



# Hyperadrenocorticism - Black holes & revelations

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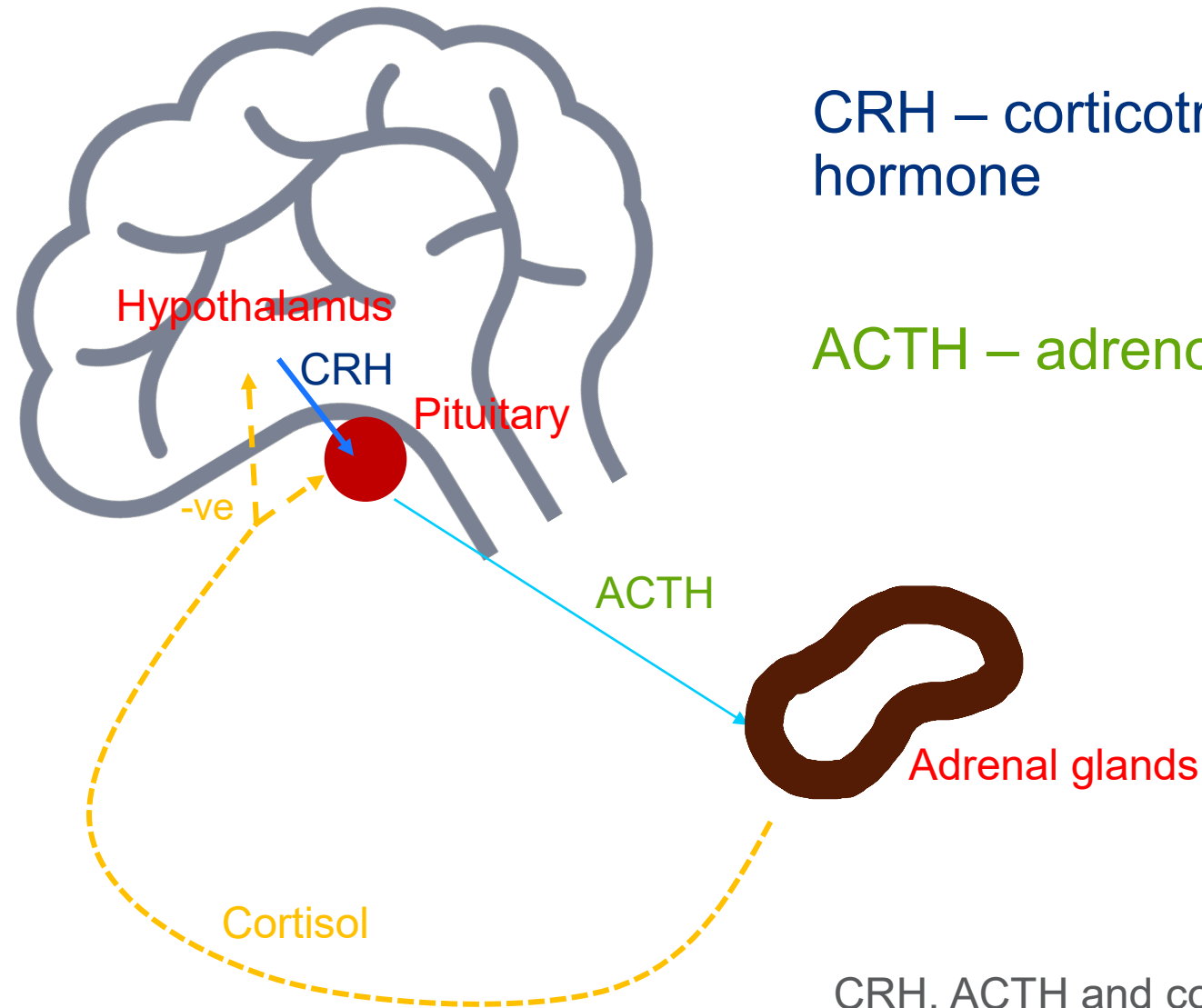
LVS, November 2023

**IDEXX**

# Conflicts of Interest & Disclaimer

- + Yvonne McGrotty is an employee of IDEXX Laboratories UK and also an employee of Anicura France.
- + *The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation, and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions, and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.*

