

Hyperadrenocorticism

References:

Feldman and Nelson, Chapter 6, "Canine Hyperadrenocorticism," in Feldman and Nelson *Canine and Feline Endocrinology and Reproduction, 3rd Edition*.

I. Etiopathogenesis:

A. History.

1. In 1932, Dr. Harvey Cushing describe 8 people with a disorder that he suggested was a result of "pituitary basophilism."
2. 6 of the 8 had basophilic pituitary adenomas.
3. The 6 had clinical features of excess cortisol.

B. Anatomy and physiology.

1. Pituitary anatomy – dogs have 3 parts:

- a. Pars distalis.
 - 1) Anterior section.
 - 2) Produces POMC (ACTH prohormone).
 - 3) Glucocorticoid negative feedback is here.
 - 4) No nerve supply – stimulated by CRH in portal circulation.
- b. Pars intermedia.
 - 1) Middle section.
 - 2) Two cell types:
 - i. A cells – stain for alpha-MSH.
 - ii. B cells – stain for ACTH.
 - 3) Negative feedback dopamine and serotonin.
 - 4) Stimulated by dopaminergic and serotonergic fibers from the brain rather than CRH form portal circulation.
- c. Pars nervosa.
 - 1) Posterior section.
 - 2) Stains for ACTH.

2. Corticotropin Releasing Hormone (CRH).

- a. Properties:
 - 1) A polypeptide of 41 amino acids.
- b. Production:
 - 1) Made and released by the hypothalamus.
 - 2) Secreted by neurons in the anterior paraventricular nuclei.
 - 3) Secreted in a pulsatile manner.
 - 4) Peaks first thing in the morning, but this has not been documented in dogs.
- c. Metabolism:
 - 1) Carried by the portal circulation system to the pituitary.
 - 2) Relatively long half life of 1 hour.
- d. Activity – stimulates the pituitary to release POMC.
- e. Regulation:
 - 1) Things that increase CRH secretion:
 - i. Arginine vasopressin.
 - ii. Angiotensin II.
 - 2) Things that inhibit CRH secretion.

- i. Oxytocin.
 - 3) Negative feedback:
 - ii. Cortisol.
 - i. Fast feedback by rate of change.
 - ii. Slow feedback by absolute level.
 - iii. Glucocorticoid drugs.
 - iv. ACTH.
3. Adrenocorticotropic Hormone (ACTH).
 - a. Properties:
 - 1) 39 amino acid peptide.
 - b. Production:
 - 1) Corticotroph cells in the pituitary make ACTH.
 - 2) Corticotrophs stain basophilic due to carbohydrate content.
 - 3) Secreted in a pulsatile manner.
 - 4) Peaks first thing in the morning, but this has not been documented in dogs.
 - c. Metabolism - fragments from precursor pro-opiomelanocortin (POMC), once broken down.
 - 1) Beta-lipotrophin (beta-LPH) – broken down to:
 - i. Gamma -LPH.
 - ii. Beta-endorphin.
 - iii. Beta-MSH.
 - iv. Met-Enk.
 - 2) ACTH – broken down to:
 - i. Alpha-melanocyte-stimulating hormone (alpha-MSH).
 - ii. Corticotropin-like intermediate-lobe peptide (CLIP)
 - 3) N-terminal fragment.
 - i. Increases in response to hypoglycemic stress.
 - ii. May be an adrenal growth factor.
 - iii. May potentiate CTH mediated steroidogenesis.
 - d. Action - stimulates adrenal cortex to produce steroids.
 - e. Regulation:
 - 1) Concentrations of all fragments increase in:
 - i. Addison's Disease.
 - ii. PDH.
 - iii. Nelson's syndrome – development of pituitary tumor after removal of adrenal glands.
 - 2) ACTH increases in response to:
 - i. Feeding.
 - ii. Pain.
 - iii. Trauma.
 - iv. Hypoxia.
 - v. Acute hypoglycemia.
 - vi. Cold exposure.
 - vii. Surgery.
 - viii. Pyrogens.
 - 3) Concentrations of all fragments decrease with adrenal tumors.
 - 4) Negative feedback:
 - i. Cortisol.
 - i. Fast feedback by rate of change.
 - ii. Slow feedback by absolute level.
 - ii. Glucocorticoid drugs.
4. Steroids.
 - a. Zona glomerulosa.

