



# Clinical Significance and Application of Cortisol

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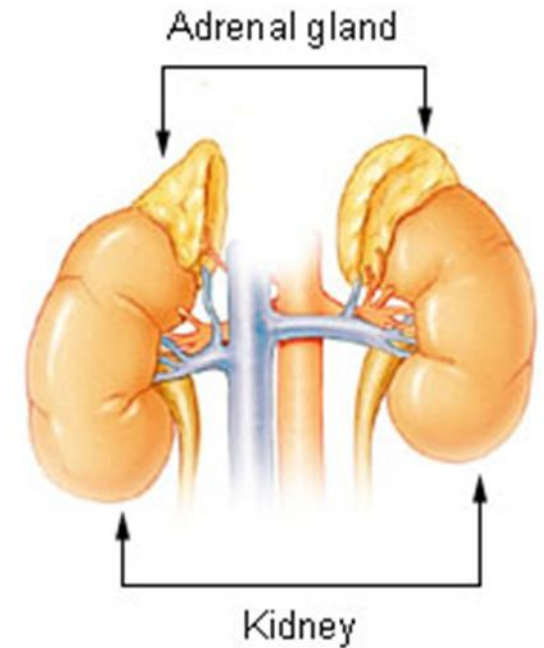
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# a. Adrenal Structure and Function

## Adrenal Gland

- ❑ A small gland located above the kidney
- ❑ Synthesises and secretes salt corticosteroids, glucocorticoids, oestrogens and androgens

