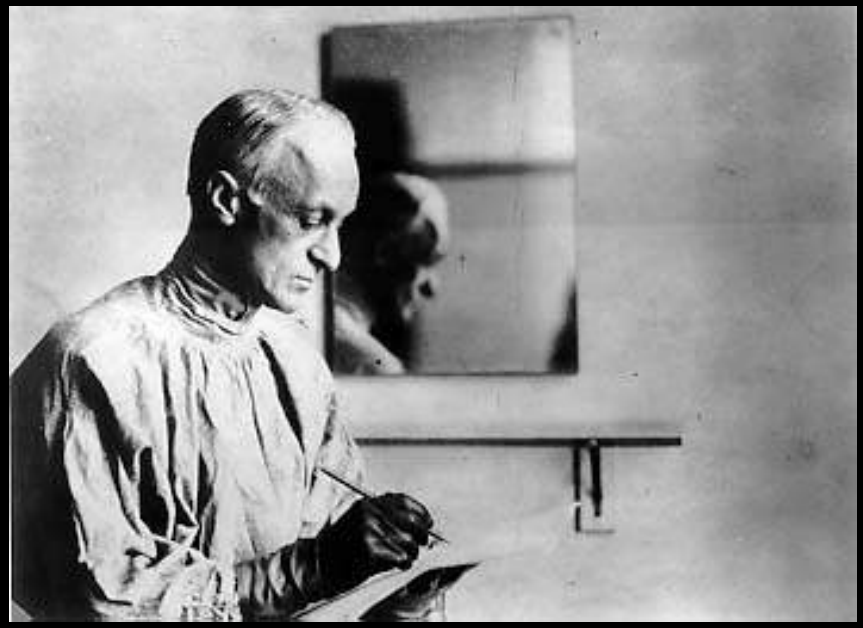
# ATYPICAL HYPERADRENOCORTICISM

Pathogenesis
Diagnosis
And
Treatment



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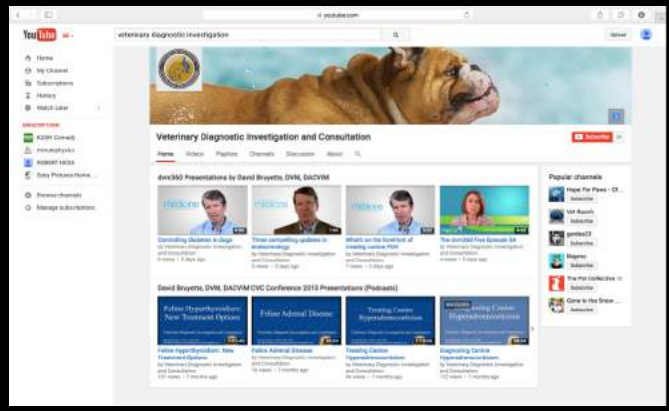


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# CANINE CUSHING'S SYNDROME ETIOLOGY

Pituitary-Dependent Hyperadrenocorticism ( 85% )

Adrenal-Dependent Hyperadrenocorticism (10-12%)

Ectopic ACTH

Food or Meal Induced Hyperadrenocorticism

Cyclic Hyperadrenocorticism

"Occult" Hyperadrenocorticism

Atypical Hyperadrenocorticism

# "CLASSIC" CLINICAL SIGNS

Pituitary-Dependent Hyperadrenocorticism ( 85% )

Adrenal-Dependent Hyperadrenocorticism (10-12%)

Ectopic ACTH

Food or Meal Induced Hyperadrenocorticism

Cyclic Hyperadrenocorticism

Atypical Hyperadrenocorticism

Lack of "Classic" Clinical Signs

Occult "Subclinical"

# DIAGNOSIS OF CANINE CUSHING'S DISEASE

- What about dogs with "classic" clinical signs
- and normal ACTH stimulation and LDDS test results ?

- 5-10% of cases seen in practice

# ECTOPIC SECRETION OF ACTH

Patients with “classic” clinical signs of HAC

Abnormal dexamethasone suppression testing
Normal to elevated endogenous ACTH
Normal pituitary imaging and PVSS

Presence of lung (most common), testicular, ovarian, adrenal, other tumors that secrete ACTH.

