

Cushing's Disease (Hyperadrenocorticism): Overview & Diagnosis

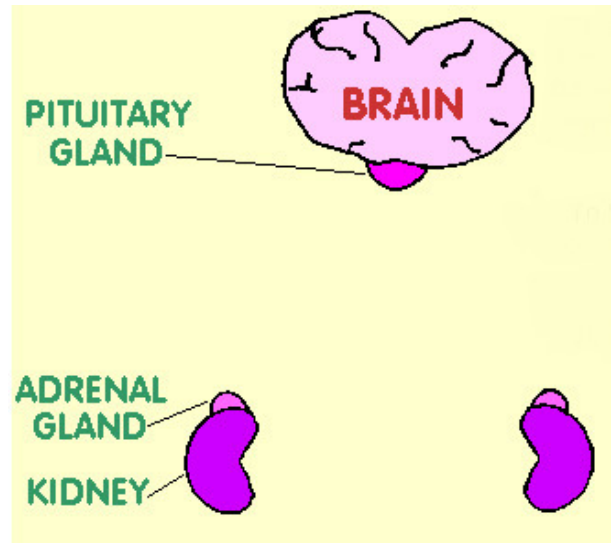
adapted from VeterinaryPartner.com; originally written by Wendy Brooks, DVM, DABVP

Cushing's syndrome is the resulting set of symptoms observed when the body is exposed to excess cortisol (or related hormones) over a long period of time. Cortisol is a hormone produced by the adrenal glands that are located atop the kidneys. Cortisol is stored in the adrenal glands and is released in times of stress, where it helps our bodies prepare for a fight or flight situation. It adjusts the metabolism to expect physical exertion by mobilizing fat and sugar stores and retaining sodium and water. It puts us in a state of break down so that our stored resources can be used quickly. However, if the body is exposed to this hormone most of the time instead of during short stressful periods only, the state of breakdown becomes debilitating.

There are several mechanisms that can lead to Cushing's syndrome and, as they are treated differently, it is important to determine which one is at work in a given animal.

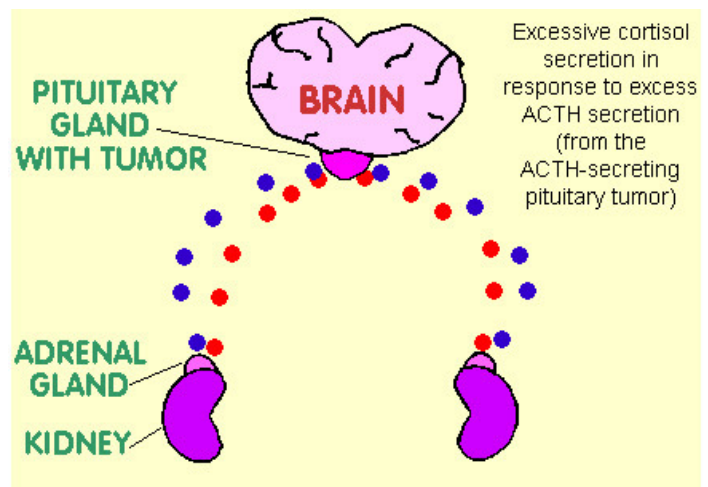
In the normal body, the pituitary gland, located at the base of the brain, can detect when cortisol levels in the blood are declining. In response, the pituitary secretes a stimulating substance, called ACTH, which causes the adrenal gland to release more cortisol. When the pituitary gland detects that cortisol levels are again appropriate, it stops its stimulatory message.

You can think of the pituitary gland as a thermostat for cortisol, though the pituitary gland regulates other hormones as well. This raising and lowering of cortisol blood level is rapidly regulated throughout the day via ACTH secretion.



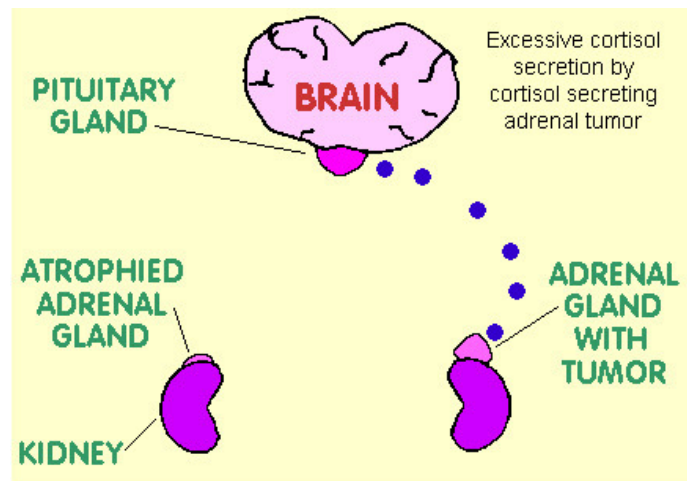
1) Pituitary-Dependent Cushing's Syndrome

