Endocrinology for Veterinary Dermatologists

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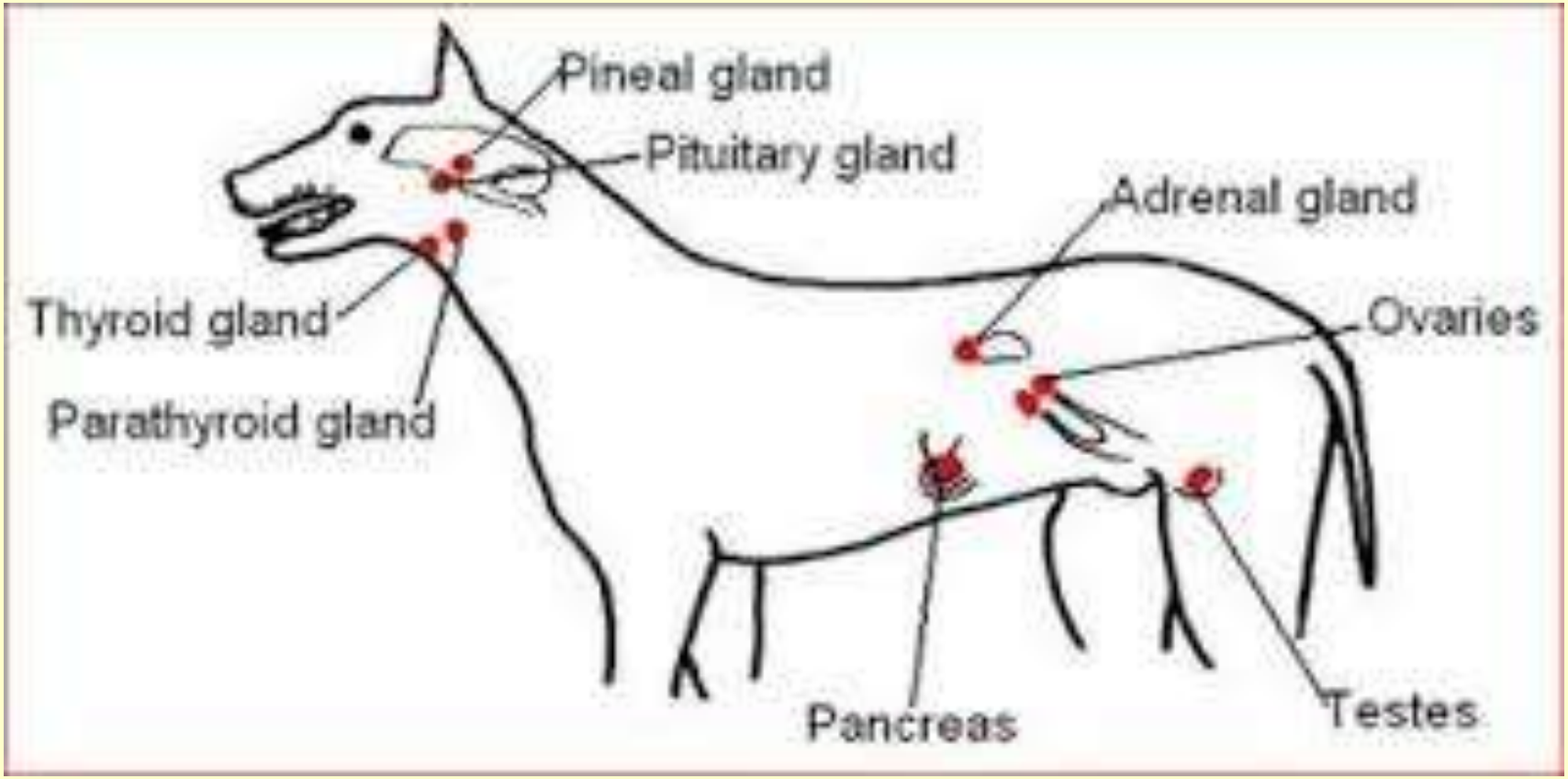
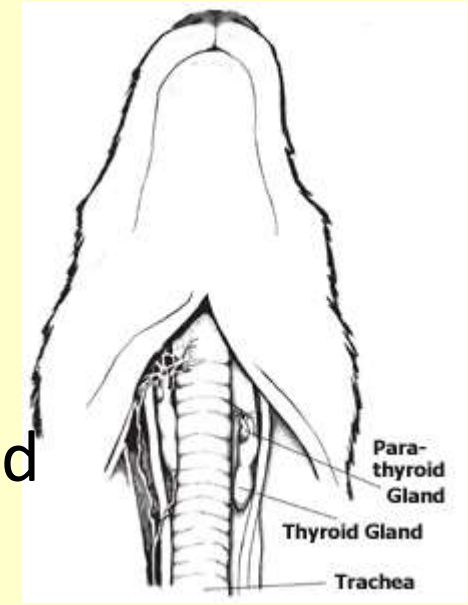
Major endocrine organs

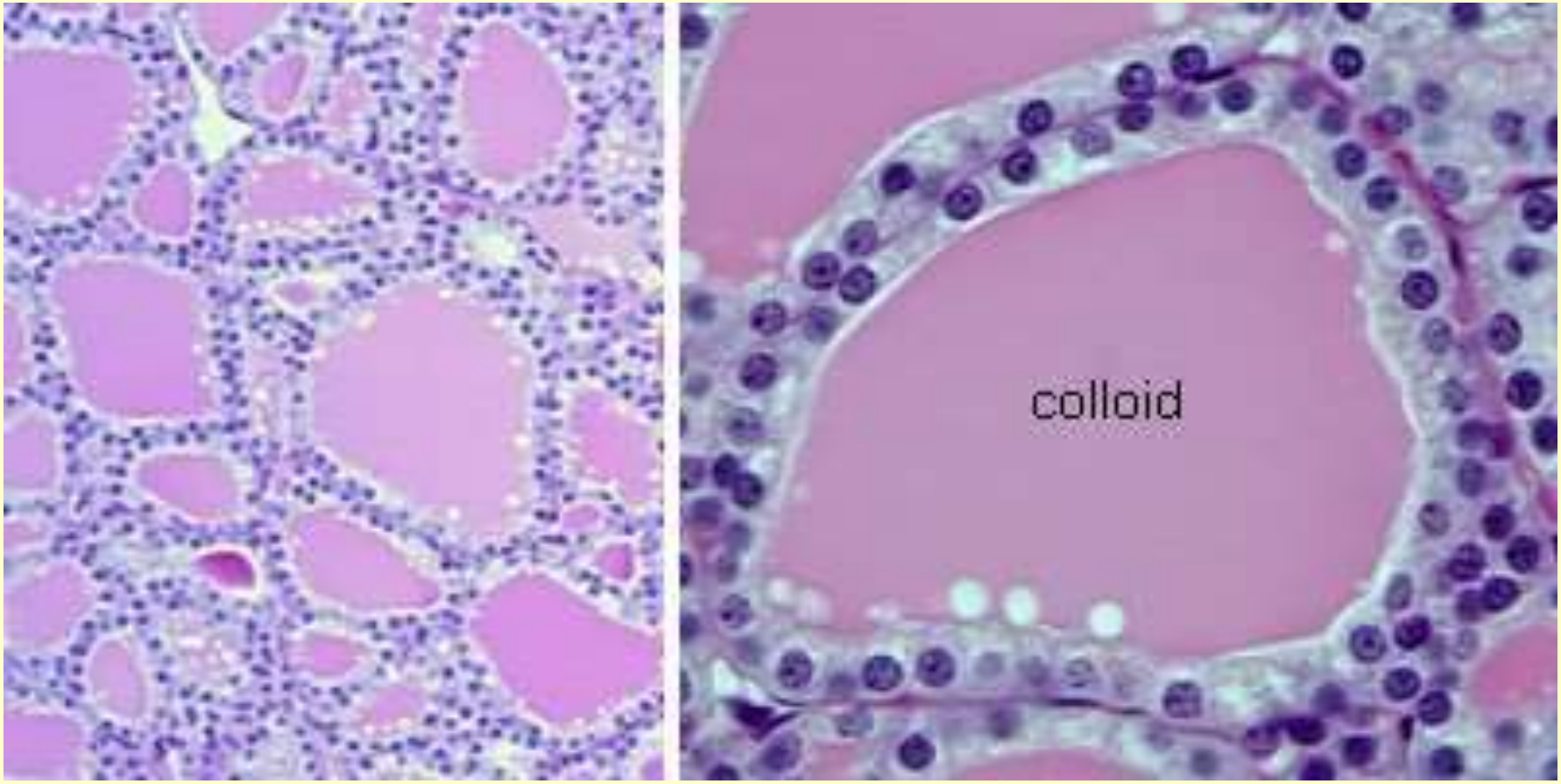


Canine Thyroid Gland

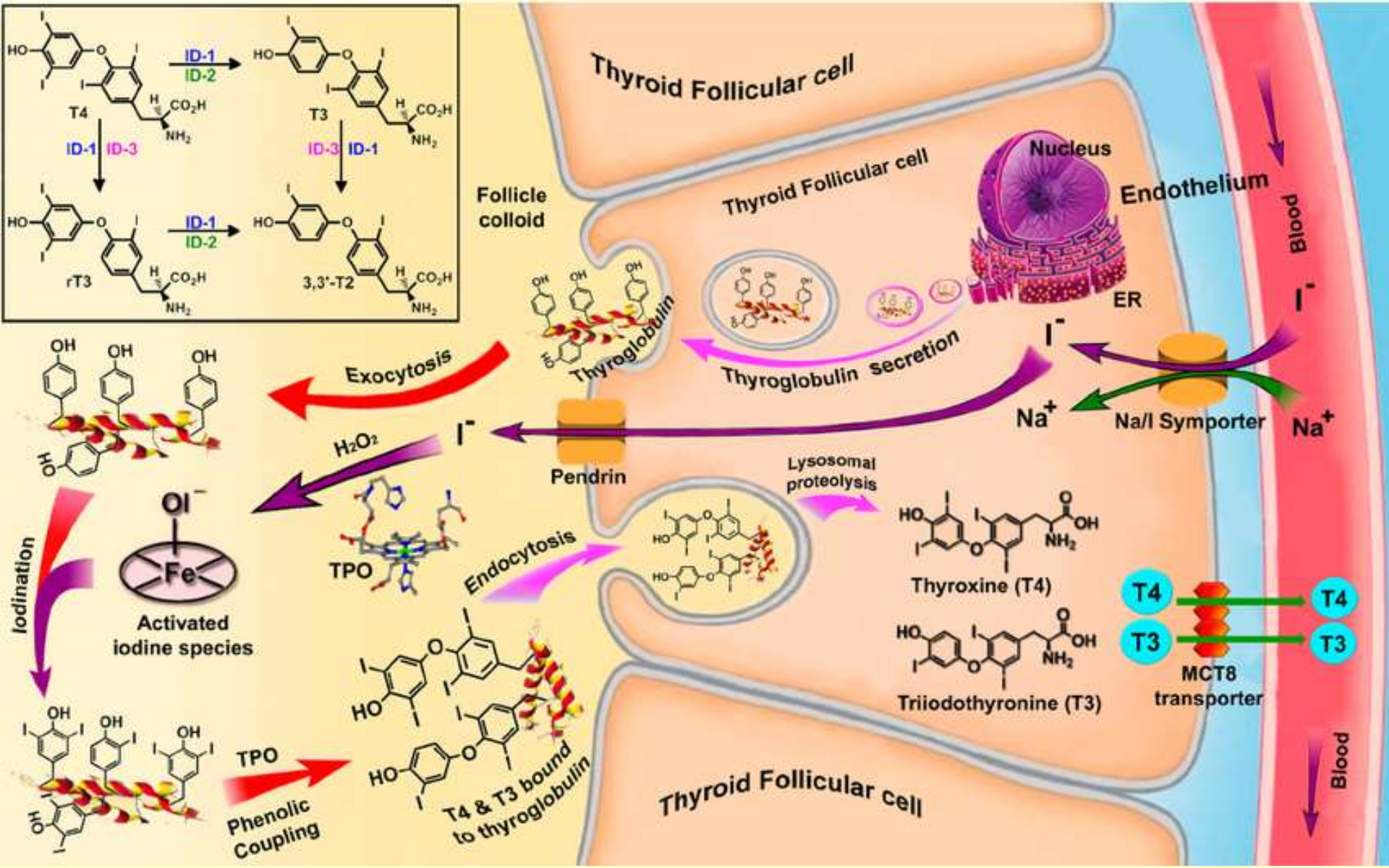


- Bilobed, located below larynx
- “accessory” thyroid tissue maybe located from base of tongue to base of heart
- Thyroid follicular cells synthesize and secrete thyroid hormones
- Parathyroid cells synthesize and secrete parathormone (parathyroid hormone)
- Parafollicular cells (C cells) secrete calcitonin