Prognosis generally poor
Incidence in the dog ?

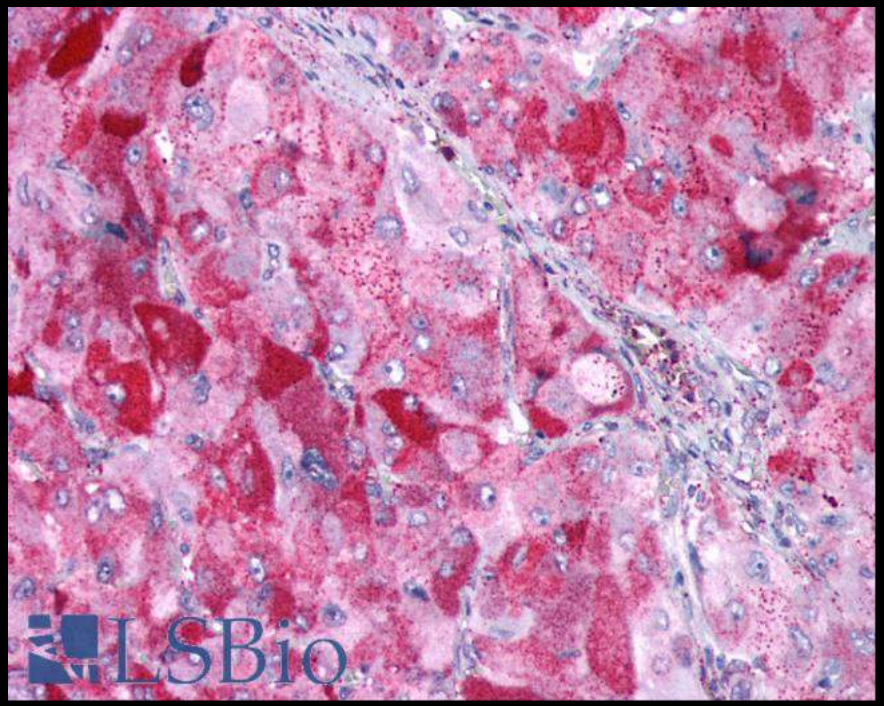
# MEAL OR FOOD-INDUCED HYPERADRENOCORTICISM

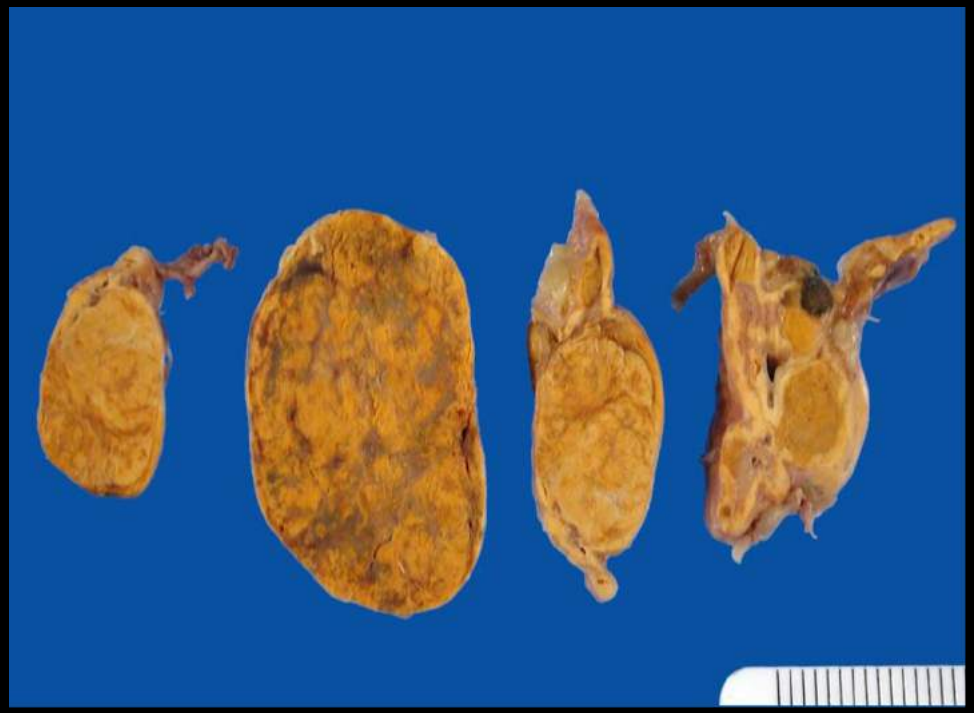
Dogs with “classic” clinical signs of HAC