This form of Cushing's disease accounts for 85% of cases. The pituitary gland basically grows a small tumor. It is generally too small to cause trouble due to its size, and it is usually benign. This tumor, however, over-produces ACTH, thus leading to over-stimulation & enlargement of both adrenal glands and an over-production of cortisol. Occasionally (10% of these patients), these benign pituitary tumors are large enough to compress the brain. In these cases, neurological signs may be observed; these cases are unusual but very hard to treat (see section on macrotumors.)



2) Adrenal-Dependent Cushing's Syndrome

In 15% of dogs with Cushing's syndrome, an adrenal tumor is directly over-producing cortisone. The tumor is often large enough to see with radiographs or ultrasound and may be malignant. There is very little or no production of ACTH from the pituitary gland and as a result the opposite adrenal gland is usually atrophied/small.



3) Overuse of Cortisone-Type Hormones

Cortisone derivatives may well be the most over-used drugs in veterinary medicine. Their anti-inflammatory actions soothes such common maladies as allergic skin disease (especially flea allergic dermatitis) and degenerative arthritis. Relief is usually rapid and many owners find themselves requesting cortisone shots or pills over and over again. In time, Cushing's syndrome can result, not from any inherent disease in the pet's system but from the effects of the hormones given over the long term.

The pituitary gland perceives the high steroid levels yielded by the medication and does not send stimulation to the adrenal glands. In time, the adrenal glands atrophy and are not able to release cortisone on their own should they be required to do so. This effect lasts as long as a period of three months after the cortisone medication has been discontinued. To allow the adrenal to gradually recover, cortisone pills are usually prescribed in a decreasing dose, rather than a sudden stoppage; an owner should never discontinue the pills suddenly.

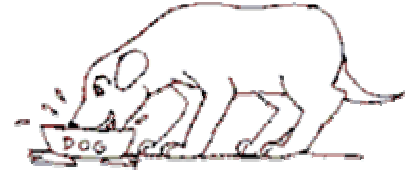
Commonly prescribed cortisone derivatives include: Vetalog, Azium, prednisone/prednisolone, dexamethasone, Depo-Medrol, triamcinolone and others. These medications have important parts to play in medicine but they must be respected and not used indiscriminately, nor discontinued suddenly after prolonged use.

Symptoms of Cushing's

There are many clinical signs associated with Cushing's syndrome (*hyperadrenocorticism*) in dogs. These signs usually come on gradually and, because of this slow onset, these changes are often written off as part of the normal aging process. Common symptoms that an owner might observe at home are:

- Drinking and urinating excessively
- Urinary incontinence

Owners often notice that lately the water bowl must be filled more frequently than in the past. Some dogs are unable to hold their bladder all night and begin crying to go outside during the night when previously this was unnecessary. Urinary tract infections may also be detected and true urine leaking may be observed.



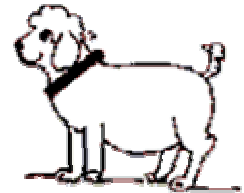
- Increased appetite

This symptom often leads dogs to beg incessantly or steal food from the garbage. It is important for an owner not to be fooled by the pet's "good appetite"; eating well is not necessarily a sign of normal health.



- Pot-bellied appearance

This symptom, seen in over 90% of Cushing's syndrome dogs, results from hormonal redistribution of body fat plus a breakdown of abdominal musculature.



- Muscle weakness

Muscle protein is broken down in Cushing's syndrome. The result may be seen as exercise intolerance, lethargy, reluctance to jump up on furniture or climb stairs.

- Skin disease

The classical signs of endocrine (hormonal) skin diseases are:

- 1. Hair loss on the main body sparing the head and legs*
- 2. Thin, wrinkled skin with poor wound healing*
- 3. Hair that does not grow back after clipping.*
- 4. Blackheads and darkening of the skin, especially on the abdomen.*
- 5. Persistent or recurring skin infections (especially if the dog is not itchy during times when the skin infection is cleared)*



Another condition of the skin that may be observed is called calcinosis cutis, in which calcium deposits occur within the skin. These are raised, hard, almost rock-like areas that can occur almost anywhere on the body.