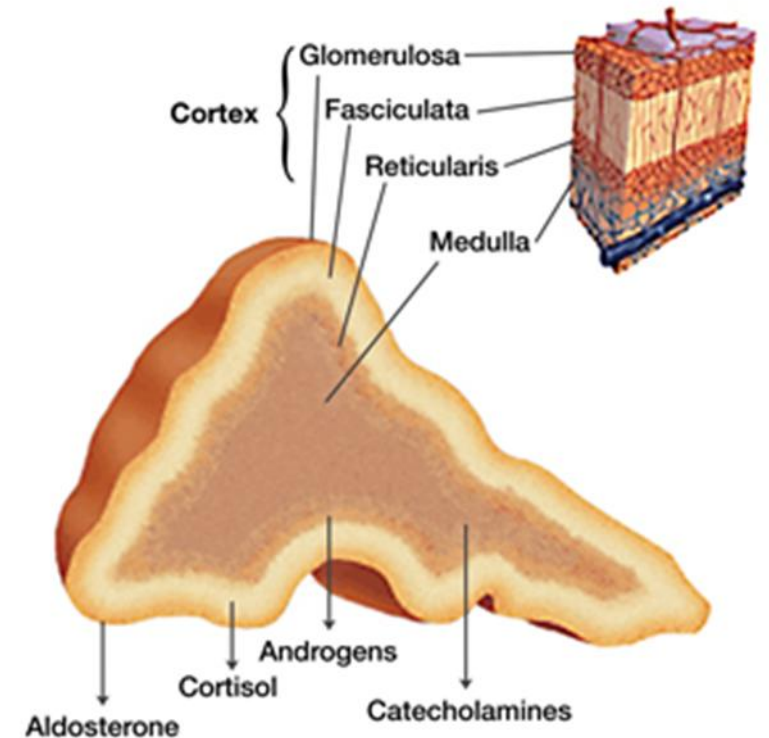
## Adrenal Gland



# a. Adrenal Structure and Function

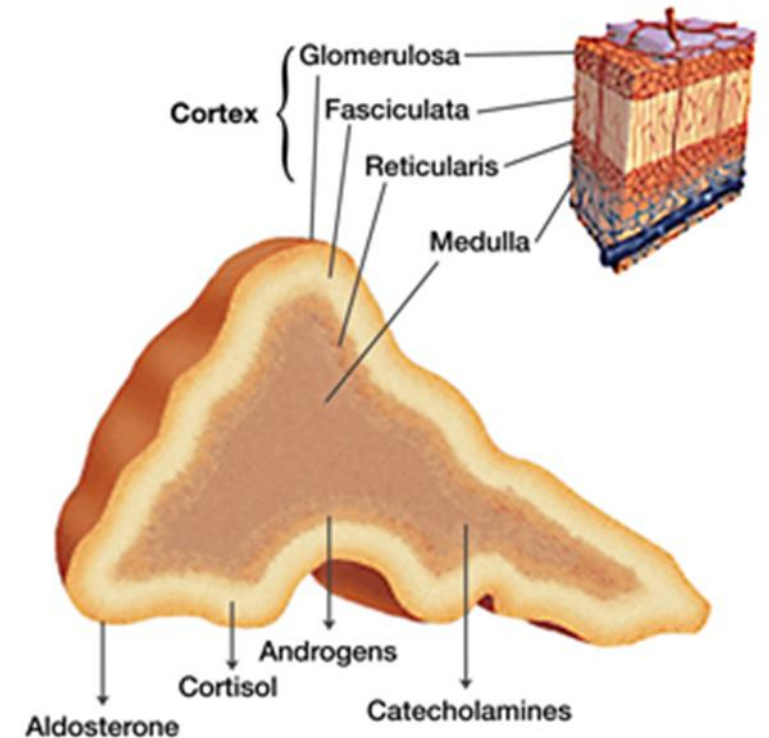
The Cortex accounts for approximately 80% of the adrenal glands and can be divided from the outside in.

- ❑ Globular Zone – Secretes salt corticosteroids, mainly aldosterone, which promote sodium and potassium retention by the renal tubules, reabsorb water and maintain water and electrolyte balance in the body in coordination with antidiuretic hormone
- ❑ The Fasciculus – Secretes glucocorticoids. Glucocorticoids regulate the biosynthesis and metabolism of sugar, fat and protein. They also have immune response suppression, anti-inflammatory, anti-shock and anti-toxin effects
- ❑ Reticular Zone – Secretes mainly sex hormones such as dehydroandrosterone and estradiol but also secretes small amounts of glucocorticoids. The main physiological effects of adrenal androgens do not occur until they are converted into testosterone and dihydrotestosterone. For females, this is an important source of androgens



# a. Adrenal Structure and Function

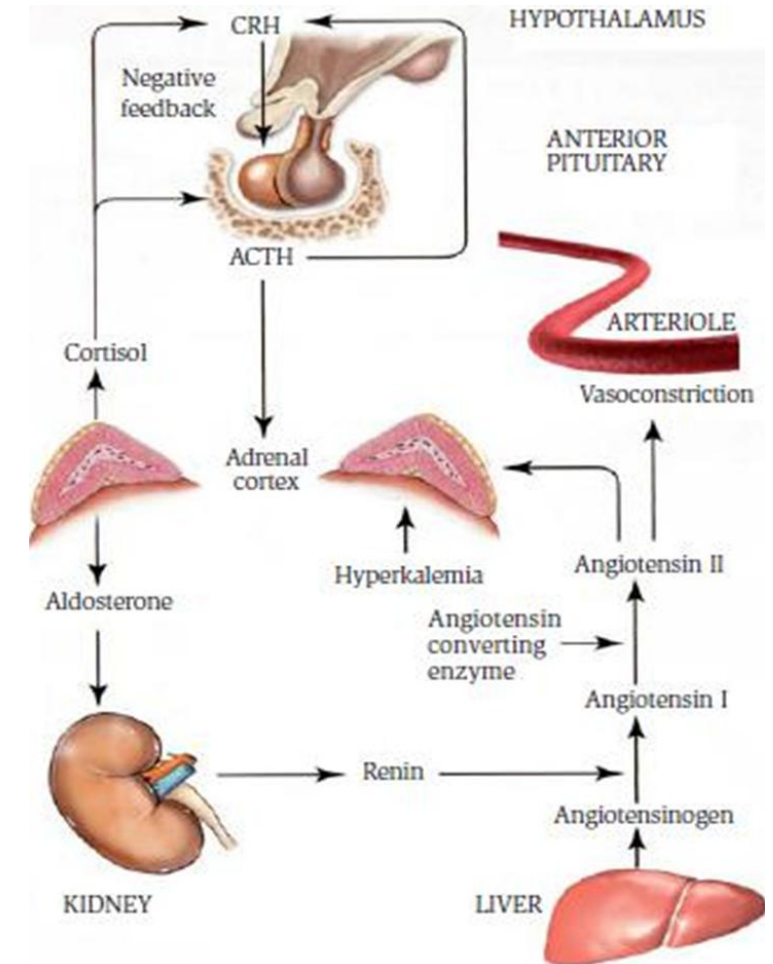
- ❑ Medulla – Located in the centre of the adrenal glands, it synthesises and secretes catecholamines (mainly epinephrine and a small amount of norepinephrine). The main action of epinephrine is on the heart muscle, causing the heartbeat to speed up and strengthen. The main effect of norepinephrine is to cause contraction of the smooth muscle of the peripheral arteries which increases blood pressure. The increased release of these hormones in a stressful state can help to raise blood pressure, speed up the heart rate, raise blood sugar, mobilise the reserves of the whole body and prepare the organism to fight against the external environment