- Normal ACTH stimulation
- Normal LDDS
- Normal UCCR
- Low plasma endogenous ACTH
- Elevated (> 100%) post prandial UCCR

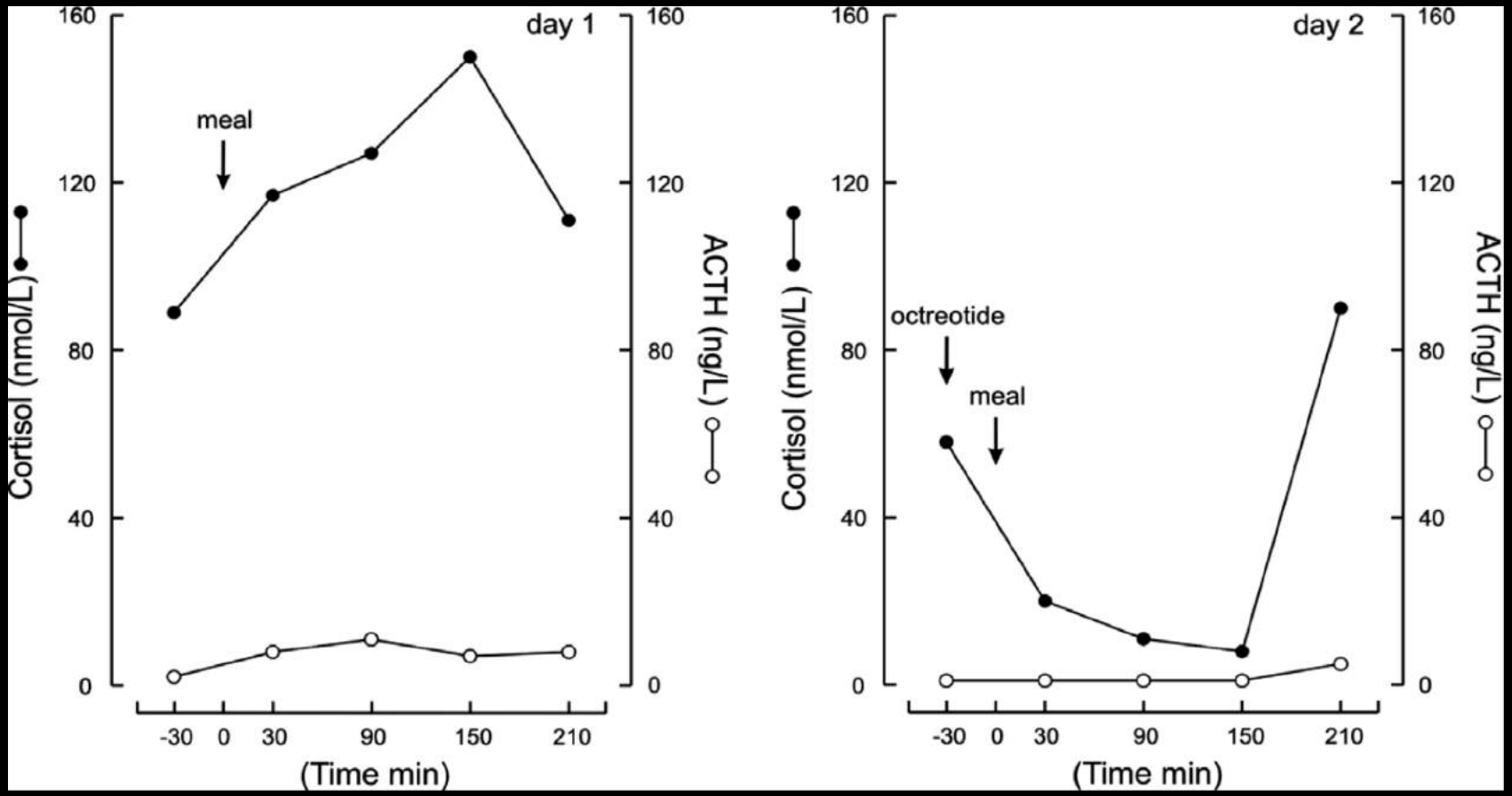
- Younger dogs
- Congenital aberrant expression of GIP receptors in the adrenal cortex