Other notable findings might include: excessive panting and shortness of breath, infertility, extreme muscle stiffness (called pseudomyotonia - a very, very rare symptom in Cushing's disease), and high blood pressure.

Advanced untreated Cushing's disease also puts a dog at risk for the following serious problems: calcium oxalate bladder stones, diabetes mellitus, and pulmonary thromboembolism.

In cats, the clinical features of Cushing's disease are similar to those in the dog: excess water consumption, muscle wasting, pot-bellied appearance, thin coat, and skin abnormalities. Some cats develop a peculiar curling-in of their ear tips. An important difference to note is that while only 10% of dogs with Cushing's disease develop diabetes mellitus, 80% of cats with Cushing's disease develop diabetes mellitus. Diabetes in an animal with Cushing's disease is difficult to control until the Cushing's disease is controlled.

Tests Suggestive of Cushing's

When an animal is presented to the veterinarian for a clinical problem, an initial "minimum database" is collected in the form of a blood panel and urinalysis, and possibly a urine culture. There are some "tip offs" to Cushing's syndrome which may be noted and added to the list of observed symptoms as evidence.

The Stress Leukogram

This term refers to the relative proportions of different types of white blood cells. There is a typical pattern produced by cortisol as the body responds to stress. This pattern is called a "stress leukogram." If this pattern is seen in a patient that does not seem stressed, excess cortisol may be present.

Elevated Alkaline Phosphatase

Alkaline phosphatase (often abbreviated ALP or SAP) is one of the so-called "liver enzymes," meaning that it is chiefly found in the liver. There is a form of this enzyme which is produced in very high levels in response to cortisol. This enzyme is not harmful in excess levels, but since such marked increases in its levels are associated with cortisol, this would be a good hint that either this patient is taking cortisone type medications or has Cushing's disease.

Elevated Cholesterol

This is a common finding in endocrine disease and, in this case, results from abnormal fat mobilization. High levels of circulating cholesterol may alter normal circulation and blood clotting.

Unconcentrated Urine and/or Bladder Infection

When a pet drinks excessive amounts of water, the extra water is passed as urine. As long as there is extra water, urine will be dilute. Because of the immunosuppression associated with Cushing's disease, evidence of bacterial infection may be present, or such evidence may be concealed by the dilution of the urine. Ideally, urine should be cultured if it is too dilute to reliably detect white blood cells or blood. Recent studies have shown that 20% of dogs with Cushing's disease have an inapparent bladder infection.

Tests Confirming Cushing's Disease

Once there is some reason to suspect Cushing's disease based on the history, physical examination, and initial laboratory testing, it is necessary to do specific testing to confirm it. There are several options. We will begin with dogs and then discuss cats.

CANINE CUSHING'S DISEASE TESTING

1) *The Low Dose Dexamethasone Suppression Test* (usually takes 8 hours in the hospital)

Dexamethasone is a cortisone-type hormone that is used therapeutically for numerous conditions. When given dexamethasone, the dog's pituitary gland will perceive that there is a steroid and shut off its stimulatory message to the adrenal glands. In the normal animal, this means that a drop in blood cortisol level will be seen 8 hours after a tiny dose of dexamethasone is given intravenously.

If there is a pituitary tumor, the pituitary is not responsive to the dexamethasone and continues to produce its stimulatory message. As a result, no drop in cortisol level is seen.

This test is currently considered the most accurate to confirm Cushing's disease; approximately 90% of dogs with Cushing's will have a positive test result.

Ideally the low dose dexamethasone suppression test (LDDST) is run in the morning. A baseline cortisol level is measured, a low dose of dexamethasone is given intravenously, and blood samples are checked again in 8 hours. Sometimes a 4-hour sample is also drawn as the pattern of suppression over the entire 8 hours may help classify the type of Cushing's disease. The pet will require at least 8 hours in the hospital.

2) *The ACTH Stim Test* (requires one to two hours in the hospital)

Central to the concept of Cushing's disease is the over-production of cortisol. It follows then that the adrenal glands of the Cushing's patient would possess large amounts of stored hormone due to their chronic stimulation. We have been talking about the stimulatory message sent from the pituitary gland to the adrenal glands. This message consists of a hormone called adrenocorticotrophic hormone, or ACTH. In this test, a dose of ACTH is given to the patient. If a larger than expected rise in cortisol levels is measured in 1-2 hours, we may diagnose Cushing's. Ideally, the patient is fasted overnight and the test is performed in the morning between 8 & 10 a.m. A blood sample is drawn, a dose of ACTH is given, and two hours later a second sample is drawn.

