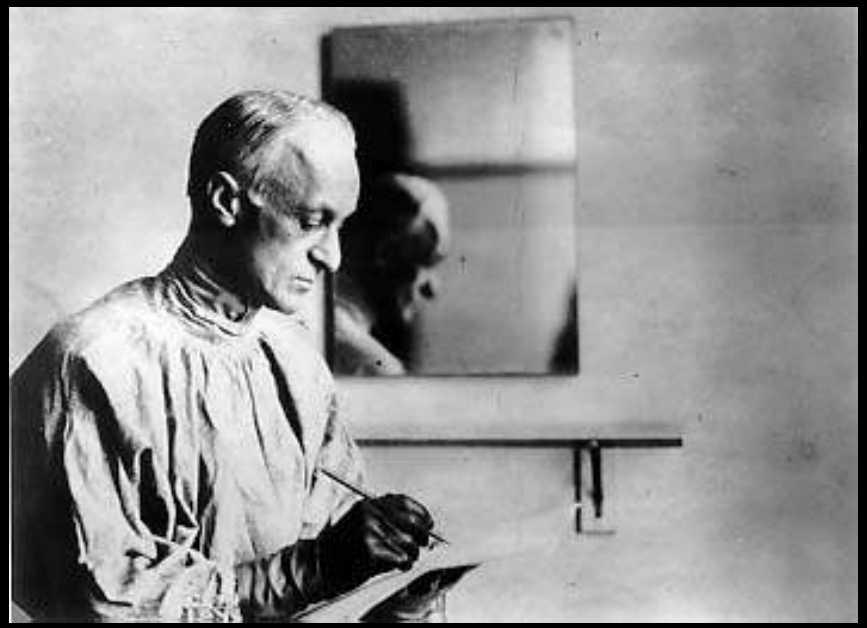
CANINE HYPERADRENOCORTICISM

Pathogenesis
Diagnosis
And
Treatment



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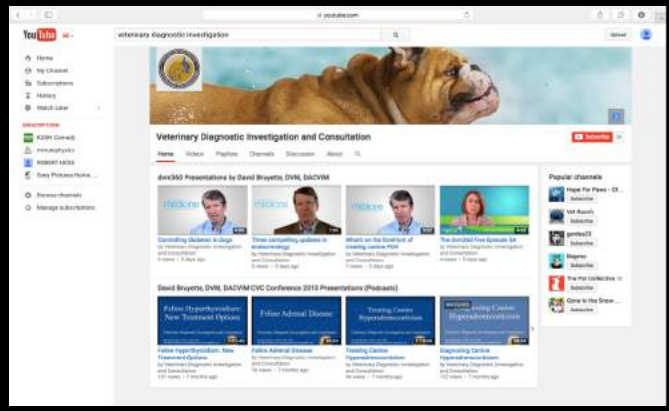

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INTRODUCTION

People:

- Third most common intracranial tumor (10-15%)
- Incidentaloma's in 1 in 6 adults (16 %)
- Clinically apparent tumor in 1 in 1000 adults
- Tumors causing Cushing's disease 1.2 – 2.4 per 1 million adults

Dogs:

- Tumors causing Cushing's disease 1.0 per 1,612 dogs
- 90,000 – 100,000 new cases/year

Histologic Lesions in 207 Canine Pituitary Glands

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Introduction

With increasing use of transsphenoidal hypophysectomy, especially for treatment of canine pituitary-dependent hyperadrenocorticism (PDH), surgical pathology has become vital for diagnosis and identification of histologic features with prognostic or therapeutic implications. To optimize the pathology of hypophysectomy specimens, archived pituitary sections from 207 dogs were reviewed to document histologic lesions.

Materials and Methods

All archived (2008-2015) pituitary sections were evaluated independent of the pathology report. Adenohypophyseal proliferations were classified as hyperplasia if <1 mm diameter without reticulin disruption (Gordon and Sweet technique), as microadenoma if 1-5 mm with disrupted reticulin framework, or as macroadenoma if >5 mm diameter. Corticotroph granularity was highlighted by periodic acid-Schiff (PAS). Immunohistochemistry (IHC) was used in selected cases for adrenocorticotrophic hormone (ACTH), growth hormone (GH), melanocyte stimulating hormone (MSH), and Ki-67.

Results

Of the 207 pituitary glands, 10 were hypophysectomy specimens; the remainder had been collected postmortem. The dogs were 115 female (81 spayed) and 92 male (59 castrated), aged 1 day-17 yr. (median, 9 yr.).

Nodular adenohypophyseal proliferations were found in 79 pituitary glands (Table 1, Fig. 1), including 36 listed as unremarkable in the postmortem pathology report. In all but 1 case (a growth hormone adenoma without apparent endocrinopathy), the proliferative cells were corticotrophs. Dogs with adenohypophyseal proliferation were older (median, 11 yr.) than unaffected dogs (median, 7 yr.). Breed or sex predilection was not evident.

TABLE 1: Features of 79 Adenohypophyseal Proliferations

Classification	Diameter (mm)	Reticulin Network	No. Dogs	Clinical or histologic evidence of PDH*
Hyperplasia	<1	Expanded	40 (51%)	17/40
Microadenoma	1-5	Disrupted	22 (28%)	16/22
Macroadenoma	>5	Disrupted	17 (21%)	12/17

*Based on PDH diagnosis on the pathology submission form or histologic evidence of adrenocortical hyperplasia.

Secondary neoplasms found in 15 pituitary glands (Table 2) included multicentric lymphoma, gliomatosis cerebri, metastatic carcinomas (nasal, urothelial, and carcinoma of unknown origin), metastatic melanoma, and local extension of ependymoma, craniopharyngioma, suprasellar germ cell tumor, and meningioma.

TABLE 2: Secondary Neoplasms in 15 Pituitary Glands

Neoplasm	Details	No. Dogs
Lymphoma	Multicentric	4 (1.9%)
Metastatic carcinoma	Urothelial, nasal, & unknown origin	3 (1.4%)
Ependymoma (3rd ventricle)	Local extension	2 (1.0%)
Craniopharyngioma	Local extension	2 (1.0%)
Metastatic melanoma	Primary tumor in oral mucosa	1 (0.5%)
Gliomatosis (oligodendroglial)	Extension from cerebrum	1 (0.5%)
Germ cell tumor (suprasellar)	Local extension	1 (0.5%)
Meningioma (suprasellar)	Local extension	1 (0.5%)

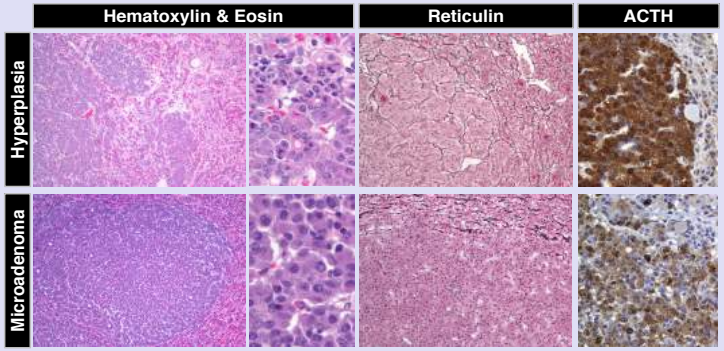
Miscellaneous lesions (Table 3) included hypophysitis, hemorrhage and necrosis, a pituicytoma, and adenohypophyseal atrophy. Craniopharyngeal duct cysts were common incidental findings, often accompanying other lesions, in 32 dogs. In 91 (44%) dogs, the pituitary gland was within normal histologic limits.

TABLE 3: Miscellaneous Pituitary Lesions in 41 Dogs

Lesion	Details	No. Dogs
Hypophysitis	Lymphocytic, GME, and blastomycosis	3 (1.4%)
Hemorrhage and necrosis	Unknown cause	4 (1.9%)
Pituicytoma	Pars nervosa	1 (0.5%)
Adenohypophyseal atrophy	Bilateral adrenocortical carcinoma	1 (0.5%)
Craniopharyngeal duct cysts	Incidental finding; sole lesion in 13 dogs	32 (15.5%)

Results (continued)

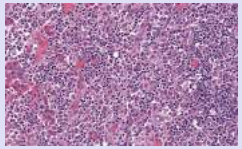
Figure 1: Comparison of Corticotroph Hyperplasia and Microadenoma



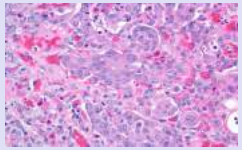
Hyperplastic nodules (top row) were multiple, usually <1 mm in diameter, and composed of hypertrophied cells with densely granulated basophilic cytoplasm. Note acidophils in adjacent normal adenohypophysis. The reticulin pattern is expanded, but intact. Cells in a hyperplastic nodule have intense ACTH immunoreactivity.

Microadenomas (bottom row) were 1-5 mm in diameter and composed of hypertrophied cells with densely granulated basophilic cytoplasm. Note acidophils in adjacent normal adenohypophysis. The reticulin pattern is disrupted. Immunohistochemistry for ACTH is positive, but weaker than in hyperplastic nodules.

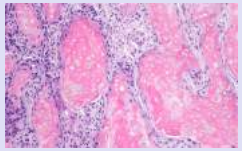
Figure 2: Secondary Pituitary Neoplasms & Miscellaneous Lesions



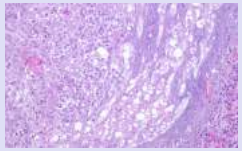
Lymphoma. The pituitary gland was enlarged by neoplastic lymphocytes that extended from hypothalamus through pars nervosa and into pars intermedia and pars distalis.



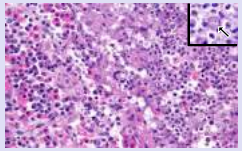
Metastatic urothelial carcinoma. Microscopic nests of neoplastic epithelial cells are scattered through the pars distalis. The hypophysis was one of many metastatic sites in this case.



Craniopharyngioma. The tumor obliterated the pituitary gland and extended into the brain of this 3-year-old dog with a 4-month history of polyuria and polydipsia.

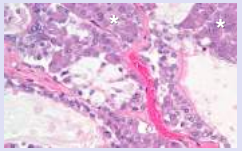


Suprasellar germ cell tumor in a 4-year-old dog. The germ cell component is in the upper left, lipid-laden hepatoid cells, in the middle. The adenohypophysis is compressed to the bottom right.