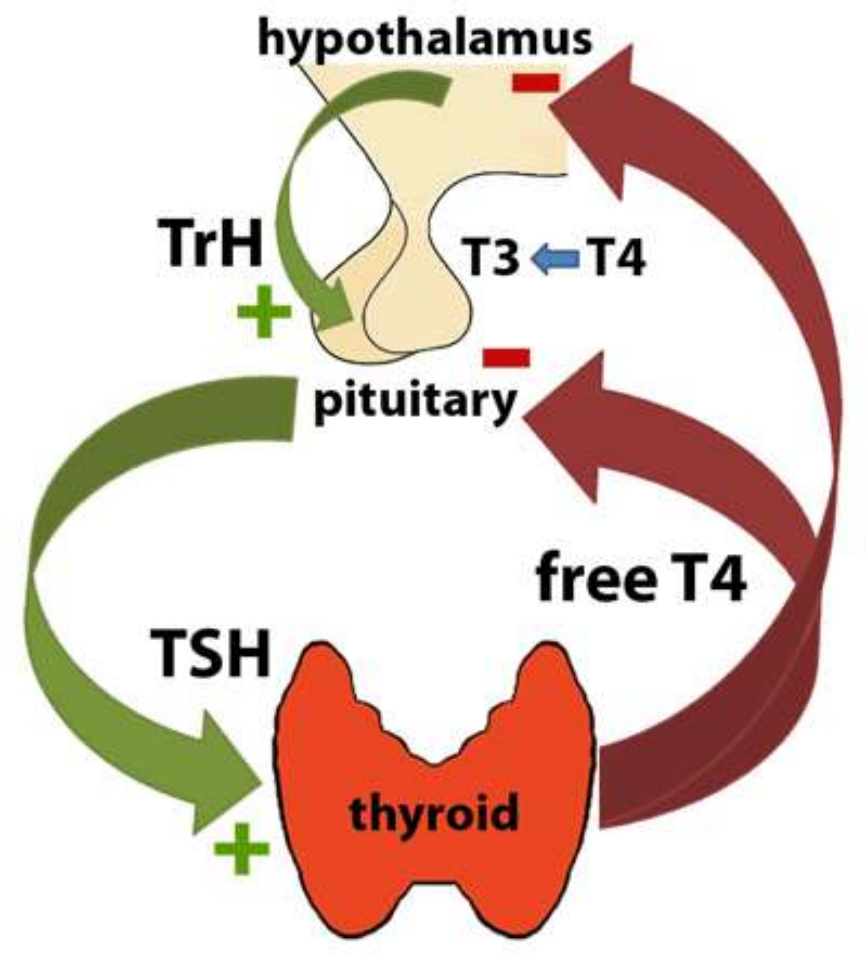
Thyroid follicles



Thyroid hormone synthesis



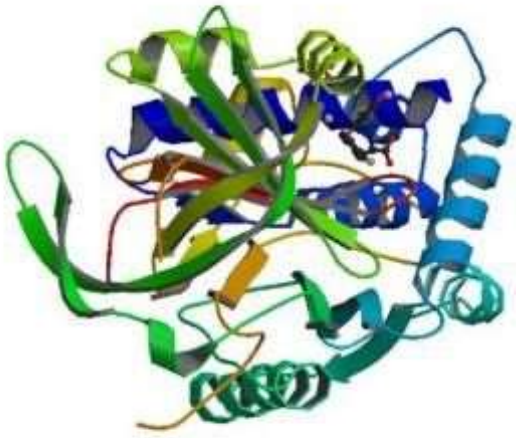
Regulation of thyroid hormones

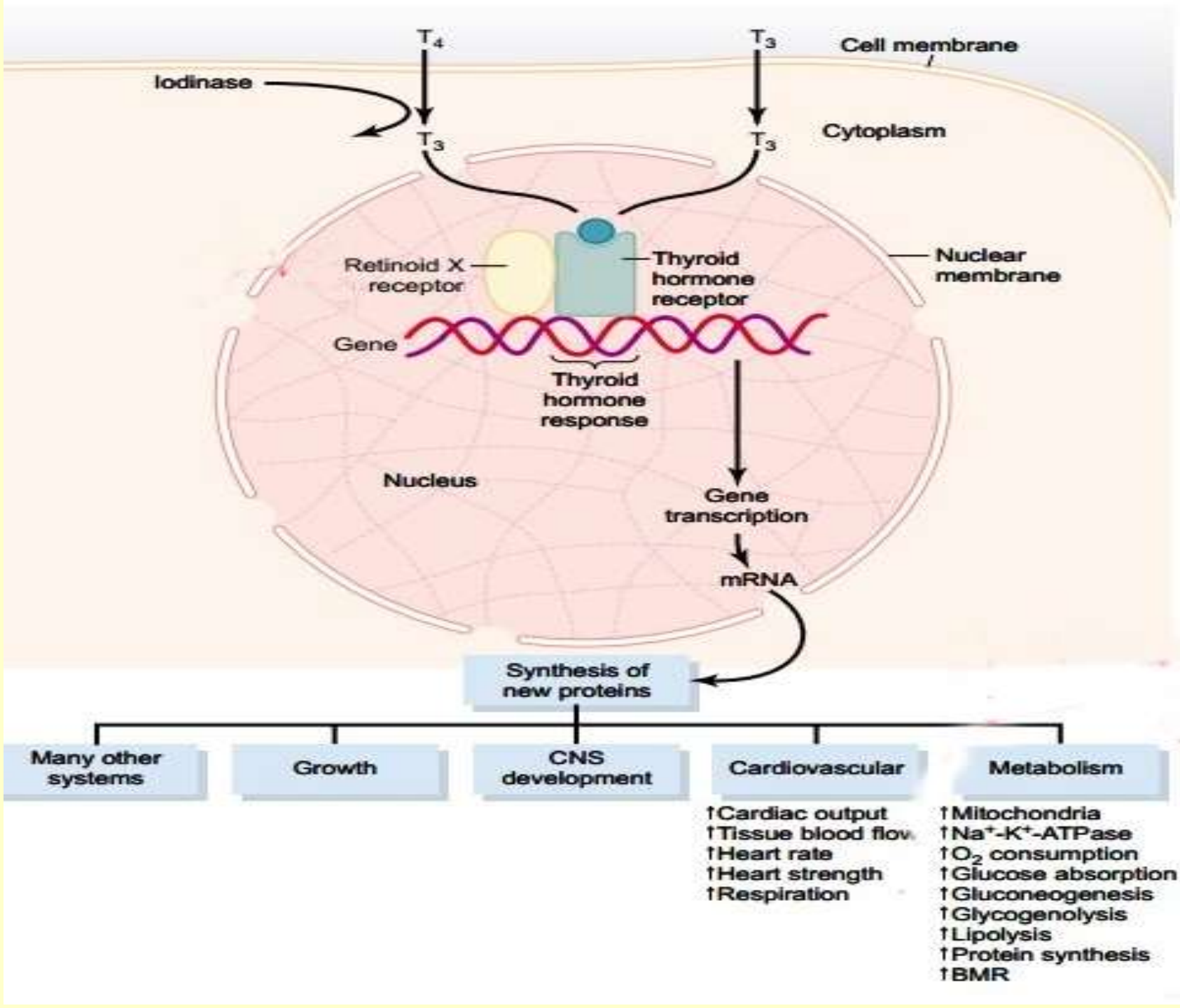


- Hypothalamic-Pituitary-Thyroid axis
- Autoregulatory (thyroid)
  - Wolff-Chaikoff block from increases in iodine
  - Increased secretion of T3 with iodide deficiency and early hypothyroidism
  - Na-Iodide Symporter activity is influenced by insulin, IL-GF, TGF-B1, TNF-a, IFN-G, IL-1, IL-6

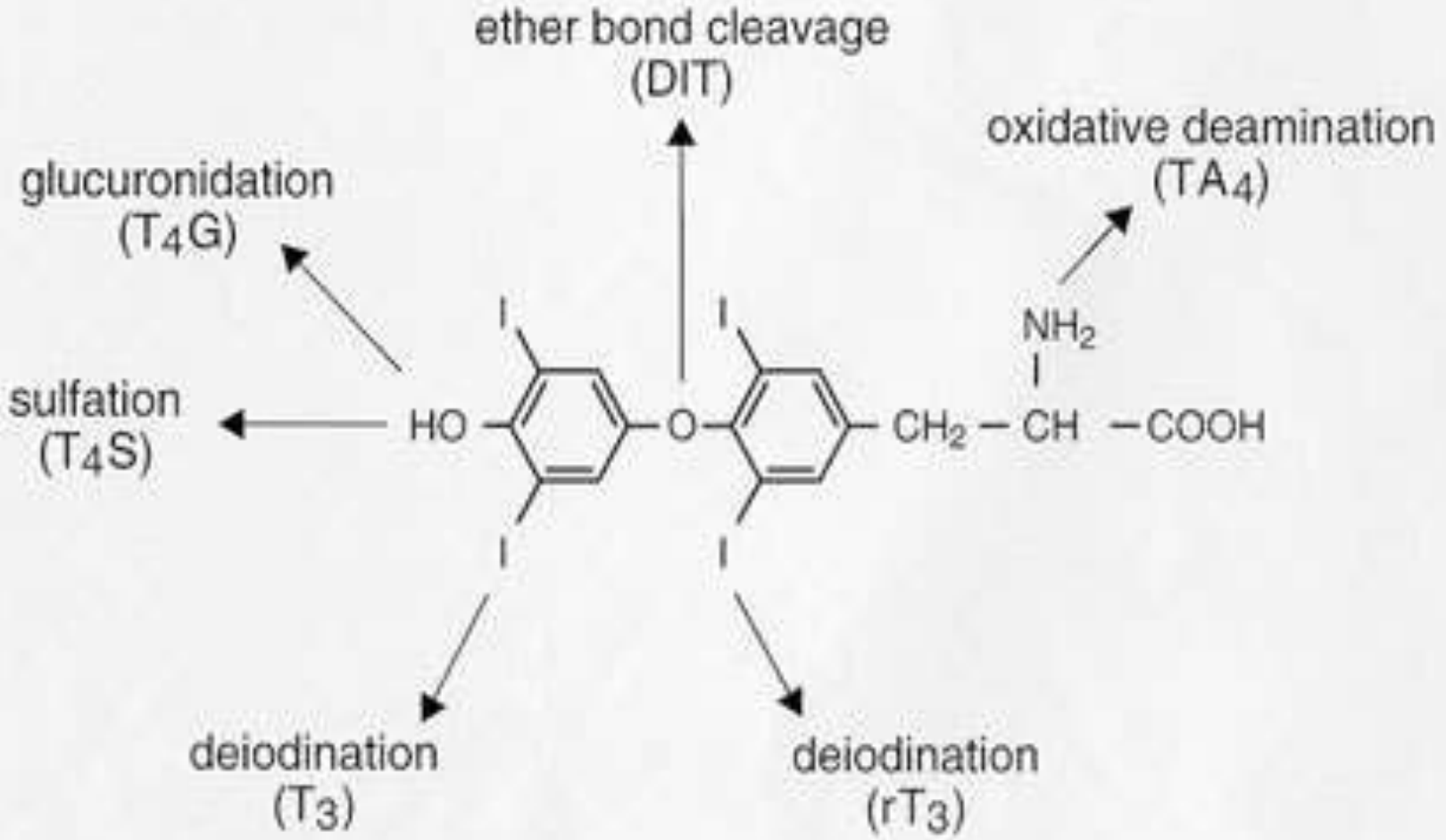
Thyroid hormones in blood

- Thyroid hormones are poorly soluble in water, circulate bound to proteins (99%)
  - Thyroxine binding globulin (not present in cats)
  - Thyroxine-binding prealbumin (transthyretin)
  - Albumin
  - Plasma lipoproteins

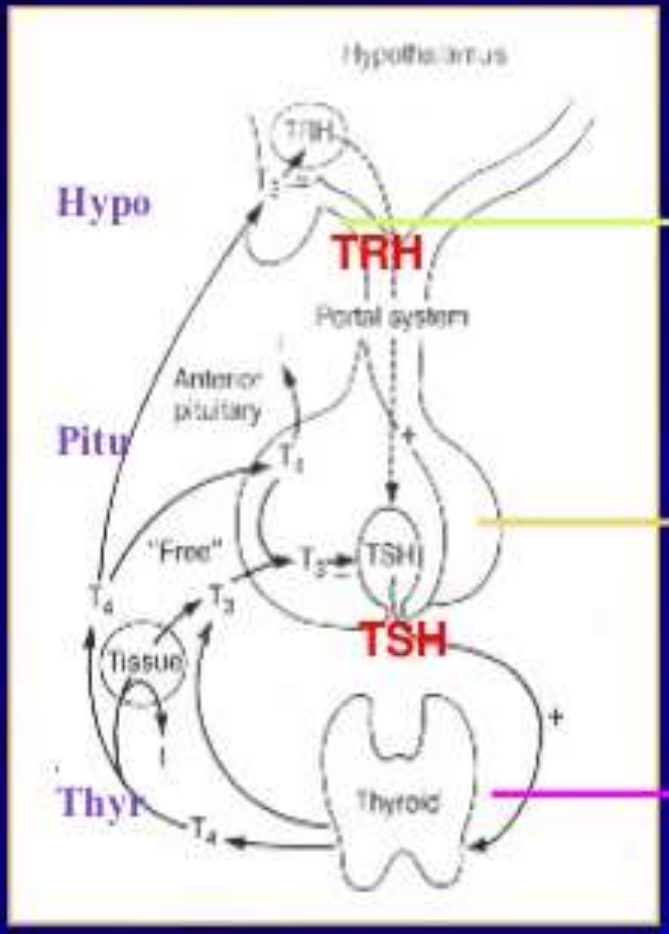



T4
T3
Cell membrane
Iodinase
T3
T3
Cytoplasm
Retinoid X receptor
Thyroid hormone receptor
Nuclear membrane
Gene
Thyroid hormone response
Nucleus
Gene transcription
mRNA
Synthesis of new proteins
Many other systems
Growth
CNS development
Cardiovascular
Metabolism
↑Cardiac output
↑Tissue blood flow
↑Heart rate
↑Heart strength
↑Respiration
↑Mitochondria
↑Na+-K+-ATPase
↑O2 consumption
↑Glucose absorption
↑Gluconeogenesis
↑Glycogenolysis
↑Lipolysis
↑Protein synthesis
↑BMR

Pathways of Thyroid Hormone Metabolism



TYPES OF HYPOTHYROIDISM



Tertiary Hypothyroidism

Secondary Hypothyroidism

Primary Hypothyroidism

Congenital hypothyroidism

- Causes
  - Iodine deficiency
    - Horses (including diets high in nitrates)
  - Thyroid dysgenesis
  - Dyshormonogenesis (iodine organification defect)
    - Abyssinian cats
  - TPO mutation
    - Toy fox terriers
    - Rat terriers
    - Tenterfield terriers
    - Spanish water dogs
    - DSH cat family

Congenital hypothyroidism

- Causes (Secondary hypothyroidism)
  - TSH deficiency
    - Giant Schnauzers
    - Scottish deerhounds
    - Boxers
    - German Shepherd dogs
    - Karnelian bear dogs
  - TSH resistance
    - Japanese cat colony

Congenital hypothyroidism – Clinical findings

- May have goiters
- Disproportionate dwarfism
  - Large broad head
  - Short thick neck
  - Protruding tongue
  - Short limbs
  - Stenotic ear canals
  - Failure to develop guard hairs
  - Delayed tooth development
  - Mental retardation
  - Weakness, hyporeflexia, hypermetria
  - Constipation
  - Myxedema

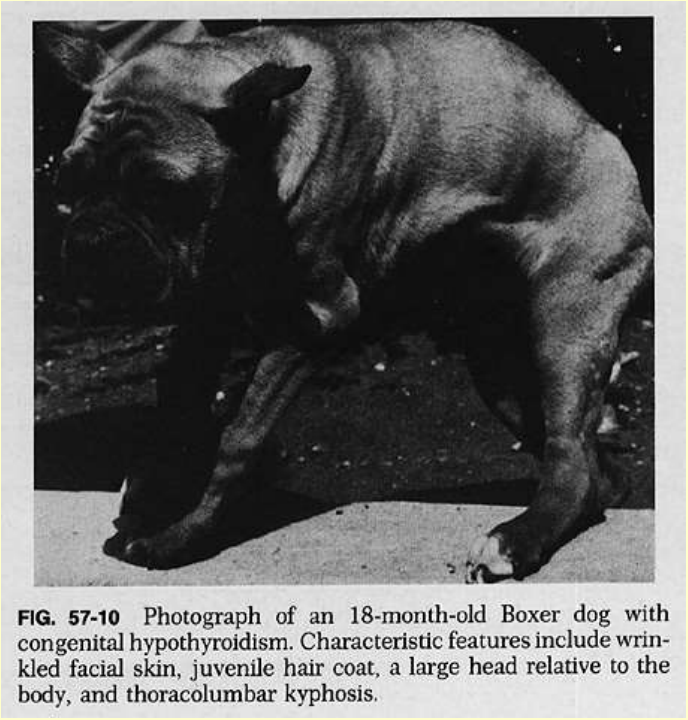
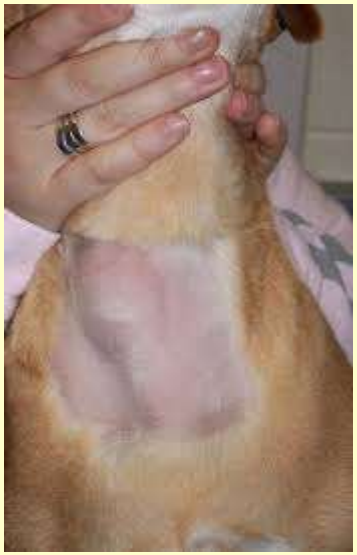


FIG. 57-10 Photograph of an 18-month-old Boxer dog with congenital hypothyroidism. Characteristic features include wrinkled facial skin, juvenile hair coat, a large head relative to the body, and thoracolumbar kyphosis.

