INTRODUCTION
Asthma in humans was defined over 40 years ago by the American Thoracic Society as, “…a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli, resulting in airway obstruction that is reversible, either spontaneously or as a result of treatment.” It is clinically characterized by episodic or persistent cough and wheeze, expiratory dysfunction, and a generalized increase in the work of breathing. Feline asthma has been recognized in the veterinary literature for over 90 years. It is a syndrome resulting in clinical signs similar to those in human asthma. The clinical signs of cough, wheeze, and exercise intolerance are the result of decreased airflow due to mucus accumulation, airway wall thickening, and bronchoconstriction. In the early stages of disease, these signs are readily reversible with appropriate therapy. Left unmanaged, the progressive condition can lead to worsening clinical signs, permanent respiratory impairment, and a decrease in life expectancy. This session will describe the pathophysiology of the clinical abnormalities observed in the asthmatic cat, and use this as the basis for a rational, patient-based approach to therapy.

EPIDEMIOLOGY
Although cats of any age can be afflicted, most cats with asthma are young to middle-aged at the time of initial presentation, with a median age of 5 years old. A previous study estimated the prevalence of asthma among all cats is less than 1% [1]. Siamese and Havana Brown breeds appear to be overrepresented, with the estimated prevalence among Siamese ~5%. Most asthmatics are otherwise healthy cats, although some cats may also present with concurrent sneezing and/or nasal discharge. Cats may present with a history of chronic, waxing and waning cough and mild to moderate exercise intolerance. These cats may have months to years of signs prior to presentation. Alternatively, some cats may be presented in acute respiratory crisis consisting of a sudden onset of dyspnea, tachypnea, orthopnea, and open-mouth breathing. Both of these presentations likely represent parts of a continuum of progressive disease.

DIAGNOSIS
The diagnosis of feline asthma is usually made on the basis of history, the constellation of clinical signs, and thoracic radiographs. No single pathognomonic clinical sign or diagnostic test exists that can be used to reliably diagnose asthma in cats. For this reason, it is important to exclude other common causes of acute dyspnea, wheeze, or coughing. These include (but are not limited to) chronic bronchitis, feline myocardial disease, pneumonia, neoplasia, pulmonary parasitism, and idiopathic pulmonary fibrosis. Of these, feline chronic bronchitis is the major differential to be considered in otherwise healthy cats with chronic cough. Although the pathogeneses of these diseases are quite different, the distinction between chronic bronchitis and feline asthma may not be absolutely necessary in mild cases of either condition.
Hematology, biochemistry, fecal flotation, and heartworm antigen and antibody tests should be performed in the evaluation of cats with chronic cough or acute respiratory impairment. In most asthmatic cats, these results will be normal, although some cats may have peripheral eosinophilia.

Radiographic findings typically include bronchial wall thickening and hyperinflation of lung fields. Right-sided cardiomegaly due to cor pulmonale may also occur. Lobular atelectasis and lung lobe torsion, particularly of the right middle lung lobe, are also occasionally found in asthmatic cats. The finding of normal thoracic radiographs does not rule out the possibility of asthma, particularly in cats with presentations consistent with acute airway obstruction.

Bronchopulmonary lavage samples, when available, can be extremely valuable in the diagnosis of feline asthma. Cytology and culture samples can be obtained via endotracheal wash (ETW) or bronchoalveolar lavage (BAL). Cytology typically reveals eosinophilic inflammation, but may also include neutrophils, mast cells, lymphocytes, and alveolar macrophages. Increased shedding of epithelial cells and mucus secretion can also be revealed through airway lavage.

Samples should be submitted for general aerobic and Mycoplasma culture. Mycoplasma organisms have been positively cultured from up to 25% of the airways of cats with bronchopulmonary disease [2]; however, the role of these Mycoplasma infections in feline asthma remains unclear.

Characteristic histopathologic changes in cats with bronchial asthma include smooth muscle hypertrophy and hyperplasia, hypertrophy of mucosal and submucosal mucus secretory cells and glands, mucosal and intramural eosinophil influx, and epithelial cell hyperplasia and erosion. Collectively, these histologic changes can be reversed with appropriate therapy early in the course of the disease. As the condition progresses, however, these changes become permanent, and result in airway wall remodeling.