- 1) The outer layer of the adrenal cortex.
 - 2) Produces mineralocorticoids.
 - i. 18-OH-corticosterone intermediate product.
 - ii. Dehydrogenated to aldosterone.
 - 3) Deficient in 17-alpha-hydroxylase (CYP17).
 - 4) ACTH has the least effect on this layer.
- b. Zona fasciculata.
- 1) Middle and thickest layer of the adrenal cortex.
 - 2) ACTH converts cholesterol to pregnenolone (rate limiting step).
 - 3) Produces glucocorticoids.
 - i. Cortisol.
 - ii. Corticosterone
 - iii. Deoxycorticosterone.
 - 4) Plasma cortisol increases within minutes of giving ACTH.
- c. Zona reticularis.
- 1) Inner and narrowest layer of the adrenal cortex.
 - 2) ACTH converts cholesterol to pregnenolone (rate limiting step).
 - 3) Produces sex hormones.
 - i. Androgens.
 - ii. Estrogens.
 - iii. Progesterones.
- d. Regulation.
- 1) Negative feedback – angiotensin
 - 2) ACTH deficiency results in adrenocortical atrophy.

C. Etiologies –

1. Four types of Cushing's Disease.
 - a. Pituitary Dependent Hyperadrenocorticism (PDH).
 - 1) Pituitary tumor that makes excess ACTH.
 - 2) 80-85% of dogs with HAC have PDH.
 - 3) 90-100% of dogs with PDH have a pituitary tumor.
 - 4) 75-85% of dogs with pituitary tumor have a pars distalis tumor.
 - 5) 15-25% of dogs with pituitary tumor have pars intermedius tumor (B cells).
 - 6) Dogs with more than one pituitary tumor have been documented.
 - b. Secretion of excess CRH by the hypothalamus, resulting in pituitary and adrenal hyperplasia – never reported in dogs and cats – rare in people.
 - c. Adrenal dependent hyperadrenocorticism (ADH) - Adrenal carcinoma or adenoma procuring excess cortisol.
 - d. Iatrogenic hyperadrenocorticism - Excessive glucocorticoid medication.
2. Other tumors outside the hypothalamus and pituitary that make excess ACTH have been reported in people but not in dogs or cats.

D. Pathogenesis .

1. PDH.
 - a. Functional pituitary tumors begin as small adenomas less 1-10 mm in diameter (microadenomas).
 - b. 50% of dogs with PDH have tumors less than 3 mm in diameter.
 - c. They are either basophilic or chromophobe.
 - d. Can be found anywhere in the anterior pituitary.
 - e. 15-25% become large (>1cm - macroadenomas).
 - f. Macroadenomas can compress or invade adjacent brain as they grow beyond the confines of the sella turcica.
 - g. Malignant tumors have been reported.

- h. Adenomatous hyperplasia occurs in people rarely but has not been defined in dogs.
 - i. Frequency and amplitude of ACTH secretion are excessive.
 - j. Adrenal glands become hyperplastic (ZF and ZR; ZG is normal).
 - k. Bilateral nodular hyperplasia occurs in 5-10% of dogs and cats with PDH
 - l. Negative feedback is relatively ineffective.
 - m. Random assay of cortisol is not effective at identifying PDH because excessive secretion of ACTH is pulsatile.
2. ADH.
- a. Adenomas and carcinomas.
 - b. Secrete excessive cortisol.
 - c. Cortisol secretion is episodic.
 - d. CRH and ACTH are suppressed.
 - e. POMC peptides except alpha-MSH are low due to negative feedback.
 - f. Normal cells in the tumorous adrenal gland as well as the contralateral adrenal gland are atrophied.
 - g. Usually continue to respond to ACTH, but the H-P axis is unresponsive to corticosteroids.
 - h. Bilateral tumors.
 - 1) Can be adenomas or carcinomas.
 - 2) Rare in the dog.
 - 3) Pheochromocytoma (medullary adrenal tumor) on one side and adrenocortical tumor on the other have been documented in several dogs.
 - i. Unilateral tumors.
3. Ectopic ACTH Syndrome.
- a. Documented in people, not dogs or cats.
 - b. Tumors secrete ACTH and cause paraneoplastic adrenal hyperplasia and HAC.
 - c. Tumors:
 - 1) Small cell carcinoma of the lung.
 - 2) Thymoma.
 - 3) Pancreatic islet cell tumor.
 - 4) Carcinoid (lung, gut, pancreas, ovary).
 - 5) Medullary thyroid carcinoma.
 - 6) Pheochromocytoma.
 - 7) Pulmonary tumorlets.
 - 8) CRH-like activity has also been documented in these cases.
4. ACTH independent adrenocortical hyperplasia.
- a. Documented in people, not dogs and cats.
 - b. Clinical features of HAC.
 - c. Subnormal morning plasma cortisol.
 - d. Suppressed ACTH stimulation.
 - e. Food intake stimulated cortisol secretion.
 - f. Lack of adrenocortical sensitivity to gastric inhibitory peptide (GIP).
5. Simultaneous PDH and ADH.
- a. Has been documented in dogs, but is extremely rare.
 - b. Testing to distinguish PDH from ADH can reveal confusing and contradictory results.
 - c. Some of the cases published as PDH and ADH might actually be PDH with adrenal nodular hyperplasia.