Pyogranulomatous hypophysitis (pars distalis) in a 3-year-old dog with systemic blastomycosis.

Inset: A yeast (arrow) in the center of a granuloma.



Craniopharyngeal duct cysts entrapped in a pituitary adenoma (asterisks) are lined by respiratory epithelium and filled with mucinous secretion.

Conclusions

- Adenohypophyseal proliferation, especially of corticotrophs, was the most common pituitary lesion, present in 79/207 dogs (38%).
- Dogs with adenohypophyseal proliferations were older than dogs without proliferation; breed or sex predilection was not detected.
- Hyperplasia and microadenoma were the most common adenohypophyseal proliferations among postmortem specimens. Macroadenoma was the most common diagnosis in hypophysectomy specimens.
- Reticulin histochemistry facilitated the distinction between hyperplasia and adenoma, especially in lesions ≤2 mm diameter or in fragmented biopsy specimens.
- Corticotrophs in hyperplastic nodules, microadenomas, and many macroadenomas were densely granulated; the granules were basophilic and PAS-positive. Larger adenomas were more likely to consist of sparsely granulated and pale eosinophilic (chromophobic) cells.
- Mitotic index was low (0-1) in pituitary adenomas, except for 1 macroadenoma with 7 mitotic figures in ten 400x fields.
- Neoplasms other than corticotroph adenomas were rare, as were non-neoplastic lesions, such as inflammation, necrosis, or severe atrophy.
- Craniopharyngeal duct cysts were common incidental lesions (15%).

Discussion

The most common diagnosis in this and previous pituitary reviews,[4,6,9] was corticotroph hyperplasia or adenoma of the pars distalis. These proliferative lesions are the major cause of spontaneous canine hyperadrenocorticism.[2,3] Other neoplastic or non-neoplastic diseases were rare as in previous studies.

Transsphenoidal hypophysectomy is increasingly used to treat dogs with PDH.[5,7,8] Histologic evaluation of pituitary biopsy specimens can provide clinically relevant information; however, their small and fragmented nature can make interpretation challenging. A systematic approach to the histologic examination of hypophysectomy specimens like that used by medical pathologists[1,10] will maximize their usefulness.

Based on this retrospective study, histopathology of canine hypophysectomy specimens should begin with HE-stained sections for initial diagnosis. In the case of adenohypophyseal proliferations, reticulin histochemistry helps to distinguish hyperplasia from neoplasia, and PAS histochemistry highlights the cytoplasmic granules of corticotrophs. An initial IHC panel with antibodies to ACTH, GH, and MSH serves to classify the proliferating cells as corticotrophs, somatotrophs, or melanotrophs, respectively. Expression of MSH also supports pars intermedia origin. Antibodies to other adenohypophyseal trophic hormones will be needed for the few cases that express none of the 3 markers. Because the mitotic index is typically low in pituitary adenomas, IHC for Ki-67 may provide a more meaningful proliferation index.

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Acknowledgements

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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

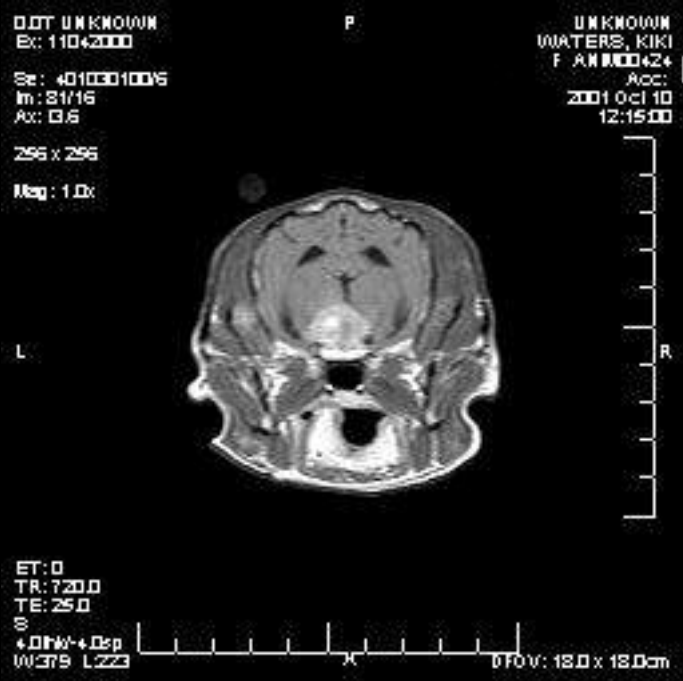
Atypical Hyperadrenocorticism

PATHOPHYSIOLOGY

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

TYPES OF PITUITARY PATHOLOGY

Pituitary carcinoma

Pituitary hyperplasia

Adenoma of pars distalis

~70% of dogs with PDH

Adenoma of pars intermedia

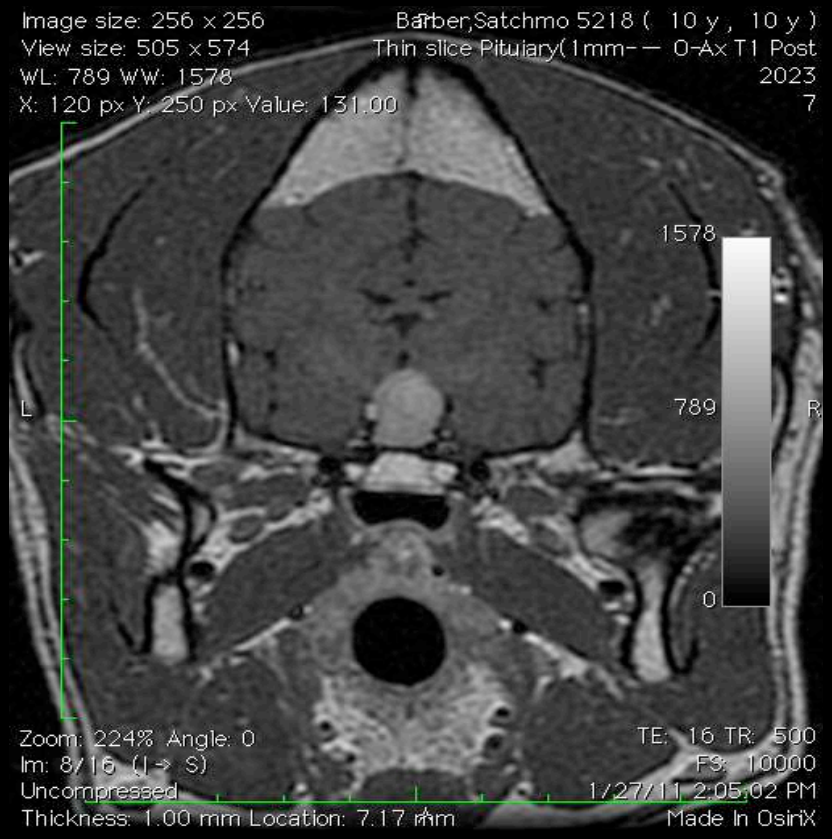
~ 20 - 30% of dogs with PDH

PITUITARY-DEPENDENT HYPERADRENOCORTICISI

Normal Pituitary Size

P/B ratio < .31

Pituitary height
3.5 – 7 mm



PITUITARY-DEPENDENT HYPERADRENOCORTICISM

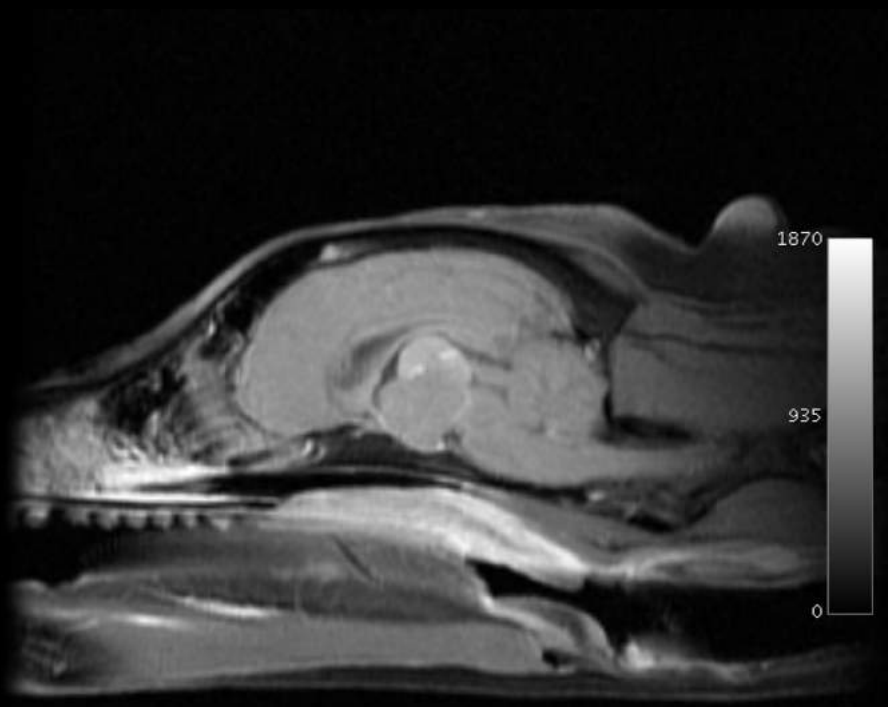
Pituitary Size

Enlarged in 55 – 68 %

P/B ratio .32 - .67

Tumors > 1 cm in 31 %

Neurologic signs with masses greater than 8.5 mm



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

ETIOLOGY OF PDH: ROLE OF DOPAMINE

Recent evidence suggests dopamine may play a role in regulation of the hypothalamic pituitary adrenal (HPA) axis

Dopamine inhibits secretion of ACTH primarily from the pars intermedia

Dopamine appears to have an inhibitory effect on proopiomelanocortin, a precursor of ACTH in the pars distalis

