Thyrotoxicosis is a term used to describe any condition in which there is an excessive amount of circulating thyroid hormone whether from excess production and secretion from an overactive thyroid gland, leakage from a damaged thyroid gland, or from an exogenous source. In most veterinary patients, thyrotoxicosis occurs from thyroid gland hyperfunction. Feline hyperthyroidism is a common endocrinopathy in middle-older aged cats and most often the cause of thyrotoxicosis seen by veterinarians. The clinical presentation of thyrotoxicosis in veterinary patients can vary tremendously from asymptomatic biochemical changes to life-threatening, multisystemic disease. In humans, one form of acute thyrotoxicosis is called thyroid storm and is a cause of significant mortality in human emergency rooms. Thyroid storm is uncommon, and the signs can go unrecognized, thus contributing to the high degree of mortality associated with this disease. In humans, thyroid storm can occur at any age. It can be present in euthyroid patients as well as treated and partially-treated hyperthyroid patients.

PATHOGENESIS
Because multiple factors appear to be involved, the exact pathogenesis of the disease is even more clouded. The rapidity and magnitude of change in the serum thyroid hormone level may be more important than the actual serum levels themselves. This would explain the occurrence of thyroid storm following radioactive iodine therapy and thyroid surgery both of which potentially damage the thyroid gland causing rapid release of hormone. Also supporting this theory is that thyroid storm has been reported to follow abrupt cessation of anti-thyroid medication or accidental thyroid hormone overdose, both resulting in the rapid rise of serum thyroid hormone levels. Additionally, non-thyroidal illness is known to be a precipitating factor for thyroid storm in human medicine. Non-thyroidal illness has been shown to alter binding of thyroid hormones to their carriers. Changes in thyroid hormone binding protein affinity could be responsible for a rapid increase of circulating free thyroid hormone available to activate cellular targets. A sudden increase of inappropriately-activated cells by thyroid hormone could certainly result in thyroid storm.

Activation of the sympathetic nervous system has been implicated in the onset of thyroid storm. Evidence supporting this is that many of the clinical signs and physiological symptoms seen in thyroid storm are similar to those seen during catecholamine excess. Additionally, medical adrenergic blockade can dramatically reduce clinical signs seen with thyroid storm, although it has not been shown to prevent it. These findings lead to the conclusion that other factors besides activation of the sympathetic nervous system are probably important in the development of clinical signs associated with thyroid storm.

There is some evidence that thyroid storm not only results from relative increases in circulating thyroid hormone, but that cellular response to thyroid hormone may be enhanced. This effect has been implicated in the cause of thyroid storm resulting from infection, sepsis, hypoxemia, hypovolemia and lactic or ketoacidosis. Similar enhanced cellular responses may be present in thyrotoxic veterinary patients. In hyperthyroid cats, increased serum concentrations of cardiac
troponin I, a marker of cardiac myocyte injury, have been demonstrated. Successful treatment of the hyperthyroidism and reduction of the serum thyroxine levels resulted in a decrease of the troponin. Additionally, thyroid hormone has been shown to increase Na+ current and intracellular Ca++ in isolated cat atrial myocytes. These data suggests that exposure to excess thyroid hormone may directly result in alteration of cellular response in the cat or at least in feline cardiac myocytes.

PRECIPITATING EVENTS
In most cases of thyroid storm in humans, a precipitating event can be identified, although no known causes are found in up to 2% of cases. The most common events are infection, thyroidal and nonthyroidal surgery, radioactive iodine therapy, administration of iodinated contrast dyes, administration of stable iodine, withdrawal of antithyroid medication, amiodarone therapy, ingestion of excessive amounts of exogenous thyroid hormone, vigorous palpation of the thyroid, severe emotional stress, and a variety of acute nonthyroidal illnesses. Common events that may precipitate thyroid storm in feline hyperthyroid patients include: radioactive iodine therapy, thyroid surgery, or vigorous thyroid palpation, causing destruction of thyroid cells and release of thyroid hormone into the circulation. Abrupt withdrawal of antithyroid medication could result in an acute elevation of circulating thyroid hormone as could the administration of stable iodine compounds which result in an initial increase of thyroid hormone synthesis in the cells. Stress and non-thyroidal illness, especially infections, are most likely important for progression of the clinical course in hyperthyroid cats to thyroid storm. Presence of any of the other causes found as precipitating factors in humans could also play a role in the precipitation of thyroid storm.

