



So, you thought it was adrenal disease... common mistakes in endocrine diagnostics.



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Conflict of Interest Disclosure:



Patty Lathan receives honoraria from Idexx, Dechra, and Boehringer Ingelheim. She also consults for Idexx and Boehringer Ingelheim.

Bill Saxon is a full-time IDEXX employee.

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ADRENAL

CUSHING'S SYNDROME PITFALLS AND TIPS

- Screening wrong patient – dog and cat
- Screening at the wrong time (when sick)
- Confusion over which screening test
- Not monitoring BP, proteinuria (other complications)
- Best monitoring practice
- Test interpretation practice (later, if we have time...)

LDDST TIMING: HOW MUCH LEEWAY IN TIMING?

- How far off from 4 and 8 hours before need to re-run test?
 - Ummmmmmmm
 - Try to be precise with 8-hr (?)
- What if dog highly stressed – okay to send home between samples?
- Sedation interfere with test?
 - Butorphanol?
 - Trazodone 3-5 mg/kg v 8-10 mg/kg

SUSPECT EEH WHEN:

- **Gastrointestinal signs**
 - Megaesophagus?
- **Albumin: globulin <1.08**
 - Over 1/3 hyperglobulinemic
 - Hypoalbuminemia more common w EEH
- **Low cholesterol (<3.43 mmol/L)**
- **Lack of stress leukogram in sick animal**
 - Lymphocyte count >1500–1750 cells/ μ L
 - Eosinophil count >500 cells/ μ L
- **Reticulocytosis without anemia**
- **Increasing Ca, decreasing BG, regurgitation...**

EEH in 30-40% of Addisonian dogs
Cats get it too.

ACTH STIMULATION TEST DOSING

- IT'S NEVER MEDICALLY WRONG TO USE THE WHOLE VIAL (250 mcg)
 - \$\$\$
- Addison's diagnosis
 - 1 mcg/kg or more
- Cushing's
 - Diagnosis
 - 5 mcg/kg
 - Monitoring
 - 1 mcg/kg (or more)

Optimal route of administration?
Acceptable routes of administration?

I'm seeing a consult this week, 9yo mixed breed dog that was diagnosed with Addison's via stim at my hosp (through ECC), started on docp and pred. Then like a month later, the pDVM did another stim and values were: pre 4.3, post 5.0

OOPS...WHY DID WE DO IT AGAIN???

I'm seeing a consult this week, 9yo mixed breed dog that was diagnosed with Addison's via stim at my hosp (through ECC), started on docp and pred. Then like a month later, the pDVM did another stim and values were: pre 4.3, post 5.0

Is that just because the dog was on prednisone? And the cortisol assay was picking that up?

Yeah, prob the pred being picked up by the cortisol assay if they gave pred before coming in the hospital. I assume the initial stim was legit?

I wasn't there for it, but our criticalist did it so I assume so

It was pre 0.3, post 0.5 or something like that, both values less than 0.1

Sorry, less than 1.0

Yeah that's convincing.

OOPS...**WHY** DID WE DO IT AGAIN???



OOPS...**WHEN** CAN I DO IT AGAIN?

- ACTH Stimulation test
 - Mistake: Using <5 mcg/dL for Cushing's test, results not positive
 - When to repeat: Next day
- LDDS
 - Mistake: Used 0.1 mg/kg instead of 0.01 mg/kg of dexamethasone, results not positive
 - (What if test is positive...?)
 - When to repeat: 1 week later?
 - Other issue: Lipemic sample, need to fast longer and repeat (...or can lab spin it down...?)
 - When to repeat: 1 week later
- LDDS following ACTH stim that's not positive: Next day
- ACTH stim following LDDS that's not positive: 1 week later?

TRILOSTANE MONITORING: TIMING

- **Pre-pill cortisol**
 - Before the next pill (12h or 24 h)
 - What if...?
 - They gave the pill?
 - They usually give the pill at 5 am
 - They ran out and it's been 2 days since dog got pill
- **ACTH stim test**
 - Start 3-5 hr after pill
 - How much leeway either side to still have accurate test?

THYROID

CANINE HYPOTHYROIDISM PITFALLS AND TIPS

- Screening healthy dogs
- Not using breed-specific reference ranges
- Over-reliance on Free T4
- Under/over reliance on TSH
- Unnecessary extended panels
- Starting dose and monitoring
- Treatment trials – not using full dose, forgetting to stop, see if signs recur
- Treatment with comorbidities – heart disease, Addison's

Assessment of the likelihood of hypothyroidism in dogs diagnosed with and treated for hypothyroidism at primary care practices: 102 cases (2016-2021)

Victoria Travail¹  | Carolina Fernandez Sanchez² | Jose M. Costo³ |
Nicola Valentine⁴ | Megan Conroy⁵  | Venessa Lee⁵ | Dimitrios Bouziopoulos⁶ |
Kathryn Bateman⁶ | Emma Gatehouse⁷ | Judith Cruzado-Perez¹ |
Danica Pollard⁸ | Valerie Lamb¹ | Florence Juvet¹ | Darren Kelly¹ 

- Retrospective, 102 dogs
- 3 ECVIM diplomates evaluated records
 - Confirmed/likely: 38%, 48%, 56%
 - Suspected but not confirmed: 6%, 23%, 12%
 - HypoT4 unlikely: 4%, 23%, 14%
 - No reason to suspect: 52%, 7%, 19%
 - *Levothyroxine supplementation not indicated in approx. 52% of cases
- **DO NOT TEST DOGS WITHOUT CLINICAL SIGNS OF DISEASE!**

