PACIFIC COAST VETERINARY SPECIALISTS

Our mission is to redefine and elevate your pet's health through collaborative, minimally-invasive, and compassionate care that supports the well-being of your pet and peace of mind for your family.

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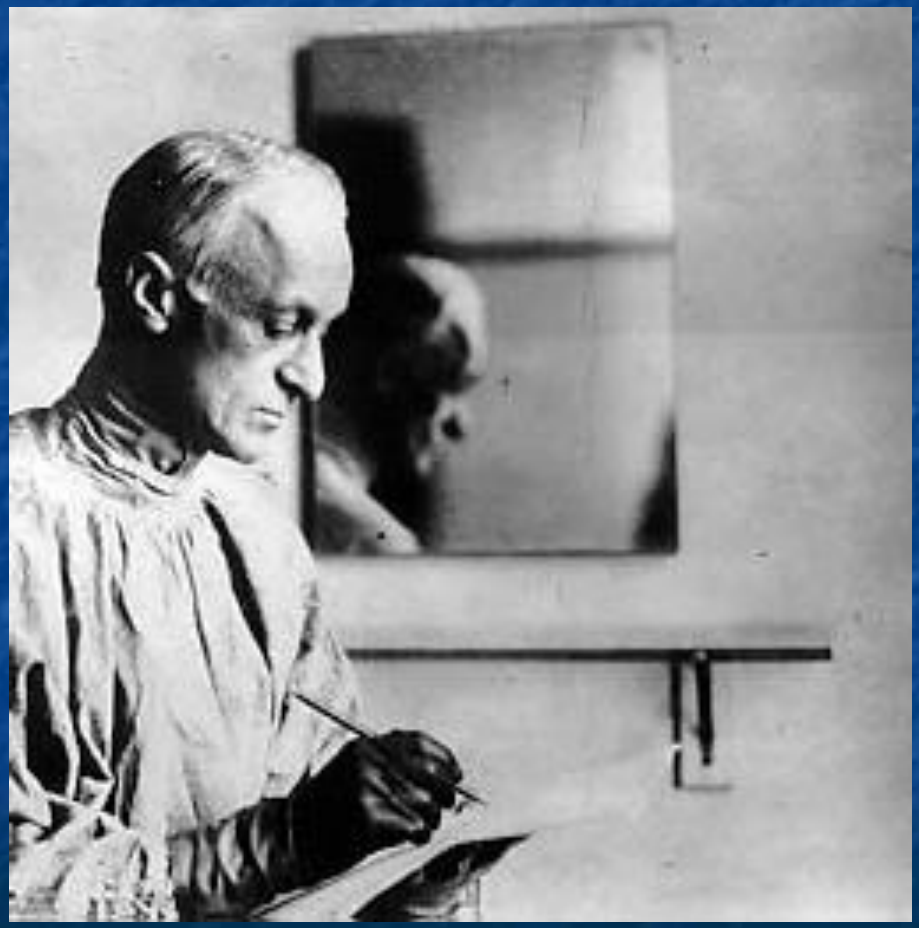
Atypical Hyperadrenocorticism

Pathogenesis
Diagnosis
And
Treatment



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”

Pathophysiology Cushing's

Lack of diurnal variation of ACTH and cortisol in dogs and cats.

Episodic secretion of ACTH.

Estimated 90,000 – 100,000 new canine cases diagnosed per year.

Pathophysiology

Chronic hypercortisolemia results in clinical signs of Cushing's Disease

Etiology of PDH

Complex

Not completely understood

Theories:

- Evidence in man supports a primary pituitary abnormality
- Most evidence in dogs supports a hypothalamic disorder

Etiology of PDH

Screening for Genetic Mutations in Canine PDH

Gs alpha
H-, K-, N-ras genes
DNA-binding domain of the glucocorticoid receptor
Tpit

No differences between control and affected dogs

Clinical Signs of Canine Cushing's Disease

- Polyuria
- Polydipsia
- Polyphagia
- Abdominal distention
- Panting
- Obesity or redistribution of body fat

Clinical Signs of Canine Cushing's Disease

- Change in activity level
- Decreased exercise tolerance
- Anestrus
- Testicular atrophy

Clinical Signs of Canine Cushing's Disease

Dermatologic

Alopecia

Cutaneous hyperpigmentation

Calcinosis cutis

Pyoderma

Comedones

Diagnosis of Canine Cushing's Disease

- Minimum data base
  - Pertinent history and clinical signs
  - Serum chemistries, complete blood count
  - Urinalysis
  - Urine culture
- Supplemental Tests
  - Abdominal radiographs ± ultrasound

Diagnosis of Canine Cushing's Disease

Screening Tests to Diagnose Cushing's:

- ACTH Stimulation Test
- Low Dose Dexamethasone Suppression Test (LDDS)
- Urine Cortisol:Creatinine Ratio (UCCR)

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 ?