6. Pathogenesis of clinical signs.
 - a. PU-PD.
 - 1) Some believe due to cortisol interfering with ADH acting at the collecting tubules (resulting in nephrogenic diabetes insipidus).
 - 2) Some believe cortisol increases GFR.
 - 3) Atrial natriuretic peptide is increased in people, but not dogs.
 - 4) Most but not all dogs with HAC have ADH deficiency (central diabetes insipidus); cortisol may interfere with release of ADH.
 - b. Pot bellied appearance.
 - 1) Increased liver size.
 - 2) Redistribution of fat to the omentum – mechanism unknown.
 - 3) Overdistended urinary bladder.
 - 4) Abdominal muscle weakness and wasting.
 - i. Increased urine volume.
 - ii. Weak detrusor muscle (glucocorticoid) and incomplete voiding.
 - iii. Chronic bladder distension further weakens the detrusor muscle.
 - c. Muscle wasting – protein catabolism due to glucocorticoids.
 - d. Hyperglycemia.
 - 1) 95% mild.
 - i. Cortisol induced gluconeogenesis.
 - ii. Insulin antagonism, resulting in decreased peripheral utilization of glucose.
 - 2) 5% severe – due to diabetes mellitus; uncontrolled HAC impedes insulin regulation.
 - e. Lack of inflammatory disease, due to anti-inflammatory effects of glucocorticoids.
 - 1) No atopy.
 - 2) No arthritis pain (though it may be present).
 - 3) No allergic respiratory disease.
 - 4) No lower urinary tract signs associated with UTI.
 - 5) These signs may return when Cushing's syndrome is successfully treated.
 - f. Immunosuppression due to high cortisol.
 - 1) Chronic pyoderma.
 - 2) Chronic urinary tract infection.
 - 3) Severe periodontal disease.
 - g. Calcinosis cutis.
 - 1) Calcium and phosphorus deposited in matrices of collagen and elastin.
 - 2) Osseous metaplasia of the deep skin layers can rarely occur.
 - h. Skin hyperpigmentation.
 - 1) Present in ADH and PDH, so increased alpha-MSH is not likely to be the sole cause.
 - i. Respiratory syndrome.
 - 1) Panting.

- i. Abdominal distension intrathoracic fat impedes diaphragmatic movement (decreased expiratory reserve volume).
 - ii. Weakness of muscles of respiration.
 - iii. Pulmonary interstitial mineralization.
 - iv. Interstitial lung disease.
 - v. Pulmonary thromboembolism(PTE).
 - 2) Coughing.
 - i. Chronic pulmonary thromboembolism.
 - ii. Collapsing trachea is a common concurrent disease.
 - 3) Cyanosis.
 - i. Alveolar hypoventilation – Pickwickian syndrome.
 - ii. Pulmonary thromboembolism.
 - iii. Pulmonary hypertension.
 - 4) Secondary polycythemia.
- j. Polycythemia.
 - 1) Secondary to hypoxia.
 - 2) Due to elevated androgens in females.
- k. Pseudomyotonia
 - 1) Rare.
 - 2) Non-inflammatory degenerative myopathy.
 - 3) Mechanism unknown.
- l. Hepatomegaly – steroid hepatopathy.
- m. Testicular atrophy.
 - 1) Cortisol inhibits release of FSH and LH by negative feedback.
 - 2) Adrenal androgen secretion is increased and testicular androgen secretion is decreased.
 - 3) Physiologic effect of adrenal androgens is negligible in males.
 - 4) Reduction in testicular androgens is significant.
 - 5) End result is feminization of males.
- n. Anestrus.
 - 1) Cortisol inhibits release of FSH and LH by negative feedback.
 - 2) Adrenal androgen secretion far surpasses normal low level ovarian androgen secretion.
 - 3) End result is virilization of females.
- o. Ectopic soft tissue calcification - skin, tracheal rings, bronchial walls, kidneys, major arteries and veins, cornea.
- p. Excessive bruising – suppressed tissue granulation in response to injury.
- q. Stress Leukogram:
 - 1) Neutrophilia and monocytosis
 - i. Steroid enhanced margination of neutrophils and monocytes.
 - ii. Decrease in normal egress of N and M from circulation.
 - 2) Lymphopenia - steroid lympholysis.
 - 3) Eosinopenia – bone marrow sequestration of E.
- r. Elevated Liver enzymes.
 - 1) ALT up due to hepatocellular damage (mild hepatic necrosis):