BREED MATTERS

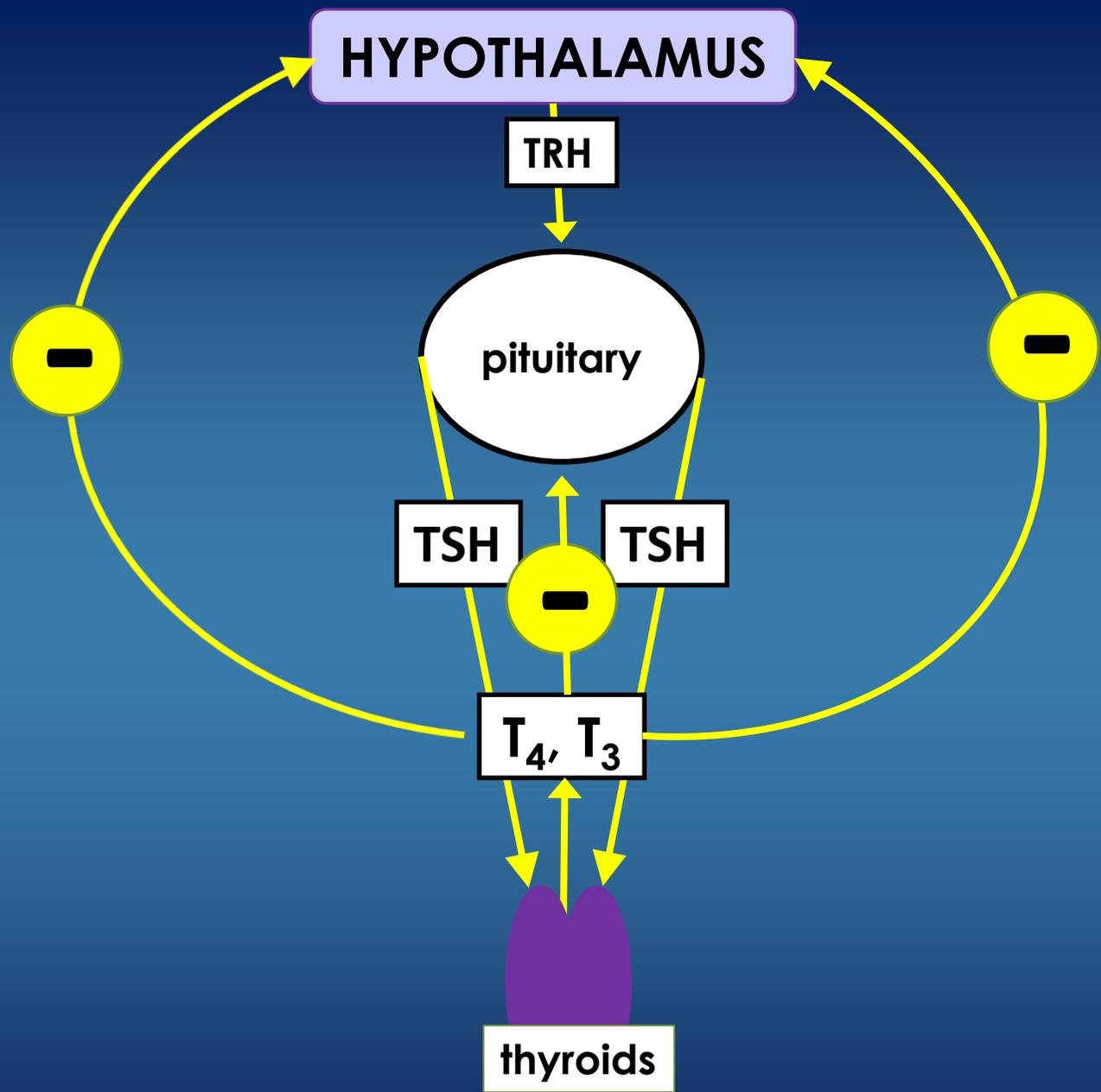
- **Normal** greyhounds
 - TT_4
 - 91% below ref interval
 - 16% below limit of detection
 - FT_4
 - 21% below ref interval
 - 13% below limit of detection
- Breed specific reference ranges if available
- Diagnose with:
 - Clinical signs, CBC/chem panel/UA, TT_4 + TSH

Not just greyhounds:

- Whippets
- Salukis
- Borzois
- Sloughis
- Basenjis
- Scottish Deerhounds
- Irish Wolfhounds
- Alaskan sled dogs