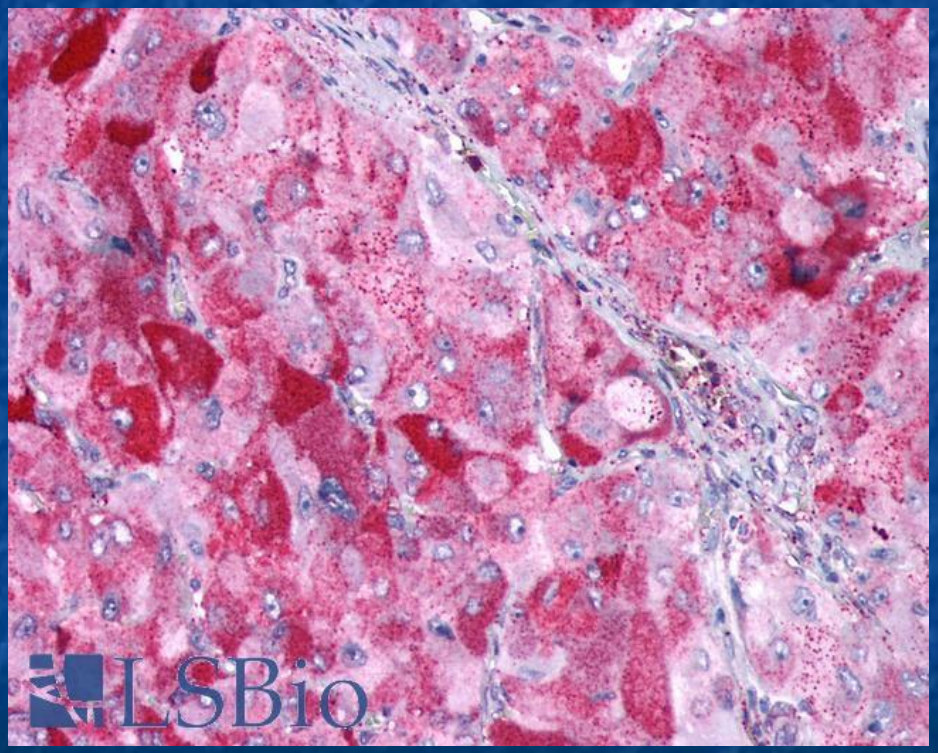
Meal or Food-Induced Hyperadrenocorticism

Dogs with "classic" clinical signs of HAC

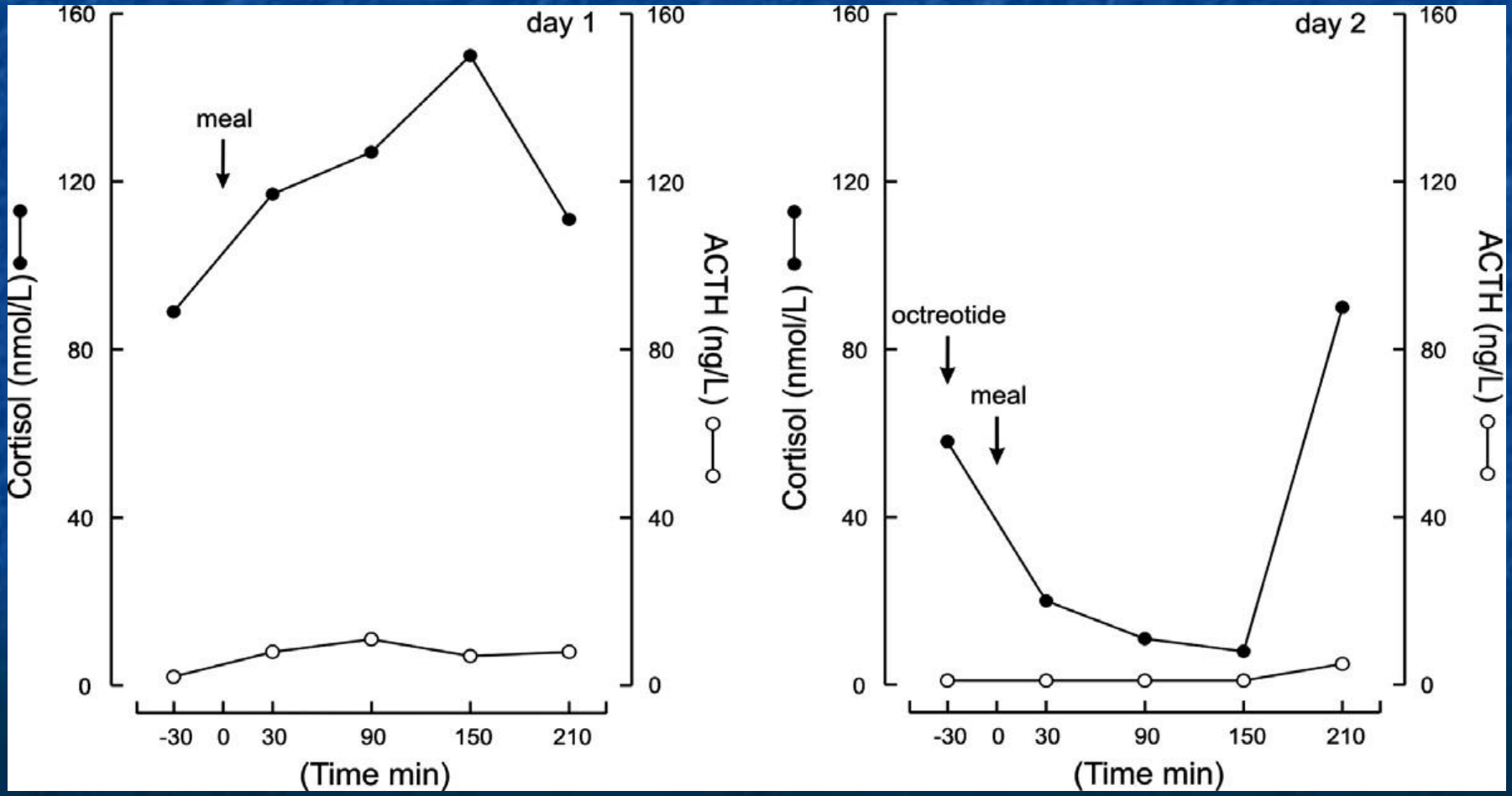
- Normal ACTH stimulation
- Normal LDDS
- Normal UCCR
- Low plasma endogenous ACTH
- Elevated (> 100%) post prandial UCCR