# Hypothalamic-pituitary-adrenal axis



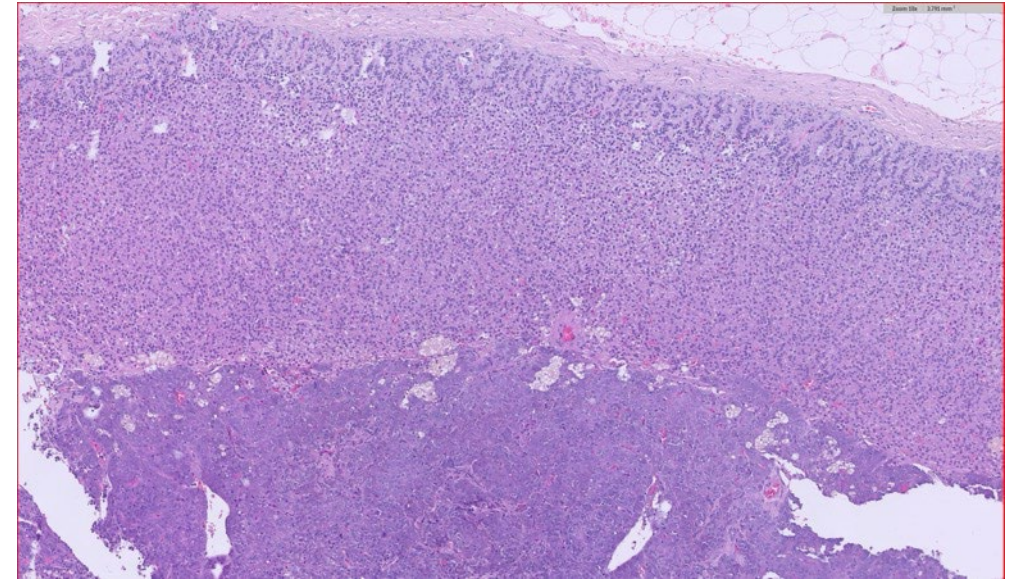
CRH – corticotropin releasing hormone

ACTH – adrenocorticotrophic hormone

CRH, ACTH and cortisol release is episodic

# Spontaneous Hyperadrenocorticism

- + Pituitary Dependent (PDH)
  - + 80-85% of cases
  - + Functional pituitary tumour (micro/macroadenoma)
  - + Occasionally pituitary hyperplasia
- + Adrenal Dependent (ADH)
  - + Functional adenomas or carcinomas
  - + 15-20% of cases
  - + Mostly unilateral
- + Other causes
  - + Ectopic ACTH secretion (neuroendocrine)
  - + Food dependent HAC



Courtesy of Louise Dawson

# Iatrogenic Hyperadrenocorticism

- Chronic use of glucocorticoids
- Topical
  - Ear preparations
  - Skin creams
  - Eye drops
- Parenteral



# Signalment

- + Any breed
  - + Border Terriers, Bichon Frise, Std. Schnauzer, Min. poodle, Boxer, Dachshund
  - + Adrenal tumours more common in large breed dogs
  - + PDH more common in smaller dogs <20kg
- + Middle-aged to old
  - + Median age is 10 years
  - + Almost all dogs >6yrs
  - + Dogs with ADH tend to be older (11.3yrs)
- + Female neutered slightly more predisposed



# Clinical Signs

- + PUPD (90% cases)
  - + Interferes with ADH action
  - + Acquired nephrogenic DI
- + Polyphagia
- + Panting
- + Pot belly
- + Symmetrical truncal alopecia
- + Comedones
- + Hepatomegaly





## Calcinosis Cutis

- + Firm white or cream skin plaques surrounded by erythema
- + Usually on neck, abdomen or inguinal skin
- + Dystrophic or metastatic



# Polydipsia/Polydipsia

- + Normal H<sub>2</sub>O intake
  - + 40-60mls/kg/day
- + Polydipsia
  - + >100 mls/kg/day in dogs
- + Don't test for HAC in patients that aren't PUPD
- + Urine SG <1.020



# Diagnostic Approach

- History (including drug therapies)
- Quantify water intake accurately
  - Confirm PUPD
- Physical examination
- Urinalysis
- Haem/bio
- Specific endocrine tests
- Imaging



# Physical Examination- Things to Check



- + Peripheral lymph nodes
- + Dermatological changes
  - + Alopecia
  - + Rat tail- consider hypothyroidism
- + Vulval discharge
- + Organomegaly
- + Rectal exam
- + Ocular changes
  - + Cataracts

# Haematological Changes

+ Most cases have

+ Eosinopenia

+ Lymphopenia

+ Erythrocytosis?

+ Thrombocytosis?

RBC	6.26	5.39 - 8.70 x10 <sup>12</sup> /L	
Haematocrit	0.468	0.383 - 0.565 L/L	
Haemoglobin	165	134 - 207 g/L	
MCV	74.8	59.0 - 76.0 fL	
<b>MCH</b>	<b>26.4</b>	21.9 - 26.1 pg	
MCHC	353	326 - 392 g/L	
Reticulocytes	53.2	<= 110.0 K/μL	
Reticulocyte Haemoglobin	25.6	24.5 - 31.8 pg	
WBC	11.3	4.9 - 17.6 x10 <sup>9</sup> /L	
% Neutrophils	85.6	%	
% Lymphocytes	9.3	%	
% Monocytes	4.8	%	
% Eosinophils	0.1	%	
% Basophils	0.2	%	
Neutrophils	9.67	2.94 - 12.67 x10 <sup>9</sup> /L	
<b>Lymphocytes</b>	<b>1.05</b>	1.06 - 4.95 x10 <sup>9</sup> /L	
Monocytes	0.54	0.13 - 1.15 x10 <sup>9</sup> /L	
<b>Eosinophils</b>	<b>0.01</b>	0.07 - 1.49 x10 <sup>9</sup> /L	
Basophils	0.02	0.00 - 0.10 x10 <sup>9</sup> /L	
Platelets	255	143 - 448 x10 <sup>9</sup> /L	

# Biochemical Changes

- + Increased ALT
  - + Swollen hepatocytes, glycogen accumulation
  - + Mild to moderate increase
- + Disproportionate increase in ALP
  - + >90% of cases
- + SiALP
  - + No use (unless negative)
  - + Diabetes mellitus, hepatopathies, anticonvulsants
- + Increased albumin?
- + Increased lipids
  - + Noted in >50% dogs with HAC

■ ∞	Glucose	5.6	3.6 - 7.0 mmol/L	
■ ∞	IDEXX SDMA	10	1 - 14 µg/dL	
■ ∞	Creatinine	46.0	44.0 - 133.0 µmol/L	
■ ∞	Sodium	152.8	135.0 - 155.0 mmol/L	
■ ∞	Potassium	4.41	3.60 - 5.60 mmol/L	
■ ∞	Na: K Ratio	34.65	28.80 - 40.00	
■ ∞	Chloride	105.8	100.0 - 116.0 mmol/L	
■ ∞	ALT	<b>374.7</b>	19.8 - 124.0 U/L	
■ ∞	ALP	<b>730.0</b>	<= 130.0 U/L	





# Urinary Changes

- SG <1.020
- UTI common
  - 50% cases at time of Dx
  - Incomplete voiding
  - Inactive sediment
- UPCr increased
  - 45% cases
  - Usually <3.0
  - May persist despite Tx

# Revelations

- + Further tests for HAC only indicated once these tests have been performed!

