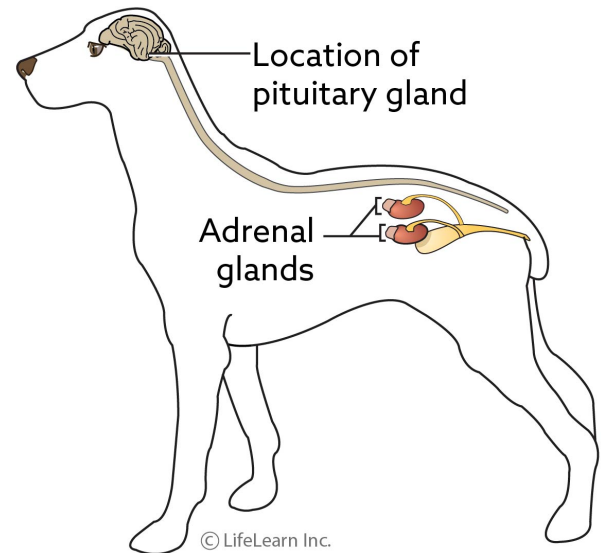


## Cushing's Disease – Testing

### What is Cushing's disease?

Cushing's disease is a condition caused by an increased production of the stress hormone cortisol by the adrenal glands. Increased cortisol production may be related to:

- excessive stimulation of the adrenal glands by the pituitary gland, usually as a consequence of a pituitary tumor (pituitary origin).
- the unregulated production of cortisol by the adrenal glands (adrenal origin).
- occasionally, administration of steroid-containing medications may result in the development of Cushing's disease (iatrogenic, or caused from medication).



The most common type of Cushing's disease is of pituitary origin. The clinical signs of Cushing's disease are similar, regardless of the underlying cause of disease. However, it is important to try to identify the type of Cushing's disease as the treatment and prognosis (outcome) differ slightly depending upon the form of the disease.

### What initial screening tests are useful to diagnose Cushing's disease?

There are characteristic laboratory changes related to Cushing's disease, which may be noted on evaluation of your pet's blood and urine samples. Not only will the documentation of such changes help in the diagnosis of Cushing's disease, these laboratory tests may also uncover other conditions related or unrelated to excessive cortisol production.

Common initial screening tests may be performed in a veterinary hospital using blood or urine samples. They include:

**Complete blood count (CBC)** (see handout "Complete Blood Count" for more information). The red blood cell, white blood cell, and platelet components in a blood sample are evaluated. Often an increase in the number of white blood cells (neutrophils and monocytes) is noted with Cushing's disease. This increase is usually related directly to the effects of excessive cortisol, but occasionally an increase in these cells may indicate underlying inflammation or infection.

**Serum biochemistry profile** (see handout "Serum Biochemistry" for more information). Serum (the liquid portion of blood) contains enzymes, proteins, lipids (fats), glucose (sugar) and metabolites. These serum components are derived from different organs such as the liver, kidney, and pancreas, and can give us an indication of the function of these organs. Specific changes in the serum biochemistry profile may support the diagnosis of Cushing's disease and may give us an indication of overall organ function.

Typical findings with Cushing's disease may include increases in blood glucose and in liver related enzymes. A certain liver enzyme, steroid alkaline phosphatase (S-ALP), increases directly in response to increased blood cortisol levels. Increases in blood lipid and cholesterol are also often noted.

**Urinalysis** (see handout "Urinalysis" for more information). Because dogs with Cushing's disease typically drink large amounts of water, the urine produced is very dilute. A special instrument called a refractometer assesses urine concentration. Infection of the bladder (cystitis) is a common finding in Cushing's disease. By looking at the cells voided into the urine, and by sending a urine sample for bacterial culture (checking for the growth of bacteria), the presence of infection can be assessed. Some dogs with Cushing's disease also have concurrent diabetes. The presence of diabetes may be detected by glucose in the urine as well as by an increased concentration of glucose in the serum biochemistry profile.