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

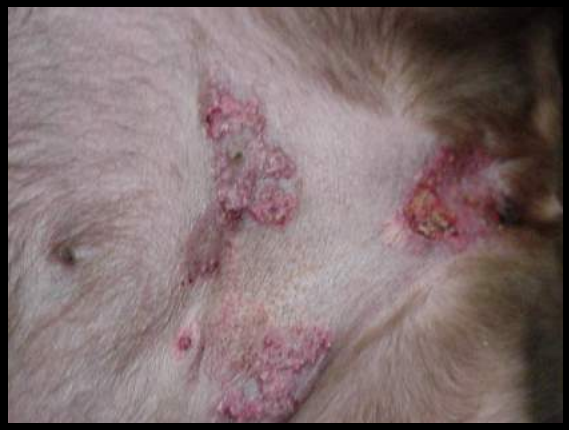
Alopecia

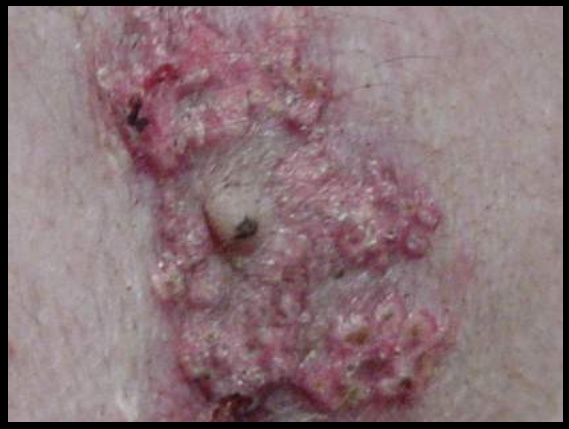
Cutaneous hyperpigmentation

Calcinosis cutis

Pyoderma

Comedones





CLINICAL SIGNS OF CANINE CUSHING'S DISEASE

Behavioral signs:

Change in greeting behavior

Change in activity level

Change in responsiveness

Abnormal sleep/wake cycles

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 CUSHING'S DISEASE IN DOGS

ACTH Stimulation Test
Low Dose Dexamethasone Suppression Test (LDDS)
Urine Cortisol:Creatinine Ratio (UCCR)
Salivary Free Cortisol Testing
Hair Cortisol Concentrations

SCREENING TESTS

Low Dose Dexamethasone Suppression Test

- Diagnostic in 90% of dogs with PDH or ADH
- Requires 8 hour testing period
- Cannot be used to diagnose iatrogenic Cushing's disease

SCREENING TESTS

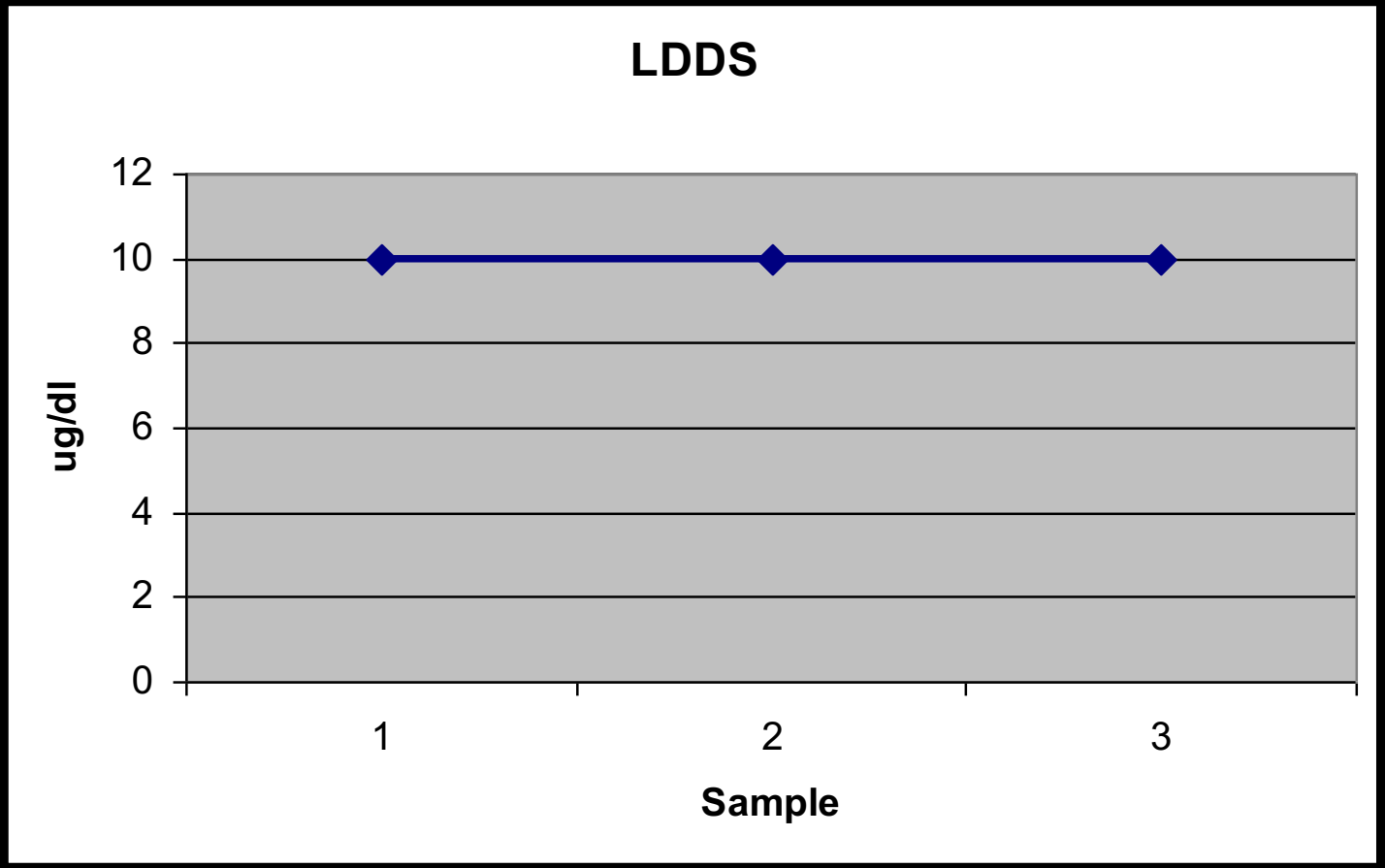
LDDS

Elevated 8 hour sample = HAC

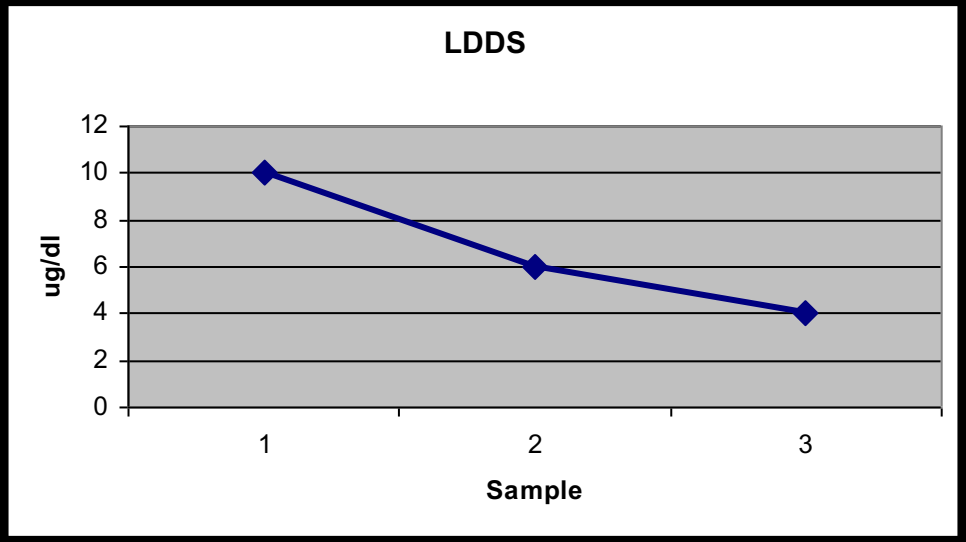
Compare 4 and 8 hour levels to Pre

50% suppression = PDH

SCREENING TESTS



SCREENING TESTS



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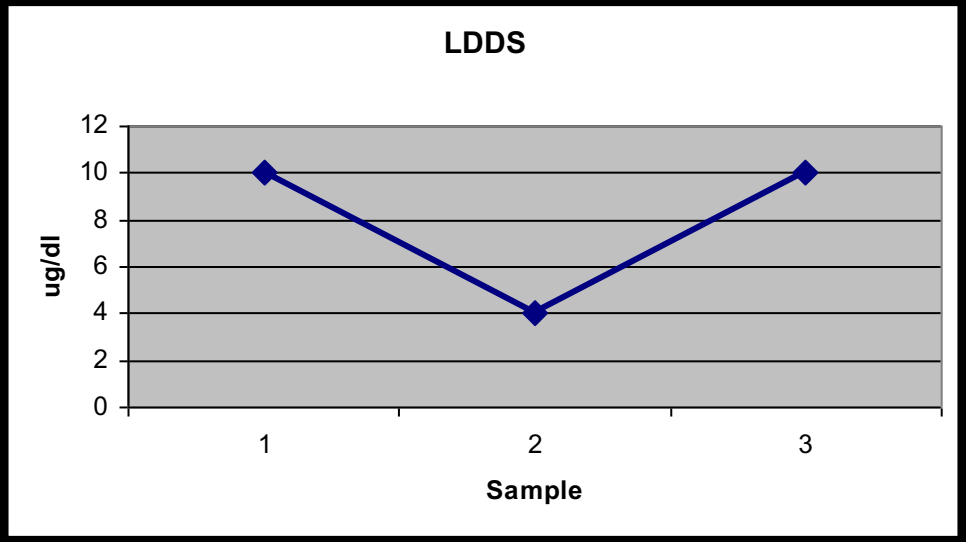
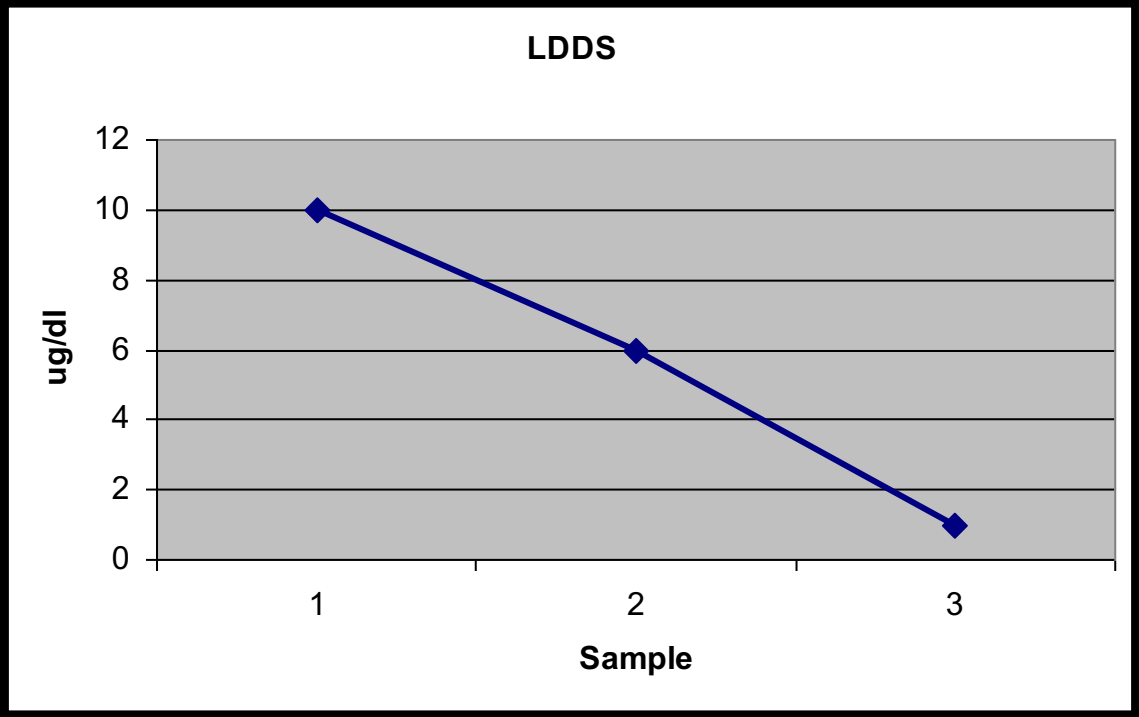