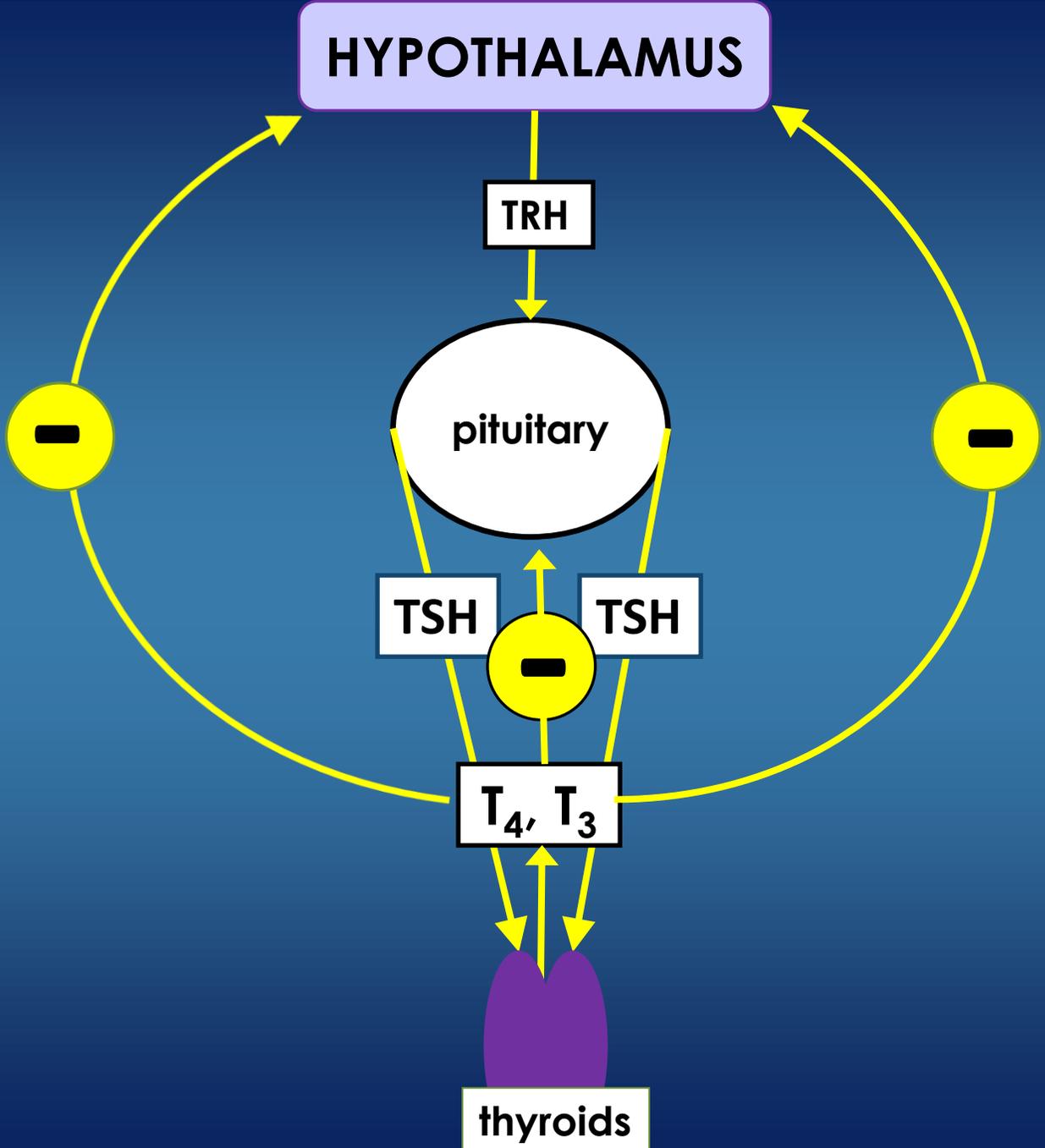
HYPOTHYROIDISM TESTING: ELIMINATE CONFUSION

- Only patients with multiple signs and supportive lab changes
- Screen with TT4 → highly sensitive, specificity ok at 77%
- Normal TT4 (almost always) excludes hypothyroidism
- Low TT4 on senior panel
 - Look for some other disease unless *everything* points to hypoT4
 - Low suspicion → repeat TT4 in 1 month
 - High suspicion → TSH, +/- FT4 (ED)
- The issue with TSH
 - Normal in 30% of hypoT4 dogs, and increased in 10-20% of normal dogs ☹️
- Treatment trial if results conflicting...use full thyroxine dose
 - 20 mcg/kg BID, 4-8 wk recheck
 - If objective improvement stop, if signs recur THEN diagnosis confirmed, restart



HYPOTHALAMIC-PITUITARY-THYROID AXIS

Hypothyroidism and Release from Negative Feedback



Hence:
Little T₄
Big TSH
Hypothyroidism

OOPS...WHEN CAN I DO IT AGAIN? (THYROID EDITION)

- Timing post-T4 supplementation
 - 4-6 hours for peak
 - Prior to last pill for trough
 - (If concerns about over- or under-treating)
- Timing post-methimazole
 - ANY (after how long on therapy?)

**OOPS...WHAT IF TREATMENT WAS STARTED
BEFORE THE DIAGNOSIS WAS CONFIRMED?**

Standard Article

J Vet Intern Med 2017;31:705–710

Effects of Levothyroxine Administration and Withdrawal on the Hypothalamic-Pituitary-Thyroid Axis in Euthyroid Dogs

V. Ziglioli , D.L. Panciera, G.C. Troy, W.E. Monroe, K.M. Boes, and K.R. Refsal

- LT4 given to euthyroid dogs x 8 wks or 16 wks
 - 30 minutes before am meal (Important Dr. Lathan?)
- TT4, TT4(ED), TSH measured q weeks during and after tx (x 16 wks)
- **STATISTICALLY “Recovered” 1 week following withdrawal**
 - TSH was higher than baseline after the 1 week period
 - 1 dog had high TSH for 14 months (but normal TT4 and FT4)
 - **Conclusion: testing 1 wk after stopping SUPPOSEDLY provides accurate assessment of thyroid function**

GIVING THE CORRECT LT4 DOSE: NOT WORKING

- Dose: 0.01-0.02 mg/kg (liquid/tablet)
- Not enough time – derm/neuro signs weeks to months to resolve
- Ensure compliance
- Rule out concurrent meds/diseases
- Use name brand or switch brands
- Give on empty stomach 1 hr before meal
- If on pill change to liquid
- Increase dose

SUSPECT FELINE HYPERTHYROIDISM WITH: PALPABLE THYROID NODULE IN 80%

• Clinical signs

- Weight loss
- Polyphagia
- Pu/pd
- Hyperactivity
- Increased vocalization
- Vomiting/diarrhea
- unkempt haircoat
- Tachycardia, tachypnea
- Apathetic <10% (lethargy, anorexia, dehydration, weakness)

• Hematology

- Erythrocytosis (mild)
- Lymphopenia, eosinopenia

• Biochemistry

- Increased ALT (>80%)
- Increased ALP (>50%)
- Azotemia (≈25%)

• Urinalysis

- Isosthenuria

HYPERTHYROIDISM TESTING: KEEP IT SIMPLE

- **Screen all cats >6 yr old whether signs or not**
 - **MCS may decrease (catabolism) without weight loss (polyphagia)**
- **TT4 (not FT4!) to screen**
 - **Usually only test necessary, increased in 90-95%**
 - **FT4 increased in 10-30% with nonthyroidal disease**
- **TT4 increased in clinical cat → diagnosis confirmed, treat**
- **TT4 increased in normal cat → retest 1 month, treat if still increased**
- **Borderline high TT4 → retest 1 month, or FT4 or TSH**
- **TT4 upper half normal range in cat >8-10 yr old → FT4 or TSH**
- **TT4 normal when suspect disease?**
 - **Repeat TT4, then FT4 (ED), TSH, last resort scintigraphy**

TSH FOR FELINE HYPERTHYROIDISM? YES! AND...

- Expected to be very low with hyperT₄
- BUT
 - Canine TSH ≠ Feline TSH ≠ Human TSH
 - Feline TSH is closer to canine TSH (cTSH) than human TSH
 - Lower limit of detection of cTSH (0.03 ng/mL) is not low enough to differentiate between hyperT₄ cats and some normal cats



Evaluation of Serum Thyroid-Stimulating Hormone Concentration as a Diagnostic Test for Hyperthyroidism in Cats

M.E. Peterson, J.N. Guterl, R. Nichols, and M. Rishniw

- 917(!!) hyperT₄ cats, 32 suspected of HyperT₄, and 131 normal
- Hyperthyroid cats
 - 98%--unmeasurably low TSH
- Euthyroid cats (suspects + normal)
 - 30%--unmeasurably low TSH
- Conclusion
 - Measurable TSH **usually** rules out hyperT₄
 - (A newer assay with a lower cut-off is more specific--Truforma)