- 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

- Incidence in dogs ?

“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

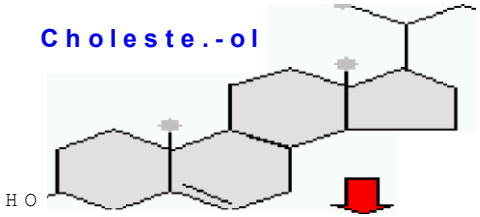
Atypical Hyperadrenocorticism

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



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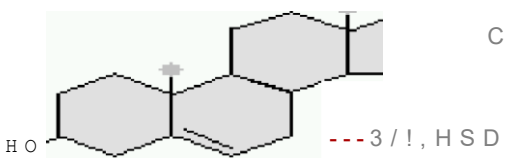

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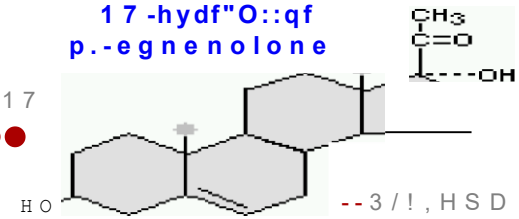

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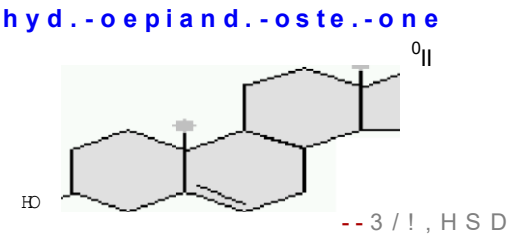
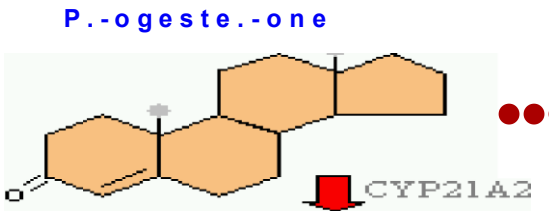
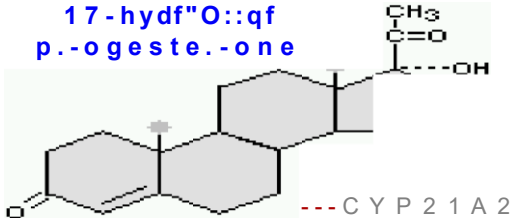
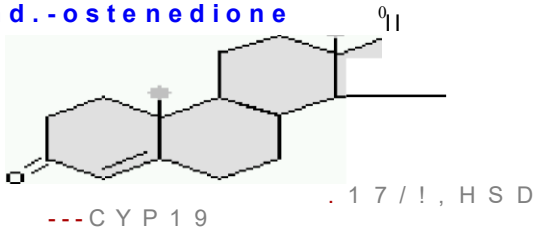
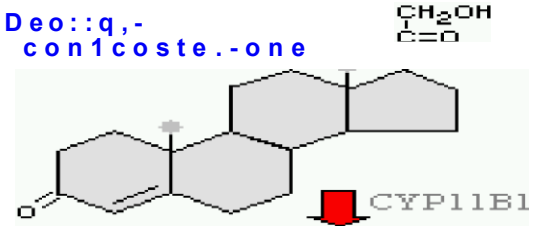
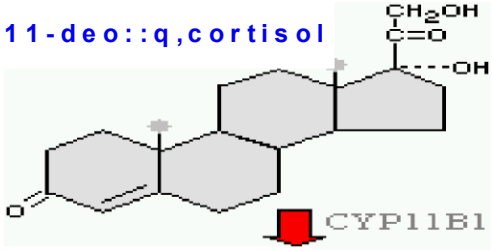