**PATHOGENESIS**

Feline asthma is believed to be similar to extrinsic (aeroallergen) asthma in humans. In this model, airborne particulate matter, irritants, or allergens trigger activity in the normal resident population of cells in the airways. These “first responder” cells include epithelial cells, mast cells, antigen presenting cells, and lymphocytes, and ultimately lead to the generation of a T-helper 2 (Th2) lymphocyte phenotype. The activation and persistence of theTh2 phenotype leads to recruitment and activation of eosinophils, mast cells, and macrophages, class switching of b-cells to IgE-secreting plasma cells, and subsequently to the ongoing disease manifestations and characteristic histologic changes.

Eosinophils are the major effector cells in both feline and human asthma. Eosinophilic inflammation in asthma is largely the result of the persistence of the Th2 lymphocyte phenotype and lymphocyte secretion of pro-inflammatory cytokines, particularly interleukin-5 (IL-5). The interaction between Th2 lymphocytes and eosinophils is an important factor in the progression of asthma, and is a target of many therapeutics utilized for feline asthma. Consequences of eosinophilic inflammation include bronchoconstriction, mucus secretion, sensitization of airway mechanoreceptors (elevating the cough threshold), and smooth muscle hypertrophy. Collectively, these changes result in airway hyperresponsiveness and airway wall remodeling. Other
effector cell changes in asthma progression include decreased phagocytosis by alveolar macrophages and epithelial cells, and generation and persistence of airway neutrophils.

**THERAPY**

The primary clinical signs in most asthmatic cats are cough, wheeze, and expiratory dysfunction. Because these signs are largely the result of airway narrowing, it is tempting to primarily treat asthmatics with bronchodilators. Successful treatment strategies must primarily address the airway inflammation, as the inflammation is responsible for both the clinical signs and the progressive histologic changes that ultimately can lead to respiratory failure. Symptomatic therapy should be a secondary goal for those signs not completely controlled with anti-inflammatory therapy. No consensus exists for the treatment of all cats with asthma. Each case should be treated individually, based on severity and frequency of clinical signs.

**Corticosteroids**

Corticosteroids are now the mainstay of asthma therapy in both humans and cats. Corticosteroids down-regulate the synthesis of pro-inflammatory cytokines, induce apoptosis in blood and tissue eosinophils, augment the activity of macrophages for apoptotic neutrophils and eosinophils, and increase bronchial epithelial cell phagocytic activity. To date, the most consistent, most reliable, and most effective treatment for feline asthma is high-dose, long-term oral corticosteroids. Oral prednisolone should be started at 2-4 mg/kg/day, initially divided BID. This dose should be maintained for 10-14 days, followed by a slow taper to the lowest effective dose that controls clinical signs, with the goal of reaching alternate day physiologic dose administration. The limitations of chronic oral corticosteroid therapy are the adverse effects, which include (but are not limited to) behavioral changes, insulin resistance, pancreatitis, polyuria and polydipsia, and immune suppression with risk of infection.

Parenteral corticosteroids can be useful in both the acute emergency presentation and chronic management of asthmatic cats. Dexamethasone (0.5-1.0mg/kg SQ/IM/IV) or dexamethasone sodium phosphate (1mg/kg IV) should be used with bronchodilator therapy (see below) for the initial management of the emergent asthmatic. Repository steroids (DepoMedrol, 10-20mg/kg IM q2-4 weeks), while not ideal for chronic anti-inflammatory therapy, can be used for short-term therapy to determine the effectiveness of corticosteroid therapy, or as a means of chronic therapy in cases in which chronic oral therapy may not be feasible.

Chronic inhaled corticosteroid therapy is now the mainstay of asthma management for most humans. Inhaled corticosteroid preparations exist as steroids alone, or combined with long-acting bronchodilators. To overcome compliance problems associated with inhalation therapy in children, spacer devices can be utilized, allowing the drug to be delivered with tidal breathing. These spacers can also be used in cats and dogs for management of chronic airway disease. Fluticasone propionate (Flovent, 110 or 220ug metered dose inhaler) can be used once a cat has been stabilized with oral or parenteral steroids. Dosing should start at 1 puff twice daily, followed by a gradual reduction in the oral or parenteral steroids. The goal of inhaled steroid therapy should be to provide a prednisone-sparing effect; however, many cats can be completely controlled with inhalation therapy.