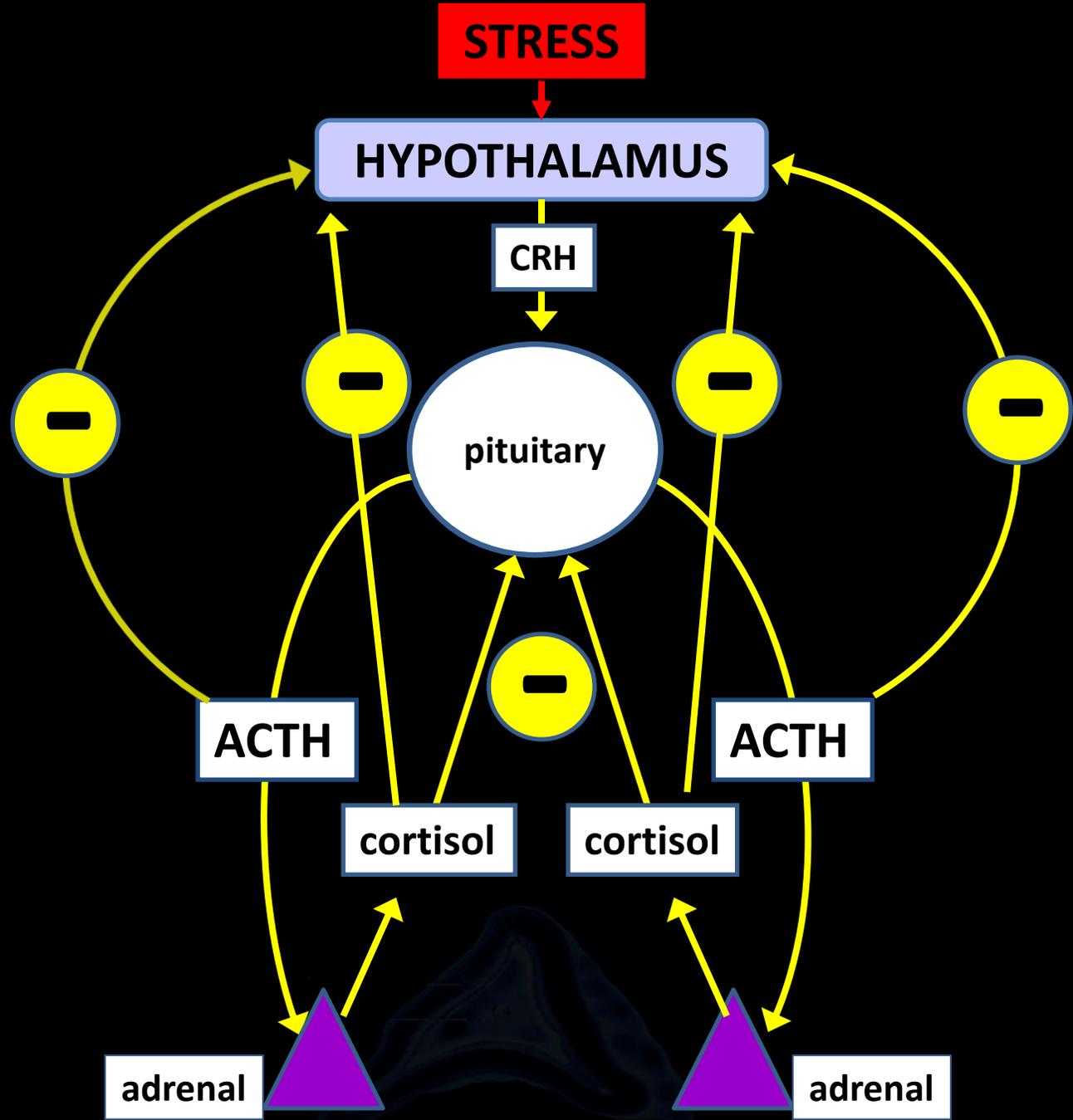
DR. LATHAN RADIOIODINE RAPID ROUND...

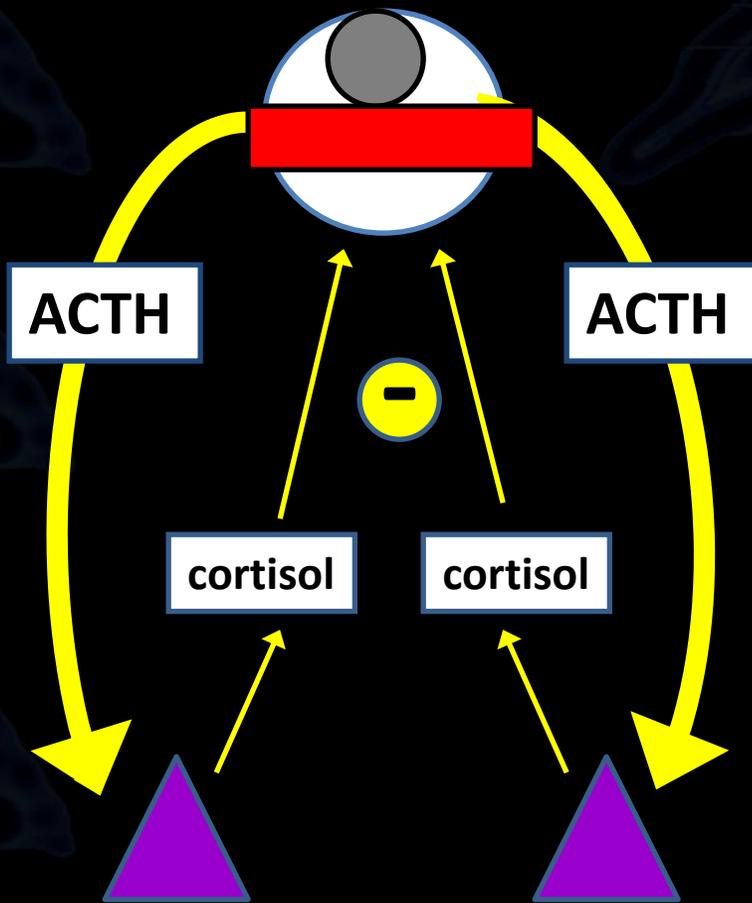
- Prophylactic T4 sup to prevent transient iatrogenic hypoT4?
- When to monitor T4 post?
- If need to supplement T4 how to determine how long?
- Impt to warn owners that some become permanently hypoT4 and need lifelong supp (what if they chose I131 cuz impossible to pill?)?