+

And only if **Cx** are supportive

# Black Holes

Endocrine tests should **ONLY** be performed when clinical signs are supportive!

Testing a sick dog for HAC is inappropriate



# Hyperadrenocorticism- Testing Pathway

Step 1

Only test dogs with supportive clinical signs.

Step 2

Perform CBC, biochemistry and urinalysis first

Step 3

Rule out or stabilise comorbidities before specific performing endocrine tests

Step 4

Specific endocrine testing only after other tests performed & results supportive

A black dog with white markings on its face, resting its head on a person's teal shirt. The dog has brown eyes and a black nose. The person is wearing a teal long-sleeved shirt. The background is a soft, out-of-focus indoor setting.

# Endocrine Testing



## Basal Cortisol

- + Not useful for the diagnosis of HAC!
- + Episodic secretion
- + Fluctuates widely
- + Significant overlap with normal animals

# Specific Endocrine Testing



Urine cortisol to creatinine  
ratio (UCCR)



ACTH stimulation Test



Low Dose Dexamethasone  
Suppression Test (LDDS)



# Urine Cortisol:Creatinine (UCCR)

- Good screening test (rules out HAC)
- Urine MUST be collected by owner at home
- False positives common
- Non-specific
- Positive result **MUST** be followed up by more specific testing

# ACTH Stimulation Test Protocol

- + Fast for 12hrs
- + Sample for basal cortisol
- + Inject tetracosactide (Cosacthen)
  - + 5µg/kg IV
- + Obtain 2<sup>nd</sup> sample 1hr later
- + Measure cortisol on both samples



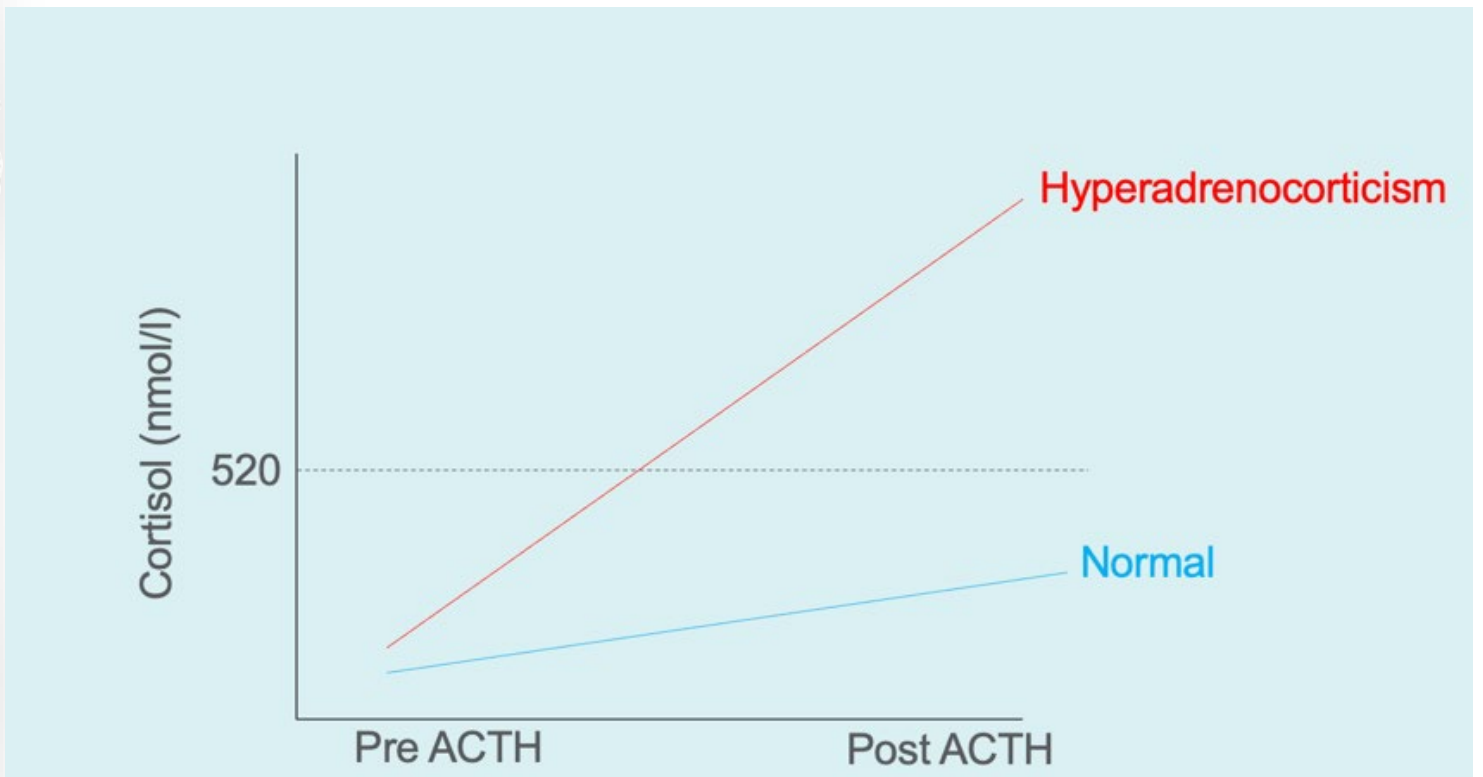
# Tetracosactide



- + Cosacthen
- + Alternative to Synacthen
  - + Keep in fridge
- + 1ml vial = 0.25mg
  - + Enough for up to 40kg dog
- + 5 µg/kg IV (0.005mg/kg)