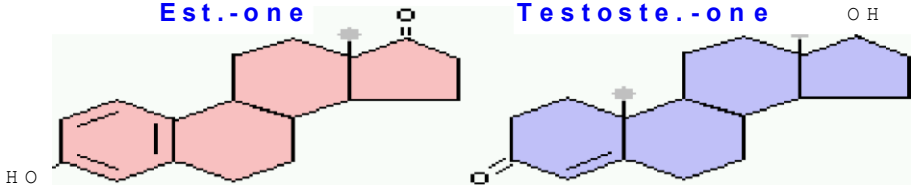


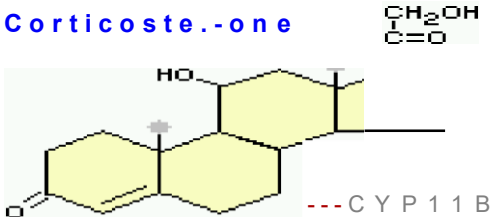


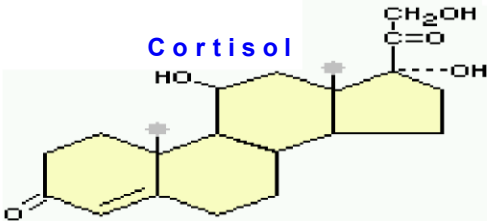


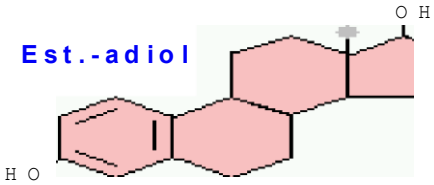


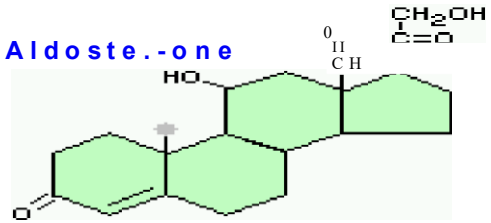












- Major progestagen
- Major mineralocorticoid
- Major glucocorticoid (species variation)
- Major gonadal estrogens
- Major gonadal androgen

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

- 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

Hair Cycle Arrest

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

Arguments against 21-OH deficiency

- No mutations in 21-OH gene

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
  - No known association with hair growth
  - Looking for any variations in this region

