection has varied from 100% to less than 25% in different trials. Overall, this experimental vaccine provided protection to approximately 50% of vaccinated cats. This work is continuing, as is work to see if ways can be developed to improve the immune response to FIPV vaccination.

Besides these traditional approaches, a group in the Netherlands has attempted to produce a FIPV vaccine using a modern recombinant carrier virus approach. Dr. Vennema and colleagues engineered the FIPV S (or spike) gene into vaccinia virus, a nonpathogenic poxvirus. The S gene of FIPV encodes the large surface protein of the virus, which is thought to be responsible for evoking an immune response. This technique produces a live, intact vaccinia virus that produces the FIPV S protein on its surface with all its own proteins. When cats were infected with the recombinant vaccinia virus as the "vaccination" process, instead of being protected they developed accelerated disease compared to unvaccinated controls.

Primucell FIP®

The latest contender in the story of FIPV vaccination is also the first commercially marketed vaccine, Primucell FIP®. This is a special type of modified-live virus vaccine, namely a temperature-sensitive mutant. It was derived from a virulent strain of FIPV, DF2, by serial passage in cell culture, followed by ultraviolet irradiation. The result is a strain of virus that can replicate well at the cooler temperatures of the oronasal cavity (31°C), but poorly at systemic body temperature (39°C). As such, it is obviously designed to be an intranasally administered vaccine. The rationale behind this approach is a sound one—"local" vaccination to induce a strong mucosal IgA response, and thereby prevent infection across the mucosal barrier right at the start. The importance of local immunity to protection against the related coronavirus, TGEV, is now well founded, lending further support to this approach for FIPV. This approach also makes sense considering the ever present problem of antibody-dependent enhancement of disease, since ideally the virus will be blocked before ever gaining entrance into the body.

Safety:

SmithKline Beecham Animal Health has done extensive safety tests of this vaccine, as well they needed to for an immune-mediated disease like FIP. They have shown that the vaccine was apparently safe when administered to cats parenterally instead of intranasally. Also, it was safely given to immunosuppressed (0.5 mg./lb. dexamethasone daily at 7, 4, and 2 days before vaccination and on the day of vaccination) or FeLV viremic cats. They also tested the vaccine in cats with pre-existing coronavirus antibodies, either due to previous FECV exposure or sublethal FIPV exposure. All the vaccinated animals "developed blood dyscrasias only rarely", "lacked abnormally high febrile responses", and no FIP according to SmithKline Beecham. They have done preliminary safety tests of the vaccine in pregnant queens and young (3 to 8 weeks of age) kittens. *However, we stress that Primucell FIP® is not approved for use in pregnant cats, nor in kittens less than 16 weeks of age.*

Efficacy:

To evaluate efficacy, cats must first be vaccinated and then challenged with virulent virus. It is also important to understand how vaccine efficacy is

properly calculated. One cannot simply look at the percentage of vaccinated animals surviving virus challenge, i.e., 17 out of 20 vaccinates surviving does not equal 85% efficacy. You must factor in the number of control (nonvaccinated) animals that also survive challenge. Thus, the true efficacy or preventable fraction (PF) calculation is:

$$PF = (IDC - IDV) \div IDC$$

(IDC=Incidence of disease in controls; IDV= Incidence of disease in vaccinates)

We have done this calculation for all the efficacy trials for which SmithKline Beecham has published data to date, evaluating challenges with 3 different strains of FIPV. The result is a (mean) efficacy equal to 69%. These efficacy trials were done on specific-pathogen free (SPF) cats under experimental conditions. As pointed out earlier, many of the FIP cases occur in multiple cat environments, not in the general cat population. Therefore, it is under these conditions that any FIPV vaccine must prove its merit.

SmithKline Beecham has evaluated Primucell FIP®'s efficacy in a group of FIPV endemic catteries. In these endemic catteries they vaccinated 50% of the cats with Primucell FIP®, and gave a placebo vaccine without FIPV to the other cats. They followed the incidence of FIP in the vaccinate and control populations for at least 6 months. Kittens born during the study were vaccinated at 6 and 9 weeks of age. Under these natural conditions, the incidence of FIP in the vaccinate and control groups was not statistically different. (In one cattery that had persistent FIP losses they vaccinated all the remaining cats, and afterward found that FIP losses stopped. The significance of this is difficult to assess since there were no unvaccinated controls in this cattery and FIP losses in multiple cat environments typically fluctuate over time.)

The discrepant results between the efficacy in SPF cats and in endemic catteries indicates that no vaccine can be considered completely proven until, over time, many doses have been administered under natural conditions to different breeds of cats in different geographic areas. SmithKline Beecham has reported safety data on 1,473 doses of Primucell FIP® that were administered by 12 practicing veterinarians. Minimal adverse reactions, such as drooling and sneezing, were reported in 176 cats, but no anaphylactic reactions were reported. But again, safety does not equal efficacy. Perhaps only time will tell just how effective Primucell FIP® will be in reducing the population-wide incidence of FIP. An efficacy trial of Primucell FIP® under experimental conditions is being done at Cornell University.