- i. Hepatocellular swelling.
 - ii. Glycogen accumulation.
 - iii. Interference with hepatic blood flow.
 - 2) Elevated SAP – usually much higher than ALT.
 - i. Glycogen deposition and vacuolization impinging in the bile canaliculi.
 - ii. Induction of SAP by liver, intestine and kidney, by cortisol – 70-100% of SAP in dogs with HAC.
 - iii. Steroid induced SAP is a specific isoenzyme.
- s. Hyperlipidemia – steroid induced lipolysis.
- t. Urinary tract infection.
 - 1) Immunosuppression due to glucocorticoids.
 - 2) Chronic bladder overdistension and incomplete voiding.
 - i. Bladder wall weakness.
 - ii. Detrusor muscle weakness.
 - iii. Large volume of urine retained as long as possible by indoor dogs
 - iv. Dilute urine increases susceptibility to lower UTI.
- u. Secondary hypothyroidism.
 - 1) Cortisol suppresses TSH secretion.
 - 2) Cortisol may also alter thyroid hormone binding to plasma proteins, to enhance clearance of thyroid hormones.
 - 3) Cortisol may decrease peripheral deiodination of T4 to T3.
- v. Osteopenia.
 - 1) Hypercalciuria.
 - 2) Suppressed intestinal absorption of calcium.
 - 3) Direct effects of cortisol on bone.
 - 4) Usually mild and of no clinical significance.

II. Epidemiology/Signalment

A. Breed.

- 1. PDH.
 - i. Poodles – 16%.
 - ii. Dachshunds – 11%.
 - iii. Terriers – 10%.
 - iv. Beagles, German shepherds, Labrador retrievers, Australian shepherds – each 5-10%.
 - v. Boston and Boxer at increased risk.
 - vi. Small breeds – 75% weigh less than 20 kg.
- 2. ADH.
 - i. No body size predisposition.
 - ii. Poodles – 15%.
 - iii. German shepherds – 12%.
 - iv. Dachshunds – 11%.
 - v. Labrador retrievers, terriers, cocker spaniels each 5-10%.

B. Age.

- 1. Middle aged to older.
- 2. Most older than 6 years.
- 3. 75% of dogs with PDH are older than 9 years.
- 4. 90% of dogs with ADH are older than 9 years.

5. Median age is 11.4 years for PDH and 11.6 years for ADH.
6. Feldman and Nelson have seen only 5 dogs less than 2 years of age.
 - i. HAC had never been reported in a dog less than 6 months of age.
 - ii. Young dogs exhibit obesity and lack of growth.

C. Sex.

1. 60% of dogs with PDH are female.
2. 60-65% of dogs with ADH are female.

III. History.

A. Onset is gradual and progressive (months to years).

B. Dogs are rarely significantly systemically ill.

C. Rarely have:

1. Poor appetite, vomiting, diarrhea.
2. Lameness due to inflammation.
3. Weight loss.
4. Sneezing and rhinitis.

D. Most common clinical signs:

1. PU-PD – 80-85%.
 - i. Most common chief complaint.
 - ii. A normal water intake is less than 40-60 ml/kg/day.
 - iii. PU-PD is greater than 100 ml/kg/day.
2. Polyphagia – 90%.
 - i. Unique to dogs – cats and people with HAC don't get it.
 - ii. Stealing food.
 - iii. Eating garbage.
 - iv. Begging continuously.
 - v. Food aggression.
3. Abdominal distension – 80%.
4. Chronic skin disease – 80-100%.
 - i. Endocrine alopecia -- head is spare – 80%.
 - ii. Pruritus – 25% - seborrhea (33%), calcinosis cutis, Demodex, pyoderma, NOT atopy.
5. Panting, heat intolerance, difficulty breathing, cyanosis.
6. Muscle weakness and wasting.
 - i. Exercise intolerance.
 - ii. Inability to jump or climb stairs.
 - iii. Can usually still jump down and go down stairs.
 - iv. Can not finish long walks due to fatigue.
 - v. Alert but not active.
7. Lethargy.
8. Apparent weight gain.
 - i. Obesity is common.
 - ii. Actual weight gain is often not that dramatic.
 - iii. Owners attribute change in body shape to weight gain.
9. Anestrus, infertility.

E. Signs of a macroadenoma affecting the hypothalamus.

1. These dogs have decreased appetite, may be adipsic.
2. Decreased mentation, stupor.
3. Cortical blindness.

F. Rare historical findings:

1. Muscle stiffness due to pseudomyotonia.
2. Droopy face due to facial paralysis (unilateral or bilateral).
3. Sudden blindness – SARDs (Sudden Acquired Retinal Degeneration).

- i. SARDs is associated with clinical signs of HAC, especially in Schnauzers.
- ii. Adrenal function tests can be diagnostic of HAC.
- iii. In most cases, HAC-like disease resolves with time and does not require therapy.