# How Does ACTH Stimulation Test Work?

- +Indirectly gauges degree of adrenocortical thickness
- +Dogs with HAC have increased thickness of adrenal cortex and have an exaggerated response to ACTH
- +Dogs with iatrogenic HAC have blunted response





# ACTH Stimulation Test

- + Not all dogs with HAC will test positive on ACTH stim
  - + Only around 50% of dogs with ADH test positive
  - + Around 80% of dogs with PDH test positive
- + False negatives
  - + Follow up with LDDST if HAC still seems clinically likely
- + False positives
  - + Stress of non-adrenal illness (up to 14%)

<b>Cortisol - Baseline</b>	<b>149.0</b>	<b>25.0 - 125.0 nmol/L</b>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<b>Cortisol - Post ACTH</b>	<b>803.0</b>	<b>125.0 - 520.0 nmol/L</b>	<input type="text"/>	<input type="text"/>	<input type="text"/>

# Advantages & Disadvantages of ACTH Stim

## Advantages

- Quick and simple to perform
- Differentiates spontaneous from iatrogenic HAC
- Baseline information for therapeutic monitoring (trilostane/mitotane)

## Disadvantages

- Poor sensitivity
  - False negatives (especially with ADH)
- False positives (non-adrenal illness)
- Doesn't discriminate between PDH and ADH

# Low Dose Dexamethasone (LDDS) Test Protocol

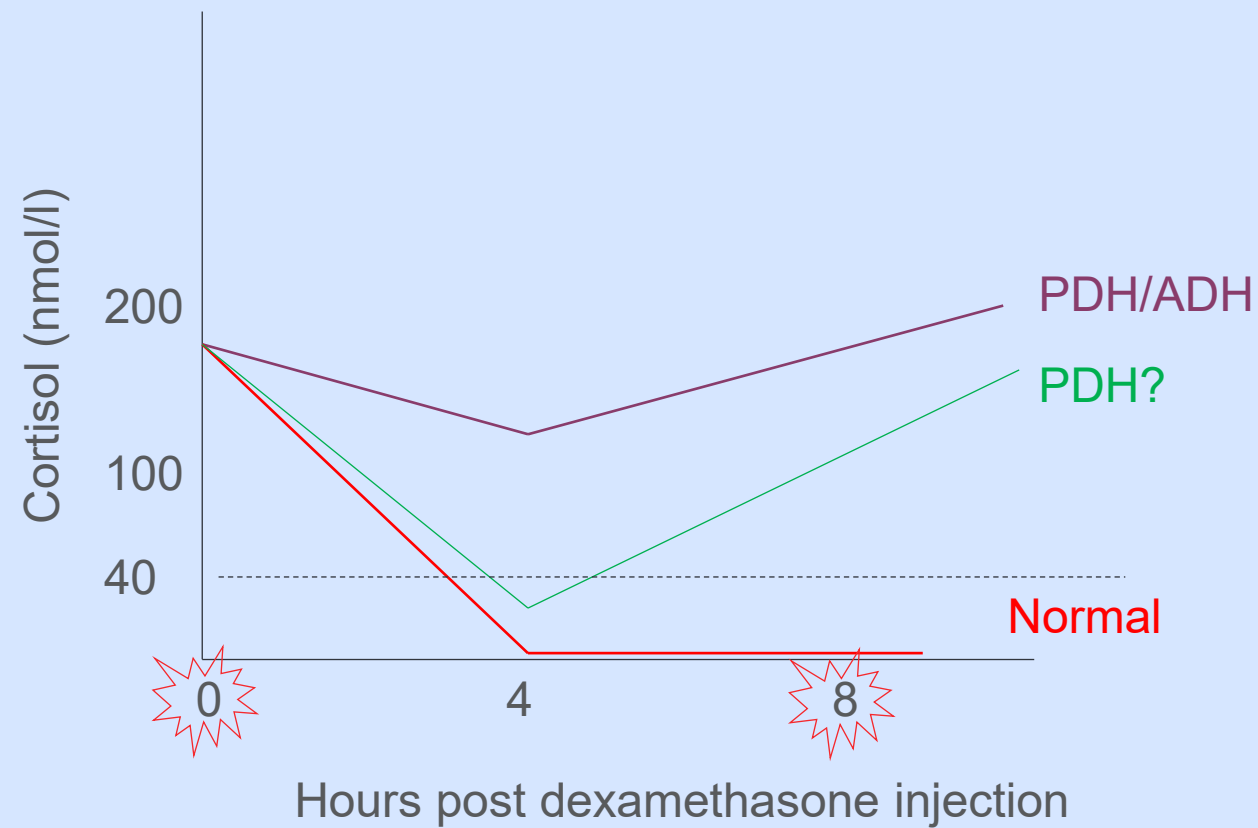
- + Fast the patient for 12 hours
- + Sample for basal cortisol (T=0)
- + Inject dexamethasone (0.015mg/kg) IV
- + Sample for cortisol at 4hrs and 8hrs after dexamethasone injection
- + Avoid stress for the duration of the test
  - + No other procedures