## b. Adrenal Modulation

All the activity of the adrenal glands is finely regulated by both the pituitary gland and the nociceptors.

- ☐ The secretion of aldosterone is regulated by renin in the kidneys
- ☐ The secretion of cortisol and androgens is regulated by the pituitary ACTH
- ☐ Adrenaline and norepinephrine are regulated by the sympathetic nervous system



## b. Adrenal Modulation

- ❑ Adrenaline secretion is not directly regulated by the pituitary gland, so there is no adrenomedullary hormone
- ❑ The secretory activity of adrenaline is directly distributed by visceral nerves

## b. Adrenal Modulation

Adrenocorticotrophic hormone (ACTH) secretion is directly regulated by the pituitary gland, with graded regulation of both ACTH and adrenocorticotropin-releasing hormone.

- ☐ Hypothalamus-pituitary-adrenal
- ☐ CRH – Adrenocorticotropin-releasing hormone
- ☐ ACTH – Adrenocorticotrophic hormone

## c. Hyperadrenocorticism

### Epidemiological Characteristics:

- ❑ Hyperadrenocorticism often occurs in middle-aged and older dogs, from 2-16 years of age, with the highest incidence in dogs 6 and 7 years of age, with no significant sex or breed differences.
- ❑ Dutch curly-tailed lion-haired dogs, Pomeranians, Samoyeds, pine lions, and toy poodles have a genetic predisposition to Cushing's syndrome
- ❑ Excessive glucocorticoids, overproduction of adrenocorticotrophic hormones from pituitary microadenomas or adrenocortical tumours and overdose of corticosteroids can lead to medically induced Cushing's syndrome (HAC)



**Abdominal hair removal, puffing**

## c. Hyperadrenocorticism

| Types of Cushing's Syndrome | Pituitary-Dependent | Adrenal Tumours  |
|-----------------------------|---------------------|------------------|
| Species                     | Australian Shepherd | Alaskan Sled Dog |
|                             | Beagle              | Cocker Spaniel   |
|                             | Dachshund           | Dachshund        |
|                             | German Shepherd     | German Shepherd  |
|                             | Labradoodle         | Labradoodle      |
|                             | Poodle              | Terrier          |
|                             | Terrier             | Toy Poodle       |

## c. Hyperadrenocorticism

### Clinical Symptoms:

- ☐ The typical clinical signs of elevated cortisol are present
- ☐ The skin is atrophic and thin with a slim, sandpaper-like appearance, easily damaged and not easily healed, with extensive melanin deposition in the dermis, epidermis or stratum corneum. The abdomen is characterised by numerous acne and increased scaling
- ☐ Skin stones are formed on the spine, abdomen or groin with superficial ulcers with intra-skin spots or bleeding
- ☐ Extensive trunk hair loss



## c. Hyperadrenocorticism

### Clinical Symptoms:

- ☐ Polyuria, secondary to polydipsia
- ☐ Increased appetite
- ☐ Enlarged liver, weakness of the abdominal muscles, enlarged and sagging abdomen
- ☐ Muscle atrophy and tremor. Spinal curvature, tendency to develop decubitus ulcers on the fly joint and elbow head
- ☐ Loss of vision and blind movement