IV. Physical Exam.

- A. Panting, dyspnea, brick red mucous membranes, cyanosis .
- B. Truncal obesity.
- C. Skin lesions.
 - 1. Skin is thin (may see blood vessels), easily wrinkled, fragile, and heals poorly. Cats can have severe skin fragility.
 - 2. Endocrine alopecia.
 - a. Head and distal extremities are spared.
 - b. Hyperpigmentation.
 - c. Much more common in dogs than in cats.
 - d. DDX:
 - 1) Hypothyroidism.
 - 2) Sertoli cell tumor.
 - 3) Granulosa cell tumor.
 - 4) Growth hormone deficiency.
 - 5) Diabetes mellitus.
 - 3. Pyoderma
 - a. 55% of dogs.
 - b. Also cats.
 - 4. Comedones (5%) – keratin plugged follicles.
 - 5. Calcinosis cutis.
 - a. Firm, irregular plaques in or under the skin.
 - b. Most often on the dorsal and ventral midlines.
 - 6. Ulcers on the hocks, elbows and sternum, due to skin fragility and unwillingness to rise.
 - 7. Hair does not regrow after clipping.
 - 8. Adult onset Demodex – dogs.
 - 9. Pododermatitis – Demodex.
 - 10. Excessive bruising.
 - a. After venipuncture.
 - b. Metal sutures placed in the abdominal wall cause bruising many years later, after development of HAC. Loss of SQ fat that used to pad the sutures.
 - 11. Up to 20% may not have skin lesions.
- D. Abdominal distension.
 - 1. Hepatomegaly. – 100%, unless there is concurrent fibrosing liver disease.
 - 2. Urinary bladder distension.
 - 3. Increased fat.
 - 4. No ascites.
- E. Muscle wasting.
- F. Lameness due to:
 - 1. Joint laxity.
 - 2. Ruptured anterior cruciate ligament.
 - 3. Medially luxating patella.
 - 4. Rarely gastrocnemius tendon rupture.
 - 5. Rare – muscle stiffness due to pseudomyotonia;
 - a. Persistent, active muscle contraction after cessation of voluntary effort.
 - b. Worse in the pelvic limbs.
- G. Atrophied testicles, clitoral hypertrophy.
- H. Blood pressure may be elevated.

- I. Neurologic abnormalities.
 - 1. Rarely facial paralysis, unilateral or bilateral.
 - 2. Rarely acute blindness if concurrent SARDs.
- J. Rare Clinical signs:
 - 1. Acute hemoabdomen or hemoretroperitoneum, due to rupture of adrenal tumor.
 - 2. Ascites due to pressure on the portal vein by adrenal tumor and portal hypertension.
 - 3. Acute dyspnea due to PTE.

V. Diagnosis .

First Round of tests:

- CBC
- General Health Profile
- Electrolytes and venous blood gases
- Urinalysis
- Urine culture

Second Round of tests:

- May do urine creatinine:cortisol to screen. If positive, continue.
- Thoracic radiographs
- Abdominal ultrasound/radiographs

Third Round of tests:

- ACTH stimulation test or Low Dose Dexamethasone test.

If further testing is needed to distinguish PDH from ADH:

- High Dose Dexamethasone Test
- Endogenous ACTH

A. CBC.

- 1. Polycythemia – primary and/or secondary.
- 2. Usually see “stress leukogram.”
 - a. Mild mature neutrophilia – 20-25%
 - b. Monocytes normal to high.
 - c. Lymphopenia – 80%.
 - d. Eosinopenia (does it really exist) ????
- 3. Thrombocytosis. – unsure why.

B. Serology:

- 1. BUN.
 - a. Usually low, due to PU-PD.
 - b. High if UTI with pyelonephritis.
 - c. Many recommend against treating HAC in dogs with concurrent renal disease, unless there is a critical reason to do so.
 - 1) Removing PU-PD can make the CRF worse.
 - 2) Reducing desire to eat can cause anorexia.
 - 3) Increased cortisol can enhance general well being, in spite of significant illness.
- 2. Liver enzymes.
 - a. ALT usually elevated, but less than 500 U/L.
 - b. SAP elevated - 90-95%.
 - 1) Higher than ALT (often greater than 1000 U/L).

- 2) Mostly the steroid induced isoenzyme (SIAP) rather than the liver SAP.
 - 3) Assay for SIAP is highly sensitive for HAC, but not very specific.
 - 4) SIAP can also be elevated in:
 - i. Primary hepatopathy.
 - ii. Other endocrine disease, such as diabetes mellitus and hypothyroidism
 - iii. Barbiturate anticonvulsant therapy.
3. Glucose.
 - a. Normal to mildly elevated – 95%
 - b. Drastically elevated – 5% of dogs with HAC have diabetes mellitus, and are often unregulated until HAC is controlled.
 4. Albumin – usually normal despite common mild proteinuria.
 5. Lipids.
 - a. Elevated cholesterol – 90%.
 - b. Elevated triglycerides – 90%. Causes other tests to be falsely high:
 - 1) Red Cell counts and indices.
 - 2) Hb.
 - 3) TP.
 - 4) Albumin.
 - 5) Bilirubin.
 - 6) SAP.
 - 7) Calcium.
 - 8) Phosphorus.
 - 9) Amylase.
 - 10) Lipase.
 - 11) Sodium.
 6. Bile Acids – mildly increased in 30% of dogs with HAC.
 7. Electrolytes - usually normal, or mildly hypokalemic due to PU-PD.
 8. Arterial blood gases – 33% are hypoxic.