SCREENING TESTS



SCREENING TESTS

ACTH Stimulation Test

- Diagnostic in 80-85% of dogs with PDH or ADH
- Can be used to diagnose iatrogenic Cushing's
- Requires a baseline sample and 1 hour (Cortrosyn) or 2 hour (IM gel) sample post ACTH administration

SCREENING TESTS

Urine Cortisol:Creatinine Ratio

- Sampling errors
- High sensitivity
- Low specificity
- High number of false positives

DISCRIMINATORY TESTS: DIFFERENTIATE PDH VS ADH

Most commonly used tests:

- High Dose Dexamethasone Suppression Test
- Endogenous ACTH concentrations
- Ultrasonic examination of adrenal glands

HIGH DOSE DEXAMETHASONE SUPPRESSION TEST

Key Points:

100% of dogs with ADH will not suppress

75% of dogs with PDH will suppress

25% of PDH dogs will not suppress

Therefore lack of suppression is non-diagnostic

ENDOGENOUS ACTH LEVELS

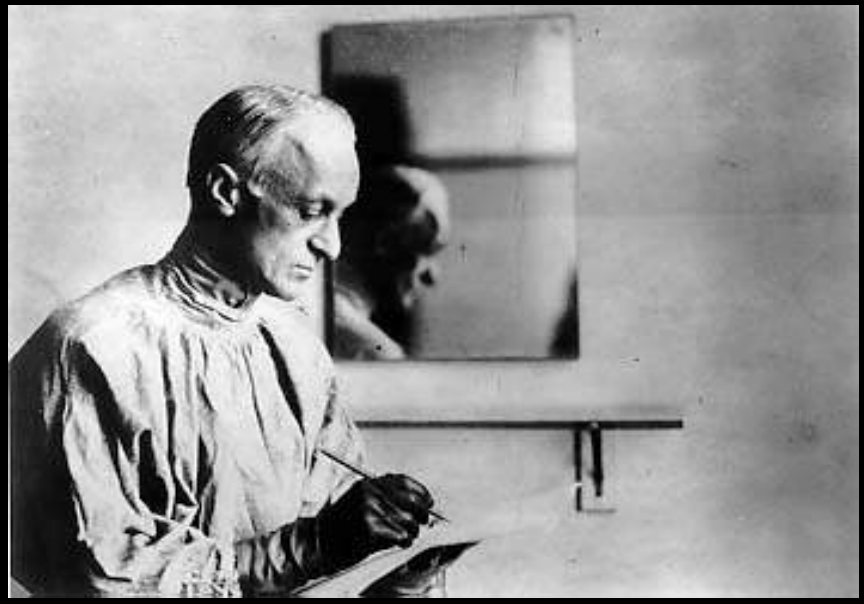
PDH dogs should have normal or increased ACTH concentrations

ADH dogs should have decreased ACTH concentrations

Some overlap occurs with normal dogs

CANINE HYPERADRENOCORTICISM

Deciding on
Treatment Options



TREATMENT OPTIONS FOR CANINE PDH

o,p’ DDD - Lysodren

l-deprenyl - Anipryl

Trilostane – Modrenal, Vetoryl

Ketoconazole – Nizoral

Bromocriptine

Metyrapone - Metopirone

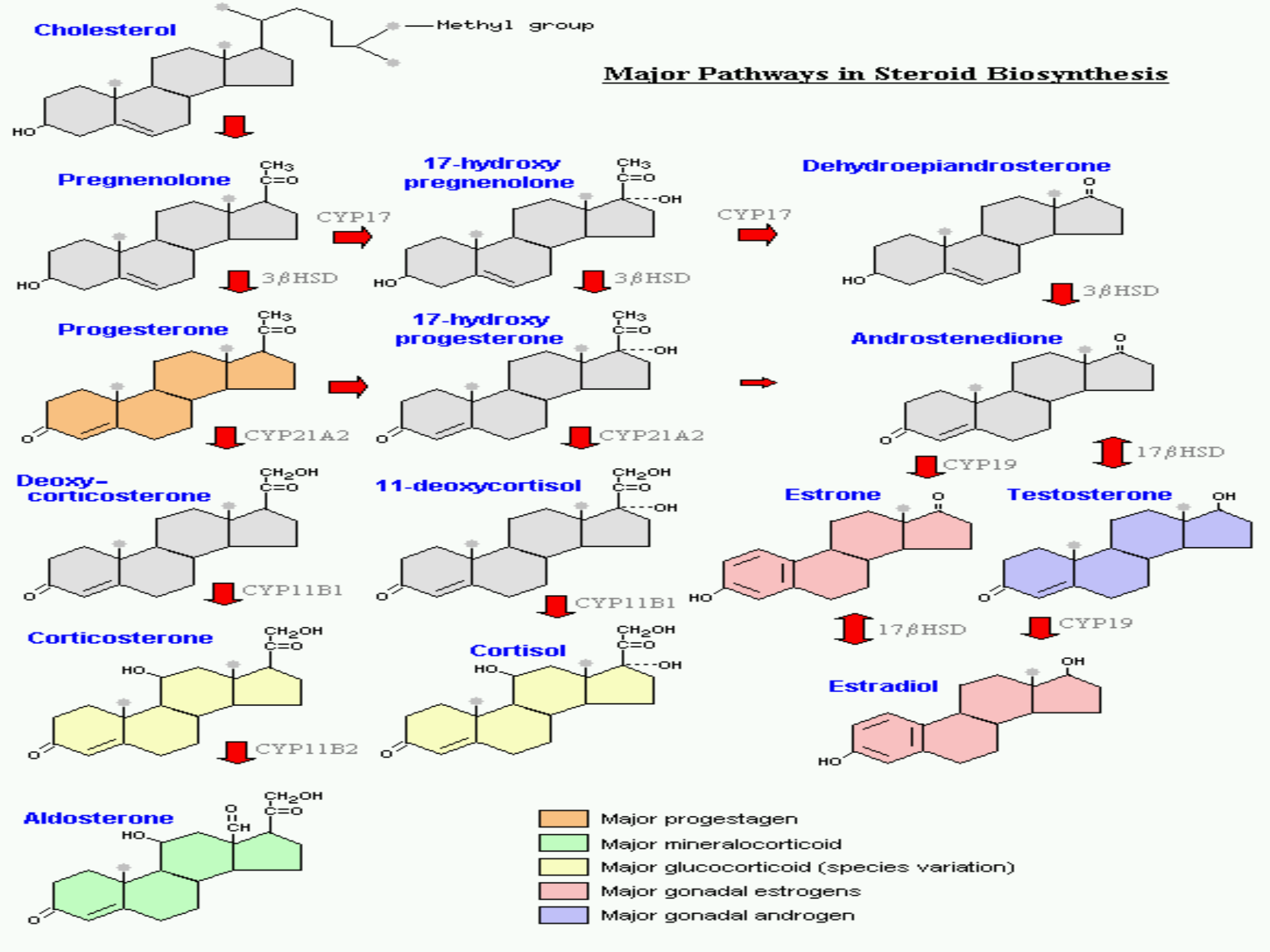
TRILOSTANE

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


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

VETORYL® (TRILOSTANE)