**Bronchodilators**
Bronchodilators should not be necessary as chronic therapy for most asthmatic cats. However, for cats in which corticosteroid therapy is not adequate to control clinical signs, bronchodilators can be used symptomatically. Bronchodilation can also be used as a short-term intervention to help clear mucus plugging in cats exhibiting ventral lung atelectasis. Another potential use for bronchodilators is as early at-home intervention for asthmatic crisis. Beta-2 agonists are the most effective bronchodilators in cats. Terbutaline (0.01mg/kg IM or SQ) can be sent home with owners, with explicit instructions for indications. Owners can be trained to administer injections in a manner similar to insulin injections. Bronchodilators can also be administered as inhalation therapy. Albuterol (90g MDI, 2 puffs) can be used with the same spacer as that used for chronic steroid therapy. Beta-2 agonists, both inhaled and subcutaneous, are relatively short acting (2-4 hours), and can have significant cardiac and systemic adverse effects. Beta-2 agonists should not be used in cats with hypertrophic myocardial disease, so proper screening for heart disease should precede dispensing of this medication. Combinations of inhaled corticosteroids and long-acting bronchodilators have been shown to be more effective in blocking airway inflammation and reversing bronchoconstriction in an experimental model of feline asthma [3]. I regularly use an inhaled combination of fluticasone propionate and salmeterol for cats that are steroid-responsive, but at risk of side effects at higher doses of inhaled or oral steroids.

Antimicrobials
Airway infection does not appear to play a major role in the pathogenesis of feline asthma. Dye et al [4] found significant positive BAL cultures in only 1 of 25 asthmatic cats (Bordetella bronchiseptica). Mycoplasma organisms may be an exception. As mentioned earlier, Mycoplasma spp have been isolated from up to 25% of cats with bronchopulmonary disease. These organisms are well adapted to serve as primary lower airway pathogens. In addition, Mycoplasma spp have been implicated as possible triggers of acute exacerbations of asthma in humans. Use of antimicrobials should be based on culture and sensitivity whenever possible. Respiratory infection should also be considered in asthmatic cats that are not responding to corticosteroid therapy.

FURTHER STUDY
Human asthmatic airways are exquisitely sensitive to the effects of histamine. Antihistamines can be effective in blocking acute signs in human extrinsic asthmatics prior to an expected provocation (e.g. pollen season). Feline airways, however, are not hyperresponsive to histamine challenge [4], and this finding suggests that antihistamines may not be effective in the management of feline asthma. Feline smooth muscle does demonstrate hyperresponsiveness to serotonin challenge [5], and serotonin is a secretory product of feline mast cells. Cyproheptadine is an antihistamine with anti-serotonergic properties, and has been demonstrated to block the smooth muscle effects of serotonin in vitro. In addition, there have been anecdotal reports of clinical benefit associated with the use of cyproheptadine (2-4mg PO BID) in feline asthmatics. Potential adverse effects of cyproheptadine can include sedation and polyphagia, and the anticholinergic effect of cyproheptadine can also contribute to airway drying and mucus thickening. Cyproheptadine may provide benefit in asthmatics as an additive therapy. Further study is needed before this can be advocated as a therapeutic for asthmatics.

Cyclosporine inhibits the synthesis and secretion of IL-2 by T-helper cells. In so doing, it inhibits T-cell activation, and blocks the development of a Th2 phenotype and the associated Th2-eosinophil interactions. Padrid et al [6] demonstrated that cyclosporine
(10mg/kg BID) was able to inhibit the lung functional derangements and the histologic changes (airway wall remodeling) in an experimental model of feline asthma. It is currently being used in human clinical trials as a steroid-sparing agent. Cost and unpredictable absorption may limit its clinical usefulness.

Immunotherapy may offer a future option for the management of asthmatic cats. Several immunomodulatory agents have been evaluated in experimental models. Some have been effective at blocking or blunting the eosinophilic inflammatory response [7, 8]. The potential for severe side effects thus far has limited the clinical utility of this option.

Tyrosine kinase inhibitors are largely known for their antineoplastic effects. However, this class of drug can also modulate allergic inflammation [9]. As with immunotherapy options, the potential for side effects, including self-limiting proteinuria, has been of concern in experimental models. Neurokinin-1 receptor antagonists, including the anti-emetic agent maropitant, may have a role in dampening neurogenic inflammation in inflammatory airway disorders. Early investigations with maropitant in an experimental model of feline asthma have not demonstrated a significant impact on airway inflammation, although a modest improvement in symptoms was observed [10].

REFERENCES