CLINICAL SIGNS
Thyroid storm is the acute exacerbation of clinical signs of thyrotoxicosis; however, the diagnosis of thyroid storm in human medicine is primarily a clinical one. In humans, it is based upon the prevalence of 4 major clinical signs. These include: fever, CNS effects from mild agitation to seizures or coma, GI-hepatic dysfunction ranging from vomiting/diarrhea and abdominal pain to unexplained jaundice, and cardiovascular effects including sinus tachycardia, atrial fibrillation and congestive heart failure. The combination of these clinical signs along with identification of a precipitating event allows for the diagnosis of thyroid storm. In cats presenting with presumed thyroid storm, many of these clinical signs also occur. Such cats often show mild-severe respiratory distress. Auscultation may reveal cardiac murmur or arrhythmia, most often a gallop rhythm. Crackles or dullness in the lung fields indicating pulmonary edema or pleural effusion, respectively, associated with congestive heart failure may also be ausculted. Additional clinical signs that may be associated with thyroid storm in cats include mild to severe hypertension. Retinopathies, including hemorrhage, edema, degeneration or even retinal detachment may be found especially in hypertensive thyrotoxic cats. Tachypnea and hypothermia may be present, and absent limb motor function may be detected as a result of thromboembolic disease occurring from acute thyrotoxicosis. Severe, acute muscle weakness and ventroflexion of the neck may be seen in acutely thyrotoxic cats, often associated with hypokalemia. Cats in thyroid storm may exhibit a myriad of neurological abnormalities ranging from hyperexcitability to stupor. Sudden death may also occur.

DIAGNOSIS
The diagnosis of thyroid storm is based upon identification of the presence of thyrotoxicosis, appropriate clinical signs, and evidence of a precipitating event. Thyrotoxicosis in hyperthyroid
cats is demonstrated by an elevated total T4 level, a total T4 level in the high normal range combined with an elevated free T4 or with lack of suppression by T3. In some cases the total T4 may be in the normal range in a hyperthyroid cat, but it is expected, that in cases of thyroid storm, the total T4 and free T4 will be above the reference range. The severity of clinical signs in hyperthyroid cats does not appear to correlate with the absolute level of circulating thyroid hormone. Therefore, as in people, the diagnosis of thyroid storm in cats probably cannot be based upon absolute serum thyroid hormone levels. In human medicine, thyroid storm is diagnosed based upon a point system assigned to each of the main clinical components: fever, CNS signs, GI signs, and cardiovascular signs, as well as, the presence or absence of a precipitating event. In hyperthyroid feline patients, thyroid storm may be diagnosed based upon the presence of clinical signs of acute thyrotoxicosis as described in the preceding paragraph. The owners should be questioned and the clinical case reviewed thoroughly in order to identify an precipitating event. If one can be found, it will further narrow the diagnosis to thyroid storm.

LABORATORY ABNORMALITIES
Laboratory abnormalities are those seen resulting from uncomplicated thyrotoxicosis; there is no distinguishing laboratory value(s) in to diagnose feline thyroid storm. In the hyperthyroid cat, hematology abnormalities may include a mild erythrocytosis, macrocytosis, and Heinz body formation. In humans with thyroid storm, a leukocytosis with left shift in the absence of active infection/inflammation has been identified. In hyperthyroid cats a mature neutrophilia, lymphopenia, eosinopenia are more commonly identified as a stress response. In hyperthyroid cats, elevated liver enzymes, a mild hyperglycemia, hyperbilirubinemia and severe hypokalemia may be seen in acute thyrotoxicosis. A decreased sodium:potassium ratio may be seen in thyrotoxic cats who present in heart failure with pleural effusions. Mild - severely elevated creatine kinase may be seen in cats presenting with thyroid storm. Radiographs may reveal an enlarged heart or evidence of congestive heart failure. Echocardiography may show hypertrophy of the left ventricular wall or left interventricular septum. Myocardial contractility deficits also may be seen.