Product Characteristics

5 , 10, 30mg, 60 and 120 mg capsules

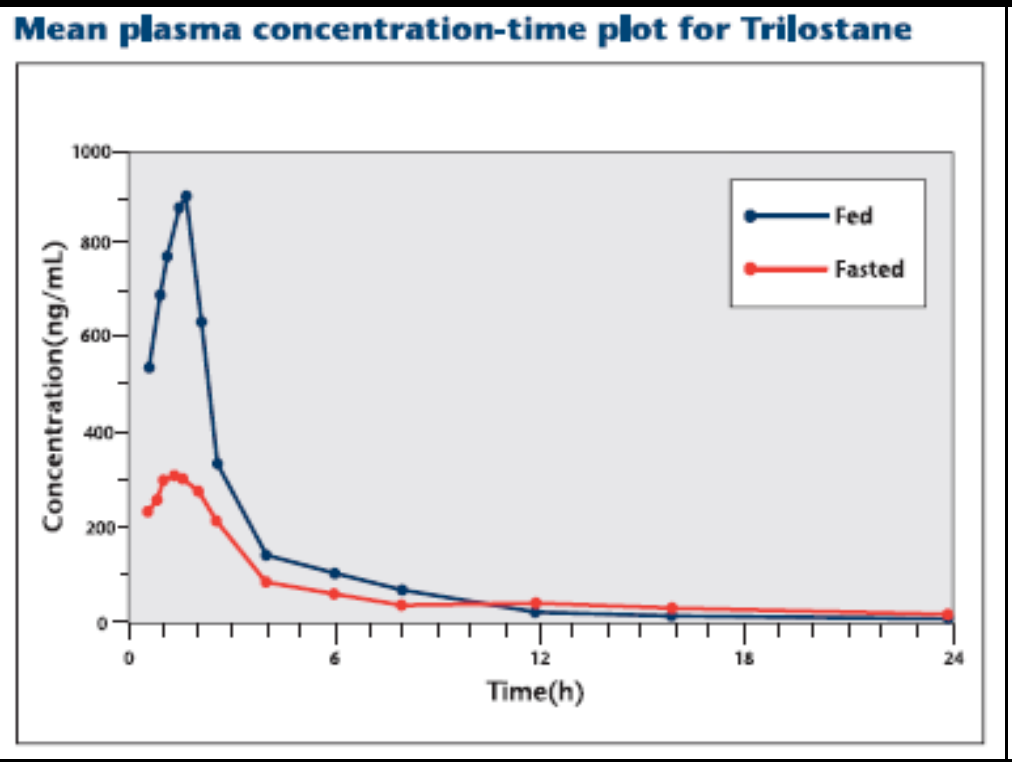
Blister packs of 30

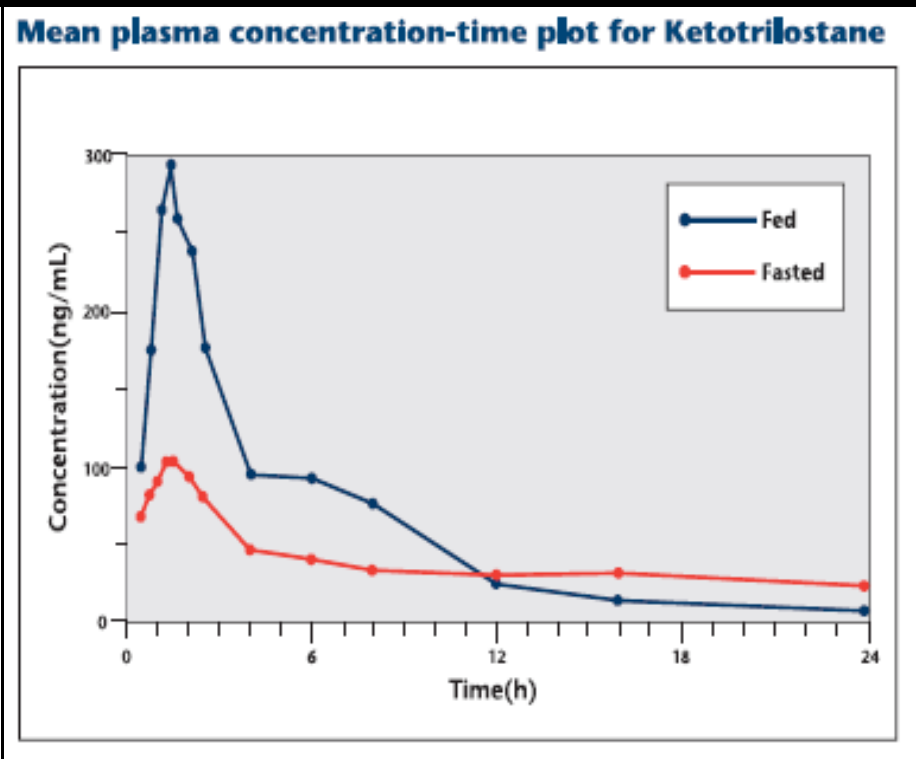
Dose 1-2 mg/kg SID

Ideally start LOW

Dose in morning – easier for monitoring

VETORYL® (TRILOSTANE) ACTIVITY

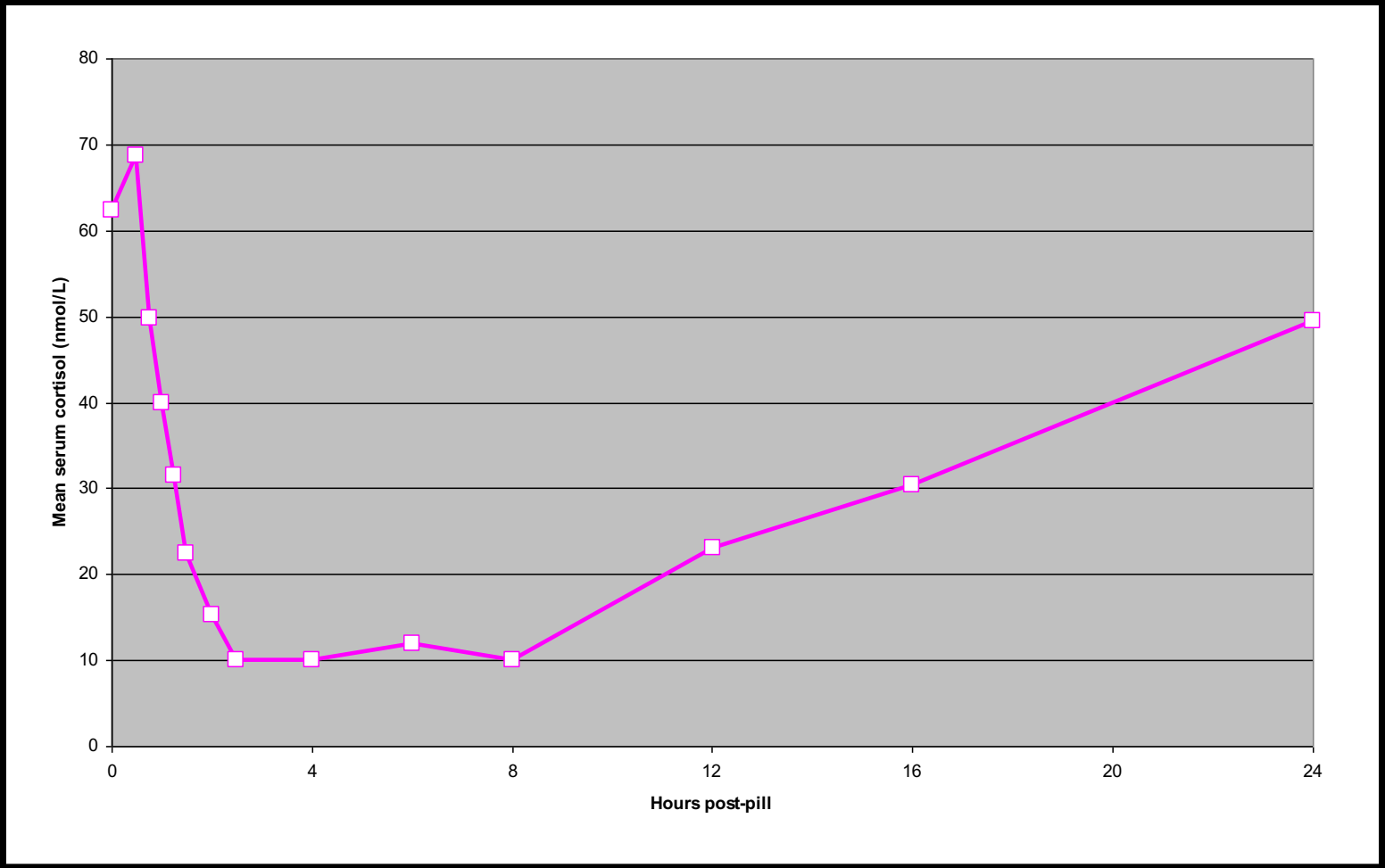




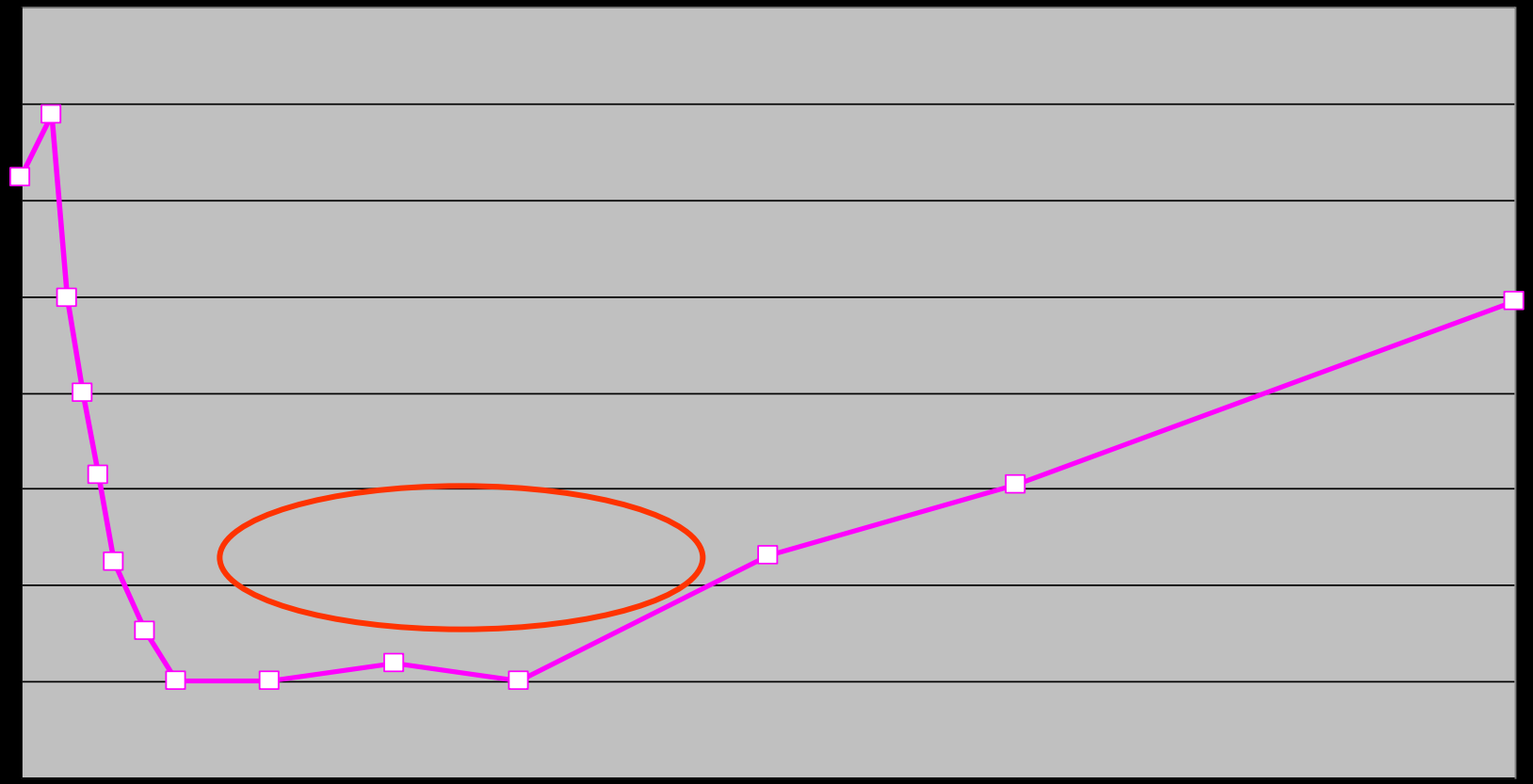
Rapidly absorbed from the gastrointestinal tract

