

# HYPERADRENOCORTICISM or "CUSHING'S DISEASE"

Cushing's Disease was named after Harvey Cushing, the physician who first described the disease in people at the turn of the century. The technical name of Cushing's disease, hyperadrenocorticism, is easier to understand if it is broken down into its component parts. The adrenal glands are located on each side of the body just in front of each kidney. The outer layer of these small glands, called the cortex, produces hormones called corticosteroids - the body's own cortisone-like chemicals. The corticosteroid that we measure with blood testing is called cortisol.

In hyperadrenocorticism, the adrenal glands produce excessive (hyper) amounts of adrenal cortical hormones (cortisols). The excess hormones in the body lead to the symptoms of the disease - excessive urination and water drinking, thin skin and haircoat, liver swelling, muscle weakness often leading to a pot-bellied appearance, panting, obesity, frequent infections, especially of the skin or urinary tract. Signs progress slowly but surely, creating more and more problems as time goes on.

These symptoms may not all occur at once. Many times in the early stages Cushing's disease resembles many other disease problems. The diagnosis may be suggested by changes in blood chemistry tests, which also help diagnose other diseases which can cause similar symptoms.

The inner layer of the adrenal glands, called the medulla, produces a set of hormones called mineralocorticoids, which regulate sodium and potassium levels in the body. This second type of hormone becomes important when we begin treating for Cushing's disease.

There are two causes of the disease. The first is a tumor of an adrenal gland. This tumor consists of excess glandular tissue which simply produces too much of its normal hormone. Adrenal tumors can be benign (non-cancerous) or malignant (cancerous).

More commonly (80-85% of the time) the tumor causing the problem is in the pituitary gland at the base of the brain. The pituitary is supposed to respond to changes in the body such as stress, day length exposure, disease and other factors, and releases a hormone called adreno-corticotrophic hormone, or ACTH, into the bloodstream. ACTH stimulates the adrenal glands to produce cortisol. In a normal dog or person, the pituitary sends an appropriate amount of ACTH into the system to produce the proper amount of cortisol to maintain health. A pituitary tumor, in contrast, produces too much ACTH, which stimulates the adrenal glands to produce too much cortisol.

Pituitary tumors can also be benign or malignant. Benign ones tend to grow very slowly, causing no problems for years other than the effects on the adrenal glands. Malignant tumors may cause trouble much sooner, but these are rare. Whether benign or malignant, if the tumor becomes large enough it will eventually damage other tissues in the brain and neurological symptoms will start to occur - seizures, blindness or behavior changes.

There are several specific test protocols that are used to diagnose Cushing's Disease and to determine which type of disease, pituitary dependant or adrenal, a dog has. They all involve testing cortisol levels before and after the administration of other hormones, to see if the adrenal and pituitary glands respond

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appropriately. An ultrasound scan of the abdomen can also be done to look for adrenal tumors. A urine test called a cortisol/creatinine ratio can be used as a screening test for Cushing's disease as well. This test is the least expensive. It's great to rule out Cushing's – if it's negative it's unlikely the dog has the disease – but we get a lot of false positives on this test. Stress increases cortisol levels and can cause false positives on all of the tests. This can be a difficult disease to diagnose, especially if the pet has other stressful or serious health problems, and sometimes multiple tests are needed.

Adrenal tumors can be surgically removed. If only a single adrenal gland is involved and removed, the other one will take over cortisol production after surgery and the symptoms of Cushing's disease will go away. Sometimes the opposite adrenal gland will eventually develop a tumor as well. This is common in ferrets but is rare in dogs and cats.

Pituitary tumors are located too deep in the brain to surgically remove. Therefore, the treatment for the 85% of Cushing's patients who have this form of the disease is medical, not surgical. Cushing's disease develops slowly, with symptoms gradually growing worse over time. Treatment for it is expensive and has risks associated with it. We generally do not recommend treatment until the symptoms warrant the risk and the cost. Regardless of the results of the blood tests if a dog does not have symptoms that are causing problems for the pet or the owner, we don't treat it.

There are three medications available. Anipryl is much safer than the other medication but is only effective in about 20% of dogs. Anipryl decreases the amount of ACTH produced by the pituitary gland. Given once daily, symptoms would begin to improve within a month. If it is helping it would then be used for the remainder of the pet's life. Periodic retesting would be needed to monitor the disease. Anipryl is fairly expensive, costing \$60-200 per month, and this cost would be ongoing. If we don't see good results we switch to another drug.

An older medication, called mitotane (Lysodren®), is more expensive initially for many dogs but may be less in the long run. It is much more effective – about 85% of dogs with Cushing's disease will respond. It also has greater risk than Anipryl. It destroys adrenal tissue so that there is less adrenal gland left to produce cortisol. Even though the pituitary is still producing too much ACTH, there isn't enough adrenal tissue left to respond.

The hard part is getting the right dosage of this medication to destroy just enough adrenal tissue but not too much. One or two doses too many can destroy so much adrenal tissue that mineralocorticoids production is affected. When this happens, sodium and potassium balance is disrupted. Vomiting, heart rhythm disturbances, collapse and even death can result. Emergency IV saline treatment is necessary if sodium levels become too low. Close monitoring is needed when using this medication.

Mineralocorticoid supplements may be needed after treatment with Lysodren - sometimes temporarily, sometimes for life. Often supplements of corticosteroid hormones are needed as well, at least for the first few days after the initial Lysodren therapy or intermittently when the dog is stressed.

With Lysodren treatment, the dog receives the drug twice daily until adrenal production drops. When the cortisol and mineralocorticoid levels drop the dog feels sick so we know it's time to stop giving it. Most of the time, within a few days to a few weeks the adrenal gland starts to recover again. As soon as adrenal hormone production starts to resume, a weekly dosage of Lysodren is initiated to maintain control. In other words, we destroy a little adrenal tissue every week after that to maintain the effect. Periodic testing for adrenal function assures good control of the disease. Unless the tumor causing the disease is one that can be removed, treatment is lifelong. Although most do well, again there can be serious side effects in a few dogs.

The last option is a new drug called trilostane (Vetoryl®). It is effective, though expensive. It has been approved for use in dogs by the FDA, unlike mitotane, which is used off label. (Mitotane is a human drug that is no longer used much in people and may soon become

unavailable to us.) Dogs on trilostane have a longer life expectancy on average than dogs on mitotane (Lysodren) – but a higher initial risk for sudden death due to treatment. Both mitotane and trilostane can cause the adrenal glands to necrose – too many adrenal cells die and decay too quickly. The risk of this is a little higher for trilostane than for mitotane, because it kills adrenal cells more quickly, and necrosis of the adrenal glands can occasionally be fatal.

As you might guess, the cost of diagnosis and treatment vary greatly depending on the dog and the size of the dog. Diagnosis alone can cost well over \$1000 in some cases. The medications are expensive. With Lysodren treatment, there is no way we can predict whether a pet will need medication for 3 days or for the rest of its life. If emergency treatment is needed for electrolyte disturbances, that alone may be several hundred dollars. Whichever drug or treatment is used, regular recheck blood tests will be needed to monitor the course of the disease.

If your dog does well on whatever medication is chosen the prognosis is good. The average lifespan after diagnosis is about two and one half years, but we have several patients who have done well on their medication for more than 5 years. Hyperadrenocorticism is considered a life-shortening disease, however, and some dogs will do much better than others. Since the disease usually occurs in middle aged or older animals, there may also be complications due to other organ dysfunction.

Please let us know if you have any questions about this disease. We want to make sure you understand it before making a decision as to treatment for your pet.