C. Urinalysis .

1. Dilute urine - isosthenuria or hyposthenuria.
 - a. Most common abnormality on UA in dogs with HAC.
 - b. 85% have USG <1.020.
 - c. USG <1.015 is common.
 - d. If water deprived, can concentrate to 1.025-1.035.
2. Glucosuria – if significant hyperglycemia.
3. Proteinuria.
 - a. UPC (urine protein:creatinine ratio) >1 in 50% of dogs who have untreated PDH but no UTI.
 - b. >1 in 31% of dogs with poorly controlled PDH, but not UTI.
 - c. >1 in 60-65% of dogs with untreated ADH, but no UTI
 - d. >1 in 20% of dogs with well controlled PDH.
 - e. >1 in 33% of dogs with ADH treated with surgery successfully (post-op).
 - f. Mean UPC 2.3 in dogs with untreated HAC.
 - g. If UPC greater than 2.5-3, the dog should be worked up for concurrent protein losing nephropathy.
4. Bacteria present in the urine sediment in a majority of dogs with HAC who also have UTI.

- D. Urine culture – should be performed on all Cushingoid animals .
1. Even if urine sediment is non-inflammatory.
 - a. UTI can be difficult to detect in dilute urine.
 - b. Excess cortisol suppresses inflammatory response in the urine sediment.
 2. Immunosuppression leads to susceptibility to UTI.
 3. Urine must be collected by cystocentesis.
 4. 40-50% of dogs with HAC have UTI at the time of diagnosis, though lower urinary tract signs (stranguria, pollakuria) are extremely rare, presumably due to the anti-inflammatory effects of cortisol..
- E. Adrenal function tests.
1. Urine creatinine:cortisol ratio.
 - a. Good screening test – few false negatives, but many false positives.
 - b. If normal, the dog does not have HAC.
 - c. If elevated, the dog has HAC or some kind of significant stress.
 - d. Urine sample best collected by the owner at home, to eliminate false positives from stress of coming to the clinic..
 2. Resting cortisol.
 - a. Not effective at detecting PDH because excessive release of ACTH is pulsatile.
 - b. Most Cushingoid dogs have normal baseline cortisol much of the time.
 3. Endogenous ACTH.
 - a. Increased with PDH.
 - b. Decreased (undetectable) with ADH.
 4. Low Dose Dexamethasone Test
 5. High Dose Dexamethasone test.
 - a. Can distinguish between adrenal nodular hyperplasia and bilateral adrenal tumors, which can look similar on ultrasound.
 6. No known antemortem test to distinguish pars intermedia PDH from pars distalis PDH.
 7. No known tests other than histopath to distinguish adrenal adenoma from carcinoma.
- F. Other hormone assays.
1. LH and FSH – low.
 2. Testosterone – lower than normal in males, higher than normal in females.
 3. Prolactin – high.
 4. Insulin – mildly high, in response to hyperglycemia; but the increase is so small and inconsistent that the test is not diagnostically useful.
 5. Thyroid tests – HAC induces secondary hypothyroidism..
 - a. TSH stimulation – suppressed.
 - b. TSH – low.
 - c. T3, T4 and free T4 low – 70% of dogs with untreated HAC.
- G. Abdominal radiographs.
1. Hepatomegaly – 80-90%.
 2. Good contrast due to abdominal fat deposition
 3. Distended urinary bladder.
 4. Mineralized adrenal mass – 5-10%.
 - a. Only 10-20% of dogs with HAC have an adrenal mass.

- b. Only 50% of adrenal tumors are mineralized, allowing them to be seen on radiographs.
 - c. Uncalcified tumors less than 2 cm in diameter are not likely to be seen on radiographs.
5. Osteopenia might be apparent.
 - a. Rarely appreciated in dogs with HAC.
 - b. One-third of bone must be lost prior to showing on rads – most HAC dogs are not this severe.
 - c. Obesity can give a false impression of osteopenia.
 - d. Epiphyseal fractures can occur in rare cases of HAC in growing puppies.
 6. Soft tissue calcification.
 - a. Calcinosis cutis - <5%.
 - b. Even more rare – renal pelvis, liver, gastric mucosa, aortic branches.