# MEAL OR FOOD-INDUCED HYPERADRENOCORTICISM



# MEAL OR FOOD-INDUCED HYPERADRENOCORTICISM



# CYCLIC HYPERADRENOCORTICISM

Patients with “classic” clinical signs of HAC

- Clinical signs are cyclic in nature
- Pituitary and adrenal function tests are generally normal

- Diagnosis via serial UCCR or salivary free cortisol during periods when clinical signs are present

- Most are pituitary in origin

# "OCCULT" HYPERADRENOCORTICISM

Patients with NO clinical signs of HAC

The Scottish Terrier and Hyperphosphatasemia

Post ACTH cortisol concentrations elevated in:

5/17 with elevations in ALP
0/17 without elevations ALP

# "OCCULT" HYPERADRENOCORTICISM

Patients with NO clinical signs of HAC

The Scottish Terrier and Hyperphosphatasemia

Post ACTH sex steroid (>/= 1) concentrations elevated in:

17/17 with elevations in ALP
Progesterone 12/17; 17 OHP 12/17
15/17 without elevations in ALP
Progesterone 12/17; 17 OHP 10/17

# "OCCULT" HYPERADRENOCORTICISM

Patients with NO clinical signs of HAC

The Scottish Terrier and Hyperphosphatasemia

Hepatic vacuolar hepatopathy

11/11 with elevations in ALP
4/5 without elevations in ALP

# "OCCULT" HYPERADRENOCORTICISM

Patients with NO clinical signs of HAC

The Scottish Terrier and Hyperphosphatasemia

With elevations in ALP

- Age: Mean of 7 years
- Sp gravity: 1.018
- Corticosteroid isoform ALP: 542 U/L (69%)

Without elevations in ALP

- Age: Mean of 2.6 years
- Sp gravity: 1.037
- Corticosteroid isoform ALP: 14.4 U/L (17%)

# "OCCULT" HYPERADRENOCORTICISM

Patients with NO clinical signs of HAC

The Scottish Terrier and Hyperphosphatasemia

Age associated increase in activation of HPA axis
No clinical signs as the increases are mild
Association between cortisol and ALP
Chronic and gradual onset of HAC may have been missed
    Urine sp gravities and pu/pd
No treatment required