- Have excluded:
  - CTSL2 gene
  - PTCH2 gene

Atypical Hyperadrenocorticism

Dogs with out "classic" clinical signs of HAC

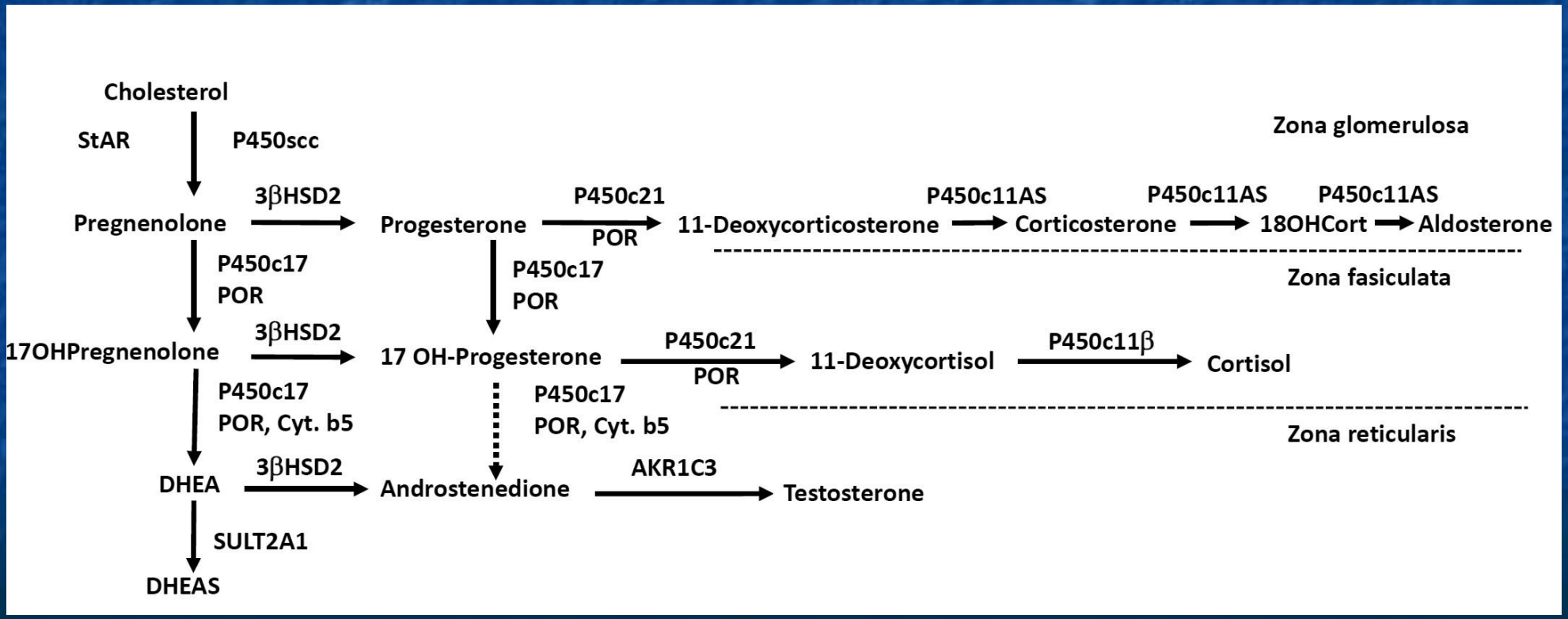
Congenital adrenal hyperplasia (human)

- 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

7Endocrine 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

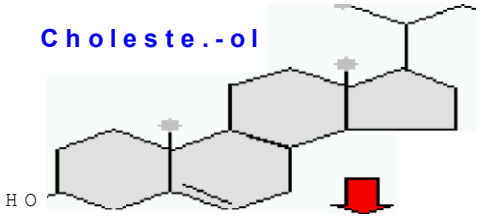
Trilostane

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



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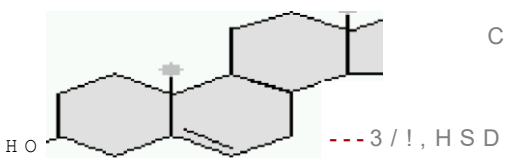

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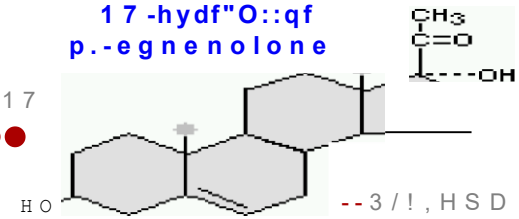

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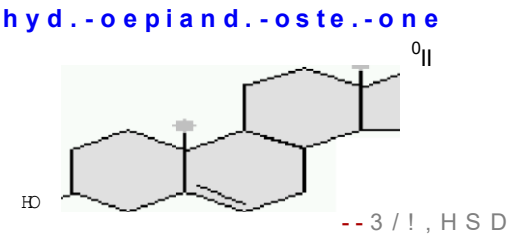
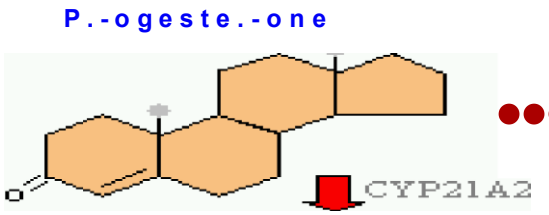
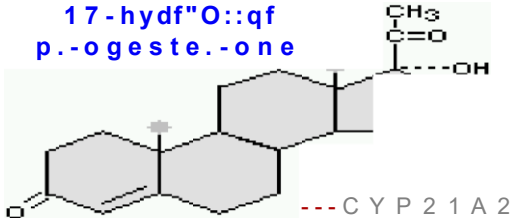
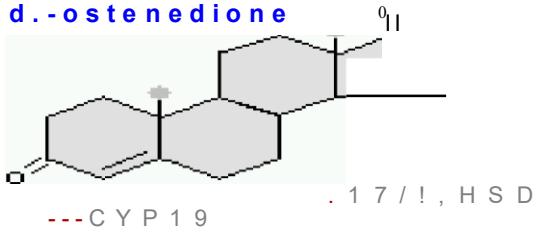
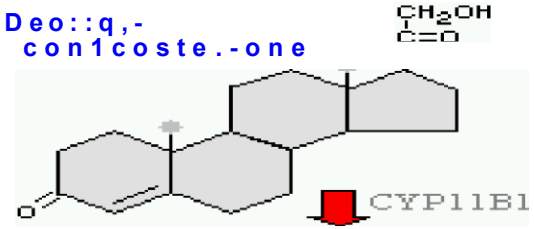
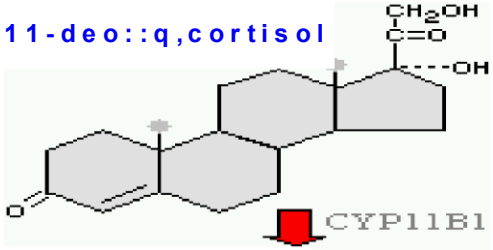