Dosing with food significantly ↑ rate & extent of absorption

VETORYL® (TRILOSTANE) ACTIVITY



VETORYL® - SAMPLING TIME



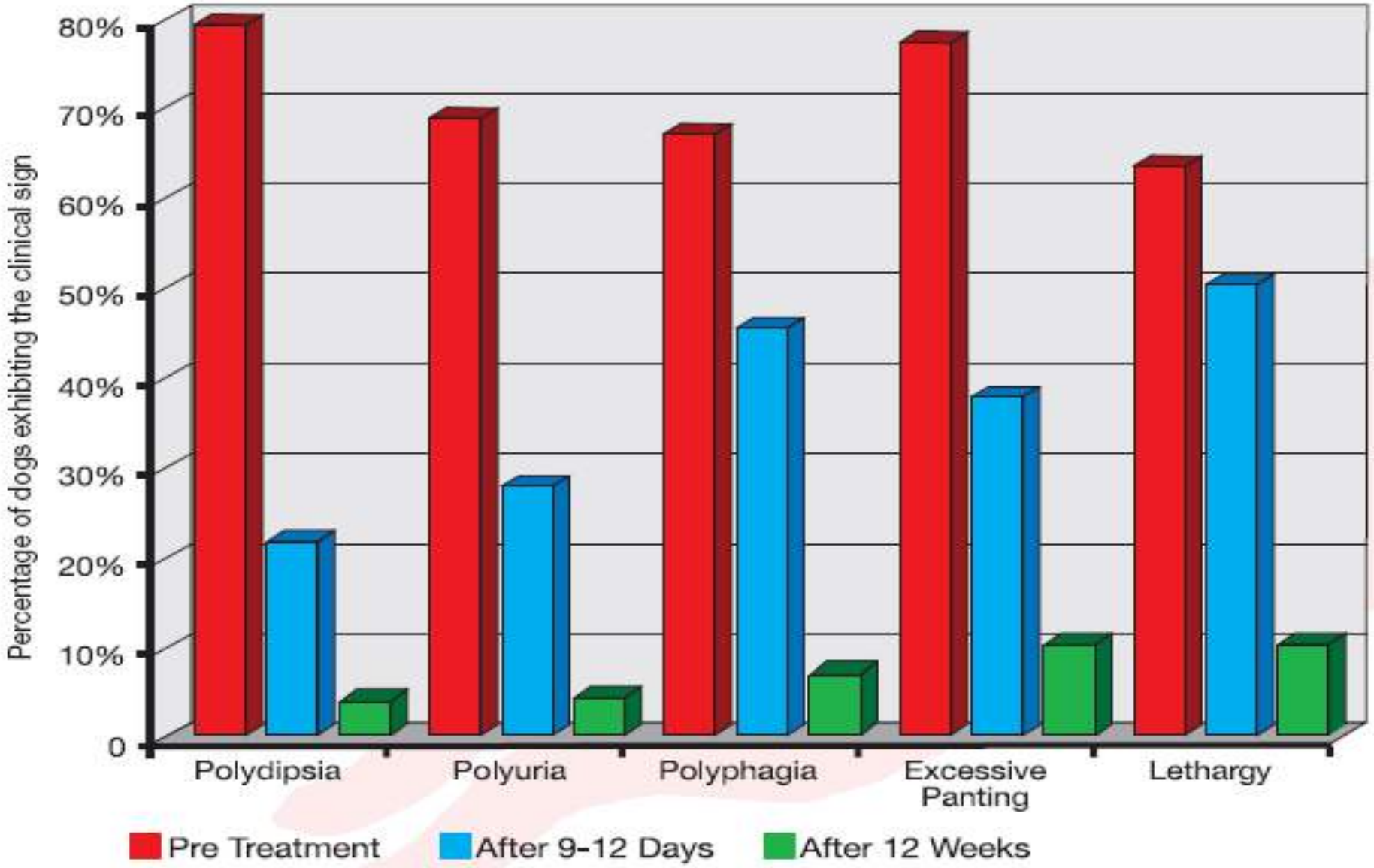
MONITORING

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

SURVEY OF OWNER PERCEPTIONS OF CHANGES IN CLINICAL SIGNS[4]



VETORYL® - ADVERSE REACTIONS

Rare reports of adrenal necrosis

- Mediated by rising ACTH levels

Unmask arthritis or inflammatory dermatitis

Sudden death

VETORYL ® – US CLINICAL STUDY

107 dogs enrolled (103 were deemed evaluable)

- Age range 6-16 years
- Body weight 3-53.5 kg

224 dogs screened

- 95 dogs w/ PDH; 5 dogs w/ FAT
  - 1 dog PDH + FAT
  - 6 dogs inconclusive localization

VETORYL ® – US CLINICAL STUDY

Conclusion –highly effective

77.3% success

Success criteria

Post-ACTH stim <9.1 ug/dL

Clinical improvement

MONITORING

Resting cortisol ?

Post-ACTH cortisol 1.5 - 9.1 µg/dL

Some recommend < 5.4 ug/dl
(4-6 hrs post dosing)

OPTIMISING VETORYL® TREATMENT

Increase in once daily dose required if:

Clinical signs not controlled

Post-ACTH cortisol > 9.1 ug/dl
(performed 4-6 hrs after dosing)

OPTIMISING VETORYL® TREATMENT

Twice daily dosing may be required if:

1. Clinical signs not controlled
2. 4 hour post-ACTH cortisol < 9.1 ug/dl and
3. ACTH stimulation test 22-24 hrs after dosing

Post-ACTH cortisol > 9.1 ug/dl

Value of ACTH Stimulation Testing ?

Pre-Vetoryl Cortisol: an improved monitoring protocol

Developed by Ian Ramsey BVSc, PhD, DSAM, Dipl. ECVIM-CA, FHEA, MRCVS, Federico Fracassi DVM, PhD, Dipl. ECVIM-CA, Nadja Sieber-Ruckstuhl PhD, Dr. med. vet, Dipl. ACVIM, Dipl. ECVIM-CA

History and clinical examination

The most important factor to consider when re-evaluating a dog receiving Vetoryl is to carefully consult with the owner regarding the dog's clinical response at home. This critical part of the assessment is often overlooked in a busy clinic but is vital to ensure good compliance, safety and optimal response to therapy.

Owners reporting at any time that their dog is unwell should be seen at their veterinary practice so that iatrogenic hypoadrenocorticism can be investigated (through cortisol results and the results of haematology, biochemistry and electrolyte analysis).

Pre-Vetoryl Cortisol

Suitable dogs

- Once- or twice-daily Vetoryl dosing
- Adrenal- or pituitary-dependent hyperadrenocorticism (HAC)
- Clinically well dogs (with or without signs of HAC)
- Calm dogs

Unsuitable dogs

- Aggressive dogs
- Stressed dogs (e.g. persistently barking)
- Unwell dogs

Appointment

- Book an appointment just before the next Vetoryl dose is due
- If the dog is normally given Vetoryl at an inconvenient time (e.g. 6 am) then ask owner to give at a convenient time from at least the day before (e.g. 9 am)
- Make sure owner has not given Vetoryl and that nothing stressful has happened that morning (e.g. vomiting, injury)
- Ensure the owner has completed the Quality of Life Questionnaire
- Take history* and examine the dog, checking for signs of HAC

Sample

- Take sample immediately after examination and before administration of Vetoryl
- 1 to 2 ml of blood in heparin or serum tube
- Can be separated and stored for up to 1 week
- Send to an external laboratory participating in an external quality assurance scheme (e.g. ESVE- or SCE- programmes) and preferably that uses a Siemens IMMULITE® – or a method that has been validated against this machine

VETORYL®

Life restored on every level

Pre-Vetoryl Cortisol: an improved monitoring protocol

Day 1
Vetoryl starting dose is approximately 2 mg/kg
Administer orally, once daily, with food

Day 10
History + Clinical examination

Clinically well

Continue Vetoryl treatment at current dose

Day 28
History +
Clinical examination

Clinically unwell

Stop Vetoryl treatment

Pre- and Post-ACTH Stimulation Test cortisols & analysis of serum electrolytes (in particular Na and K) immediately

Pre- and Post-ACTH Stimulation cortisols <1.5 ug/dl

Pre- or Post-ACTH Stimulation cortisols >1.5 ug/dl

Clinical signs probably due to hypocortisolism or hypoadrenocorticism
Treat symptomatically as required[5]

Unlikely to be hypocortisolism
Investigate other causes

Restart Vetoryl at lower dose when clinical signs of HAC recur or Post-ACTH cortisol > 5 ug/dl

Restart Vetoryl when well

Clinical signs of HAC[1]

No clinical signs of HAC

Pre-Vetoryl Cortisol*

1.5 ug/dl — 5.0 ± 15% ug/dl

Pre-Vetoryl Cortisol*

0 ug/dl — 1.5 ug/dl — 5.0 ± 15% ug/dl

If Pre-Vetoryl Cortisol values do not match the clinical picture contact Dechra Technical Services

Increase dose frequency[3]
or
Increase dose[4]

Re-evaluate case[2]
Consider lower dose[4]

Continue Vetoryl treatment at current dose

Re-evaluate case
Consider dividing current dose equally between morning and evening doses
If already dosing twice daily then consider small dose increase[4]

RETURN TO DAY 1

RE-EXAMINE IN 3 MONTHS AND RETURN TO DAY 28

RETURN TO DAY 1

TRILOSTANE

Twice a day dosing

0.2 – 2.5 mg/kg q 12 hours

3.0 – 3.5 mg/kg q 12 hours

TRILOSTANE VS LYSODREN

Survival Times

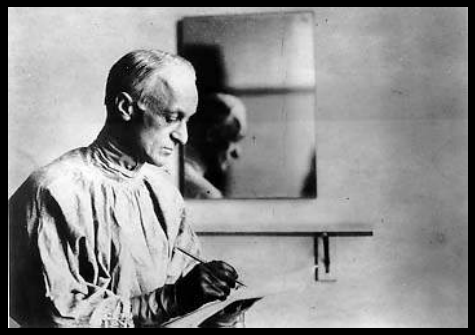
- Lysodren
  - 750 days
  - 720 days (non-selective)
- Trilostane
  - 930 days (BID)
  - 900 days (qD)
  - 662 (qD)

Upcoming Clinical Trials

1) SOM230, 2) CDK Inhibitor, or 3) Chimeric molecule

Based on clinical, hormonal and imaging data may proceed to surgery or continued monitoring

Microarray analysis looking for candidate genes



Acknowledgements:

Harvey Cushing, MD

Effects of hypophyseal transplantation following total hypophysectomy in the canine. Quart Jour Exper Physiol. 389-400, 1909

Experimental Hypophysectomy. Bull Johns Hopkins Hosp. 127-169, 1910.