# ATYPICAL HYPERADRENOCORTICISM

Dogs with “classic” clinical signs of HAC

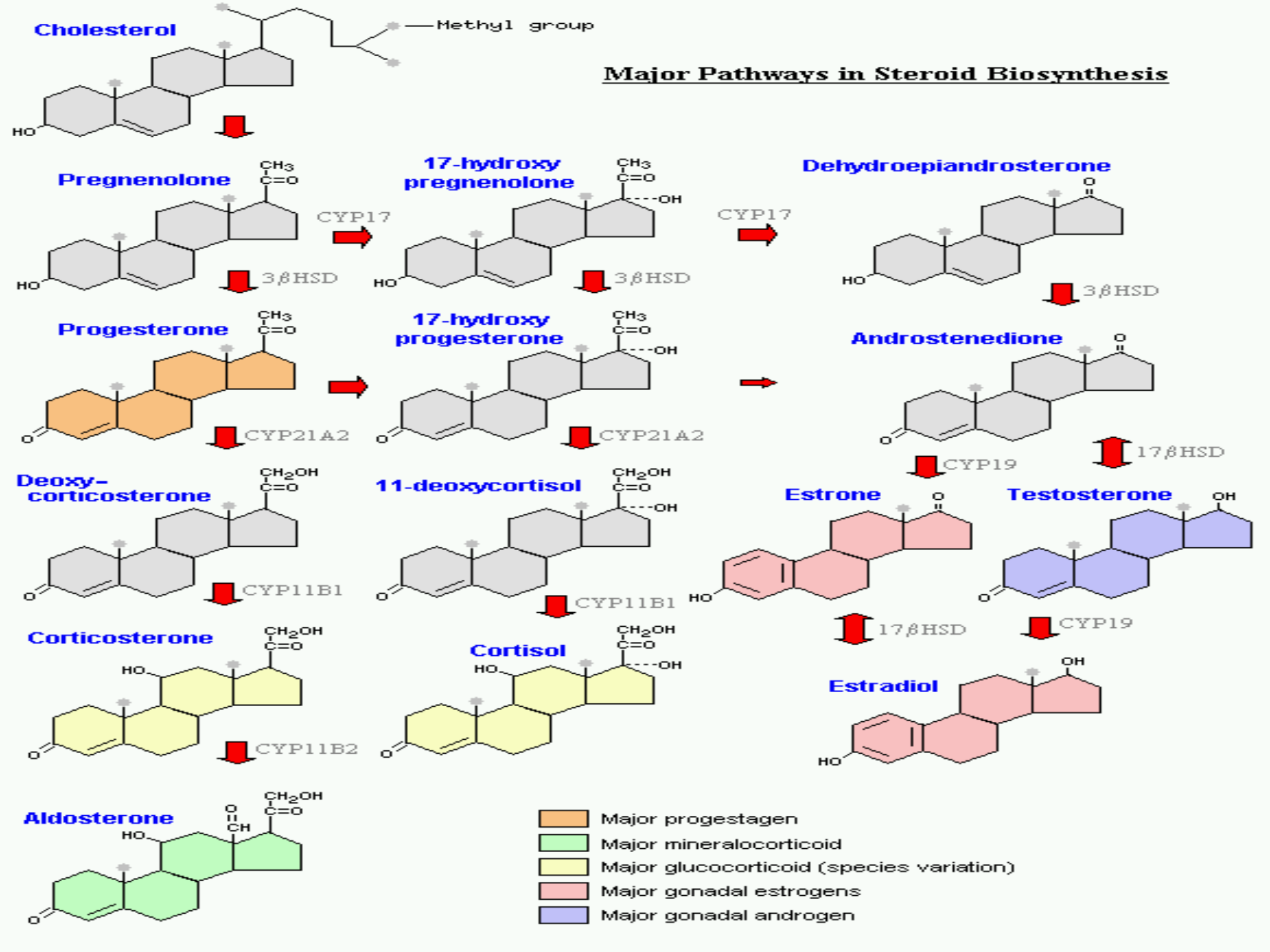
Normal or suppressed cortisol response to ACTH

Normal LDDS

Elevated progesterone and 17 OHP

Diagnosis via ACTH stimulation measuring cortisol, progesterone and 17 OHP pre and post

Rule out presence of an adrenal mass


Major Pathways in Steroid Biosynthesis
Cholesterol
Methyl group
Pregnenolone
CYP17
17-hydroxy pregnenolone
CYP17
Dehydroepiandrosterone
3βHSD
3βHSD
3βHSD
Progesterone
17-hydroxy progesterone
Androstenedione
CYP21A2
CYP21A2
CYP19
17βHSD
Deoxy-corticosterone
11-deoxycortisol
Estrone
Testosterone
CYP11B1
CYP11B1
17βHSD
CYP19
Corticosterone
Cortisol
Estradiol
CYP11B2
Aldosterone
Major progestagen
Major mineralocorticoid
Major glucocorticoid (species variation)
Major gonadal estrogens
Major gonadal androgen

# ATYPICAL HYPERADRENOCORTICISM

Dogs with “classic” clinical signs of HAC

Most commonly seen in dogs with adrenal tumors

Progesterone and 17 OHP bind to the glucocorticoid receptor in the peripheral tissues resulting in clinical signs and bind to GR receptors in the pituitary suppressing ACTH release.