FELINE HYPERTHYROIDISM: DON'T FORGET

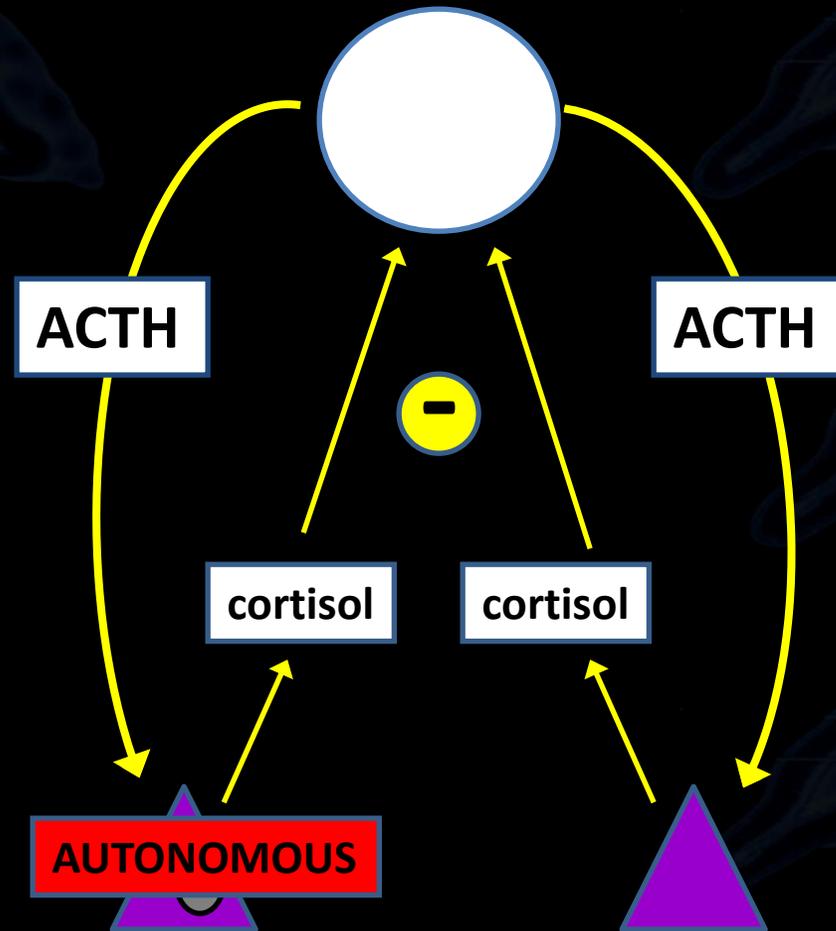
- Importance of avoiding iatrogenic hypoT4
- Affect of non-thyroidal illness on freeT4
- Continue monitoring BP (at least 6 mo) if normal at diagnosis
- Treat adequately with CKD
- NTproBNP can differentiate thyrotoxic v primary cardiomyopathy
 - Should be normal 3 mo after euthyroid if thyrotoxic

TEST INTERPRETATION PRACTICE

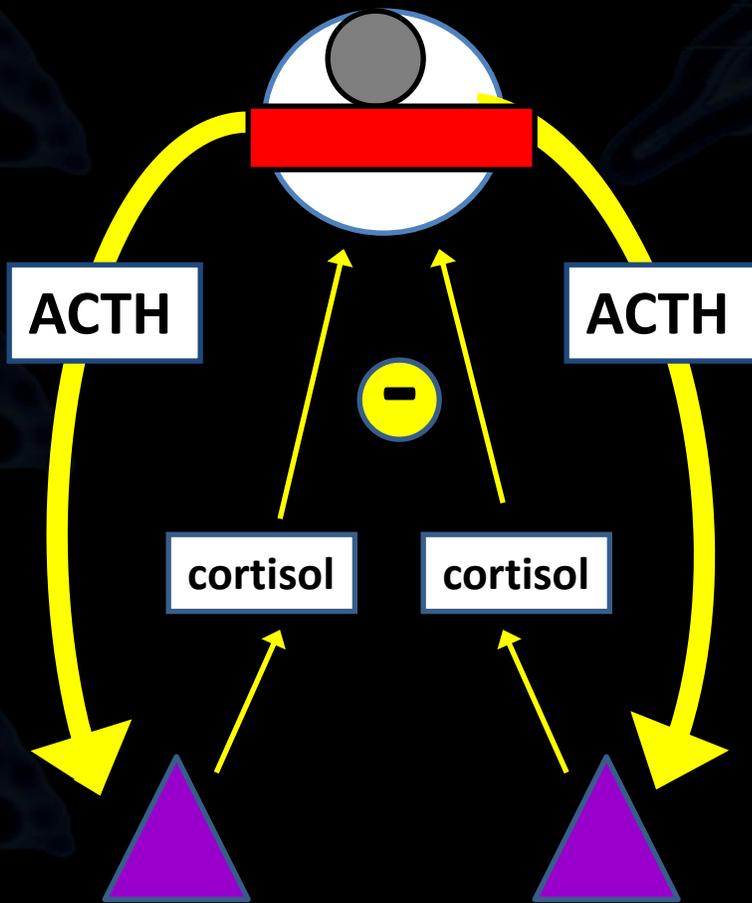




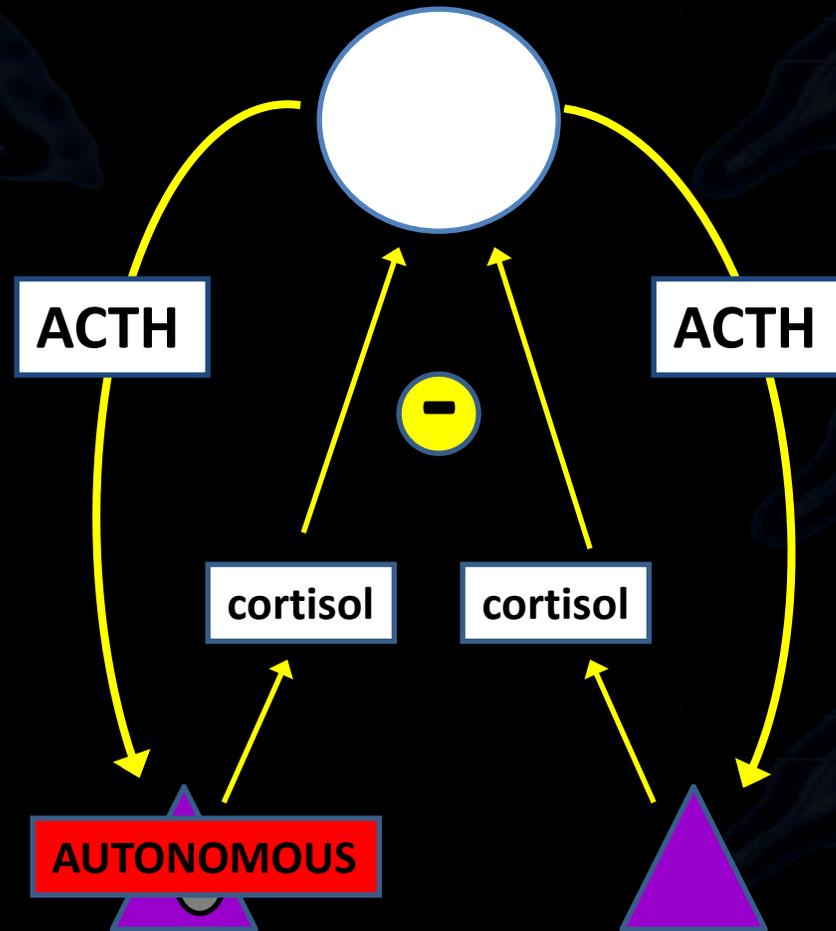
Pituitary Tumor
 ↑ ACTH
 Bilaterally ↑ adrenals
 ↑ cortisol