# LDDS test

- + Dexamethasone is anticipated to suppress CRH and ACTH for several hours and therefore reduce cortisol production
- + Assesses the entire hypothalamic-pituitary-adrenal axis
- + ADH – cortisol secretion is **not** expected to be suppressed
- + PDH – cortisol secretion **may or may not** be suppressed

# Low Dose Dexamethasone Suppression Test



Courtesy of Stephen Jordan

# Advantages & Disadvantages of LDDS

## Advantages

- + Good screening test
  - + 90-95% dogs with PDH test positive
  - + Almost 100% ADH
- + May confirm PDH
  - + Suppression at 3-4hrs

## Disadvantages

- + Low specificity
  - + Especially in sick dogs (40-50%)
  - + More likely to produce false positives
- + Takes longer to perform (8hrs)

# Comparison of Tests- Neither test is ideal!

## ACTH Stim

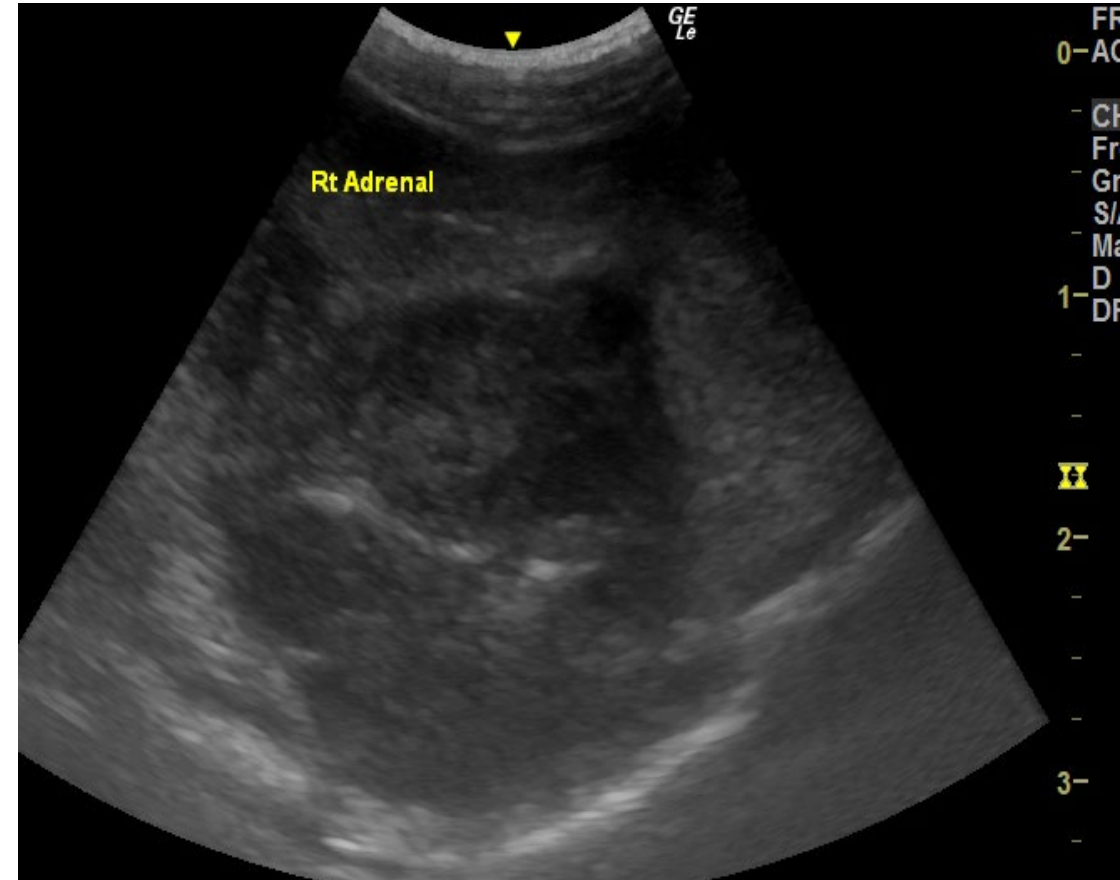
- + Quick test (1hr)
- + Low sensitivity
  - + High rate of false negatives
- + Moderate risk of false positives
  - + Especially diabetes mellitus
- + Tests for iatrogenic HAC

## LDDS Test

- + Long test (8hrs)
- + High sensitivity
  - + Low rate of false negatives
- + Lower specificity
  - + Risk of false positives
- + Does not test for iatrogenic HAC

# Additional Diagnostics - Abdominal Ultrasound

- + Adrenal enlargement
  - + Unilateral vs bilateral
  - + Increased size after trilostane Tx
  - + Not all dogs have adrenal enlargement!
  - + Not all adrenal masses are functional
- + Look for adrenal mass
  - + Carcinoma
  - + Aldosteronoma
  - + Pheochromocytoma
  - + Incidentaloma
- + Not a diagnostic test for HAC





# Cushing's Diagnostic Prediction Tool

Journal of Veterinary Internal Medicine

Open Access



STANDARD ARTICLE | Open Access |

## Development and internal validation of a prediction tool to aid the diagnosis of Cushing's syndrome in dogs attending primary-care practice