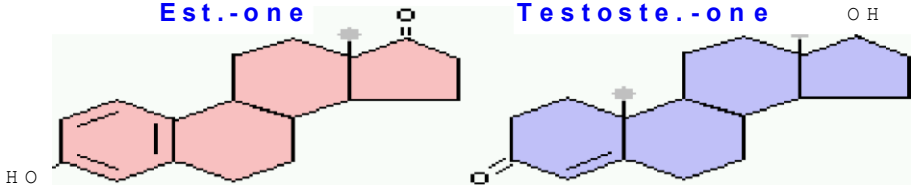


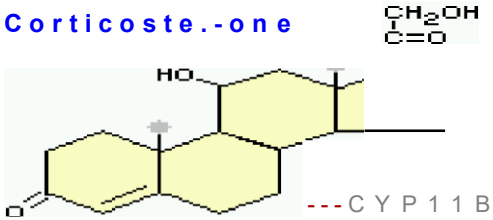


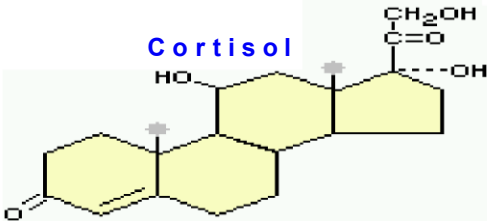


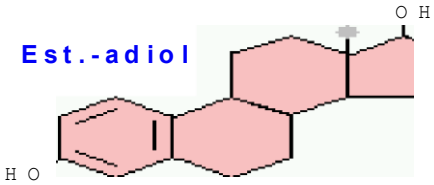


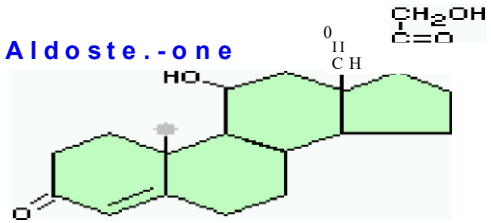












- Major progestagen
- Major mineralocorticoid
- Major glucocorticoid (species variation)
- Major gonadal estrogens
- Major gonadal androgen

Vetoryl® (trilostane)

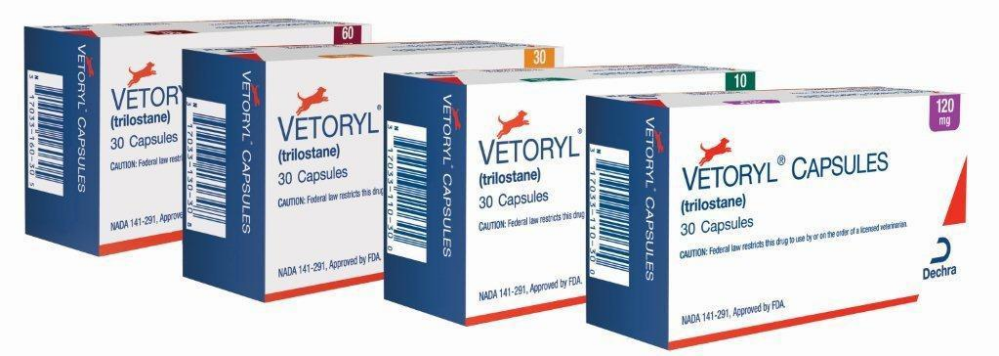
Product Characteristics

10, 30mg, 60 and 120 mg capsules

Blister packs of 30

Dose 1-2 mg/kg SID

Ideally start LOW



Dose in morning – easier for monitoring

Vetoryl® Monitoring

Electrolytes & ACTH stimulation test (4-6 hours post dosing)