Clinical and hormonal abnormalities reverse with surgical removal, adrenal enzyme blockers or adrenolytic agents.

# ATYPICAL HYPERADRENOCORTICISM

Dogs with “classic” clinical signs of HAC

May also be the result of HAC via:

- Relative enzyme deficiency as a result of adrenal hyperplasia or neoplasia
- In some dogs with PDH the POMC fragments may be increased leading to selective stimulation of adrenal sex hormone production
- Abnormal expression of LH, GIP on adrenal tissue
- Excess LH in neutered dogs
- Hyperplasia into nodule formation

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X (Hair Cycle Arrest)

- Adult Onset Growth Hormone Deficiency
- Growth Hormone Responsive Alopecia
- Castration Responsive Alopecia
- Adrenal Hyperplasia Like Syndrome
- "Coat Funk" of Malamutes
- "Black Skin" Disease of Pomeranians

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

Signalment:

Breeds Affected: Nordic breeds, toy and miniature poodles, Pomeranians

Both sexes affected regardless of neuter status

Hair loss as early as 1 year

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

- Bilaterally symmetric alopecia
- Tends to spare head and front limbs
- Cutaneous hyperpigmentation
- NO systemic signs

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Initial Pomeranian Study

- 7 affected dogs
- 12 unaffected (but related dogs)
- 19 non-Pomeranian control dogs

ACTH stimulated 17 OHP higher in affected than unaffected Pomeranians.

ACTH stimulated 17 OHP and progesterone higher in affected and unaffected Pomeranians vs controls.

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Similar results in Alaskan Malamutes

Suggested a partial 21-hydroxylase deficiency with adrenal hyperplasia (low cortisol resulting in rising ACTH)

- Would explain the hormone abnormalities
- Would explain the findings seen in unaffected vs affected Pomeranians
- Would explain response to castration (debulking)
- Would explain response to medical therapies

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Arguments against 21-OH deficiency

No mutations in 21-OH gene

16 Pomeranians

30 control dogs (other breeds)

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

Candidate gene on chromosome 15

Small segment with 10 genes

Have excluded:

CTSL2 gene

PTCH2 gene

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

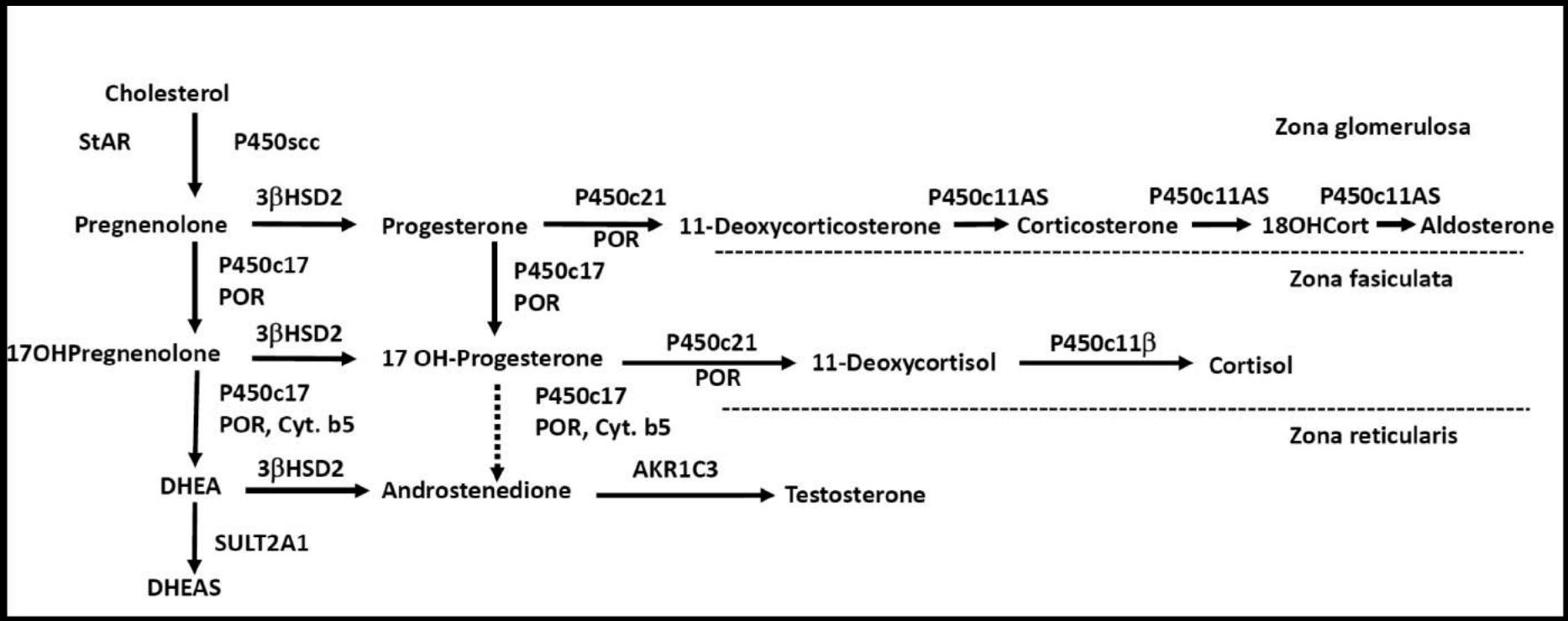
Congenital adrenal hyperplasia (human)