Adrenal Tumor
 One ↑ ↑ adrenal
 ↑ cortisol
 ↓ ACTH

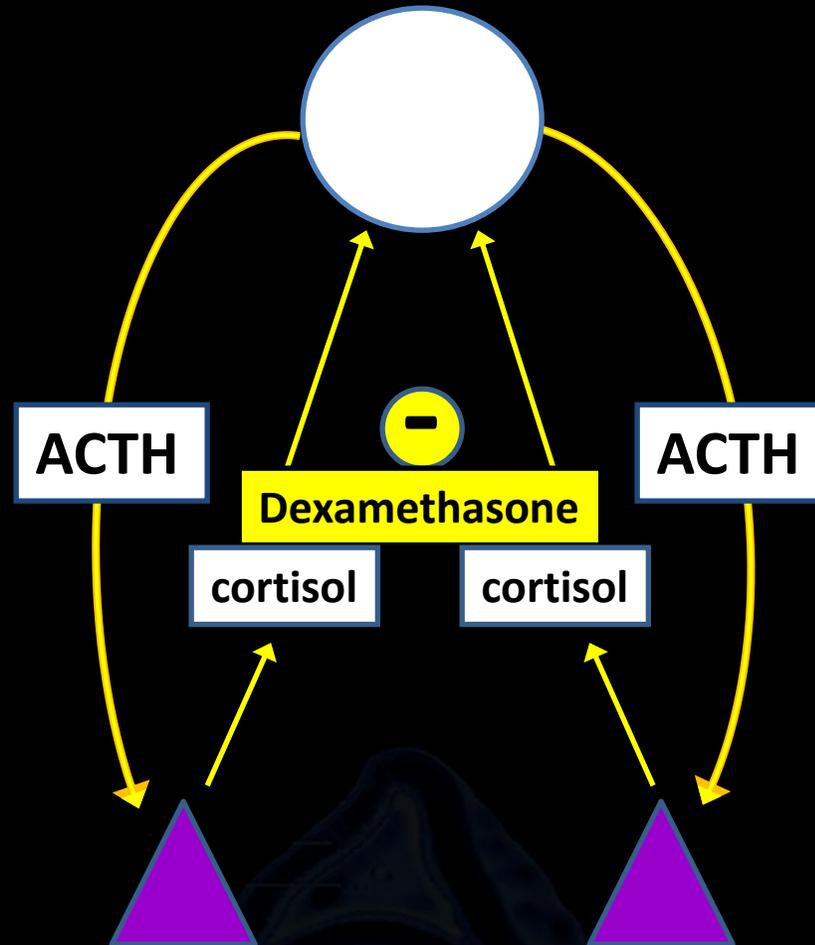


Pituitary Tumor
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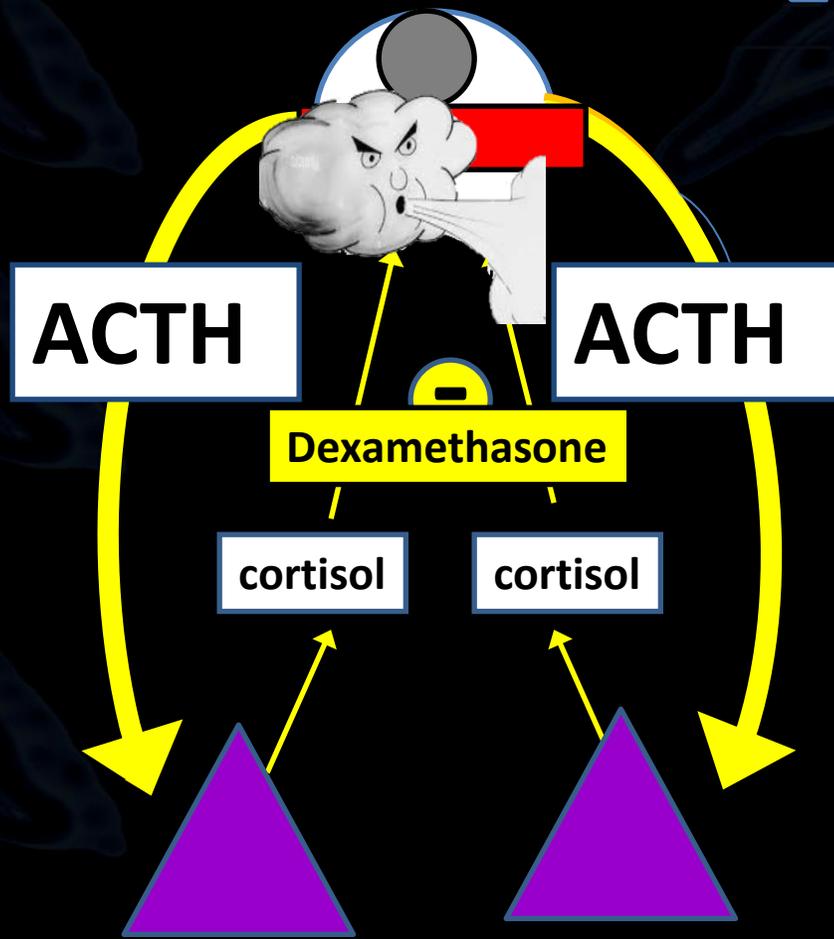