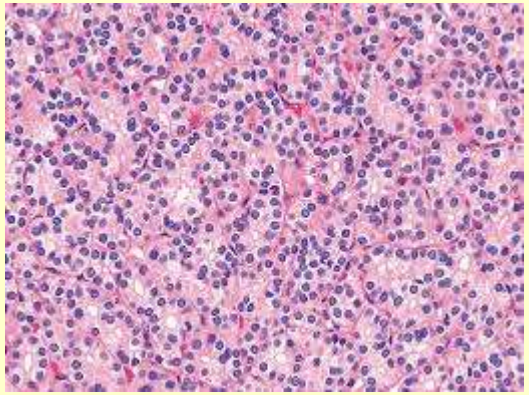
Iodine deficiency & Hypothyroidism

- Decreases in TT4 not seen in adult beagles until dietary iodine < 50 ug/d
- All meat diets may cause
- Puppies fed diets with high iodine for 45 days developed hypothyroidism (Wolff-Chaikoff block)



Goitrogens

- Foods: cabbage, broccoli, kale, rape
- Anti-thyroid medications: propylthiouracil, methimazole
- Potentiated sulfonamides
  - Inhibit iodine conversion to iodide, inhibit binding of iodide to thyroglobulin, interfere with coupling of iodothyrosines
  - Decreased TT4, fT4, TT3, fT3, rT3 and increases in TSH may be seen within 2 weeks; may take > 3 weeks to return to normal after treatment is stopped



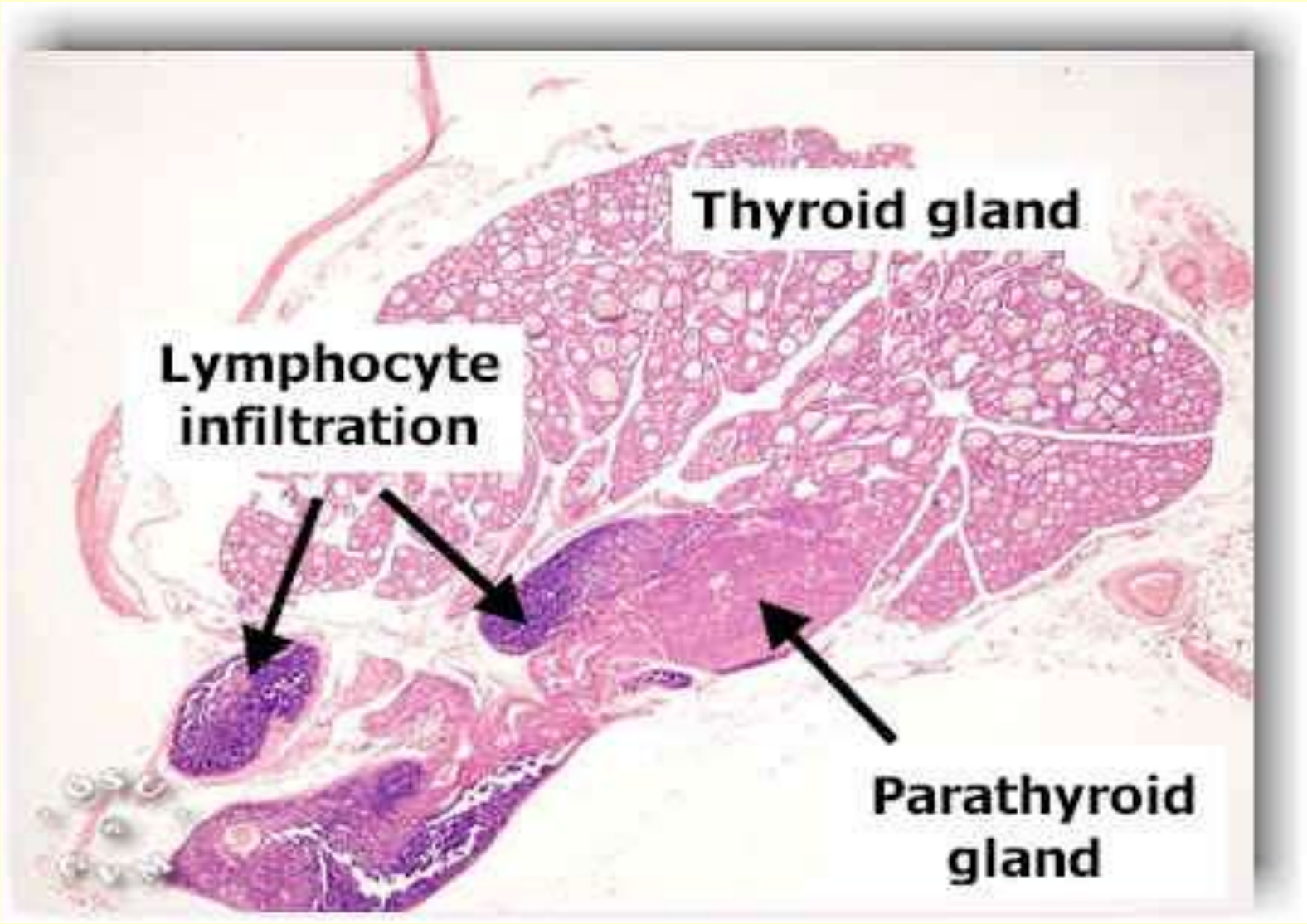
Canine Lymphocytic Thyroiditis

- Genetic and environmental factors likely involved
- Polygenic in beagles
- Autosomal recessive in a family of Borzoi dogs
- Doberman pinchers, English Setters, Rhodesian Ridgebacks, Giant Schnauzers – associated with MCH complex DLA class II haplotypes
- Gorden Setter, Hovawart, Rhodesian Ridgeback – genome-wide association analysis identified a major hypothyroidism risk locus on chromosome 12, includes 3 genes (LHFPL5, SRPK1 and SLC26A8)
- Orthopedic Foundation for Animals (OFA) maintains a thyroid registry based on measurements of fT4, TSH and TG-autoantibody testing at $\geq$ 12 months
- Anti-thyroglobulin levels increase during summer and following vaccinations (antigen mimricky? Damage to thyroid?)

Canine Lymphocytic Thyroiditis

- Four stages
  - Subclinical thyroiditis (+ autoantibodies to TG and/or T4, T3, focal lymphocytic infiltrates) (usually starts around 2 years of age)
  - Antibody positive subclinical hypothyroidism (antibody positive, >60% destruction of thyroid mass, compensatory increases in TSH maintain normal T4 levels)
  - Antibody positive overt hypothyroidism (>80% destruction of thyroid tissue, decreased T4 levels, increased TSH levels) (~ 4 years of age)
  - Non-inflammatory atrophic hypothyroidism (thyroid tissue replaced with fibrous and adipose tissue, few if any lymphocytes, undetectable anti-TG antibodies) (dogs 5-8 years old at this stage)
- Humoral and cell-mediated immunity are involved
- Thyroglobulin (TG) is major antigen, 17% of tested dogs have anti-TPO antibodies
- Antibody-dependent cytotoxicity is involved with destruction of follicular cells
- CD4+ cells also involved (CMI)

Canine Lymphocytic Thyroiditis

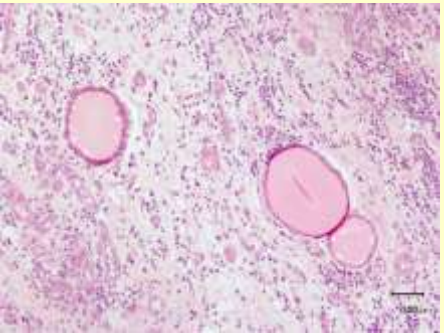


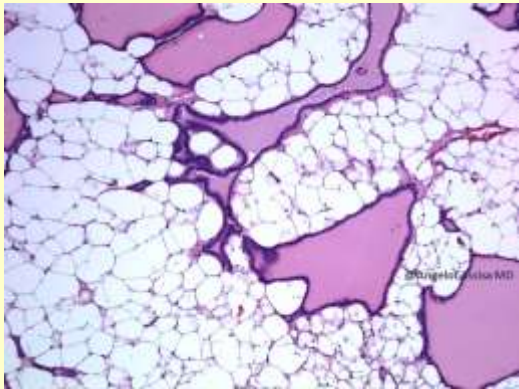
Polyglandular Autoimmune Syndromes

- Concurrent development of more than one immune-mediated endocrine disease
- Humans – most common is PGAIS Type II = Schmidt syndrome with hypoadrenocorticism, autoimmune thyroiditis and diabetes mellitus
- Dogs – hypothyroidism and hypoadrenocorticism (4% of dogs with Addisons are also hypothyroid)
- Dogs- hypothyroidism with diabetes mellitus (0.5% of hypothyroid dogs have DM)
- Dogs-hypothyroidism with orchitis (reported in a colony of beagles)

Idiopathic Thyroid Gland Atrophy

- Approximately 50% of dogs diagnosed with hypothyroidism are negative for autoantibodies to TG, T4 and T3 and lack lymphocytic infiltration of glands
- Thyroid follicles degenerate and are replaced with adipose tissue
- May occur as a primary degenerative disorder or as end-stage of lymphocytic thyroiditis (stage IV)





Hypothyroidism – clinical signs

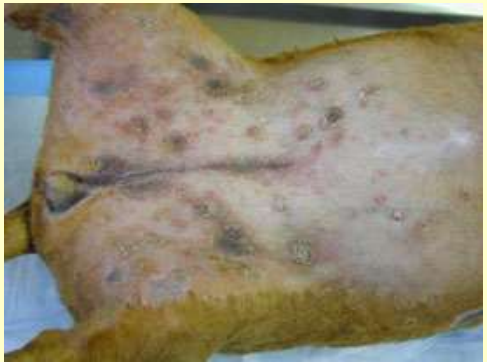
- 15% decrease metabolic rate: lethargy, mentally dull, “lazy”, heat-seeking, weight gain
- Premature telogen, decrease anagen hair growth
  - Hair loss caudal thighs, ventral thorax, bridge of nose, tail
  - One study beagles 1/3 decrease hair shafts w/o alopecia
  - Post-clipping alopecia
- Decrease cutaneous EFAs, decrease cutaneous PGE2
- Increased hyaluronic acid in dermis→ myxedema

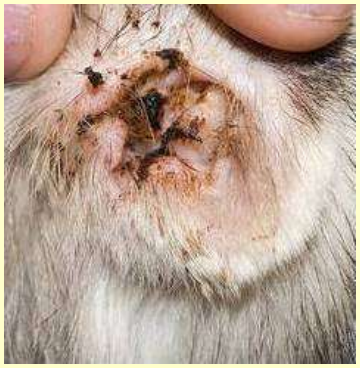




Hypothyroidism & immune system

- Decrease ratio CD4:CD8
- Suppressed humoral immunity
- Predisposition to skin and ear infections, demodex
- Increases in acute phase proteins, circulating immune complexes, alpha-globulins, beta-2-globulins, gamma-globulins (= systemic inflammatory responses)

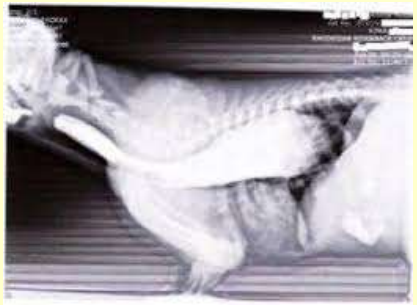





Hypothyroidism & neuromuscular disorders

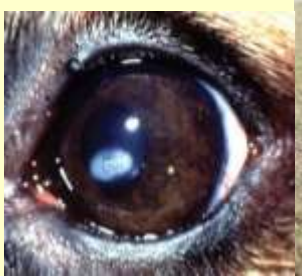
- Causes
  - Nerve entrapment
  - Demyelination (disrupted Schwann cell metabolism)
  - Impaired axonal function
  - Vascular encephalopathy (infarcts, hyperlipidemia)
  - Immune-mediated attack on acetylcholine receptors
  - Myofiber degeneration (especially type II myofibers)
- Signs
  - Peripheral neuropathy (weakness, ataxia, suppressed reflexes)
  - Cranial nerve deficits, palsy, circling/head tilt
  - Laryngeal paralysis, megaesophagus, myasthenia gravis
  - Myxedema coma

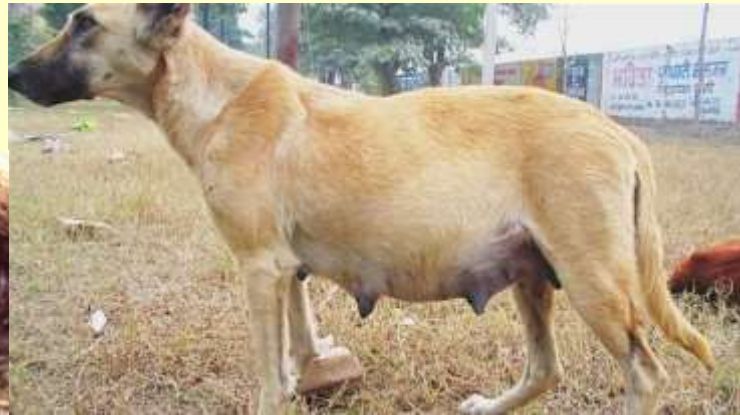




Hypothyroidism—other effects

- Reproduction
  - Prolonged parturition, reduced puppy survival
  - Weak or silent estrus cycle
  - Galatorrhea (increase secretion of prolactin)
- Cardiac function
  - Bradycardia – sinus bradycardia, 1st and 2nd degree heart blocks
  - Weak apex beat – decreased amplitude of P and R waves, inverted T waves
  - Increased left ventricular end systolic diameter, prolonged pre-ejection period
  - Decreased cardiac output, increased systemic vascular resistance
  - Decreased cardiac muscle ATPase activity, decreased beta-adrenergic receptors
- Corneal lipid deposits
- Decreased tear production
- Constipation
- Behavioral changes



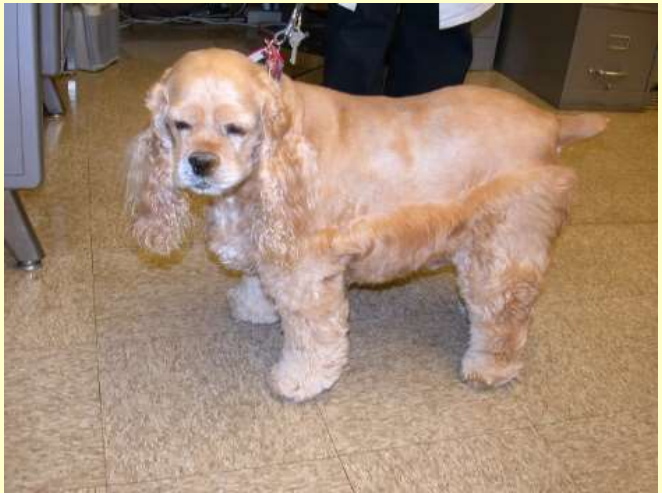


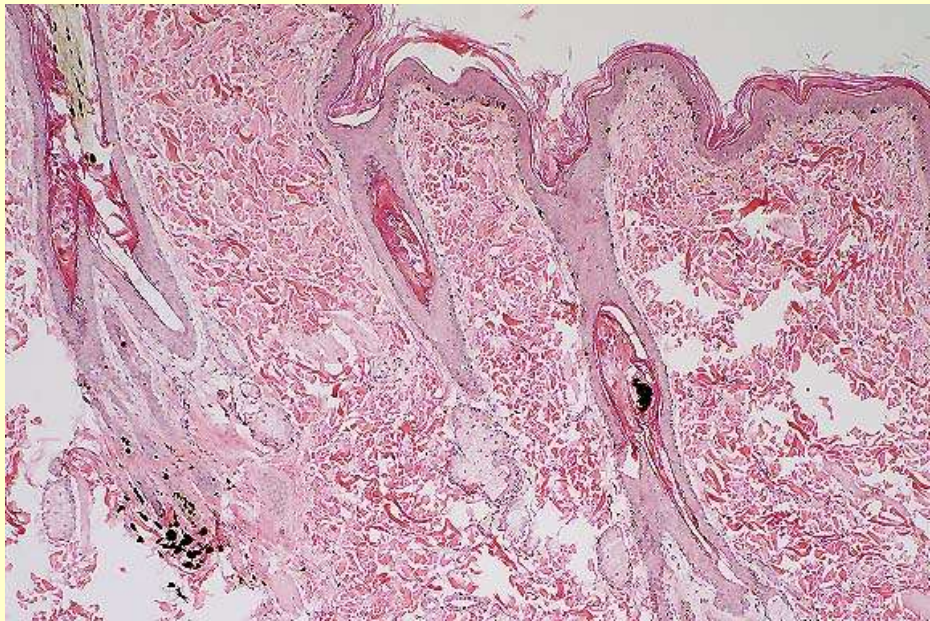
Hypothyroidism-Laboratory Findings

- Normocytic, normochromic, non-regenerative anemia
  - Decreased erythropoietin, effects on stem cells
- Increased leptocytes (target cells) (hypercholesterolemia)
- Normal to increased platelet counts
- Has NOT been associated with reduced factor VIII related antigen (von Willebrand factor)
- Hypercholesterolemia, hypertriglyceridemia, also increases in VLDL, LDL and HDL (reduced lipioprotein lipase and hepatic lipase activity
- Mild hypercalcemia (reduced excretion, increased absorption)
- Mild increases in LDH, AST, ALT, ALP and creatine kinase
- Proteinuria (uncommon)

Hypothyroidism-Dermatopathology

- Increased kenogen (hairless telogen) with decreased anagen and catagen
- Increased tricholemnal keratinization
- Follicular atrophy
- Epidermal hyperplasia
- Vacuolated arrector pili





Radiographic Abnormalities

CONGENITAL hypothyroidism

- Delayed epiphyseal ossification
- Scalloping of vertebrae
- Short, broad skull
- Delayed dentition
- Valgus deformities

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FIG. 57-12 Lateral radiograph of the thoracic spine of a Boxer dog with congenital hypothyroidism. The epiphyses are underossified and the intervertebral spaces appear widened. Caudal beaking of the vertebral bodies is present.