H. Thoracic radiographs.

1. Airway and interstitial mineralization of the lungs – more common in dogs with respiratory signs.
 - a. Airway mineralization – 75%.
 - b. Interstitial mineralization – 25%.
 - c. Those with interstitial mineralization are more likely to be hypoxic.
2. Metastasis of adrenal carcinoma – requires both laterals and VD/DV (3 views).
3. Signs of PTE – solitary or multiple.
 - a. Hypovascular lung regions.
 - b. Alveolar infiltrates due to atelectasis, hemorrhage, infarction.
 - c. Interstitial infiltrates (soft tissue density).
 - d. Enlarged pulmonary arteries.
 - e. Right sided heart enlargement.
 - f. Pleural effusion.
4. Osteopenia, soft tissue calcification might be apparent – see abdominal rads.

I. Abdominal ultrasound.

1. Adrenal glands.
 - a. Gas in the gut can obscure interrogation of the adrenal glands, as can deep chested body conformation.
 - b. Left is easier, because it is more caudal.
 - c. US should be used to differentiate ADH from PDH, NOT to screen for HAC.
 - d. Adrenal size is best estimated by measuring the width of the left adrenal gland.
 - 1) 7.5 mm the upper limit of normal.
 - 2) PDH dogs usually have width 7.5-10mm.
 - e. The left adrenal gland is peanut shaped, and the right is oval shaped.
 - f. Hypoechoic relative to renal cortex.
 - g. PDH.
 - 1) Bilaterally normal or large adrenal glands.
 - 2) Normal shape to plump/rounded.
 - 3) May have hyperechoic nodules.
 - h. ADH.
 - 1) One large/abnormally shaped adrenal gland.
 - 2) One normal, thin (atrophied) or non-visualized adrenal gland.
 - i. Not decreased in length.
 - ii. Medulla may appear normal with thin cortex.
 - 3) Bilateral tumors are possible.
 - 4) Carcinomas are usually larger than adenomas.
 - i. Masses greater than 2 cm in diameter tend to be malignant.

- ii. Almost all masses greater than 4 cm in diameter are malignant.
 - 5) Invasion of local tissues or distant metastasis would suggest carcinoma.
 - i. Invasion of: vena cava, liver, kidney., aorta.
 - ii. Mets in the liver.
 - 6) Visualization of the right adrenal gland and not the left is stronger evidence for ADH than vice versa.
 - 7) 50% of both adenomas and carcinomas are mineralized.
- i. Adrenal tumors can not reliably be distinguished from nodular hyperplasia by ultrasound.
 - 1) Nodular lesions tend to be more often:
 - i. Nodular hyperplasia.
 - ii. Adenoma.
 - iii. Metastasis.
 - 2) Echogenicity of nodules not specific for type of lesion.
- j. Some adrenal masses are found incidentally when doing abdominal US for other reasons, when there are no signs of Cushing's disease (non-functional adrenal mass).
 - 1) DDx:
 - i. Adrenal cyst.
 - ii. Myelolipoma.
 - iii. Hemorrhage.
 - iv. Nonfunctional adrenal adenoma or carcinoma.
 - v. Pheochromocytoma.
 - vi. Metastasis.
 - vii. Granuloma.
 - 2) These tumors are often not removed, unless functional pheochromocytoma causing clinical signs.
 - i. Invasive tumors often can not be removed, except by the most bold surgeon.
 - ii. Non-invasive tumors often never cause problems.
 - 3) Recheck one month.
 - 4) If no significant growth, then recheck again in 3 months.
 - 5) If no growth, then every 6-12 months.
 - 6) Rapid growth may indicate need for surgery.

J. Abdominal CT.

- 1. Useful for identifying adrenal tumors and assessing for local metastasis and appropriateness of surgery.
- 2. Not always useful for diagnosing PDH. 50% of dogs with PDH have tumors less than 3 mm in diameter.

K. Pulmonary scintigraphy.

- 1. Interstitial mineralization seen on bone phase scintigraphy.
- 2. Diffusion impairment to blood oxygen seen on pulmonary perfusion scan.

L. CSF tap.

- 1. Might be done if neurologic signs of macroadenoma.
- 2. CRF is low with PDH and ADH.
- 3. ACTH normal.

E. Histopathology.

- 1. PDH pituitary histopath.
 - a. Identifying pituitary tumors on histopathology may take special training.