TREATMENT
Treatment of thyroid storm is aimed at controlling the four major problematic areas: 1) to reduce the production/secretion of thyroid hormones, 2) to counteract the peripheral effects of thyroid hormones, 3) to provide systemic support, and 4) to identify and eliminate the precipitating factor.

The thioimidazole compound, methimazole, inhibits iodine incorporation into tyrosyl residues of thyroglobulin and thus prevents the synthesis of active thyroid hormone. In this way, methimazole should be the first line of defense against thyroid storm. However, it does not prevent the secretion of already formed thyroid hormones. Methimazole may be given orally, transdermally, or even rectally in cats. The dose should be toward the high end in cats that have normal renal function at 5 mg twice/daily. If there is suspected renal insufficiency or failure, the methimazole dose should be reduced in half.

Methimazole will block the formation of new active thyroid hormone, but other therapy must be instituted in order to prevent further secretion of formed hormone that is stored in high concentrations in the thyroid gland. This can be done by treatment with stable iodine compounds such as potassium iodine. These compounds, in large doses, can also decrease the synthesis rate of thyroid hormone. They must be given 1 hour after methimazole administration since a large load of iodine will initially stimulate thyroid hormone production.
Potassium iodate, a more stable form of potassium iodine, has been used successfully in cats and may be given at 25 mg every 8 hours. Instead of potassium iodide, lipid-soluble radiographic contrast agents containing stable iodine such as, iopanoic acid, may be given. Such compounds have been used in hyperthyroid cats as an ancillary treatment for hyperthyroidism. Iopanoic acid or diatrizoate meglumine may be given at 100 mg PO bid. Although iopanoic acid is available in parenteral form, oral dosing is safer since it is a very hyperosmolar agent. These compounds have the additional advantages of blocking peripheral conversion of T₄ to T₃, blocking T₃ binding to its receptor, and inhibiting thyroid hormone synthesis.

The most rapid relief of signs caused by thyroid storm is by medications that block the adrenergic receptors such as propranolol and atenolol. The nonselective beta blocker, propranolol most commonly used as a sympatholytic in human medicine, is inherently difficult to use in cats due to its poor oral bioavailability and short half life, requiring dosing q 8 hours. The use of propranolol has been superseded by that of atenolol in cats because of its selectivity and the once daily dosing regime. However, propranolol has been shown to inhibit the peripheral conversion of T₄ to T₃, although this effect happens slowly. Therefore, its use may be advantageous in severely thyrotoxic cats. Additionally, it may be used intravenously. Propranolol should be used toward the high end of the dose to ensure beta-adrenergic blockade at 5 mg PO q 8 hrs or 0.02 mg/kg IV over 1 minute. Alternatively, the selective α adrenergic blocker, atenolol, may be used at 1 mg/kg q 12-24 hour. In acute situations, the short acting α blocker, esmolol, may be used intravenously at a loading dose of 0.5 mg/kg IV over 1 minute; followed by a constant rate IV infusion of 10-200 mcg/kg/minute.

The third arm of treatment for thyroid storm involves reversing the effects of thyroid hormones on the body. Fever should be treated by the judicious use of ice packs and fans. Volume depletion is another common systemic effect of thyroid storm and this should be treated aggressively with crystalloid fluid replacement. As many cats have concurrent cardiomyopathy, they should be thoroughly evaluated for heart failure to ensure judicious fluid use. Heart failure therapy should be instituted if it is present. Colloid therapy is generally not indicated unless severe GI disease or other syndrome resulting in low oncotic pressure is present. Serum potassium levels should be closely monitored, and potassium supplementation should be added as necessary remembering that some patients with thyroid storm become acutely hypokalemic and demonstrate severe muscle weakness. Dextrose supplementation of 5-10% should be considered as well as B vitamin supplementation to combat potential thiamine deficiency in hyperthyroid cats.