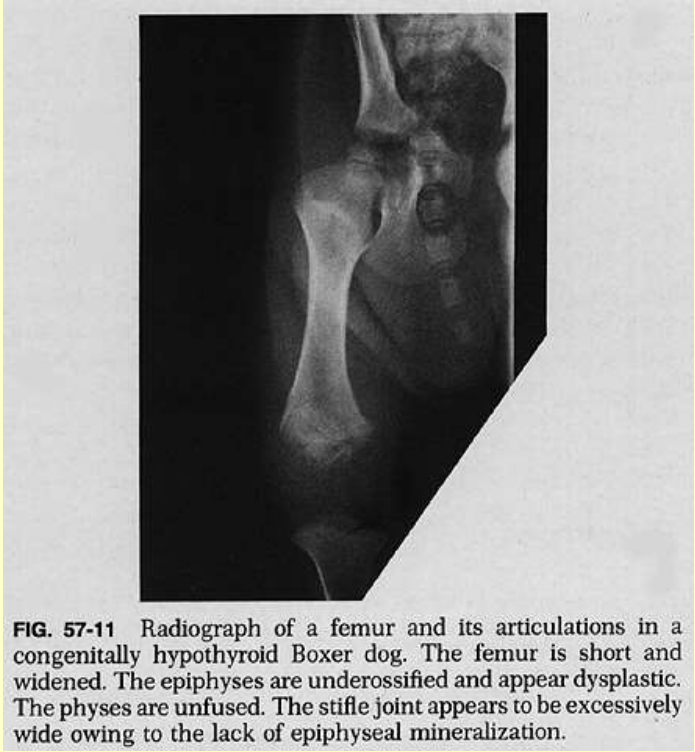
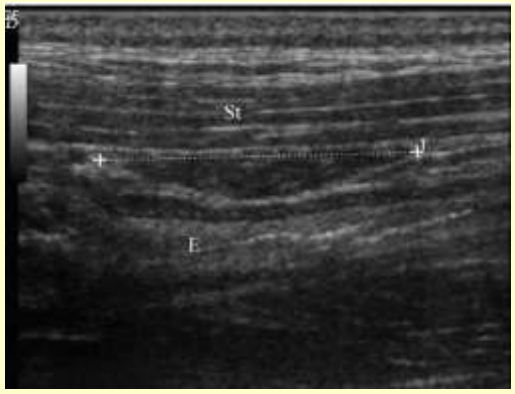
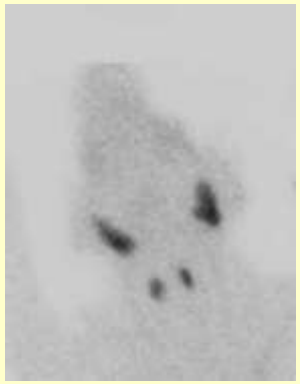


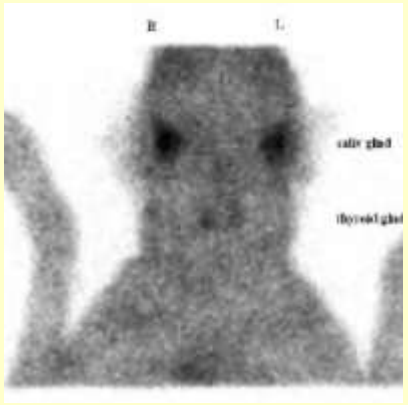
FIG. 57-11 Radiograph of a femur and its articulations in a congenitally hypothyroid Boxer dog. The femur is short and widened. The epiphyses are underossified and appear dysplastic. The physes are unfused. The stifle joint appears to be excessively wide owing to the lack of epiphyseal mineralization.

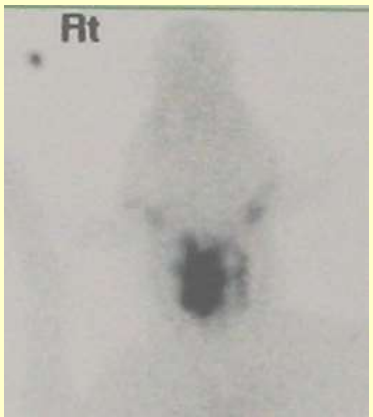
Diagnostic Imaging

- Ultrasonography
  - Decreased thyroid volume and hypoechogenicity (compare to sternothyroid muscle)
- Nuclear scintigraphy (Technetiium-99m-pertechnetate)
  - Normal uptake of thyroid gland compared to submandibular salivary glands is 1:1
  - Hypothyroid dogs have little to no-uptake UNLESS due to iodination defect or potentiated sulfonamides then increased uptake









Thyroid hormone testing

- Baseline TT4
  - Methods include radioimmunoassays, chemilumniescent immunoassays, enzyme-linked immunosorbent assays
  - Most commercial labs use ChLIAs—work well
  - Snap tests use ELISA – variable reliability
  - Storage and shipment in glass can falsely increase levels
  - Levels are stable when stored in plastic tubes for 8 days room temperature
  - Anti-T4 autoantibodies can cause spurious values however are uncommon (in <2% of dogs tested for hypothyroidism)
  - Hyperlipidemia and hemolysis may affect ChLIA and ELISA
  - Normal value rules out hypothyroidism except in dogs with anti-T4 antibody false elevation
  - Note – healthy sighthounds and working Alaskan sled dogs have lower TT4 levels

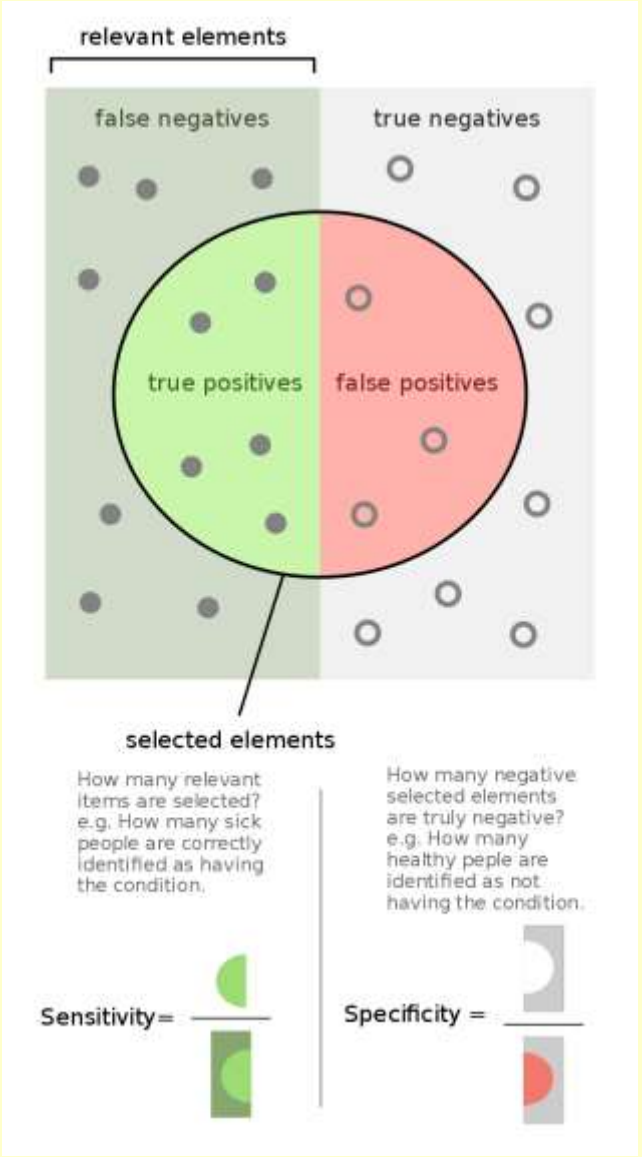
SI “System International Units” and “Traditional Units”

- TT4 µg/dL x 12.87 = nmol/L (SI units)
- Cortisol µg/dL x 27.59 = nmol/L (SI units)

https://www.dcpah.msu.edu/sections/endocrinology/WEBCD.ENDO.REF.002.pdf

Thyroid hormone testing – TT4

- Low TT4 may be found in euthyroid sick dogs
- “Gray range” – balance between sensitivity and specificity
  - 62 health dogs had TT4 of 1.0-3.3 ug/dL
  - 51 hypothyroid dogs had TT4 of 0.0 – 1.5 ug/dL
  - Cutoff of <1.5 increases sensitivity but decreases specificity
  - Cutoff of <1.0 has higher specificity but lower sensitivity



Thyroid Hormones – TT3

- RIAs or ChLIAs
- Anti-T3 antibodies can falsely increase or decrease, occur in ~6% of dogs suspected as being hypothyroid
- Of little value in diagnosis of hypothyroidism
  - Most T3 is intracellular
  - Early in hypothyroidism may have increased secretion of T3
  - Maybe helpful in Greyhounds – normal greyhounds have low TT4 and fT4 however TT3 values are in “normal reference range” similar to other breeds

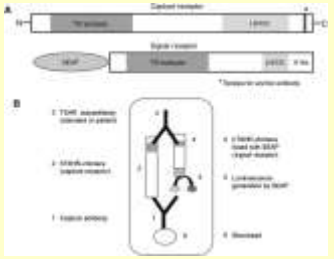
Thyroid hormones – fT4

- fT4 values less likely to be affected by non-thyroidal illnesses (when decreased has higher specificity than TT4 for hypothyroidism)
- Gold standard is equilibrium dialysis – only performed in research laboratories
- Commercial laboratories usually use “Modified equilibrium dialysis” (MED) which has diagnostic accuracy of 86-93% compred to 75-85% for TT4
- Serum should be shipped in plastic tubes
- Anti-T4 antibodies do not interfere with ED or MED, do interfere with analog-based assays (some RIA and ChLIA assays calculate fT4 based on a formula that uses TT4 data)
- fT4 values are lower in sighthounds and working Alaskan sled dogs

Thyroid hormones – fT3, rT3

- Diagnostic value of these assays has not been critically evaluated in dogs

TSH assays and diagnosis of hypothyroidism in dogs



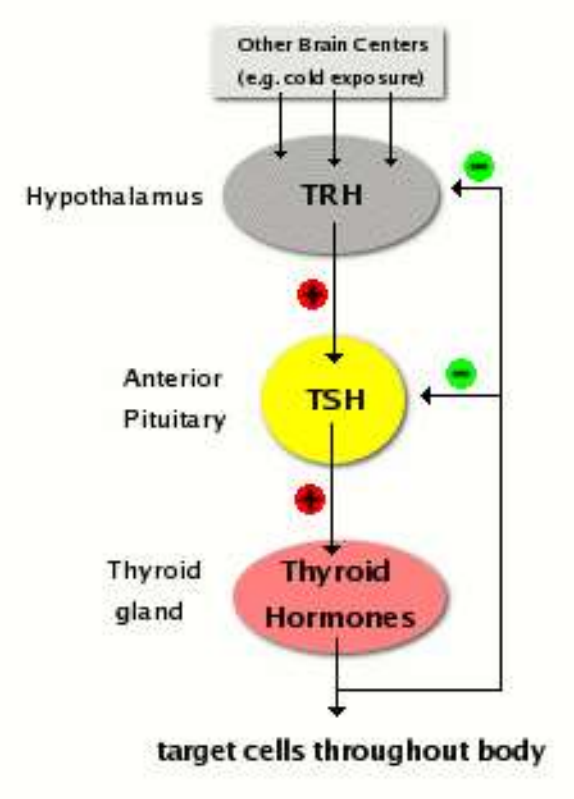
- TSH is glycoprotein, alpha subunit is identical to that of LH, FSH and chorionic gonadotropin
- Beta subunit is unique for TSH
- Human assays do not work for dogs
- ChLIA is most commonly used assay for dogs
- 20-40% of hypothyroid dogs have TSH in reference range; overall sensitivity of TSH for detection of hypothyroidism is 63-82%
- Combination of high TSH with low TT4 or low fT4 has specificity of 90% for diagnosis of canine hypothyroidism (however potentiated sulfonamides treatment results in same profile or even higher values for TSH)

TSH Stimulation Test

- Pre and 6 hour post administration of 0.1 IU/kg IV
- Pre and post TT4 < 1.5 ug/dL confirms diagnosis of hypothyroidism
- Post TT4 > 2.5 ug/dL → euthyroid
- "Gray Zone" post TT4 of 1.5-2.5 µg/dL
- Post TT4 > 1.5x baseline value → euthyroid

TRH Stimulation Test

- Pre and 4 hour post TT4 measurements
- TRH given at dose of 10 ug/kg or 200 ug/dog IV
- Normal dogs post > 1.5-2.0 ug/dL
- Hypothyroid dogs post < 1.5 ug/dL



Thyroid Autoantibodies (ATA)

- ATAs present in ~50% of hypothyroid dogs
- ATAs do not correlate with thyroid function or even with severity of lymphocytic inflammation of thyroid glands
- Longitudinal study of 171 dogs with ATA and normal fT4 and TSH for one year
  - 20% developed decrease fT4 or increased TSH at retest
  - 65% had similar values at retest
  - 15% reverted to negative ATA; fT4 and TSH remain normal
- Of most value is anti-TG; primary value of testing for anti-T3, anti-T4 is to explain unusual/unexpected test results
- May be helpful in screening breeding animals for genetic risk of developing lymphocytic thyroiditis

Thyroid hormones: effects of non-thyroidal factors

- Age
  - TT4 decreases by 21-29% after 6 years
  - mean TSH increases in older dogs
- Breed
  - Sighthounds and working Alaskan sled dogs have lower TT4 and fT4 levels
  - Post-racing TT4 further decrease is seen
- Sex hormones
  - Testosterone decreases thyroid-binding protein (↓TT4)
  - Progesterone may increase protein binding (↑TT4, TT3)