# c. Hyperadrenocorticism

## Cushing



## Sertoli Cell Tumour



## c. Hyperadrenocorticism

### Clinical Symptoms:

- ☐ Shortness of breath (inorganic material deposited in the lungs)
- ☐ Urinary tract infections
- ☐ Decreased fertility
- ☐ Osteoporosis prone to fracture
- ☐ Symptoms of Aldosteronism – Disturbance of water and salt metabolism, sodium and water retention, increased excretion of potassium and chloride, later manifestation of hypokalemia and hypochloremic alkalosis, such as muscle weakness, irritability, excessive drinking, polyuria, convulsions, and persistent hypertension
- ☐ Adrenal Sex Hormone Hypersecretion Disorder – Female dogs are androgynous or pseudonegative dogs



## c. Hyperadrenocorticism

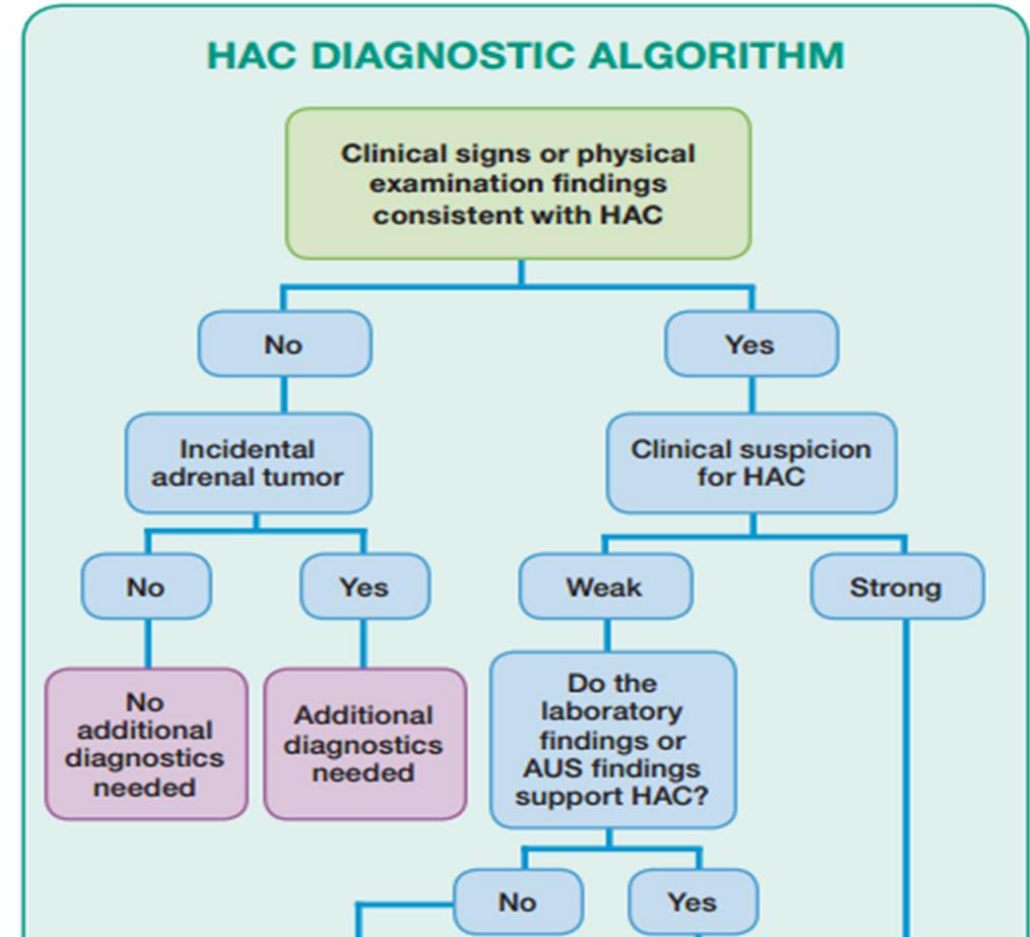
### Laboratory Tests

- ☐ CBC – Leukocyte picture on steroids, slight increase in red blood cells
- ☐ Biochemistry – Elevated ALKP, ALT, CHOL, GLU
- ☐ Urinalysis – Presence of protein, blood, bacteria, leukocytes, decreased urine specific gravity (<1.020)