"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 ?

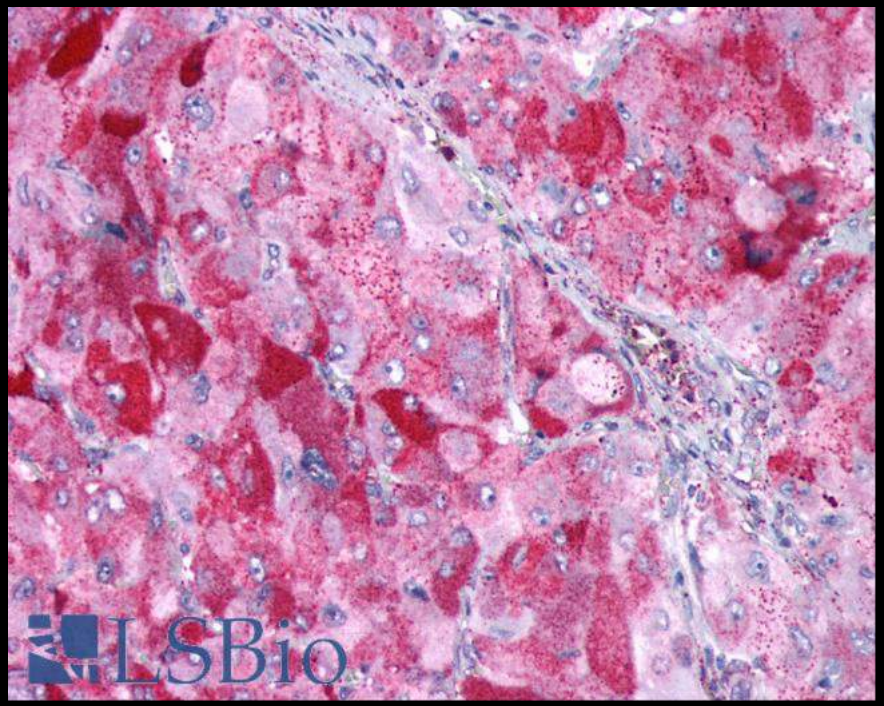
MEAL OR FOOD-INDUCED HYPERADRENOCORTICISM

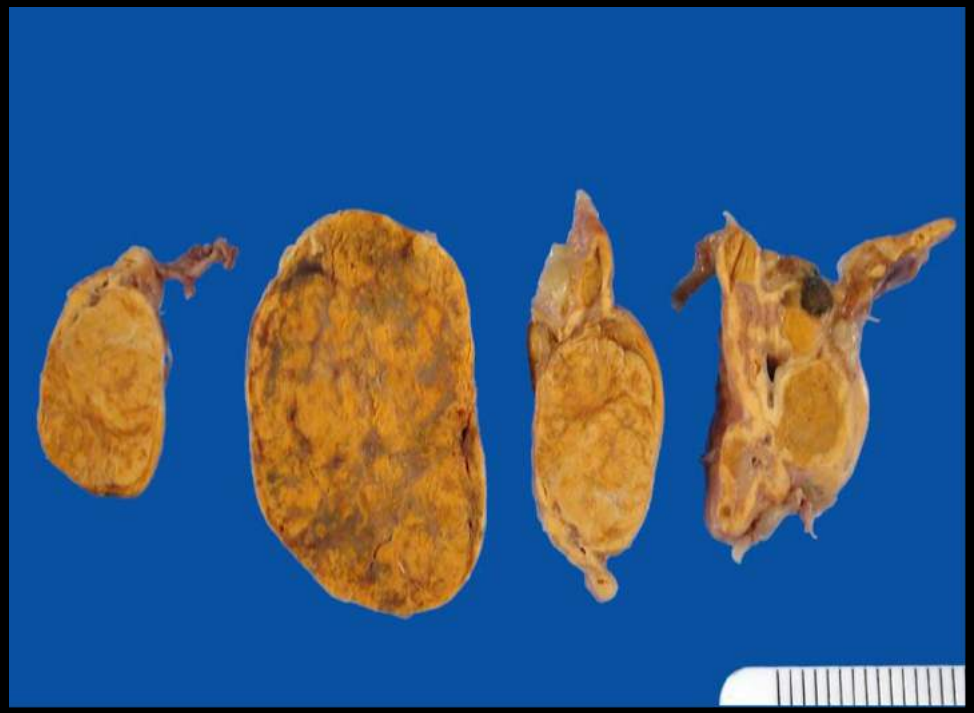
Dogs with “classic” clinical signs of HAC

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

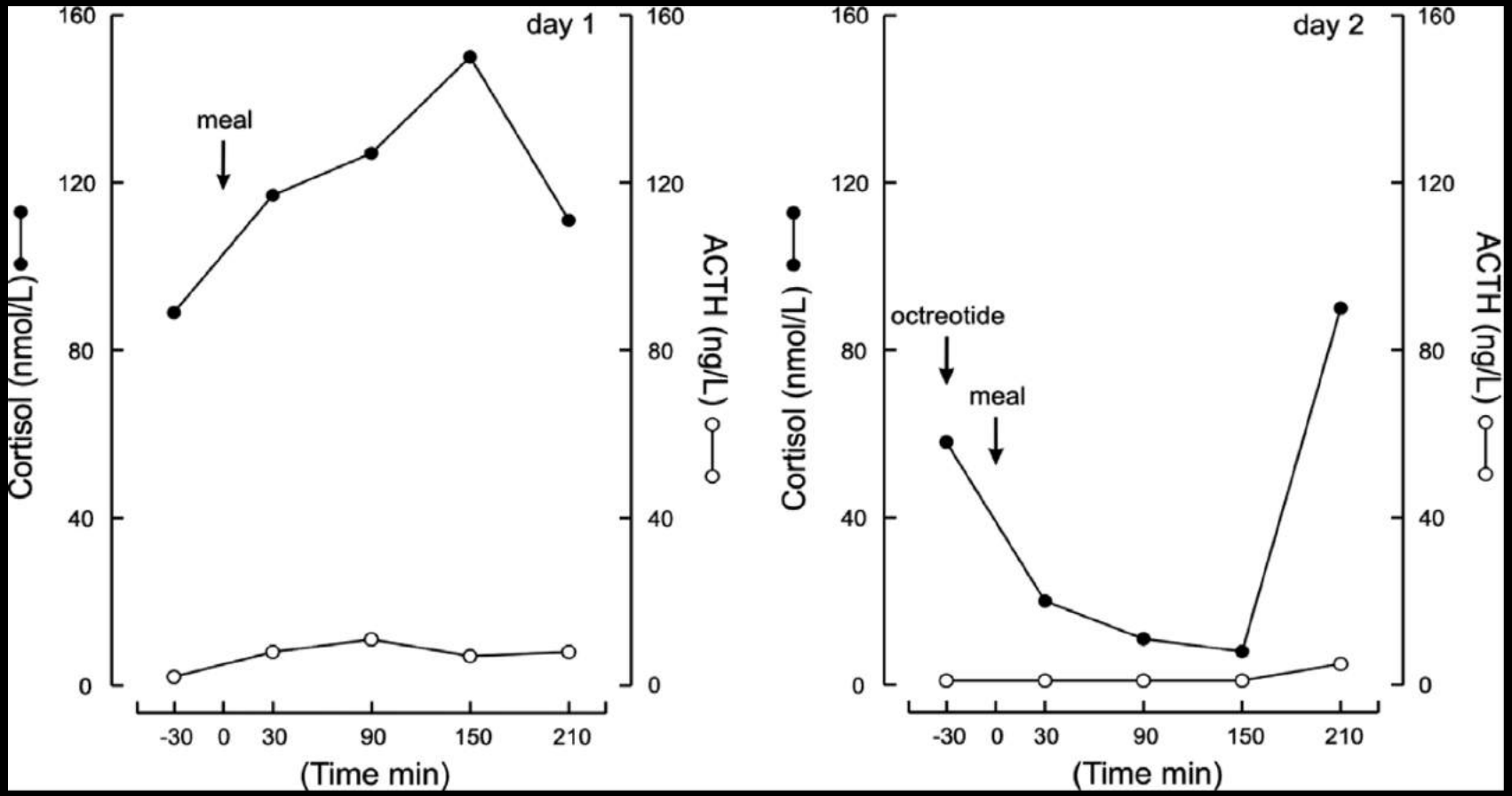
- Younger dogs
- Congenital aberrant expression of GIP receptors in the adrenal cortex