Thyroid hormones: effects of non-thyroidal factors

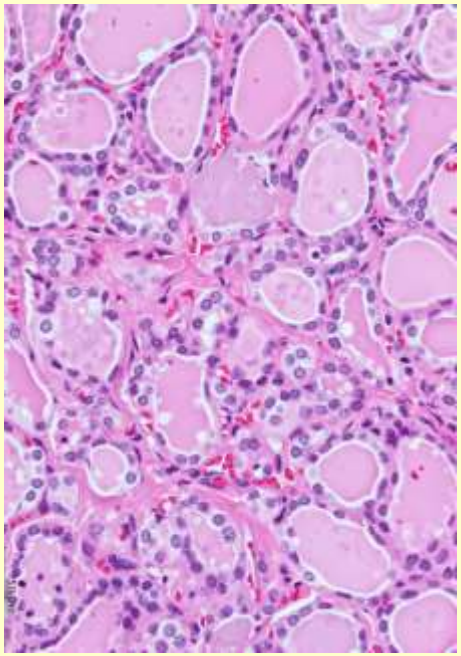
- Diurnal rhythm
  - possible peak TT4 and fT4 midday
- Euthyroid sick syndrome
  - Decreased TSH secretion
  - Decreased synthesis T4
  - Decreased protein binding
  - Inhibition of T4 → T3 de-iodination
  - Fasting > 48 hr decreases TT3

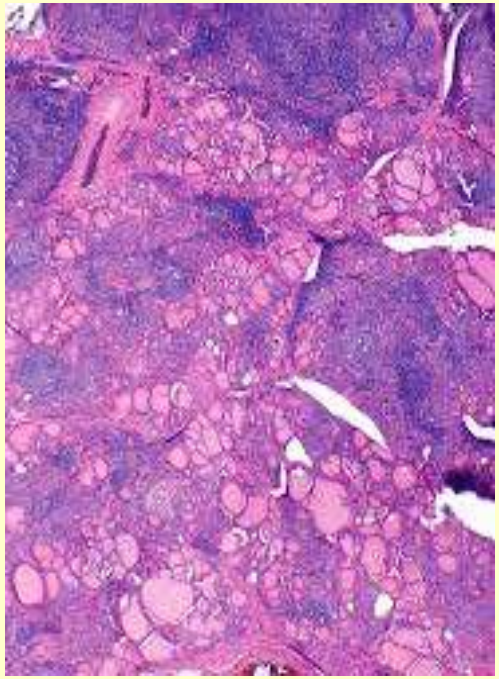
Thyroid hormones: effects of drugs

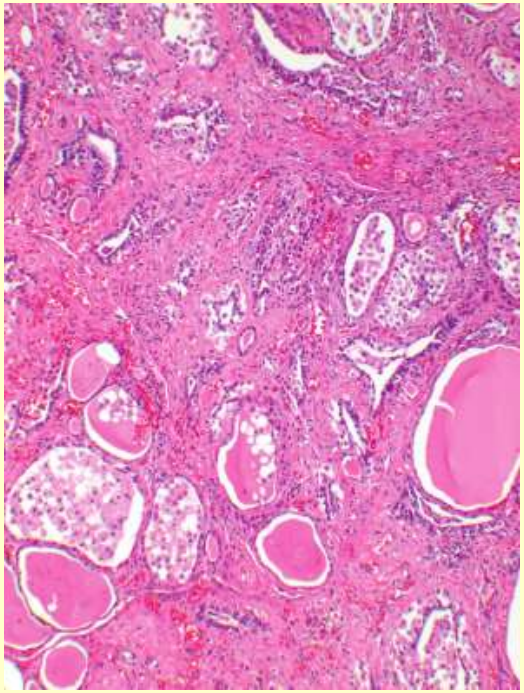
- Glucocorticoids
  - Decrease TT4, fT4, normal TSH
- Phenobarbital
  - Decrease TT4, fT4, normal TSH
- Potentiated sulfonamides
  - Decrease TT4, fT4, TT3, fT3, increase TSH
- Clomipramine
  - Decrease TT4, fT4
- Aspirin
  - Decrease TT4, fT4

Thyroid Biopsy

- Provides documentation of thyroid pathology
- 80% destruction of thyroid tissue before clinical hypothyroidism







Response to treatment trial

- Improvement can occur because of direct effects of thyroid hormones – especially true for hair regrowth
- If improve with treatment trial to confirm diagnosis stop treatment
  - if signs recur diagnosis is confirmed and restart supplementation
  - If signs do not recur the dog had a thyroid-responsive condition

Treatment of Hypothyroidism

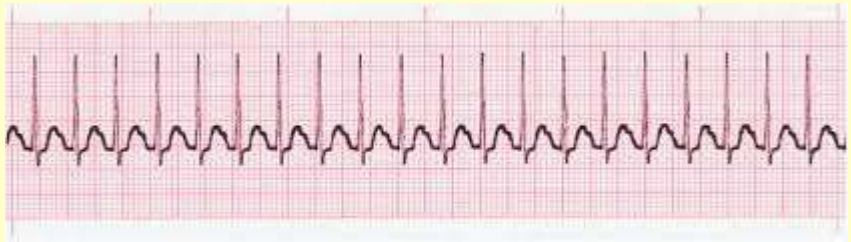
- Synthetic levothyroxine
  - Plasma half-life of TT4 is 9-14 hours
  - Usual recommended dose is 0.02 mg/kg PO q 12 hours
  - Peak concentrations of TT4 is at 3.8 $\pm$ 2 hrs
  - 75% good response with dose of 0.022 mg/kg once daily or divided q 12 hours
  - Body surface area dose is 0.5 mg/M^2
  - Maximum dose 0.8 mg q 12 hours
  - Giving with food reduces absorption
  - New drug approval process requires potency of 95-105% of label dose – products tested for humans may not be absorbed the same by dogs

Responses to Treatment

- Mental status improved within a few days
- Clin Path findings improve within one month
- Cardiac and neurological improvement 1-3 months
- Skin and haircoat improvement 1-3 months
- Reproductive improvement 3-10 months
- RECHECK TT4 ± TSH 4-6 hours post-pill (follow normal routine regarding feeding)—should be 3-6 ug/dL
- If dosed once daily also check a pre-pill TT4 (should be >1.5 ug/dL)

Thyrotoxicosis

- Signs may include PD/PU, urinary incontinence
- Increased panting
- Nervousness, anxiety, tachycardia, aggressive behavior, polyphagia, weight loss
- Reduce dose if post-pill TT4 is > 6 ug/dL



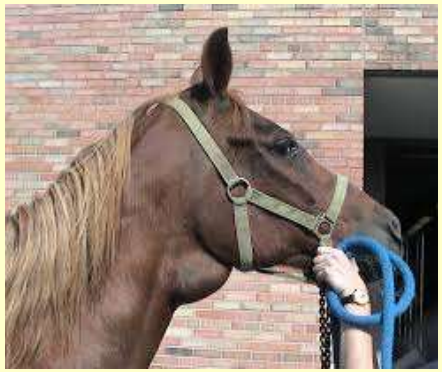
Special Considerations – Concurrent disease and treatment of hypothyroidism

- Cardiac disease
  - Start with 25-50% of normal dose
  - Re-evaluate cardiac function and clinical signs before increasing dose
- Hypoadrenocorticism
  - Stablize on mineralocorticoids and glucocorticoids first
- Diabetes Mellitus
  - Monitor closely for hypoglycemia
- Myxedema coma
  - Injectable levothyroxine 4-5 ug/kg q 12 hours
  - Supportive care

Feline Hypothyroidism

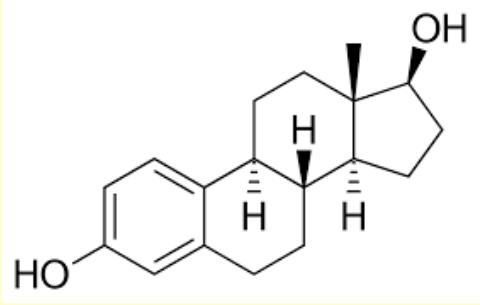
- Congenital cases due to iodination defects
  - Supplement with 0.05-0.1 mg L-T4 once daily
- Post I-131 treatment: monitor, many become euthyroid within 2-3 months
- If secondary to methimizole treatment reduce dose

Equine Hypothyroidism



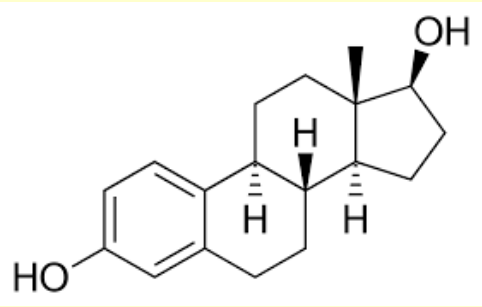
- Rare in adults—adenomas non-functional
- Foals of dams that consumed goitrogens may respond to L-T4 supplementation
- Foals with congenital hypothyroidism and dysmaturity syndrome
  - Prolonged gestation
  - Flexural limb deformities
  - Prognathism
  - Fine, silky haircoats
  - Grave prognosis

Steroid Hormones

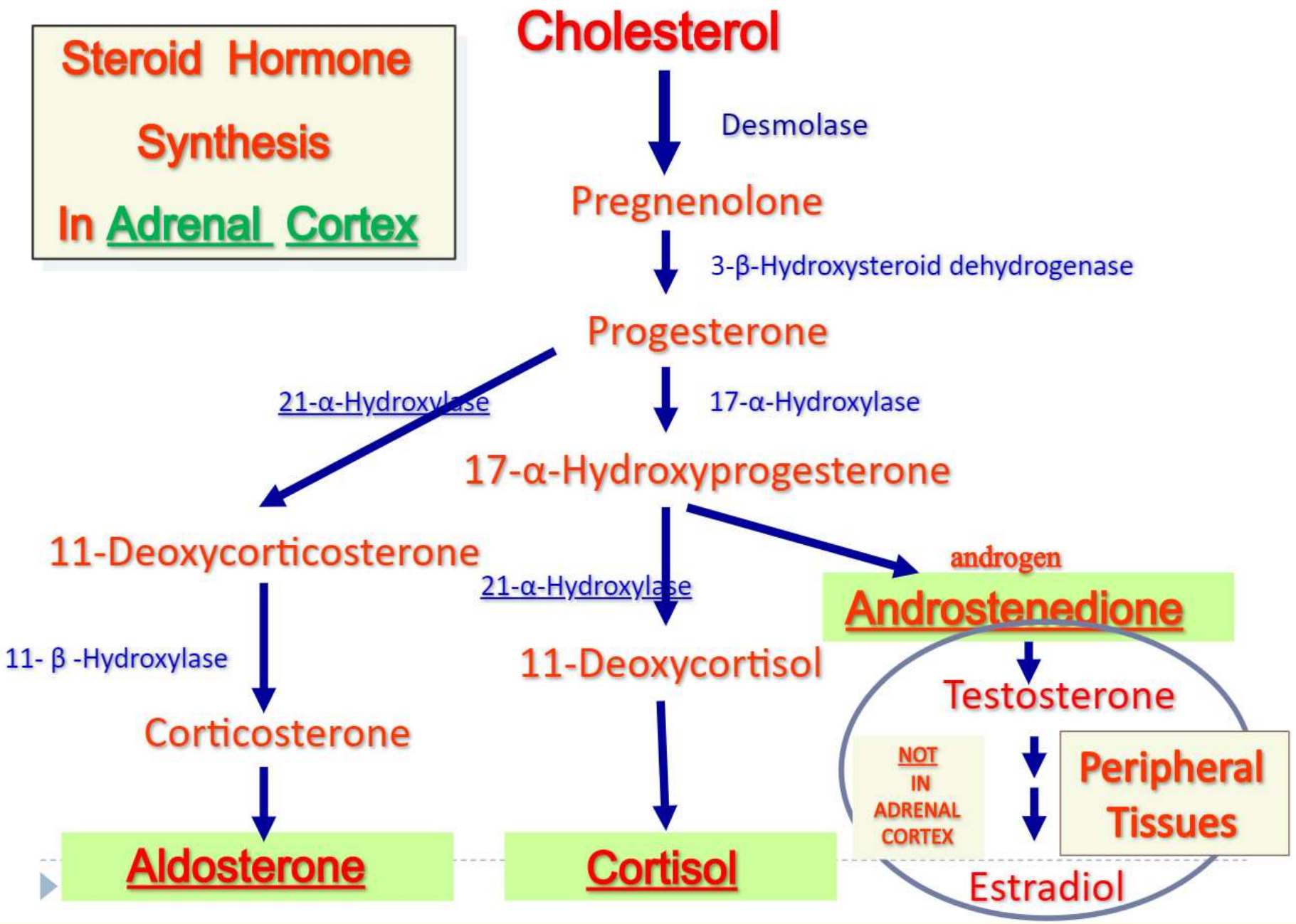


- Types of steroid hormones
  - Glucocorticoids: cortisol is major one produced
  - Mineralocorticoids: aldosterone is major one produced
  - Sex hormones
    - Androgens: androstendione, testosterone
    - Estrogens: estradiol and estrone
    - Progestogens: progesterone
- ALL steroid hormones are derived from cholesterol
  - Differ in ring structure & side chains
- Steroids are lipid soluble & transported in blood bound to specific plasma proteins
  - Cortisol: corticosteroid binding globulin (transcortin)
  - Aldosterone: albumin
  - Sex steroids: sex hormone-binding protein

Steroid Hormone Synthesis

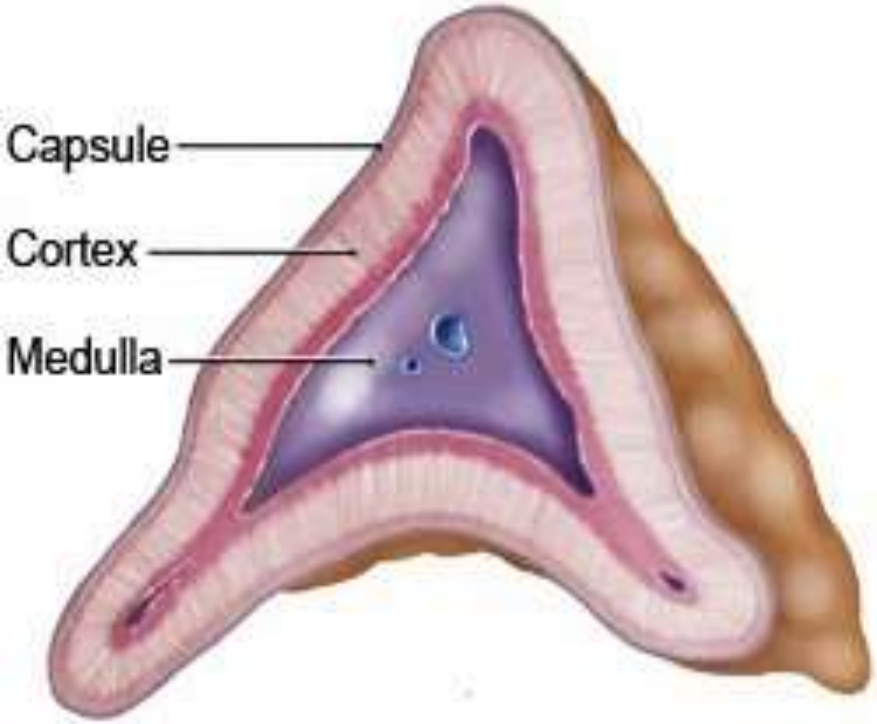


- Cholesterol sources include LDL and HDL from blood
- Cholesterol can also be synthesized by adrenal glands from acetate (acetyl CoA pathway)
- Movement of cholesterol into the inner membrane of mitochondrium is regulated by a transport protein = StAR (steroidogenic acute regulatory protein)
- The next step is the conversion of cholesterol to pregnenolone through actions of cholesterol desmolase, also known as side-chain cleavage enzyme, P450scc, CYP11A – this is the rate limiting step of steroid hormone syntesis