Imogen Schofield , David C. Brodbelt, Stijn J. M. Niessen, David B. Church, Rebecca F. Geddes, Noel Kennedy, Dan G. O'Neill

First published: 16 September 2020 | <https://doi.org/10.1111/jvim.15851> | Citations: 1

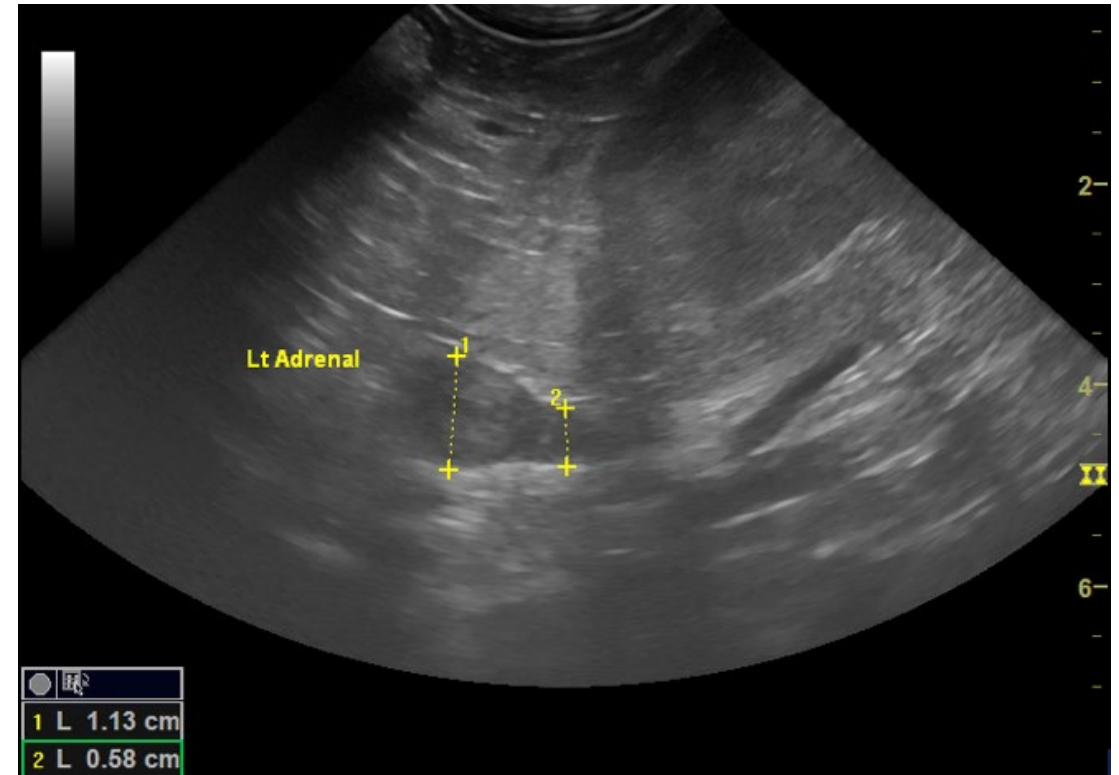
# Differentiation Tests

- + Adrenal ultrasound?
  - + Bilateral enlargement with PDH
  - + Unilateral enlargement with ADH
- + Endogenous ACTH?
  - + Low levels with ADH
  - + High/normal levels with PDH
- + High dose dex suppression test?
  - + Suppression- PDH
- + Advanced imaging
  - + CT or MRI



# Ultrasound

- + Adrenal enlargement
  - + Unilateral vs Bilateral
  - + Hyperadrenocorticism
    - + PDH vs ADH
    - + L Adrenal width >7.5mm
  - + Aldosteronoma
  - + Pheochromocytoma
  - + Incidentaloma
  - + Enlarged with trilostane Tx
- + Check for metastases
  - + Liver
  - + Invasion of vena cava



# Endogenous ACTH Assay

- + Meticulous sample handling
- + No use in diagnosis of HAC
  - + Episodic secretion
- + Differentiates PDH from ADH
  - + Low levels with ADH
  - + High levels in PDH



# MRI and CT

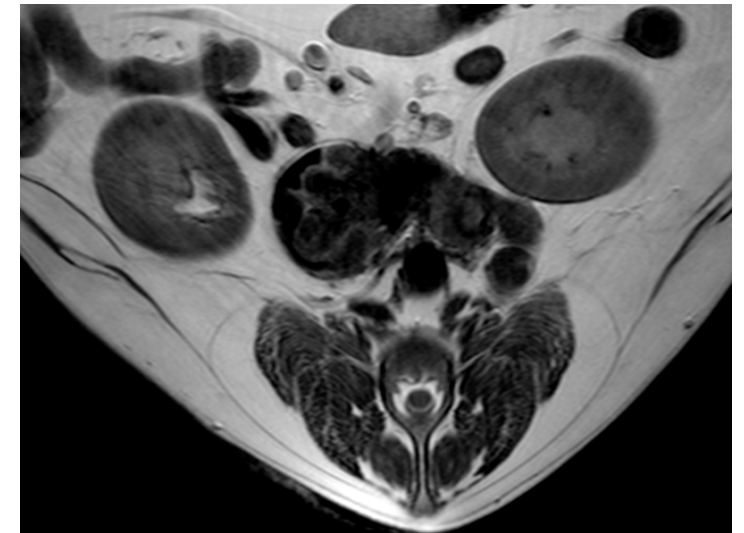
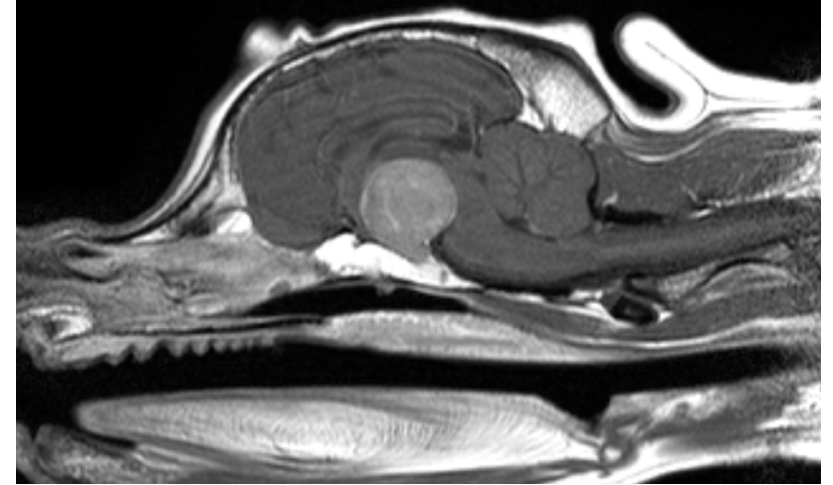
## + Pituitary tumours