One possible reason for the apparent lack of efficacy in endemic catteries is the 16-week-old recommended age of vaccination. A recent study by Drs. Addie and Jarrett from Scotland has shown that transmission of feline coronaviruses can occur as young as 4 to 6 weeks of age. The results of this study are consistent with results previously reported from our laboratory by Dr. Cheryl Stoddart. SmithKline Beecham Animal Health scientists are currently evaluating the use of Primucell FIP® in younger kittens, but the vaccine is currently licensed for use at 16 weeks of age, with boosters in 3 to 4 weeks, and then yearly.

A final comment regarding vaccination and testing—Dr. Jay Gerber of SmithKline Beecham Animal Health reports that Primucell FIP® vaccination of seronegative cats will induce low positive coronavirus titers as measured by ELISA. This will pose a particular problem for cattery owners who are striving, in part by serologic testing, to maintain a coronavirus-free population. ■

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(continued on page 8)

Synbiotics' FIP Test

Synbiotics Corporation has been working on a new laboratory test to identify cats that have been infected with feline infectious peritonitis (FIP) virus. This test, based on anti-idiotypic technology, is still going through the licensure process, but as of early April 1991 it had not yet been approved by the USDA. Recent prerelease advertisements in veterinary and lay publications have resulted in numerous calls to the Feline Health Center and the Diagnostic Laboratory about this test. This brief report is to inform you of the development status of this test.

Synbiotics kindly supplied the Diagnostic Laboratory and the Feline Health Center with kits for evaluation of specificity and sensitivity. Unfortunately, during this evaluation, some problems were identified, as happens with any new test. We have shared our results with Synbiotics Corporation and are confident that these problems will be addressed.

According to Gregory Soulds, Synbiotics' vice president of marketing, sales, and commercial development, his company plans to "expand the scope of its independent clinical studies to broaden the experience base with the new anti-idiotypic assay technology among opinion leaders and academic institutions." He further states, "It is anticipated that these results should be available in the next few months and release of the product could be as early as August 1991."

"Synbiotics apologizes for the fact that the delayed product launch resulted in premature advertisement for the product,"commented Soulds. "However, we feel that the additional studies will better insure the broad acceptance of this important new technology in the long run."

Once this kit receives USDA approval and is released, we would hope to re-evaluate the final version of the kit, and the results of that evaluation will be shared with our readers. ■

The Cat's Meow

The best method we have devised for **anesthetizing vicious cats** is to use a small non-human primate squeeze back cage. The fractious cat is dumped from its carrier into the cage. The cage is then closed. The false back is moved forward until the cat is physically restrained and injected with a low dose of ketamine HCL. After chemical restraint it can be easily removed from the cage for examination or treatment. These cages can be purchased or otherwise obtained from laboratory animal facility warehouses at low or no cost because most of them are no longer used for holding monkeys.—*Dr. Matt J. Kessler, Puerto Rico*

Send your practical tips and ideas on feline health management to:

Cornell Feline Health Center
The Cat's Meow
College of Veterinary Medicine
Ithaca, NY 14853

Correction—

On page 2 of Volume 6, Number 1— The end of the first paragraph should read "exposed sulfhydryl groups", not "exposed serum hepatitis groups".

Feline Seminar Is Scheduled

The Cornell Feline Health Center and Cornell College of Veterinary Medicine's Continuing Education Office are sponsoring the third annual Feline Seminar from August 2 to 5. Topics and speakers tentatively scheduled include:

Thursday, August 1:	
4-6 pm	Registration
Friday, August 2:	
7:30-8:30 am	Registration
8:30 am -5 pm	Clinical Neurology, Neurologic Examinations and Case Studies —*Dr. A. deLahunta*
5-6 pm	Wine and Cheese Social
Saturday, August 3:	
8:30-10 am	Clinical Toxicology—*Dr. Larry Thompson*
10:30-12 noon	My 30 Favorite Drugs—*Dr. Lauren Trepanier*
1-3 pm	Practical Management of Clinical Signs—*Practitioner Panel*
3:30-5 pm	Radiology of Clinical Signs—*Dr. Kathy Beck*
Sunday, August 4:	
8:30-10 am	Bacterial Diseases—*Dr. Patrick McDonough*
10:30-12 noon	Clinical Genetics—*Dr. John Saidla*
1-3 pm	Declawing: Surgery and Other Alternatives—*Practitioner Panel*
3-5 pm	Free Time
5-9 pm	Picnic and Blue Grass Entertainment
Monday, August 5:	
8:30-10 am	Infectious Disease Update—*Dr. Fred Scott*
10:30-12 noon	Report from FeLV/FIV Colloquium on Tests & Vaccines—*Dr. Fred Scott*
1-2 pm	Management of Infectious Diseases—*Practitioner Panel*
2-4 pm	Ophthalmology—*Dr. Ron Riis*
4 pm	End of Seminar

Additional details on the Feline Seminar are available by contacting Linda Ritzler, Office of Continuing Education, College of Veterinary Medicine, Ithaca, NY 14853 or calling (607) 253-3200.