Adrenal Tumor
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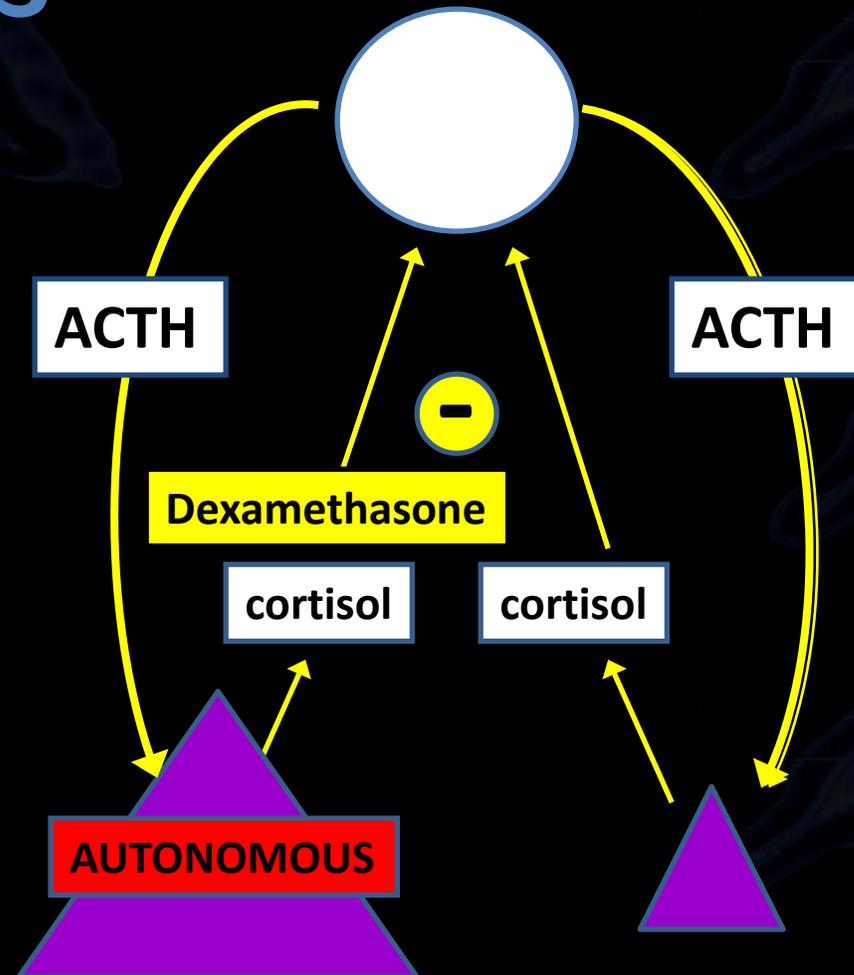
LDDS: Normal Patient



LDDS



Pituitary Tumor
↑ ACTH
Bilaterally ↑ adrenals
↑ cortisol



Adrenal Tumor
One ↑ ↑ adrenal
↑ cortisol
↓ ACTH

Baseline cortisol

Premise:

Dogs with hypoadrenocorticism should have very minimal (or no) baseline cortisol production. If the baseline cortisol is above a given concentration (2-3 $\mu\text{g}/\text{dL}$; 55 – 83 nmol/L), the dog does NOT have hypoadrenocorticism.

CAN ONLY RULE-OUT HYPOADRENOCORTICISM!

Baseline Cortisol: Clinical Use



**CANNOT DIAGNOSE HYPOADRENOCORTICISM WITH A
BASELINE CORTISOL CONCENTRATION.**

Rule-out Hypo-AC

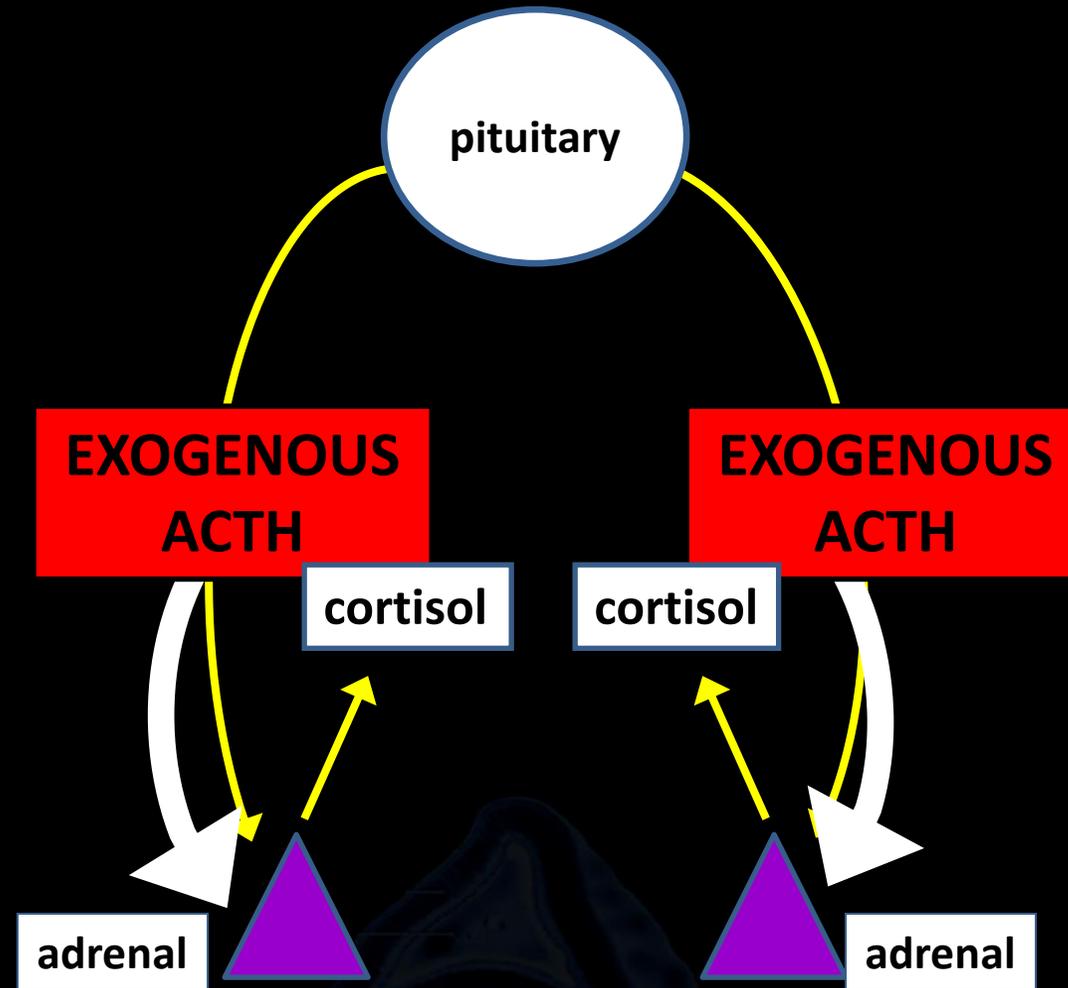
- Baseline $>2.0 \mu\text{g/dL}$ (55 nmol/L), Hypo-AC very unlikely
- If $< 2.0 \mu\text{g/dL}$, need to run ACTH-stim test