- + MRI superior to CT?
- + 50% dogs with PDH have detectable mass
- + Continue to grow despite treatment

## + Adrenal tumours

- + CT
- + Detects invasion of vena cava
- + Useful prior to possible adrenalectomy

Courtesy of Jacques Penderis



A black and white photograph of a dog lying down on grass. The dog's head is in the foreground, and its body extends towards the background. The word "Treatment" is overlaid in white text, centered over the dog's face. A white horizontal line is positioned below the text.

# Treatment

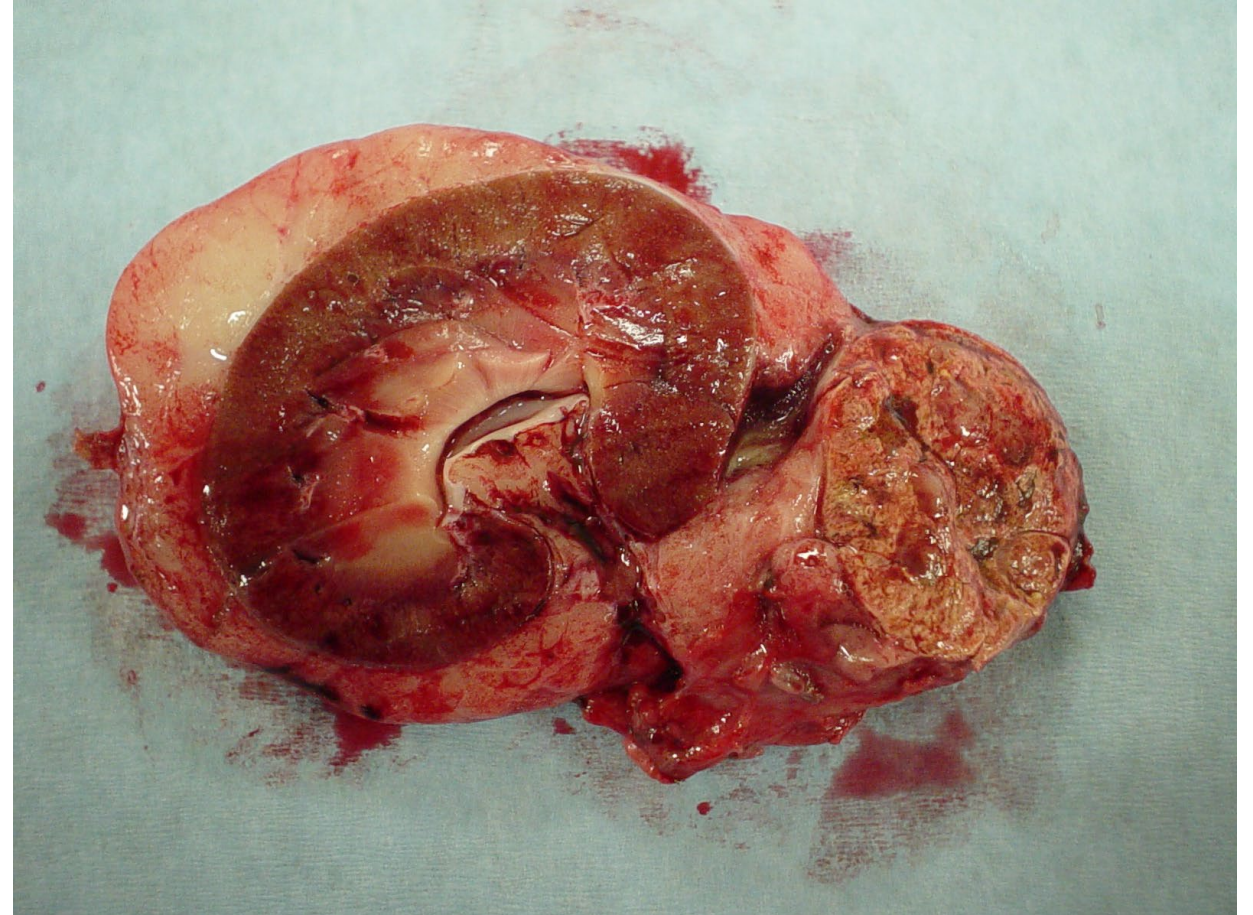
# Treatment of HAC- Trilostane

- + Competitive  $3\beta$  hydroxysteroid dehydrogenase blocker
  - + Blocks cortisol synthesis
  - + Blocks sex hormones
  - + Lesser effect on mineralocorticoids
- + Well tolerated
- + 2 to 5mg/kg PO q24hrs
- + For both PDH & ADH
  