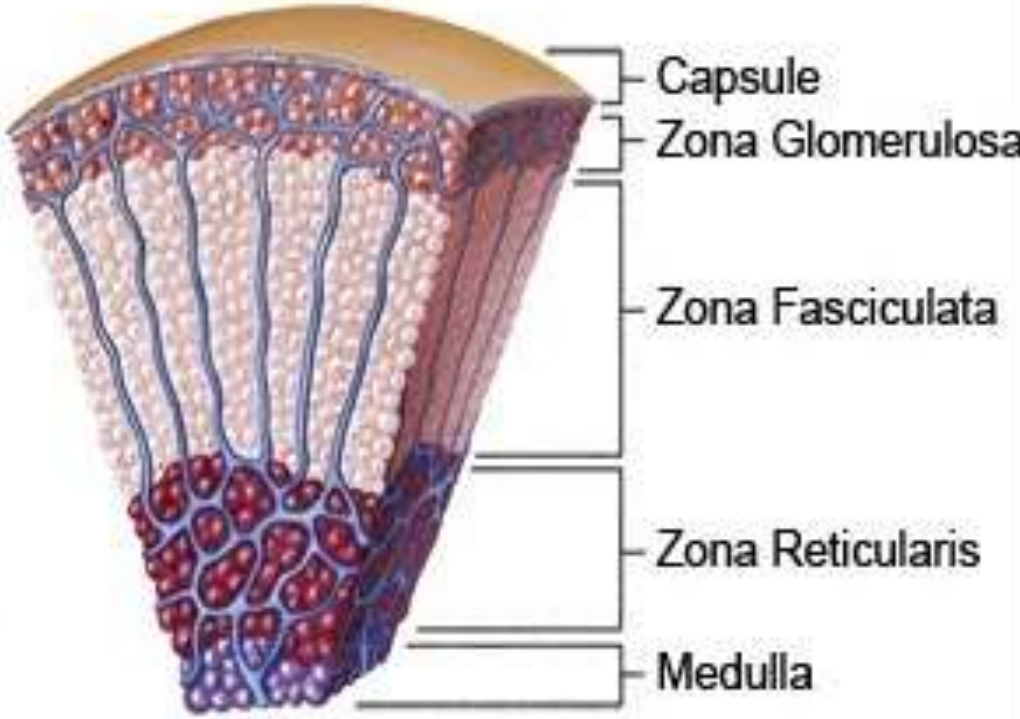

Steroid Hormone Synthesis In Adrenal Cortex
Cholesterol
Desmolase
Pregnenolone
3-β-Hydroxysteroid dehydrogenase
Progesterone
21-α-Hydroxylase
17-α-Hydroxylase
17-α-Hydroxyprogesterone
11-Deoxycorticosterone
21-α-Hydroxylase
androgen
Androstenedione
11- β -Hydroxylase
11-Deoxycortisol
Testosterone
Corticosterone
NOT IN ADRENAL CORTEX
Peripheral Tissues
Aldosterone
Cortisol
Estradiol

Adrenal Gland Cross Sections

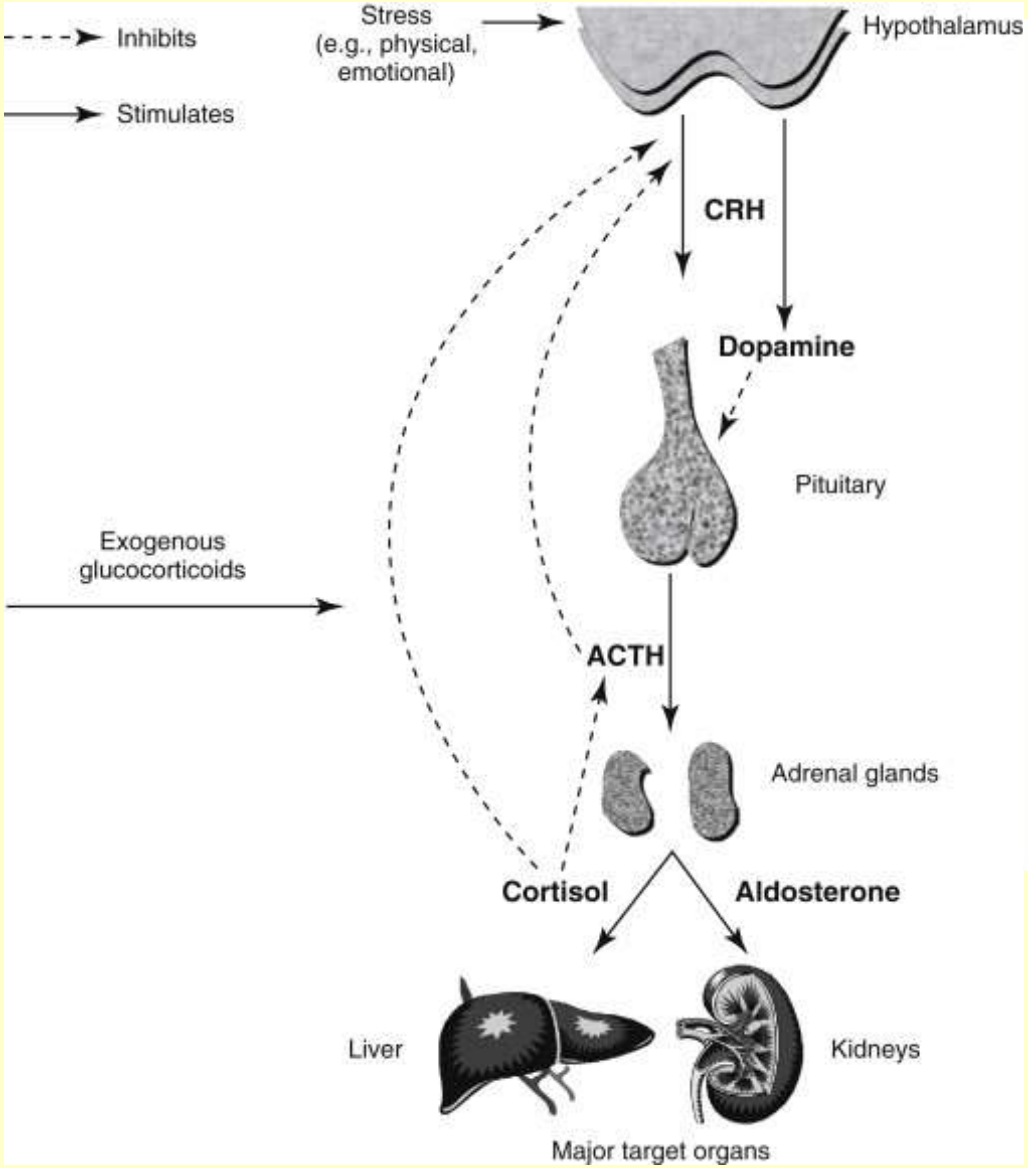
Transverse Section

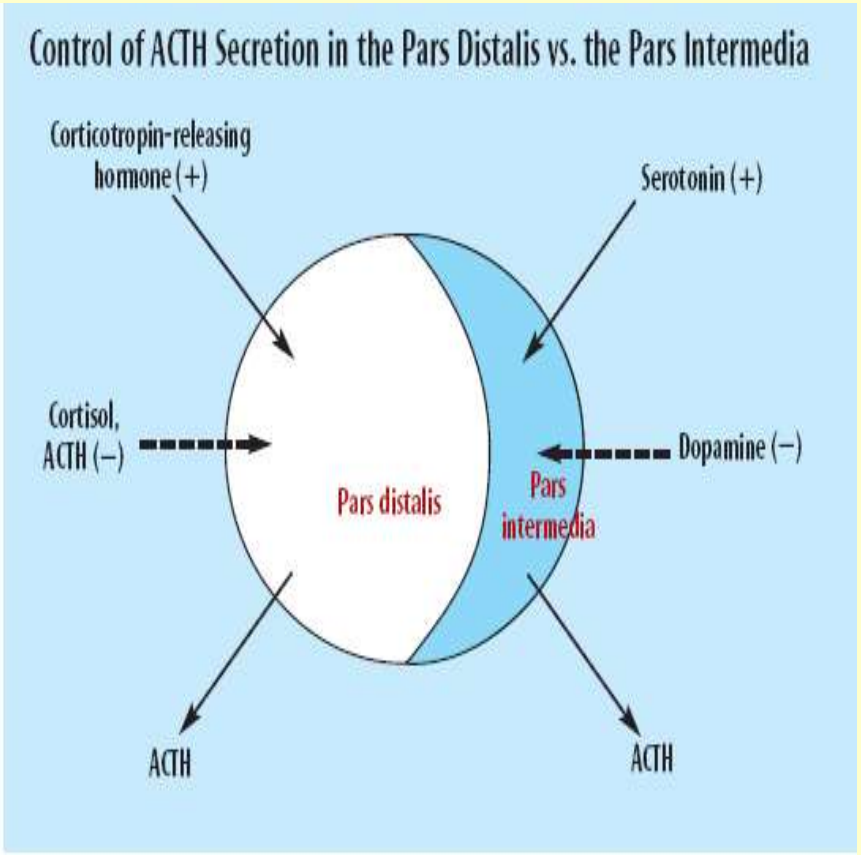


Microscopic Section



Regulation of glucocorticoid synthesis



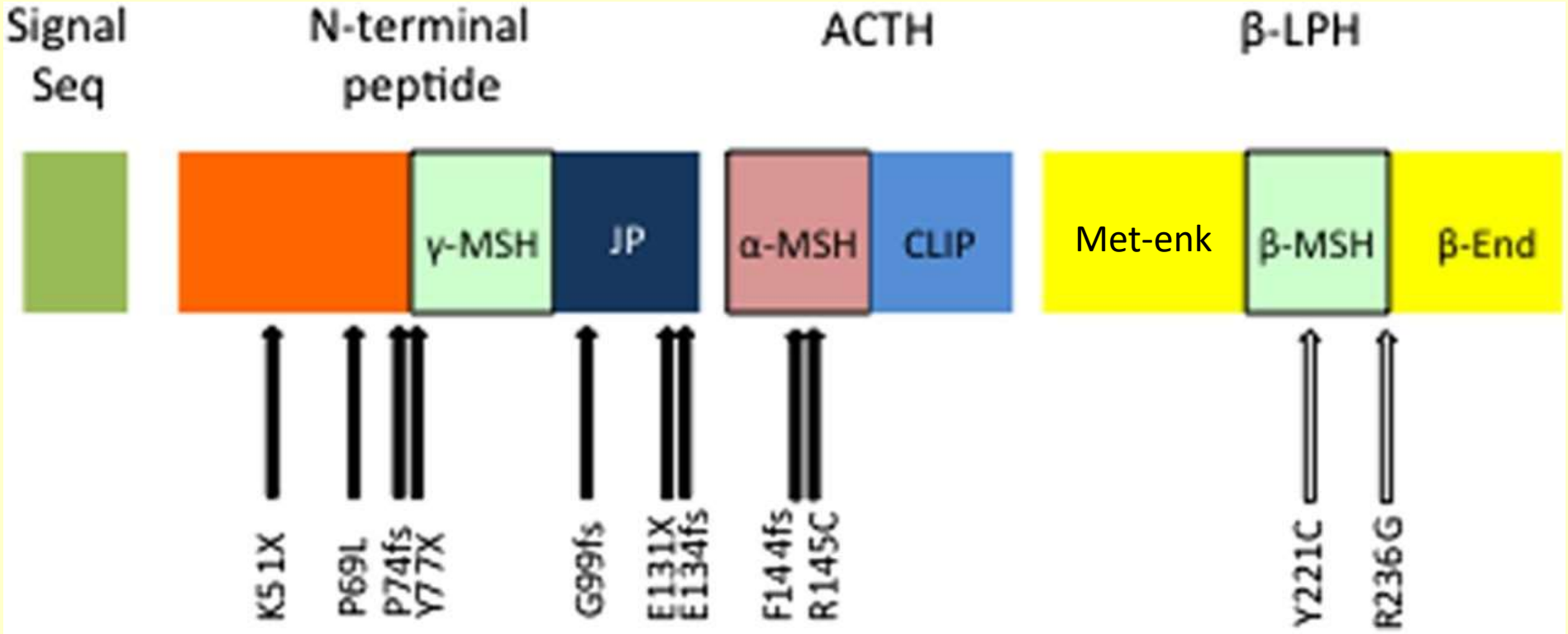


Dogs – dysfunction/adenomas of pars distalis

Horses—dysfunction/adenomas of pars intermedia

Proopiomelancortin (POMC)

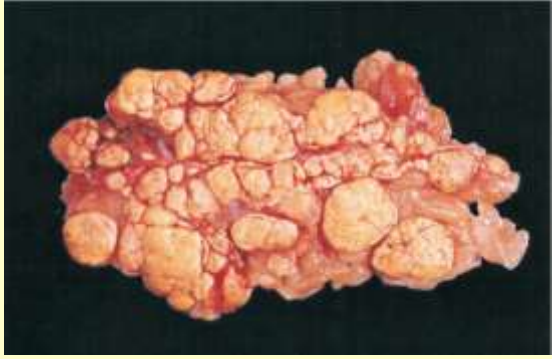
- Synthesized by pituitary corticotrophs
- Processed into smaller biologically active fragments including ACTH and beta-lipotropin



Cushing's Disease

- Harvey Cushing (1869-1939) was an American neurosurgeon, pathologist and writer
- 1912 reported clinical signs of Cushing's disease as "polyglandular syndrome" (pituitary, adrenal, pineal and/or ovarian influences)
- 1932 published additional findings as "The basophil adenomas of the pituitary body and their clinical manifestations"
  - Obesity
  - Diabetes mellitus
  - Hirsutism
  - Adrenal hyperplasia

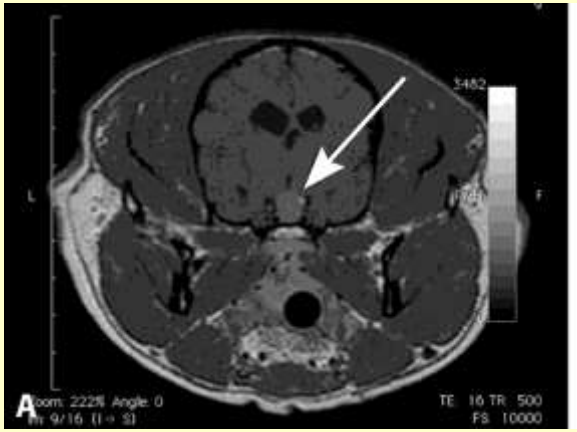
Cushing's Disease

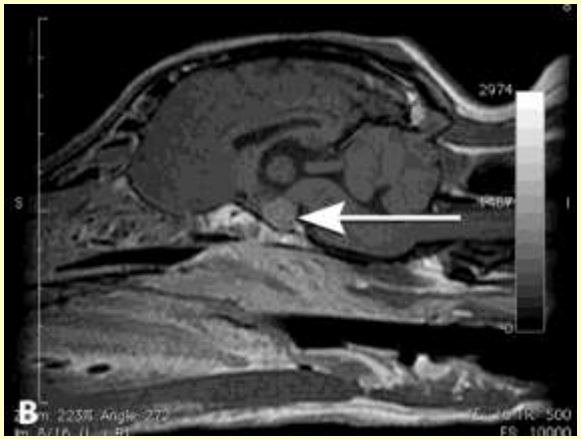


- Excess ACTH production by pituitary adenoma
- Excess ACTH production from hyperplastic pituitary (excess CRH or increase levels of serotonin)
- Adrenocortical tumor secreting excess cortisol
- Food-dependent cortisol secretion
- Ectopic sources of ACTH secretion
- Iatrogenic exogenous glucocorticoids