- ☐ ACTH Stimulation Test – Can determine the type of diagnosis, >20 µg/dL in case of endogenous HAC
- ☐ Low-Dose Dexamethasone Suppression Test – Determines the diagnosis, >1 µg/dL in 8h hour test
- ☐ High-Dose Dexamethasone Suppression Test – To determine the type of diagnosis, <1.4 µg/dL for pituitary-dependent and >1.4 µg/dL for adrenocortical tumours
- ☐ Endogenous Plasma Adrenocorticotrophic Hormone Concentration – >40 pg/mL for pituitary-dependent HAC and <20 pg/mL for adrenocortical tumours

# c. Hyperadrenocorticism

## Diagnostic Process

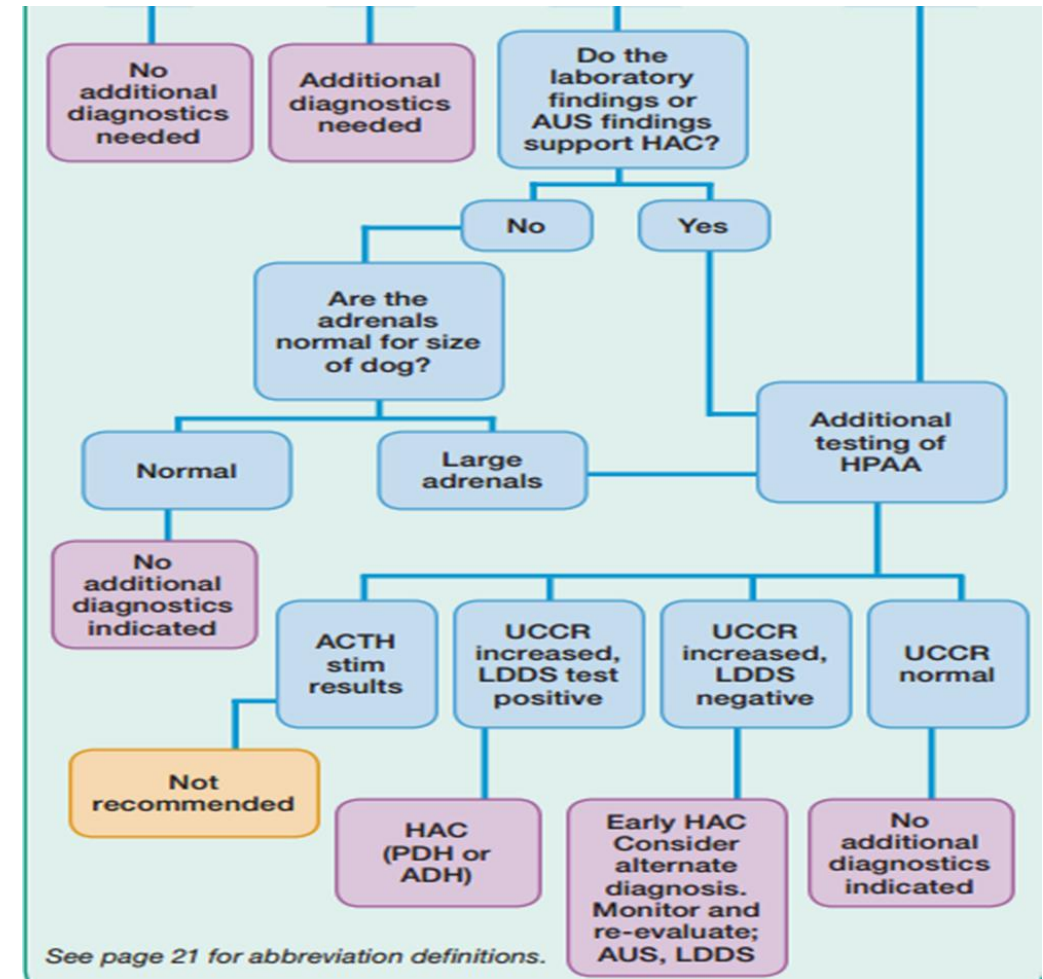
- ☐ ACTH – Adrenocorticotrophic hormone
- ☐ ALP – Alkaline phosphatase
- ☐ ATH – Adrenocortical tumour hyperadrenocorticism
- ☐ AUS – Abdominal ultrasound
- ☐ HAC – Hyperadrenocorticism
- ☐ HDDS – High-dose dexamethasone suppression
- ☐ HPAA – Hypothalamic-pituitary-adrenocorticol axis
- ☐ LDDS – Low-dose dexamethasone suppression
- ☐ PDH – Pituitary-dependent hyperadrenocorticism
- ☐ UCCR – Urine cortisol : creatinine ratio