**Urine cortisol/creatinine ratio.** The amount of cortisol being lost in the urine is increased with Cushing's disease. This cortisol can be measured and compared to the amount of creatinine, a normally occurring urinary component that is produced at a constant rate. The urine cortisol/creatinine ratio is usually elevated with Cushing's disease. However, stress and other illnesses may also increase this ratio. While an increased urine cortisol/creatinine ratio is suggestive of Cushing's disease, it cannot absolutely confirm the diagnosis.



A refractometer measures the specific gravity (or the concentration) of the urine.

**"It is very important to know the type of disease so that an effective treatment plan can be formulated and the possible outcomes can be predicted."**

If a large number of changes characteristic of Cushing's disease are found with these initial screening tests, then more extensive diagnostic tests will be required to confirm the diagnosis of Cushing's disease and to establish the type of Cushing's disease that your pet has. It is very important to know the type of disease so that an effective treatment plan can be formulated and the possible outcomes can be predicted.

### **What do the more extensive and specific diagnostic tests involve?**

The more extensive tests may include an adrenocorticotropic hormone (ACTH) stimulation test, dexamethasone suppression tests, and/or endogenous ACTH concentrations.

## How does the ACTH (Adrenocorticotrophic Hormone) stimulation test work?

ACTH is a hormone naturally produced by the pituitary gland (a gland located in the brain). The purpose of ACTH is to tell the adrenal glands when and how much cortisol to produce. As the blood level of cortisol increases, it causes the pituitary gland to decrease its production of ACTH, which results in a lowering of the cortisol level. The ACTH stimulation test mimics this natural stimulatory pathway and demonstrates the capacity of the pet's adrenal glands to produce cortisol in response to an injection of synthetic ACTH.

This test requires two blood samples. The first blood sample is taken, then an injection of synthetic ACTH is given, and the second blood sample is taken 2 hours following the injection. When the levels of cortisol in the two samples are compared, they may show a normal response, an exaggerated response, or very little response.

## What do we expect to see if the patient has Cushing's disease?

With pituitary origin Cushing's disease, we normally see a markedly increased cortisol level following the synthetic ACTH injection. This exaggerated response occurs because the adrenal glands have been over-stimulated with naturally occurring ACTH secreted by the diseased pituitary (pituitary origin Cushing's disease). These adrenal glands are therefore highly responsive to stimulation by the synthetic ACTH. With adrenal origin Cushing's disease, an exaggerated cortisol level after the synthetic ACTH injection may also be seen.

**"Since the ACTH stimulation test may be positive in both types of Cushing's disease, the test confirms that your pet has Cushing's disease, but not the type or cause."**

Since the ACTH stimulation test may be positive in both types of Cushing's disease, the test confirms that your pet has Cushing's disease, but not the type or cause of Cushing's disease. Some dogs with Cushing's disease of either pituitary or adrenal origin do not respond to the ACTH stimulation test and additional diagnostic testing is required to confirm a diagnosis.

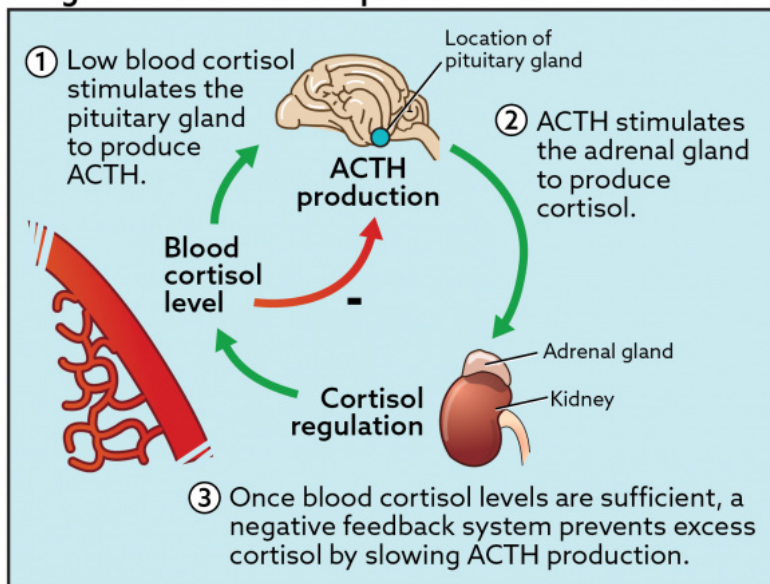
Dogs that are showing signs of Cushing's disease due to the effects of corticosteroid containing medications (called iatrogenic Cushing's syndrome) will show either a very mild response or no response to synthetic ACTH injection. This type of muted response, in conjunction with a history of medication use, is confirmatory for iatrogenic Cushing's syndrome.