90% due to 21-hydroxylase deficiency

Cholesterol side chain cleavage enzyme
17a-hydroxylase
11B-hydroxylase
3B-hydroxysteroid dehydrogenase
StAR defect
P450 oxidoreductase

# ATYPICAL HYPERADRENOCORTICISM

Adrenal Steroidogenesis



# ATYPICAL HYPERADRENOCORTICISM

Laboratory Concerns

Non adrenal illness

19/29 (66%) normal cortisol post ACTH

8/19 (42%) elevated post progesterone

6/19 (32%) elevated post 17 OHP

Case selection

High index of suspicion that adrenal disease exists

# ATYPICAL HYPERADRENOCORTICISM

Laboratory Concerns

- Post Treatment Hormone Analysis
  - Clinical improvement with worsening hormonal concentrations
- Measurement of sex steroids
  - LC or GC/MS
  - Endocrine Society
  - ELISA vs RIA vs chemiluminescence

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

Treatment Options

- Melatonin
- Medroxyprogesterone acetate
- Growth hormone
- Trilostane
- Lysodren
- Deslorelin (GNRH agonist)
- Fulvestrant (estogen receptor blocker)

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

Melatonin

- Mechanism of action unknown
- Effects on estrogen receptors
  - Conflicting data on estrogen receptors
- Approximately 40% of patients initially respond
- Alopecia may recur while on therapy

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

Medroxyprogesterone acetate (Pomeranians)

- Progestin induced increases in IGF-1
  - Partial hair regrowth in 3/8
  - Complete hair regrowth in 1/8
  - No change in IGF-1 in affected or unaffected Pomeranians
  - IGF-1 increased in non Pomeranians

# ATYPICAL HYPERADRENOCORTICISM

Dogs with out "classic" clinical signs of HAC

Alopecia X

Deslorelin (GNRH agonist)

- 20 dogs with hair cycle arrest
- Hair regrowth in 3 months in 12/16 intact males
- No hair regrowth in any neutered female