- + Give with food
- + Give in morning
  - + To facilitate monitoring tests



# Surgical Treatment

- + Adrenalectomy
- + Functional adrenal mass
- + Pre-op CT recommended







# Monitoring

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# Monitoring

- + Day 10-14
- + Don't fast the patient
- + Start ACTH stim test 2 -4 hrs post-pill
- + Measure cortisol on pre and 1hr post sample
- + Repeat at 4 weeks then 12 weeks

# Therapeutic Goals

- + Post-ACTH cortisol >40nmol/L but <200nmol/L
- + Resolution of clinical signs
  - + PUPD resolves first
  - + May take months for skin changes to improve



<b>Cortisol - Baseline</b>	86.1	25.0 - 125.0 nmol/L	<input type="text"/>
<b>Cortisol - Post ACTH</b>	141.0	125.0 - 520.0 nmol/L	<input type="text"/>

> [Vet Rec. 2016 Dec 10;179\(23\):597. doi: 10.1136/vr.103744. Epub 2016 Nov 1.](#)

## Pre-trilostane and three-hour post-trilostane cortisol to monitor trilostane therapy in dogs

L Macfarlane <sup>1</sup>, T Parkin <sup>2</sup>, I Ramsey <sup>3</sup>

Affiliations + expand

PMID: 27803375 PMCID: [PMC5256409](#) DOI: [10.1136/vr.103744](#)

Research article | [Open Access](#) | [Published: 27 December 2018](#)

## Comparison of two prepill cortisol concentrations in dogs with hypercortisolism treated with trilostane

[Felicitas Boretti](#), [Caterina Musella](#), [Wanda Burkhardt](#), [Claudia Kuemmerle-Fraune](#), [Barbara Riond](#), [Claudia Reusch](#) & [Nadja Sieber-Ruckstuhl](#) 

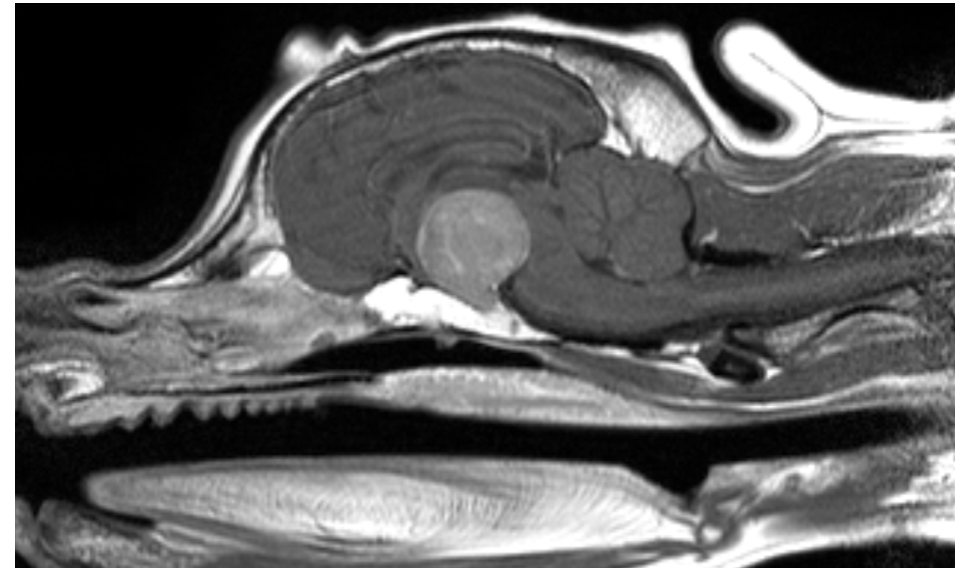
[BMC Veterinary Research](#) **14**, Article number: 417 (2018) | [Cite this article](#)

# Pre-Pill Cortisol

- + Sample collected immediately before trilostane Tx is due
- + Only useful for well animals
- + Do not use in animals that are very stressed
- + Must send to reference laboratory for analysis

# Complications of Treating HAC

- + Unmasking steroid responsive diseases
  - + Arthritis
  - + Atopy
- + Rapid expansion of pituitary tumour
  - + Neurological signs
- + Adrenal necrosis?
  - + Hypoadrenocorticism
- + Adrenal gland enlargement
  - + After trilostane therapy



Courtesy of Jacques Penderis

# HAC- Black Holes

- + Don't test for HAC in dogs that do not have supportive clinical signs
- + HAC would be very unlikely in a dog less than 6yrs old
- + Do not test for hyperadrenocorticism in sick animals or dogs with unstable comorbidities e.g., diabetes mellitus
- + Don't perform endocrine testing before CBC, biochemistry, and urinalysis



# HAC- Revelations



- Increased ALP without supportive signs of HAC is not an indication for HAC screening
- Abdominal ultrasound cannot be used to diagnose hyperadrenocorticism
  - Not all adrenal masses are functional
  - Not all HAC patients have adrenal enlargement
- Cortisol reference ranges are not the same as therapeutic ranges
- Endocrine tests cannot be interpreted in absence of clinical context



Any Questions?