Another use for the ACTH stimulation test is to monitor your dog's response to therapy for Cushing's disease. Periodic ACTH stimulation tests during the initiation and maintenance phases of treatment will be required. As your dog responds to treatment, the increases in cortisol will become less exaggerated in response to injection of synthetic ACTH.

## How does the low-dose dexamethasone suppression test work?

In a healthy dog, ACTH is secreted by the pituitary gland and stimulates the adrenal glands to produce or secrete cortisol. As the blood cortisol level increases, it causes the pituitary gland to lower its production of ACTH, which results in a lowering of the blood cortisol level – this is called a negative feedback loop. This feedback loop is capable of causing rapid changes in blood cortisol levels in response to the body's needs. Mimicking what happens naturally, when healthy dogs are given an injection of synthetic cortisol (dexamethasone), the production of ACTH is suppressed, as is the production of cortisol. The Low Dose Dexamethasone Suppression Test requires three blood samples. The first sample is taken prior to dexamethasone injection, and the second and third samples are taken 4 and 8 hours after injection.

### Negative feedback loop



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## What do we expect to see if the patient has Cushing's disease?

With Cushing's disease, this negative feedback loop is diminished or lost because cortisol is high all the time. If the patient has pituitary origin Cushing's disease, the negative feedback mechanism is only diminished, so we expect to see a small decrease in the 4- or 8-hour cortisol levels from the pre-injection sample. With adrenal origin Cushing's disease, the negative feedback loop is lost, so we do not see any reduction in blood cortisol concentrations at either the 4- or 8-hour cortisol levels.

**"In most instances, the low dose dexamethasone suppression test will allow the diagnosis of Cushing's disease to be made..."**

In most instances, the low dose dexamethasone suppression test will allow the diagnosis of Cushing's disease to be made, and will indicate of the type of Cushing's disease (pituitary versus adrenal origin) that is present.

## How does the high-dose dexamethasone suppression test work?

This test works on the same principle as the low dose test, and is used when no reductions in cortisol levels are seen on the low dose test. The purpose is to determine definitively which type of Cushing's disease we are dealing with. In rare instances with pituitary origin Cushing's disease, the negative feedback loop is more resistant to the effects of dexamethasone. A higher dosage of this synthetic cortisol may be required to overcome this resistance and demonstrate the negative feedback mechanism. If there is a reduction in cortisol levels at either 4 and/or 8 hours after the higher dose of dexamethasone, then we have diagnosed pituitary origin Cushing's disease. If the levels do not budge from the high values of the pre-injection sample, then the diagnosis is adrenal origin Cushing's disease.

## Endogenous ACTH concentrations:

Endogenous (originating from within the body) ACTH concentration can be measured in blood samples as a screening test for the diagnosis of Cushing's disease. With pituitary origin Cushing's disease an increased concentration of endogenous ACTH will be found in the blood. With adrenal origin Cushing's disease, or with iatrogenic Cushing's disease (caused by cortisol containing medications), the amount of endogenous ACTH in the blood will be decreased. Unfortunately, the concentrations of ACTH found in blood with these different types of Cushing's disease may overlap and not allow a clear differentiation of the cause of the disease.

**"A combination of these tests either will allow us to make a diagnosis of Cushing's disease, or will allow us to rule out the disease in your pet."**

In most instances, a combination of these tests either will allow us to make a diagnosis of Cushing's disease, or will allow us to rule out the disease in your pet. Occasionally, additional testing such as abdominal radiographs (X-rays) or ultrasound may be required to determine whether an adrenal tumor is present.

In very rare instances, referral to a veterinary facility with MRI (magnetic resonance imaging) or CT (computed tomography) imaging may be needed to rule out or demonstrate the presence of pituitary or adrenal tumors. Your veterinarian will help you determine which testing method is best for your pet.

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