- b. 50% of dogs with PDH have tumors 3mm or smaller, and are often not grossly visible.
 - c. No usually encapsulated but are often surrounded by a rim of compressed pituitary cells.
 - d. Compact sheets of well granulated basophilic cells in a sinusoidal arrangement.
 - e. Crouke's changes – perinuclear hyalinization from chronic exposure to high cortisol.
2. PDH adrenal histopath.
- a. Bilateral adrenal hyperplasia of ZR and ZF.
 - b. Increased adrenal weight.
 - c. ZG is usually normal.
 - d. Nodular hyperplasia usually in the ZF, when present.
3. ADH adrenal histopath.
- a. Classification of adrenal tumors as benign or malignant is challenging.
 - b. Difficult to distinguish normal from hyperplastic from adenoma from adenocarcinoma.
 - c. Difficult to distinguish adrenal medullary from cortical tumor.
 - d. Adenomas.
 - 1) Usually encapsulated, grossly visible, and range from 1-6 cm.
 - 2) Usually less than 75% of the kidney size.
 - 3) ZF predominates, followed by ZR.
 - 4) 50% are partly calcified.
 - e. Carcinomas.
 - 1) Usually greater than 50% of kidney size.
 - 2) Often larger than the kidney.
 - 3) May not be encapsulated.
 - 4) Highly vascular.
 - 5) Necrosis, hemorrhage and cystic degeneration are common.
 - 6) 50% are partially calcified.
 - 7) Degree of dysplasia varies a great deal.
 - 8) Vascular or capsular invasion and local invasion predict malignant behavior.
 - 9) Can invade:
 - i. Ipsilateral kidney and its vessels.
 - ii. Liver.
 - iii. Caudal vena cava (especially the left adrenal gland).
 - iv. Aorta (especially the right adrenal gland).
 - v. Retroperitoneum.
 - vi. Portal vein.
 - 10) Can metastasize to:
 - i. Liver.
 - ii. Lungs.
 - f. Atrophied adrenal gland.
 - 1) ZR is virtually absent.
 - 2) Clear ZF cells.
 - 3) ZG normal.
4. Skin histopathology.
- a. Atrophy of adnexae – hair follicles, pilosebaceous apparatus.
 - b. Keratin accumulation in the follicles.
 - c. Increased melanocytes in the stratum corneum, basal epidermis, and dermis.
5. Liver histopathology – very specific for steroid hepatopathy.

- a. Liver is grossly large, pale and friable.
- b. Centrilobular hepatocytic vacuolation; a few large vacuoles that displace the nucleus to the periphery.
- c. Glycogen accumulation in the Periportal hepatocytes.
- d. Low grade hepatocellular necrosis.
- e. Electron microscopy:
 - 1) Progressive alteration to plasma membranes of cells and organelles.
 - 2) Abundant glycogen.
 - 3) Few mitochondria in hepatocytes.

VI. Treatment.

--primary reason for treatment is to control problematic clinical signs.

--if tests are diagnostic of HAC without clinical signs, do not treat.

--Cushing's Syndromes is a constellation of clinical signs, and can not be diagnosed without clinical signs.

--all effective treatments can be harsh, and can harm asymptomatic dogs.

A. Primary medical therapy.

- 1. Mitotane.
- 2. Trilostane.
- 3. Ketoconazole.
- 4. Antihypertensives.
 - a. Used only if hypertension persists after HAC is well controlled.
 - b. Systolic BP usually decreases significantly after HAC is controlled.
 - c. Some dogs do remain hypertensive and proteinuric after HAC is well controlled. For these dogs, ACE inhibitors are used first.

B. Secondary medical therapies.

- 1. Serotonin antagonists.
 - a. Cyproheptadine.
 - b. Helps only with Pars intermedia PDH (15-25% of dogs with PDH, 10-20% of dogs with HAC).
 - c. If effective, response is often partial.
- 2. Dopamine agonists.
 - a. Bromocriptine, L-deprenyl, pergolide.
 - b. Helps only with Pars intermedia PDH (15-25% of dogs with PDH, 10-20% of dogs with HAC).
- 3. ADH analogs – may help control PU-PD when it is not totally controlled by primary therapy.
 - a. DDAVP nasal drops.

C. Surgery.

- 1. Adrenal Surgery for ADH.
- 2. Pituitary surgery for PDH.

D. Treat sequellae.

- 1. Antibiotics for UTI.
 - a. Treat for a minimum of 4 weeks.
 - b. Urine culture 2-3 days after stopping antibiotics.
 - c. Mid-treatment cultures can be done for UTIs which prove difficult to resolve.
 - d. If initial post-treatment culture is negative, repeat urine culture in 1 month.

VII. Monitoring

A.

VIII. Sequella/Prognosis

A. Sequellae.

1. Secondary endocrinopathies.
 - a. Excess cortisol inhibits normal function of pituitary and hypothalamus.
 - b. Inhibits release of:
 - 1) TSH – secondary hypothyroidism.
 - 2) GH – failure to grow, GH deficiency alopecia.
 - 3) FSH and LH - failure of females to cycle, and testicular atrophy.
2. Hypertension – if untreated.
3. Glomerular sclerosis and protein losing nephropathy – if untreated.

B. Prognosis.

1. If pseudomyotonia, response to therapy is variable.

IX. Public Health Significance – none.