# c. Hyperadrenocorticism

## Diagnostic Process

- ☐ ACTH – Adrenocorticotrophic hormone
- ☐ ALP – Alkaline phosphatase
- ☐ ATH – Adrenocortical tumour hyperadrenocorticism
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## c. Hyperadrenocorticism

### Treatment:

- ☐ Drugs – Trilostane, Metiradione
- ☐ Symptomatic Treatment – Ketoconazole
- ☐ Radiation Therapy – Pituitary tumour
- ☐ Surgical Procedure – Adrenal tumour removal

## d. Hypoadrenocorticism

Hyperalgesia refers to primary or secondary adrenocortical insufficiency, a condition also known as Addison's syndrome.

### Epidemiological Characteristics:

- ❑ It generally occurs in young and middle-aged female dogs at an average age of 4 years
- ❑ Standard Poodles, West Highland White Terriers, Great Danes, Old Shepherds, Portuguese Waterfowl Hunters, Nova Scotia Duck Retrievers and Irish Soft Coated Terriers are the breeds most commonly affected



## d. Hypoadrenocorticism

### Causes of Disease:

- ☐ The cause of primary adrenocortical insufficiency is usually idiopathic, as the cause of the disease is not obvious and may be due to immune-mediated destruction of the adrenal cortex or to infection, haemorrhagic infarction, tumour metastasis, trauma and amyloidosis
- ☐ Secondary adrenocortical insufficiency is most often caused by destructive damage to the pituitary gland or hypothalamus, chronic use of exogenous glucocorticoids or megestrol acetate



## d. Hypoadrenocorticism

### Clinical Symptoms:

- ☐ Symptoms usually appear suddenly or intermittently and vary in severity
- ☐ Intermittent loss of appetite, diarrhoea, black stool syndrome, vomiting, weight loss
- ☐ Weakness, depression, muscle weakness, tremors, drowsiness
- ☐ Arrhythmia, dehydration, bradycardia with progressive development, shock, weak pulse



## d. Hypoadrenocorticism

### Laboratory Tests:

- ☐ CBC – Non-regenerative anaemia
- ☐ Biochemistry – AST, ALT, Ca, K, CREA, BUN elevated. P, Na, Cl, CHOL, GLU decreased
- ☐ Sodium to potassium ratio <27:1
- ☐ Urinalysis – Presence of ketones, urine glucose, decreased urine specific gravity (<1.030)
- ☐ ACTH Stimulation Test – <1 µg/dL in primary hypoadrenocorticism
- ☐ Plasma Adrenocorticotrophic Hormone Concentration – >500 pg/mL in primary, <20 pg/mL in secondary
- ☐ Decreased plasma aldosterone



Electrolyte levels are important, but not a definitive test for Addison's.

Primary Addison's involves changes in electrolytes while Atypical and Secondary do not.

An ACTH stim test is the only definitive test for diagnosing Addison's.

# d. Hypoadrenocorticism

## Diagnosis

Detection of basal serum cortisol values below the normal range was evaluated in combination with cortisol assay values after ACTH stimulation to confirm the diagnosis of Addison's disease.