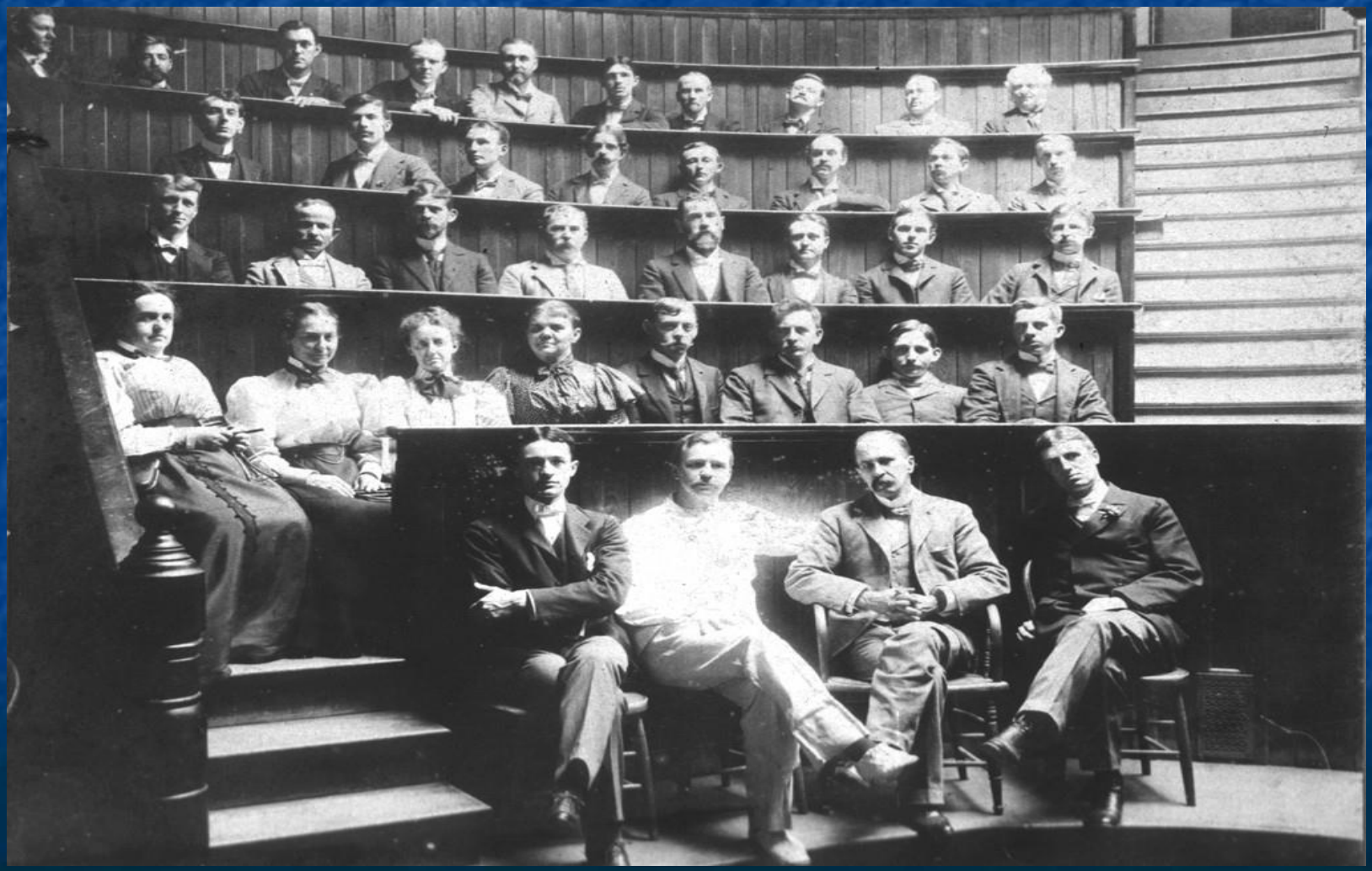
- Pre-treatment
- 10 days, 4 weeks, 12 weeks
- Every 3 months
- Each dose adjustment

Assess clinical signs

Vetoryl® - Adverse Reactions

- Rare reports of adrenal necrosis
  - Mediated by rising ACTH levels
- Unmask arthritis or inflammatory dermatitis
- Sudden death