Less expensive

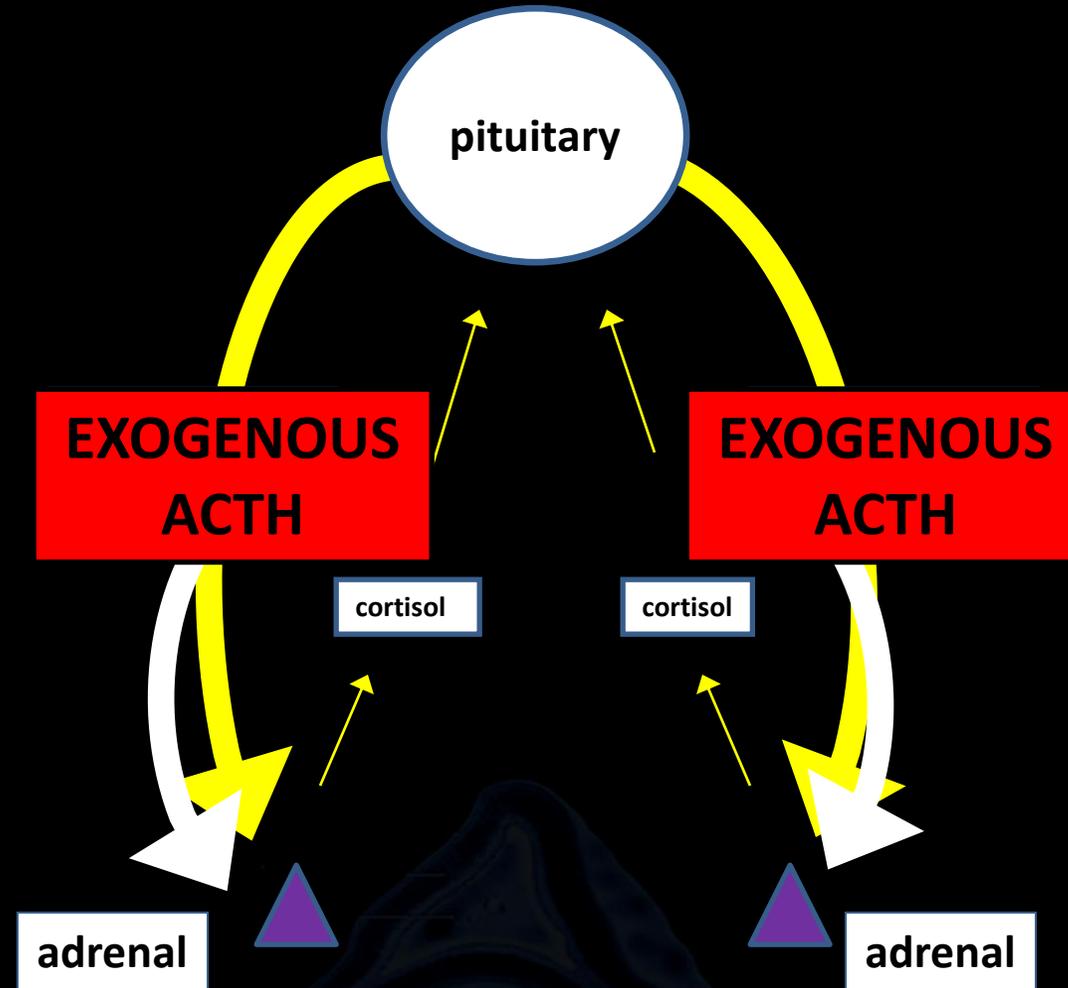
Non-critical patients (time)



ACTH Stimulation Test: Normal Dog



ACTH Stimulation in an Addisonian



ACTH Stimulation Test Interpretation

- **Post-sample: $<2.0 \mu\text{g/dL}$ ($<55 \text{ nmol/L}$)**
 - **Diagnostic of Hypo-AC**
 - (IF no recent exposure to glucocorticoids)
 - **Primary, Secondary, OR Iatrogenic**
- **Post-sample: $>2 \mu\text{g/dL}$ ($<55 \text{ nmol/L}$)**
 - **NOT Addison's**
- **Post-sample: $2.0 - 5.0 \mu\text{g/dL}$ ($55 - 138 \text{ nmol/L}$)**
 - **Suspicious for steroid use in last month**

 **Endocrinology**

7/3/15

1:38 AM



Cortisol - Pre ACTH	<0.2	µg/dL
Cortisol - Post ACTH	a. <0.2	µg/dL

a.

ACTH Reference Range:

Canine:	Feline	
2 - 6	0.5 - 5	Pre-ACTH (resting) cortisol
6 - 18	5 - 15	Post-ACTH cortisol
18 - 22	15 - 19	Equivocal post-ACTH cortisol
>22	>19	Post-ACTH cortisol consistent with hyperadrenocorticism
<2	<0.5	Post-ACTH cortisol consistent with hypoadrenocorticism
1 - 5	n/a	Desired pre- and post-ACTH cortisol on lysodren therapy

ACTH response test is only clearly positive (>22) in 30% of dogs with hyperadrenocorticism (HAC); equivocally positive in another 30% of dogs with HAC, and normal in 40 % of dogs with HAC.* If the ACTH response test is normal and HAC is still suspected, proceed with a low-dose dexamethasone suppression test.

Dogs with iatrogenic Cushing's disease will have flatline response test results in the low end or below the normal reference range.

Both HAC and hypoadrenocorticism are rare diseases in cats.

*Reference: Feldman and Nelson; Canine and Feline Endocrinology and Reproduction. 3rd ed. W.B.Saunders Co., 2004.

- **Dr. Lathan wouldn't a non-fussy eACTH assay be great?**
- **How would that help?**
- **Would you use it?**

THANK YOU!

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