## Treatment:

- ☐ Supportive therapy
- ☐ Medications
- ☐ Corticosteroids – Prednisolone sodium succinate, dexamethasone
- ☐ Salt Corticosteroids – Hydrocortisone hemisuccinate, fludrocortisone, etc.
- ☐ Monitoring of electrolytes, urea nitrogen, creatinine

## e. Adrenocortical Function Tests

### ACTH Stimulation Test

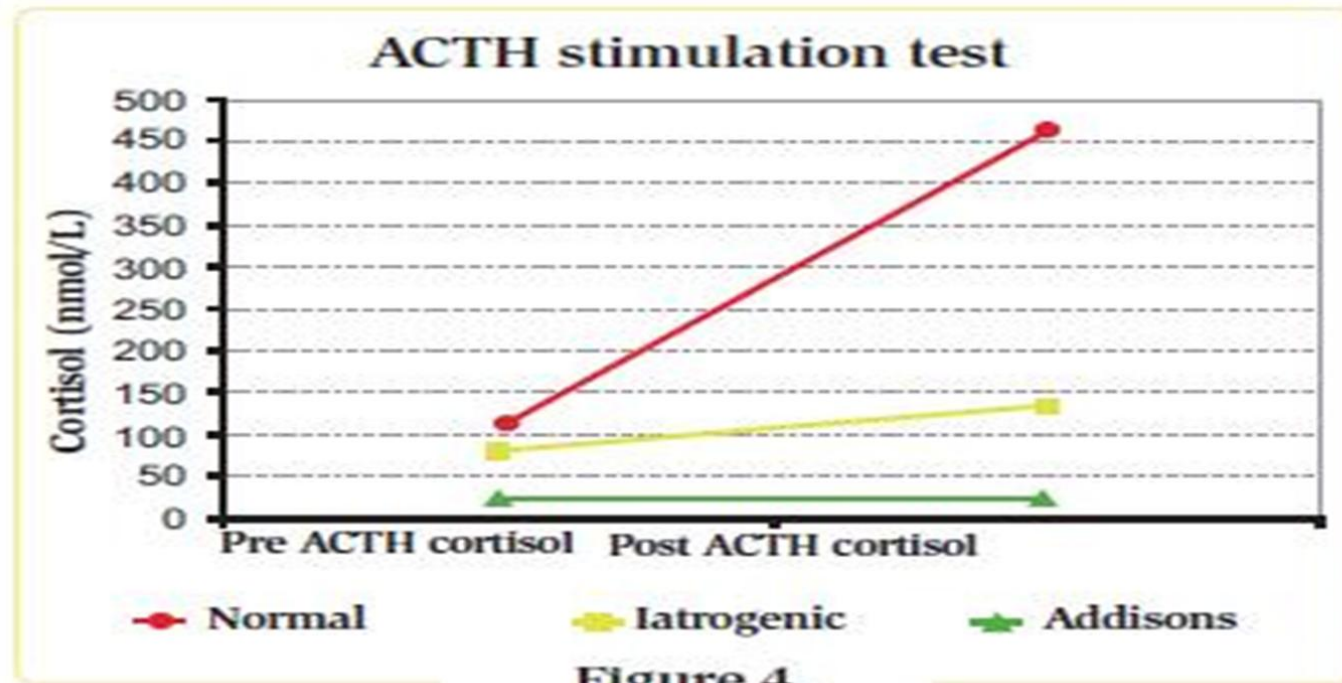


Figure 4.

ACTH stimulation test. Lines depict a normal response, a response consistent with Addison's disease, and a response that is most consistent with exposure to exogenous corticosteroids.

# e. Adrenocortical Function Tests

## ACTH Stimulation Test

Intramuscular injection of ACTH 2.2 IU/kg up to 40 IU and cortisol is measured 2 hours later.

| Pre-Stimulation Cortisol Value | Cortisol Values After Stimulation | Diagnostic Significance     |
|--------------------------------|-----------------------------------|-----------------------------|
| <55nmol/L                      | <55 nmol/L                        | Addison's Disease           |
|                                | 55-166 nmol/L                     | Inconclusive                |
| 55-166 nmol/L                  | 55-166 nmol/L                     | Inconclusive                |
|                                | 166-500 nmol/L                    | Normal                      |
|                                | 550-663 nmol/L                    | Possible Cushing's Syndrome |
|                                | >663 nmol/L                       | Cushing's Syndrome          |

# e. Adrenocortical Function Tests

## Low-Dose Dexamethasone Suppression Test

Intravenous 0.01 mg/kg is administered and cortisol values are measured at 4 hours and 8 hours later.