Pituitary Dependent Hyperadrenocorticism-Dogs

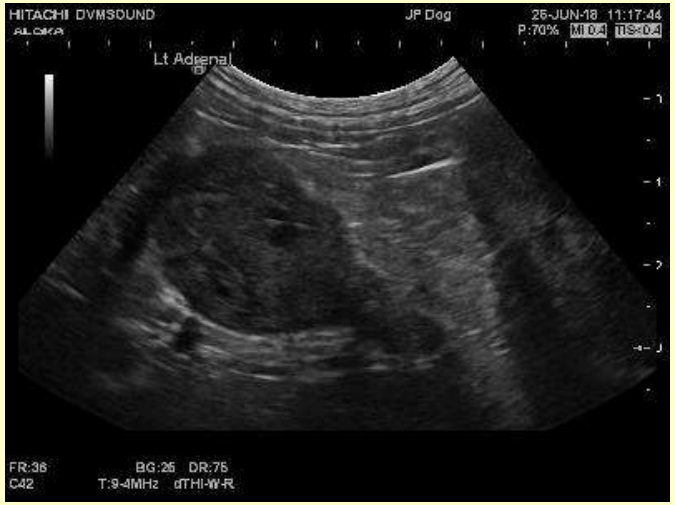
- 85-90% of dogs with HAC
- Microadenomas < 10 mm
- Macroadenomas > 10 mm
- Pars distalis (71-80%)
- Pars intermedia (20-29%)
  - Variable responses to negative feedback
- Hyperplasia – may be secondary to imbalance of neurotransmitters (e.g. ↑ levels of serotonin)

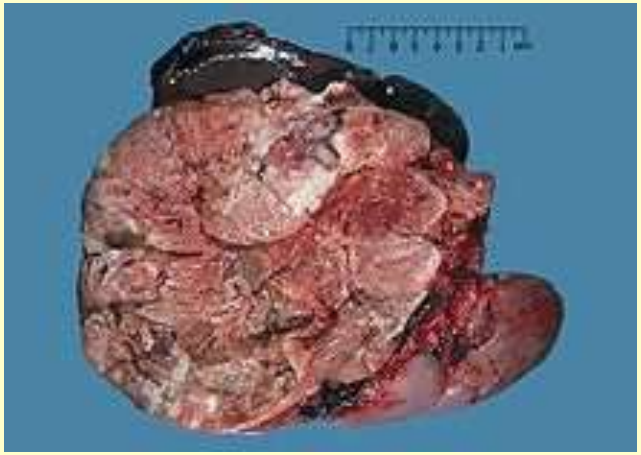




Adrenal tumors – dogs

- 10-15% of dogs with HAC
- Atrophy of contralateral gland
- Arise from zona fasiculata or retricularis
- Adrenocortical carcinomas frequently invade surrounding tissues (e.g. vena cava)



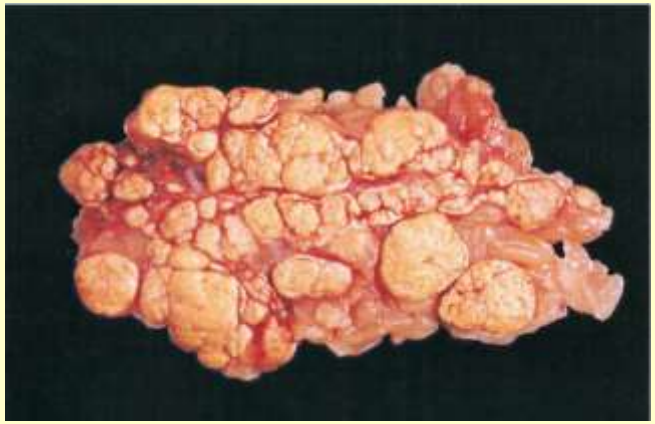


Ectopic ACTH Syndrome

- Dogs
  - Hepatic carcinoma
  - Neuroendocrine neoplasia
  - Unknown source in one dog
- Humans
  - Pulmonary oat cell carcinoma
  - Thymoma
  - Pancreatic islet cell tumor
  - Carcinoid tumor
  - Thyroid medullary CA
  - Pheochromocytoma

Food-dependent adrenocortical nodular hyperplasia

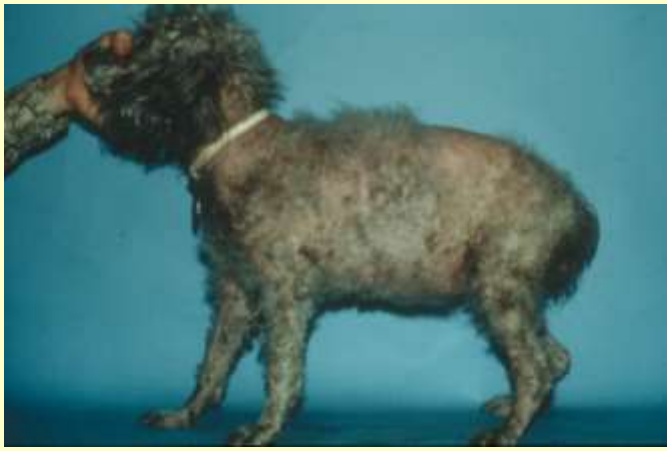
- Humans
  - Enhanced adrenal responsiveness to aberrant receptors in adrenal cortex
    - GIP (gastric inhibitory polypeptide)
    - Vasopressin
    - Beta-adrenergic
    - Luteinizing hormone
    - Serotonin
    - Angiotensin-1



- Dogs
  - Receptors for GIP, LH and vasopressin found in adrenal cortex
  - One case report of food-induced HAC associated aberrant adrenal GIP receptors

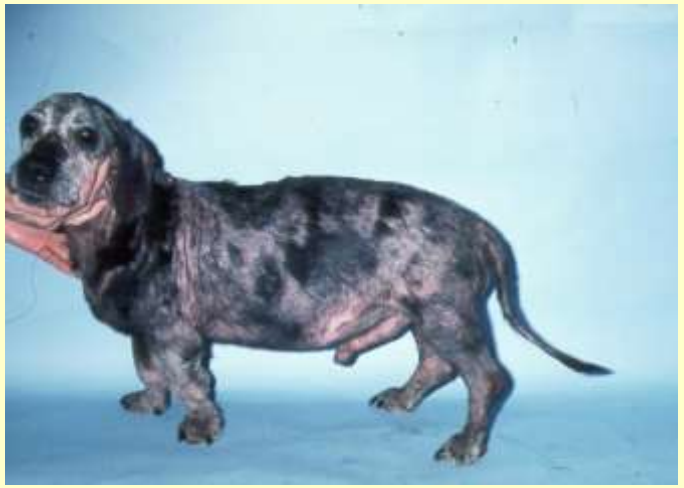
Canine HAC – risk factors

- 89% > 6 years
- 75% > 9 years
- 92% of Adrenal tumors > 9 yrs
- ↑ females
- Miniature poodles, boxers, dachshunds, ?terriers, ?beagles, ?GSDs
- 75% of PDH < 20 kg
- 50% of ATs > 20 kg



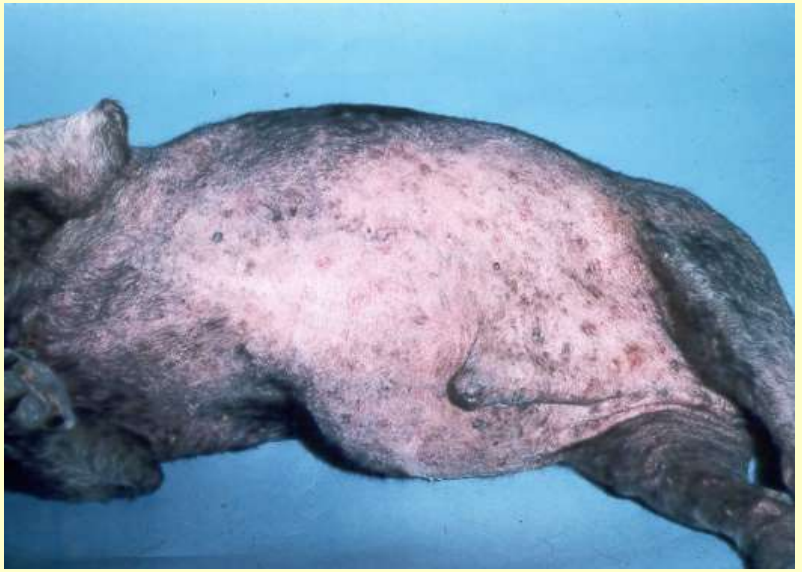
Canine HAC: clinical signs

- Common findings
  - PU/PD/PP
  - Panting
  - Hepatomegaly
  - Abdominal distension
  - Alopecia
  - Muscle weakness
  - Muscle wasting
  - Hypertension



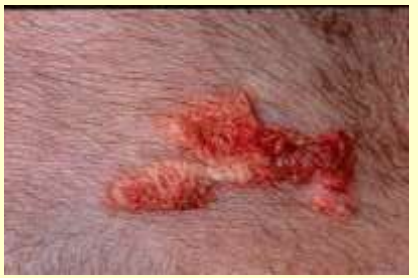
Canine HAC: clinical signs

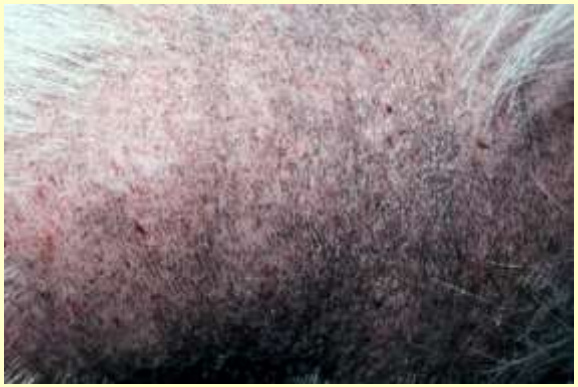
- Other findings
  - Lethargy
  - Hyperpigmentation
  - Comedones
  - Pyoderma
  - Thin skin
  - Poor hair regrowth
  - Incontinence
  - Diabetes mellitus

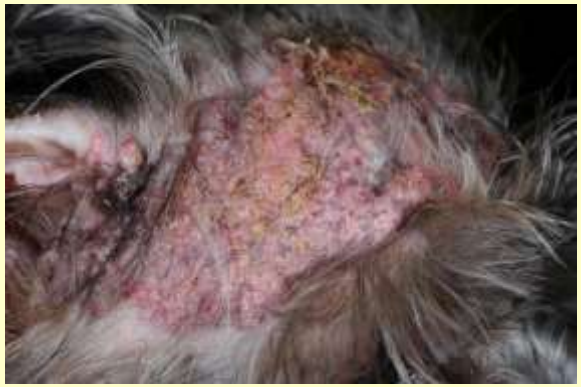


Canine HAC: “uncommon” signs

- Bruising
- Thromboembolism
- Ruptured ligaments
- Facial nerve palsy
- Calcinosis cutis
- Pseudomyotonia
- Testicular atrophy
- Anestrus







Signs that would not be expected in dogs with HAC

- Vomiting
- Diarrhea
- Sneezing
- Coughing
- Pain
- Bleeding

Pathophysiology: HAC--PU/PD

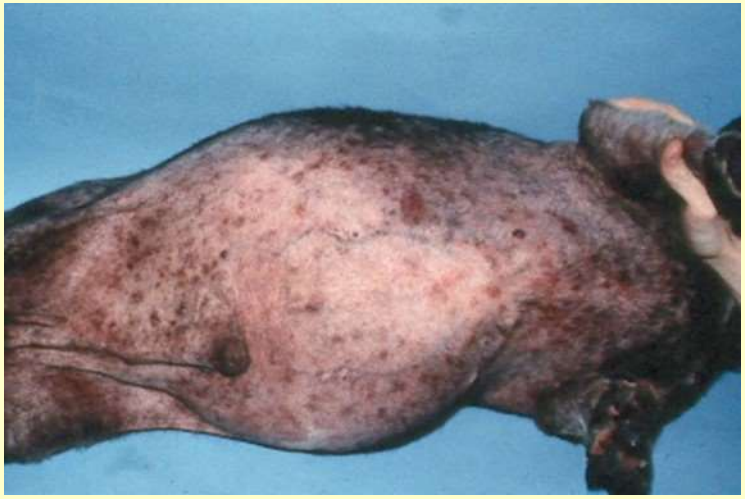
- Normal water intake for dogs is 60-90 ml/kg/day
- ~80% of dogs with HAC drink >100 ml/kg/day
- Causes
  - Abnormal sensitivity to ADH
  - Reduced renal responsiveness to ADH
  - Compression of hypothalamus→ diabetes insipidus

Pathophysiology: HAC--PP

- Direct effect on hypothalamus

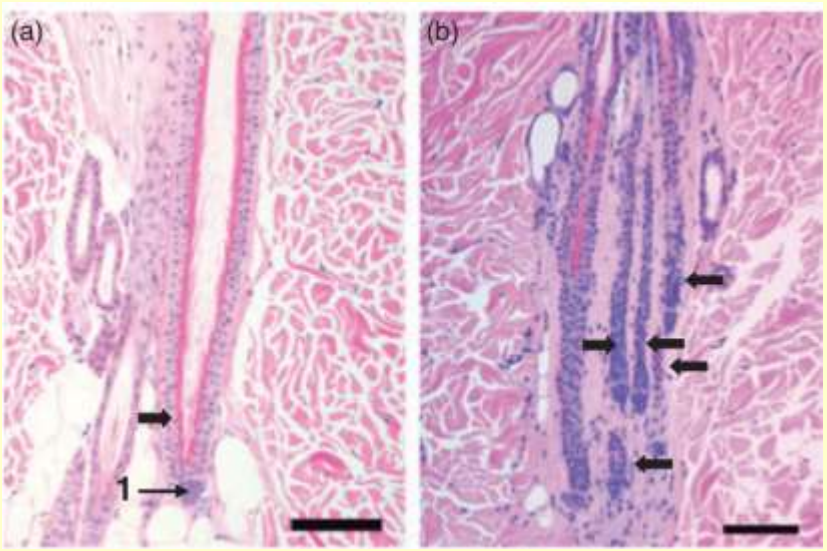
Pathophysiology: HAC—pot-belly

- Hepatomegaly (glycogen accumulation)
- Weak abdominal muscles (protein catabolism)
- Fat redistribution (intraabdominal)
- Bladder distension