Registration fee - $300

ICU Respiratory Therapy for Sick Cats

Editor's Note: The following is excerpted from a presentation given by Drs. Dougherty and Ludders at the Feline Seminar sponsored by the Cornell Feline Health Center and Office of Continuing Education at Cornell University in 1990.

Because of their size, temperament, physiology, response to drugs, and unique disease processes, cats can pose a challenge to veterinarians who provide intensive care for sick cats. The art and science of veterinary intensive care have progressed tremendously over the past 10 years. This briefly describes aspects of respiratory therapy for the sick cat.

Blood Gas Analysis

The best way to evaluate pulmonary function is to collect an arterial blood sample for analysis. However, a venous blood sample does provide acid/base information and it can indicate whether cardiac output and perfusion is adequate. A sufficient volume of arterial blood should be collected so that the heparin in the syringe does not dilute either the partial pressure of oxygen or carbon dioxide.[1] Since heparin is acidic it can also affect pH analysis if an insufficient volume of blood is collected.

Electrolytes are affected by and can affect acid/base balance. For animals requiring intensive therapy it is important to monitor and manage electrolytes such as sodium, potassium, calcium and chloride. Until now measurement of electrolytes has required expensive equipment, a variety of reagents, and the time to prepare plasma samples for analysis. The development of dry chemistry units has solved many of the short comings associated with the use of wet analysis systems.

Ventilatory Support

A cat needs to be ventilated when there is evidence of hypoventilation. Hypoventilation occurs when minute ventilation is less than normal [minute ventilation is the product of Tidal Volume (V_T) X Respiratory Frequency (f)]. Analysis of an arterial blood sample will show an increased P_aCO_2 in an animal that is hypoventilating (>45 mmHg). Ventilatory support can be provided with an ambu bag, a reservoir bag on an anesthesia machine, or a mechanical ventilator. To be effective, ventilatory support requires that the animal be intubated. Some guidelines for ventilator therapy are:

Tidal volume = 1-15 ml./kg.
Respiratory rate = 8 -20
Minute ventilation = 150-250 ml./kg./min.

Oxygen Therapy

An animal needs oxygen therapy when there is evidence of hypoxemia, which is usually defined as a P_aO_2 less than 60 mmHG. This is not an absolute value as the amount and type of hemoglobin markedly affects the oxygen carrying capacity of blood. Signs of hypoxemia include cyanotic or grey mucous membranes, tachypnea, tachycardia and orthopnea. The exact signs that an animal will show depend on its general condition. Cyanosis can be difficult to detect because it is influenced by the type and amount of incident light, the amount and type of hemoglobin in the patient's blood, and the ability of the observer to detect shades of red and blue.

Therapy can be provided with an oxygen cage or by nasal insufflation of oxygen.[2] Steel cylinders are the most commonly used means for supplying oxygen. The most commonly used cylinder sizes are the E, G, H or K cylinders. The larger cylinders need to be securely fastened to a wall or secured in a hand truck designed for steel cylinders.

It is possible to use a gas such as compressed air or nitrogen rather than oxygen as the driving gas for a ventilator. The advantage to this arrangement is that the oxygen is used just for oxygen therapy rather than as power to the ventilator, which usually requires

high pressure and gas flows. A disadvantage to using 100% oxygen ($FIO_2 = 1.0$) is that over time it is toxic to the lungs and can cause pathologic changes that reduce and eventually stop gas exchange. This is usually evidenced by a progressive decreasing P_aO_2 despite a high FIO_2. The lung eventually becomes so damaged that the exchange of carbon dioxide is impaired and P_aCO_2 progressively increases, evidence that the animal is in respiratory failure. Safe and adequate oxygen therapy can be provided with a FIO_2 of 0.4. The upper limit for safe oxygen therapy is 60%. However, these are only guidelines; the animal's condition, disease process and its progress, and cardiopulmonary function dictate ventilatory therapy.

If an oxygen cage is used for oxygen therapy, steel cylinders can be used as the source of oxygen. An oxygen meter should be used to assist in monitoring and controlling the oxygen concentration in the cage. After flushing oxygen into a cage, an oxygen flow rate of 3 to 5 L./min. is usually adequate for maintaining the oxygen concentration at 40% if the cage is relatively free of leaks. At these flow rates a H cylinder of oxygen will last from 38 to 23 hours, respectively. Factors such as the leakiness of the cage, frequency with which the cage is opened for other therapeutic measures, and the frequency with which the cage is flushed with oxygen will shorten the delivery time of a cylinder. ■

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FIP Vaccination *(continued from page 4)*

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