|       | Cortisol Base Value | Cortisol Value After 4 Hours      | Cortisol Value After 8 Hours         |                       |
|-------|---------------------|-----------------------------------|--------------------------------------|-----------------------|
| LDDST | Normal              | <39 nmol/L<br>(1.4 ug/dL)         | <39 nmol/L<br>(1.4 ug/dL)            | Normal                |
|       | Normal or increased | >39 nmol/L<br>and >50% base value | >39 nmol/L and<br>>50% base value    | Cushing's<br>syndrome |
|       | Normal or increased | <39 nmol/L or <50%<br>base value  | >39 nmol/L<br>and >50% base<br>value | PDH                   |
|       | Normal or increased | >39 nmol/L or >50%<br>base value  | >39 nmol/L<br>and <50% base<br>value | PDH                   |
|       | Normal or increased | <39 nmol/L or <50%<br>base value  | >39 nmol/L<br>and <50% base<br>value | PDH                   |

# e. Adrenocortical Function Tests

## Low-Dose Dexamethasone Suppression Test

### Caution:

- ☐ LDDST does not differentially diagnose medical-derived and primary Cushing's syndrome
- ☐ LDDST at 8 hours does not differentiate pituitary-dependent Cushing's (PDH) from adrenal tumour Cushing's
- ☐ Stress caused by the animal's restricted activity, fluctuations in its own cortisol levels and non-adrenal disease may also affect the outcome. Cortisol levels in these animals may be suppressed leading to erroneous results
- ☐ LDDST cannot be used for response monitoring in case therapy
- ☐ Response monitoring during treatment is generally done with ACTH stimulation assays

# e. Adrenocortical Function Tests

## High-Dose Dexamethasone Suppression Test

Intravenous 0.1 mg/kg dexamethasone is administered and cortisol values are measured at 4 hours and 8 hours.

|       | Cortisol Base Value | Cortisol Value After 4 Hours   | Cortisol Value After 8 Hours   |                                                                        |
|-------|---------------------|--------------------------------|--------------------------------|------------------------------------------------------------------------|
| HDDST | Normal or increased | <39 nmol/L or <50% base value  | >39 nmol/L and >50% base value | PDH                                                                    |
|       | Normal or increased | >39 nmol/L and >50% base value | <39 nmol/L or <50% base value  | PDH                                                                    |
|       | Normal or increased | <39 nmol/L or <50% base value  | <39 nmol/L or <50% base value  | PDH                                                                    |
|       | Normal or increased | >39 nmol/L and >50% base value | >39 nmol/L and >50% base value | More tests are needed to distinguish PDH and adrenal dependent disease |

## e. Adrenocortical Function Tests

TABLE 3. Diagnostic Tests That Differentiate PDH & ATH

| DIAGNOSTIC TEST           | RESULTS INDICATING PDH                                                                       | RESULTS INDICATING ATH                                                                          |
|---------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>LDDS Test</b>          | 4-hour cortisol < 1 mcg/dL (varies with laboratory) or < 50% of basal cortisol concentration | Test does not identify ATH*                                                                     |
| <b>HDDS Test</b>          | 4-hour cortisol < 1 mcg/dL (varies with laboratory) or < 50% of basal cortisol concentration | Test does not identify ATH*                                                                     |
| <b>ACTH Concentration</b> | Upper 50% or greater than reference range                                                    | Below reference range                                                                           |
| <b>Ultrasound</b>         | Bilateral adrenomegaly or normal adrenal size                                                | Asymmetric adrenal glands (characterized by adrenal mass and small contralateral adrenal gland) |

\* Lack of suppression does not confirm ATH because approximately 25% of dogs with PDH fail to exhibit suppression upon LDDS or HDDS testing.

# **InSight<sup>®</sup> Canine-IA**

## **Cortisol**

## **Rapid Quantitative Test**

Woodley have developed a rapid, accurate and reliable, highly sensitive detection method for Cortisol in dogs.

The InSight Canine-IA Cortisol Rapid Quantitative Test is a fluorescence immunoassay used with the InSight Canine-IA Veterinary Immunoassay Analyser for quantitative determination of canine or Cortisol concentration in canine serum or plasma.

Cortisol is a hormone that regulates metabolism and is used to help diagnose adrenal disorders.

It can be stored at room temperature.



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# Thank You