Given that the Low Dose Dexamethasone Suppression test is more accurate, when might we run this test instead? It turns out that this is the only test that can be used if the iatrogenic form of Cushing's disease is suspected. This test is also crucial in monitoring patients with Cushing's disease, depending on which medications are used. This test is more specific than the low dose dexamethasone suppression test meaning that the strongly positive dogs definitely have Cushing's disease (false positives are unusual) but since it is not a very sensitive test, the University of California Veterinary School no longer recommends this test to determine whether or not a dog has Cushing's disease. This is, as mentioned, the test that is used to monitor the treatment of Cushing's disease, however, and a dog being treated for Cushing's disease will likely look forward to many ACTH Stimulation tests ahead.

3) *The Urine Cortisol/Creatinine Ratio*

This is a screening test for Cushing's disease; a positive test here does NOT confirm Cushing's syndrome but a negative test DOES rule it out. In this test, a single urine sample is collected to determine the relative amounts of cortisol and creatinine (creatinine is a protein metabolite that is constantly excreted in urine). If there is a high ratio - a relatively high amount of cortisol being excreted - further testing is in order. Ideally for this test the urine sample is collected at home so that cortisol secreted in response to the stress of visiting the vet's office does not interfere with results.

FELINE CUSHING'S DISEASE TESTING

The testing situation is similar in cats, though the ACTH Stim test is generally not considered useful.

1. *The Low Dose Dexamethasone Suppression Test*

This test is similar to the way it is performed with dogs, but the dose of dexamethasone required to test a cat is higher as cats are more resistant to the effects of steroids. The test still requires eight hours in the hospital and the cat should be relaxed and kept quiet. If the cat is the type to experience a great deal of stress in the vet's office, consider the urine cortisol:creatinine ratio.

2) *The Urine Cortisol/Creatinine Ratio*

This test provides an excellent screening test for Cushing's disease in cats and can be performed to include a high dose dexamethasone suppression test to further categorize the Cushing's disease so as to best determine treatment. The owner should bring urine samples collected first thing in the morning on three consecutive mornings. Having the sample collected at home removes the possibility of interference from vet visit-induced stress. The first two samples are used to determine if the cat has Cushing's disease and the ratios are averaged. On the second day (after the second sample is brought in) dexamethasone pills are given to the cat at home and the sample from the third day is used to determine the type of Cushing's disease the cat has.

Collecting a cat's urine at home is easier than it sounds. The cat is confined overnight and in the morning is allowed access to the litter box. The easiest way to collect the urine is to place a sheet of cellophane over the box. The cat will crinkle this scratching but only a small amount need be caught on the cellophane. A syringe can be used to suck up the sample and store it for transport to the veterinary clinic. Non-absorbent beads (instead of regular litter) are also available from the vet.

No blood drawing is needed and the cat does not have to come to the vet for the test. The problem is that urine cortisol:creatinine ratios may generate false positives. For this reason, the low dose dexamethasone suppression test is listed by most experts as the screening test of choice for cats.

It is important to note a diagnosis of Cushing's disease but it is equally important to consider that successful treatment of Cushing's disease is about control of symptoms. If the symptoms do not warrant control, then treatment should be postponed until they are more problematic. After it has been determined that a pet has Cushing's disease, it is important to determine the type of Cushing's disease (adrenal vs. pituitary tumor). The next section in this series reviews how this is done. Treatment options and prognosis are highly dependent on the type of Cushing's disease the pet has.

Classifying Cushing's Syndrome: Pituitary vs Adrenal

Adrenal or Pituitary Cushing's? Why do we Care?

Once a pet has been confirmed as having Cushing's syndrome, the next step is to determine which form of Cushing's syndrome the pet has since treatment and prognosis are different for each form. As described, there are two forms, commonly abbreviated PDH and AT. PDH stands for pituitary dependent hyperadrenocorticism and accounts for 85% of canine and feline Cushing's patients. In PDH, there is a pituitary tumor, often extremely small, causing over stimulation of the adrenal glands. AT simply stands for adrenal tumor. Adrenal tumors can be benign or malignant. Testing to determine the type or form of Cushing's disease is called discriminatory testing. This type of testing is done AFTER the diagnosis of Cushing's disease has already been made. Here are some issues and concerns where the type of Cushing's disease the pet has becomes an important matter:

- If there is an adrenal tumor, there is a 50% chance that it is malignant. It is helpful to know if the pet has a condition with this kind of a malignancy rate, especially if surgery is being considered.
- If the patient is known to have an adrenal tumor, this knowledge will direct the doctor on how and where to look for tumor spread to determine if the patient has cancer or not. On the other hand, if the patient is known to have a pituitary tumor, it becomes more relevant to image the brain to look for evidence of pressure on the brain.
- Medication protocols are completely different for adrenal tumors versus pituitary tumors.
- Surgery protocols are completely different for adrenal tumors versus pituitary tumors.
- Approximately 85% of Cushing's patients will have pituitary dependent disease while approximately 15% will have adrenal tumors. This statistic appears to be valid in dogs and cats.

So What Tests will Tell us What Type of Cushing's Syndrome is Present?

1. The Low Dose Dexamethasone Suppression Test (LDDST)

If one is lucky, the same test used to determine if Cushing's disease is present can also classify the Cushing's disease so that no further tests are needed. To get the information needed, a 4-hour sample is drawn in addition to the pre-dexamethasone sample and the 8-hour sample. If the cortisol level suppresses to a level below 50% of baseline at 4 hours, only to escape to a level high enough to indicate a positive result, only a pituitary tumor is possible. While pituitary tumors do not always show this kind of classic suppression at four hours, adrenal tumors never do. If suppression is seen in the 4-hour sample, further testing is not needed, though this is the only pattern that is distinctive enough to obviate further testing. Approximately, 60% of patients with pituitary tumors can be identified with the Low Dose Dexamethasone Suppression test.

2) Imaging

With pituitary-dependent disease, both adrenal glands are being overstimulated. Therefore, they should both be symmetrical in size and shape, and most likely enlarged. With an adrenal tumor, one gland will be severely atrophied and possibly undetectable while the other one is enlarged and possibly misshapen. This makes imaging of the adrenal glands an accurate way to distinguish types of Cushing's. Ultrasound, MRI, or CT scan can be used, but ultrasound is the most readily available and least costly. Sedation is generally not needed for abdominal ultrasound whereas CT and MRI require general anesthesia and referral to a specialty clinic.

An added benefit of imaging includes looking for evidence of malignancy should an adrenal tumor be identified. Malignant tumors tend to invade the vena cava, the largest vein in the body. Ultrasound has been found to be extremely accurate in evaluating for this complication. Imaging also allows for measurements of the adrenal glands to be taken. Glands that measure greater than 4 cm in length are highly suspicious of being malignant.

It is important to note that ultrasound can never be used to make the initial diagnosis of Cushing's syndrome as there is too much variability in the size of normal adrenal glands. Imaging is best used on patients already known to have Cushing's syndrome for whom classification is needed.

3) The High Dose Dexamethasone Suppression Test (HDDST)

This test is similar to the low dose dexamethasone suppression test except that a higher dose of dexamethasone is used and the patient having the test is already known to have Cushing's disease through prior testing. The idea behind this test is that a patient with a pituitary tumor will show suppression in circulating cortisol when exposed to the high dose of dexamethasone (though suppression does not occur with the low dose). If an adrenal tumor is present, suppression does not occur. Unfortunately, the theory does not hold well enough to make this a reliable test; 20-30% of pituitary tumors will fail to suppress even with the high dose. Further, this test cannot identify patients with adrenal tumors; it is able to confirm about 70-80% of patients with pituitary disease. The remaining patients will need further testing.

4) Endogenous ACTH Level

This test is felt by many to be the most accurate method of classifying Cushing's, but the problem is that the test is technically difficult to run. Serum from the patient must be frozen when transported to the lab and must not thaw. The hormone ACTH is very fragile and may not survive the trip. The idea with this test is that a patient with a pituitary tumor will have high ACTH levels, as this is what the tumor is secreting. A patient with low or no measurable ACTH levels has an adrenal tumor as the pituitary is trying its best not to stimulate the over-active adrenal tumor.

Is it Reasonable to Play the Odds and Not Do Further Testing?

Since 85% of canine patients with Cushing's syndrome have a pituitary tumor, it is not unreasonable to play the odds and treat for a pituitary tumor. The risks in doing so is that if the patient does not readily respond to medication it will be impossible to know if the medication dose simply needs adjustment or if the patient has an adrenal tumor and a completely different treatment is needed. A great deal of time and effort could be wasted by pursuing the wrong therapy.