# *TRILOSTANE*

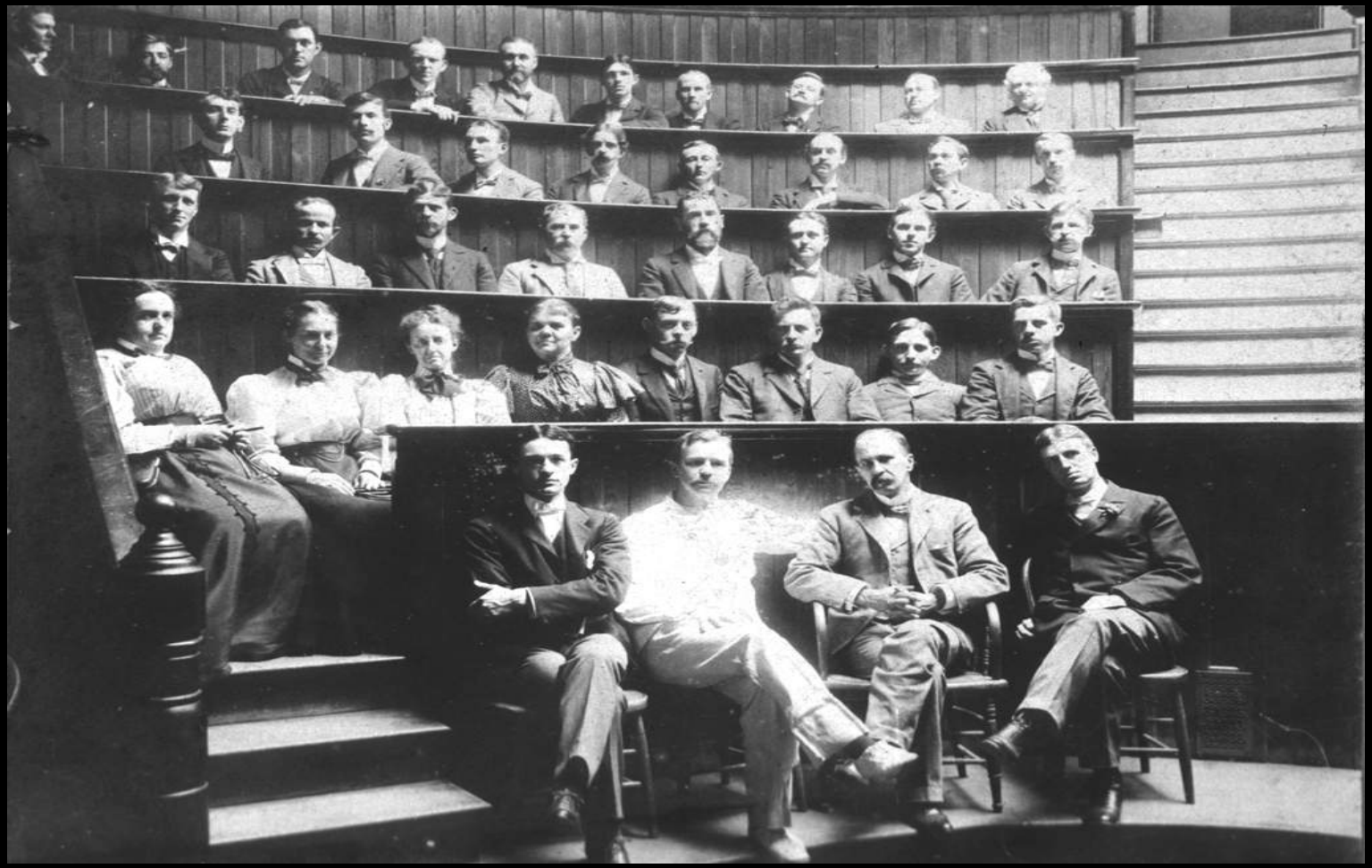
Adrenal enzyme inhibitor

- Similar to ketoconazole and metyrapone

Inhibitor of 3β-hydroxylase

- Rapid reductions in cortisol concentrations
- May also affect aldosterone concentrations
  - ↑ K and ↓ Na concentrations

# MAKING THE CHOICE



## Goals of Any Therapy

Address Primary Disorder

Control of Clinical Signs

Prevention of Treatment Related Side-Effects

Cost

Does it require treatment ?

Therapy tailored to the individual patient

History

Physical examination

Laboratory evaluation

Severity of clinical signs

# Treatment Options

## What I Do

Melatonin – Initial Treatment

Trilostane – Melatonin failures

Sweater – Safe and effective

# CONCLUDING THOUGHTS

***With Clinical Signs***

We must always rule out:

Cushing's syndrome: ACTH stim *and* LDDS

Adrenal steroid testing

Sex steroid secreting adrenal tumors

***With No Clinical Signs***

Adrenal steroid testing

Sweater

Trilostane

# CONCLUDING THOUGHTS