Making the Choice



Goals of Any Therapy

Address Primary Disorder

Control of Clinical Signs

Prevention of Treatment Related Side-Effects

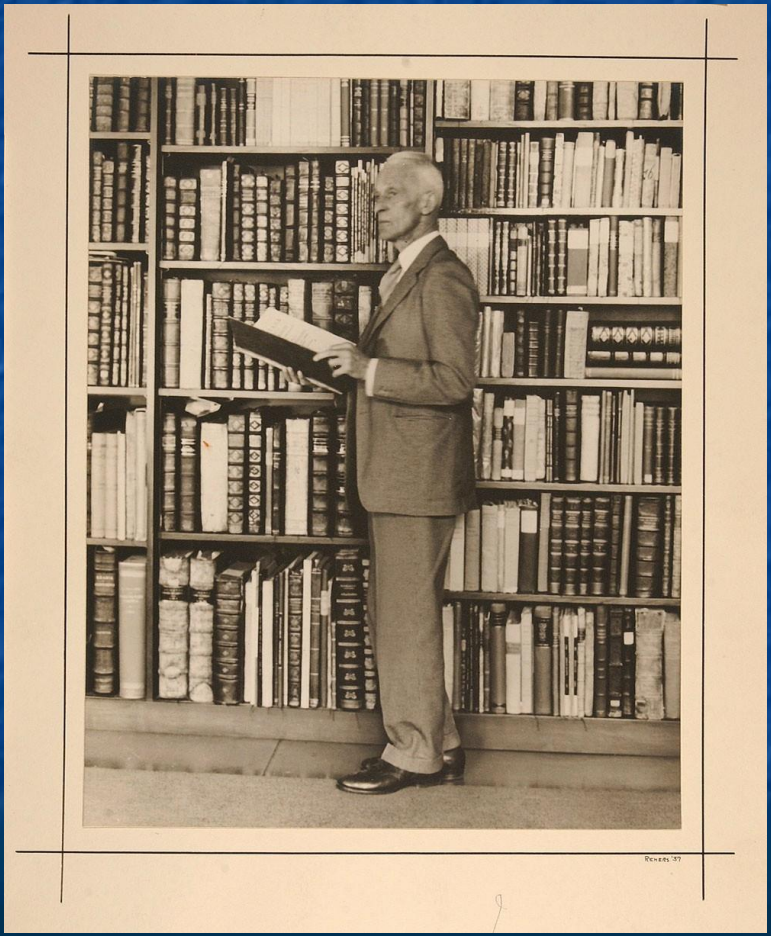
Cost

Does it require treatment ?

Therapy tailored to the individual patient

- History
- Physical examination
- Laboratory evaluation
- Severity of clinical signs

Not all dogs and/or all signs will show a complete response to any therapy for AH



Treatment Options

What I Do

Melatonin – Initial Treatment

Trilostane – Melatonin failures

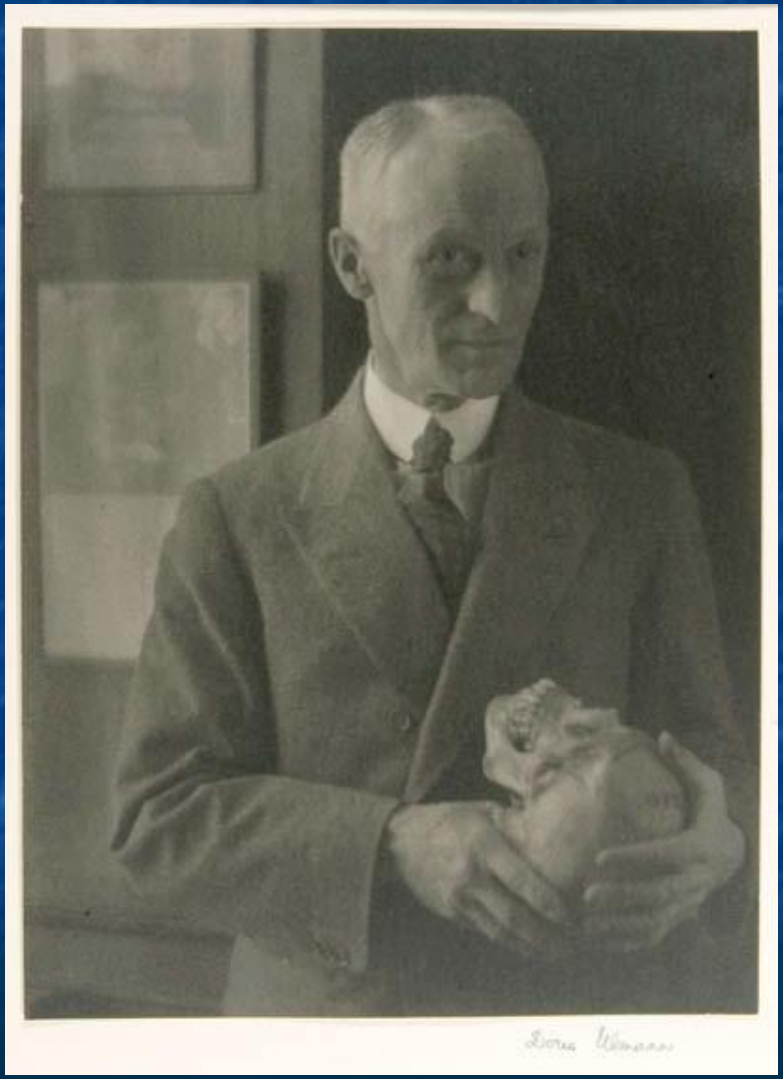
Sweater – Safe and effective

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