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

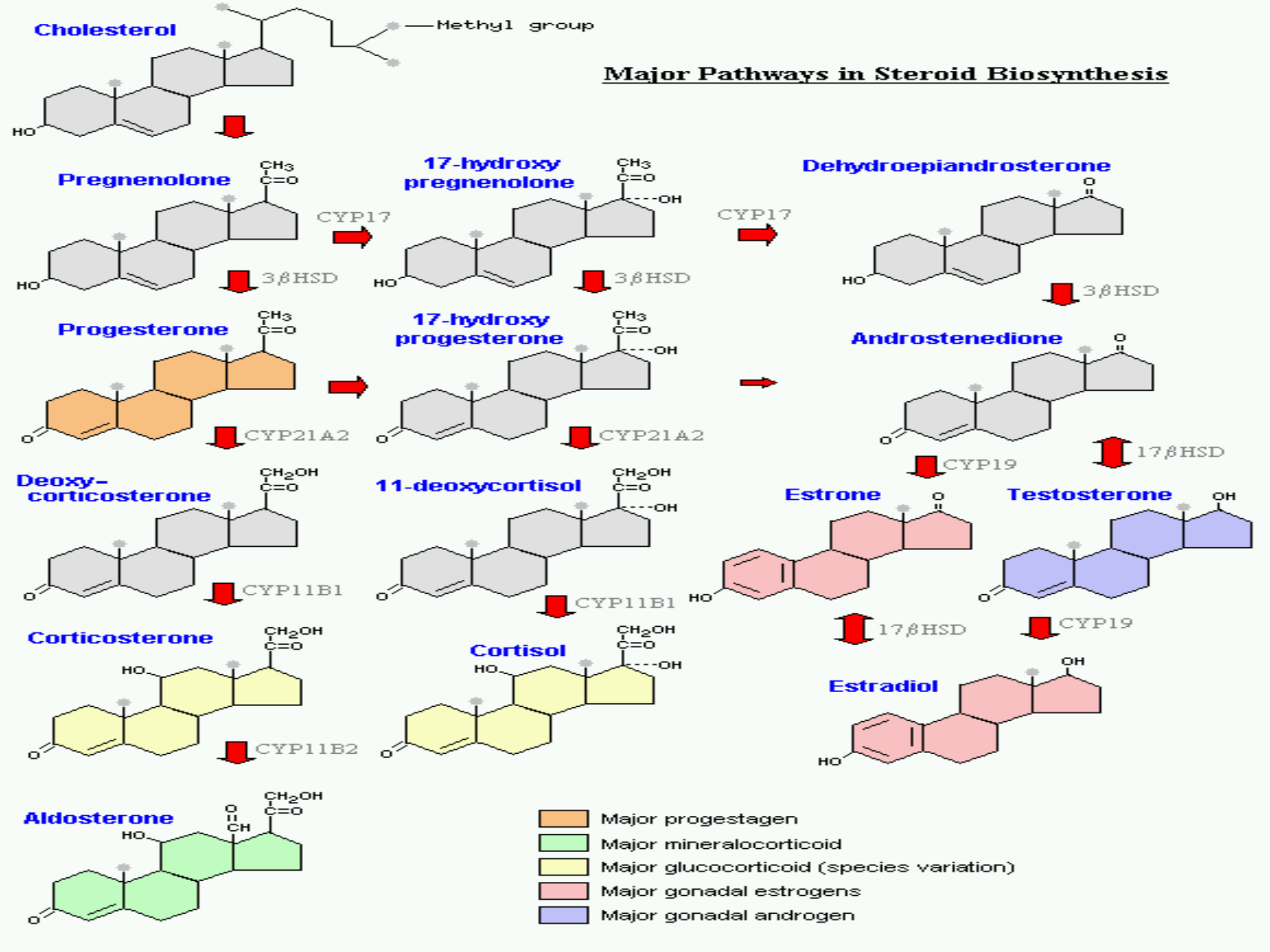
Normal or suppressed cortisol response to ACTH

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

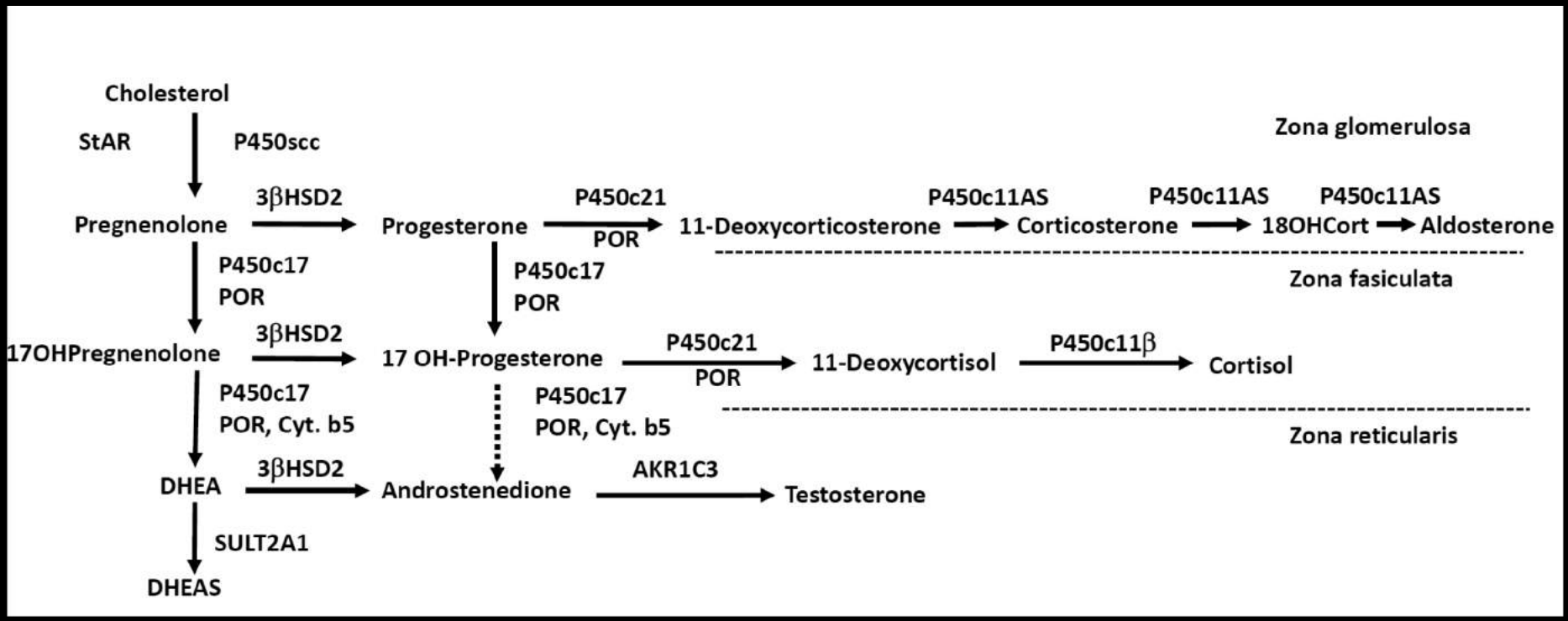
Congenital adrenal hyperplasia (human)

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

TRILOSTANE

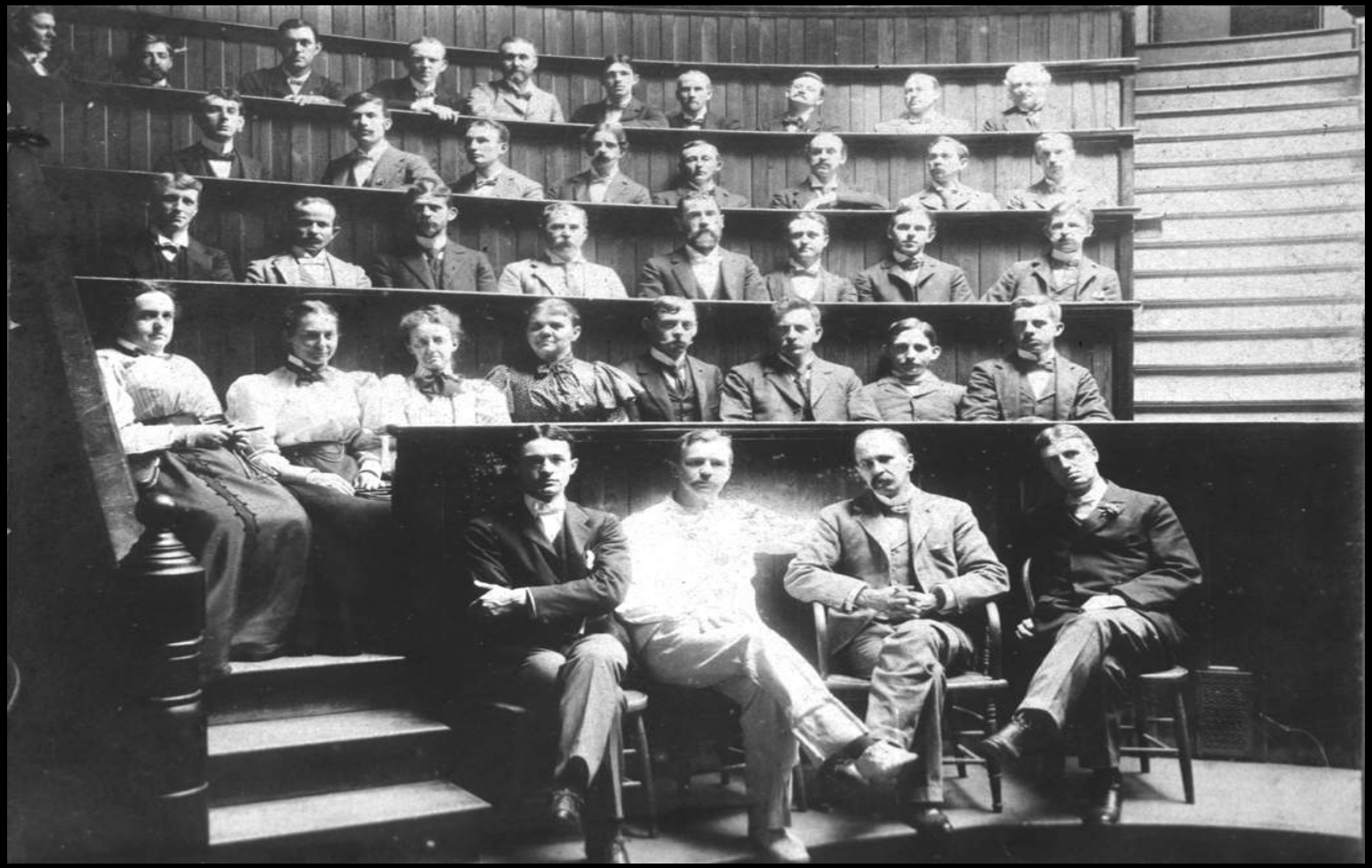
Adrenal enzyme inhibitor

- 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