Pathophysiology: HAC—alopecia

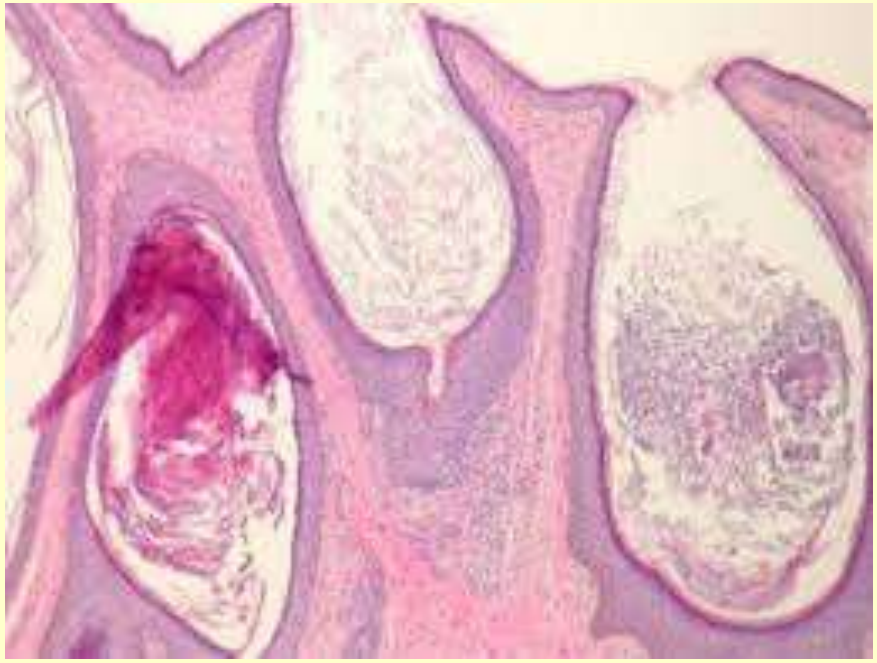
- Prolonged telogen
- Atrophy of hair follicles and adnexa



Vet Dermatol 2012; 23: 206-e44

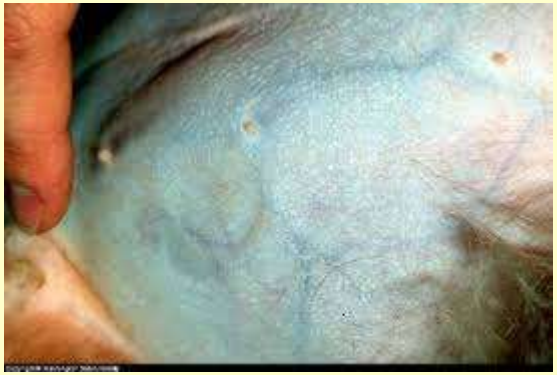
Pathophysiology: HAC—comedones

- Empty hair follicles distended with keratin and glandular secretions



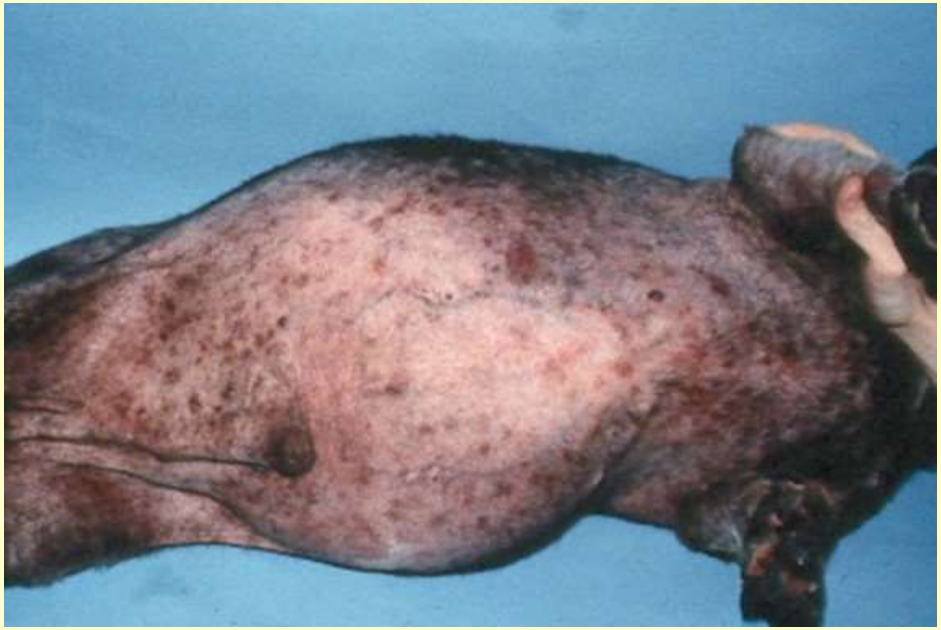
Pathophysiology: HAC—thin skin/cutaneous fragility/stria

- Decreased synthesis of collagen I and III
- Epidermal and piloglandular atrophy
- Decreased synthesis of mucopolysaccharides



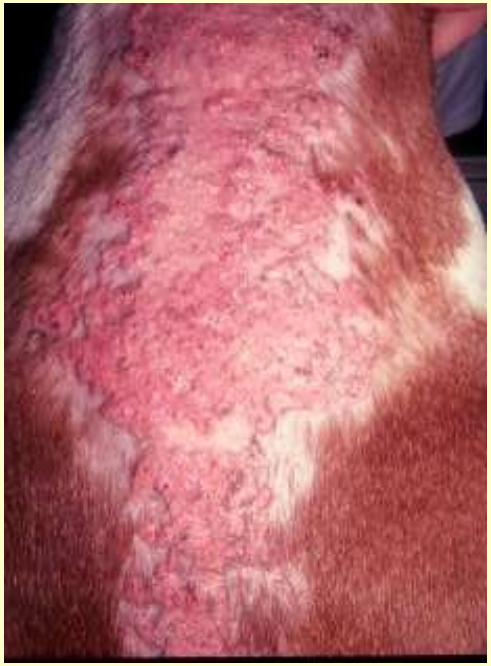
Pathophysiology: HAC—bruising, phlebectasias (dilated veins)

- Loss of collagen support
- Increased fragility of blood vessels



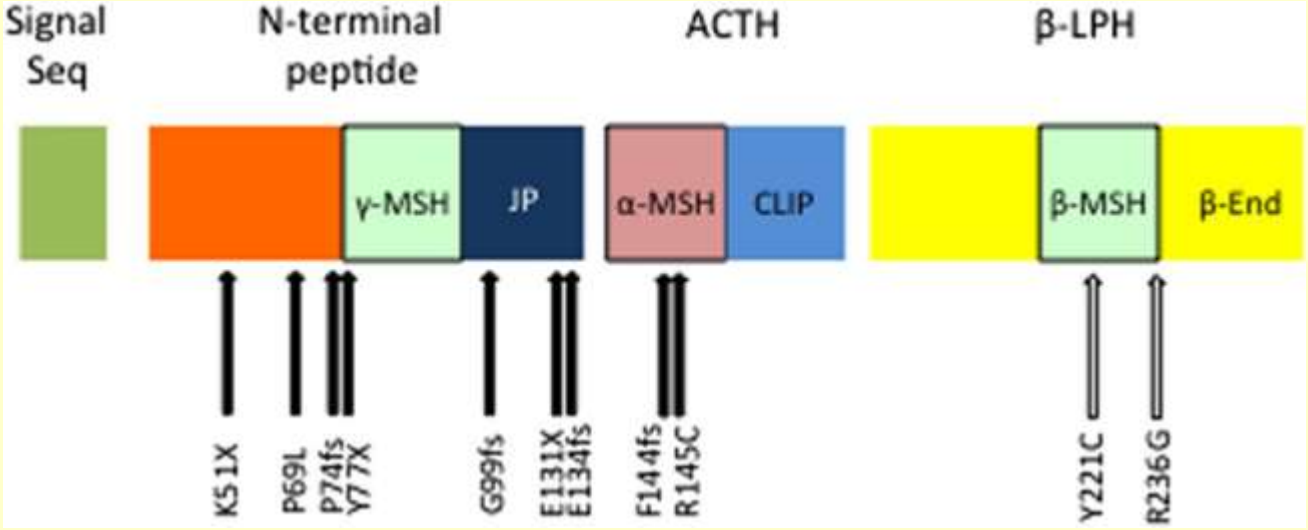
Pathophysiology: HAC—calcinosis cutis

- Abnormal collagen fibrils
- Secondary hyperparathyroidism
- Occurs in 2-40% of dogs, may progress to osseous metaplasia
- May also see calcification of pulmonary interstituim, trachea, bronchi and even other tissues (calcific band keratopathy)



Pathophysiology: HAC--hyperpigmentation

- Increased alpha-MSH
- Increased # of melanocytes
- Increased production of melanin

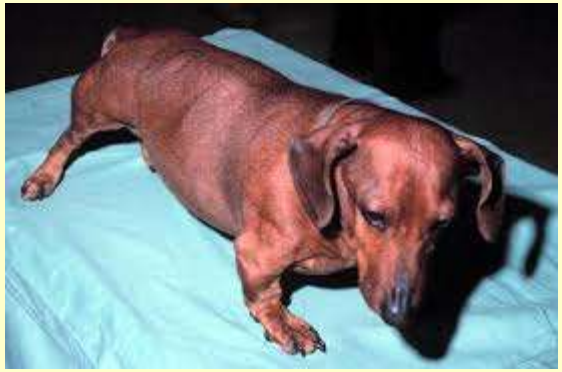


Pathophysiology: HAC—panting

- Muscle weakness
- Decreased lung compliance (e.g. due to calcification)
- Pressure on diaphragm from abdominal enlargement
- Thromboembolism
  - Increased levels of procoagulatory factors II, V, VII, IX, X, XII and fibrinogen and decreased anti-thrombin
  - Obesity, hypertension, polycythemia, blood stasis, damaged endothelium

Pathophysiology: HAC—myotonia/pseudomyotonia

- Muscle contractions continue after activity
- Pathology primarily affects type 2 muscle fibers
  - Variable sizes
  - Focal necrosis
  - Fiber splitting
  - Fatty infiltrates
- Neurologic
  - Demyelination
  - Chronic neuropathy
- EMG: bizzare high frequency discharges



Pathophysiology: HAC—CNS signs

- Expanding pituitary tumors
- Listlessness
- Inappetance
- Behavioral changes
- Disorientation
- Stupor
- Pacing/circling
- Ataxia
- Seizures

Pathophysiology: HAC—Blindness/ Sudden Acquired Retinal Degeneration Syndrome

- Compression of optic chiasma by pituitary tumor
- Changes in ocular blood flow
- Retinal health affected by increased concentrations of IL6, insulin, nitric oxide, triglycerides, and/or adiponectin

Pathophysiology: HAC—Hypertension

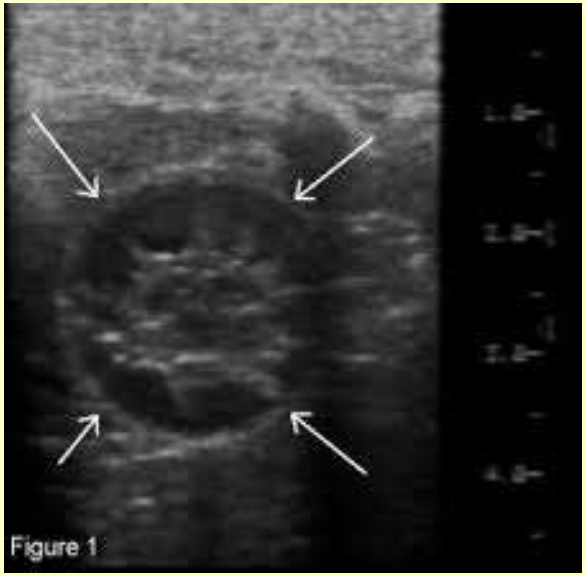
- Affects 31-86%
- Mean BP 150-202 mm Hg
- ↑ Renin
- ↑ vascular sensitivity to catecholamines
- ↓ prostaglandins (vasodilators)
- ↑ deoxycorticosterone and aldosterone

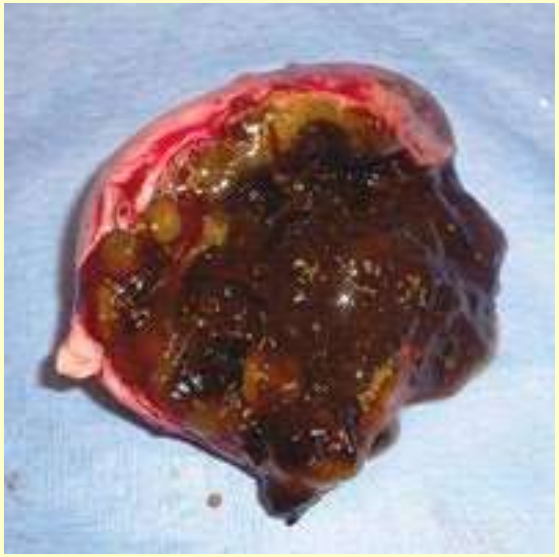
Pathophysiology: HAC—testicular atrophy

- Decreased concentrations of testosterone
- ? Decreased FSH and LH

Pathophysiology: HAC—Gallbladder mucocele

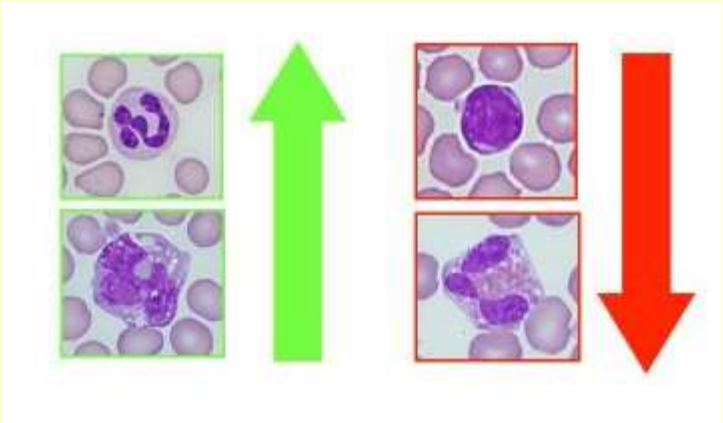
- 21-23% of dogs with GBM have HAC
- Hyperlipidemia = risk factor





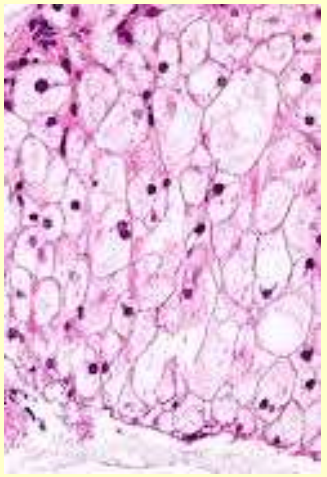
Complete Blood Cell Counts

- Mild polycythemia
- Thrombocytosis
- “Stress Leukon”
  - Neutrophilia & Monocytosis
    - Degressed egress
    - Capillary demargination
  - Lymphopenia
    - Lympholysis
  - Eosinopenia
    - Bone marrow sequestration



Chemistry Profile

- Alkaline phosphatase
  - Steroid induction of CIALP
  - Increased production of other isoezymes
- Alanine Aminotransferase
  - Hepatic swelling (glycogen accumulation)
  - Decreased bloodflow
- Bile acids
  - Cholestasis, 30% have increased pre- and post-prandial bile acids
- Hypercholesterolemia & Hypertriglyceridemia
  - Lipolysis, reduced clearance



Chemistry Profile

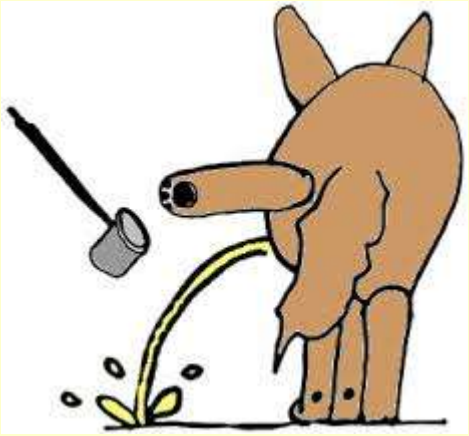
- Hyperglycemia
  - Insulin antagonism
  - Increased hepatic gluconeogenesis
  - Decreased peripheral ultilization
- Decreased BUN
  - Polyuria
- Calciuria, phosphaturia
  - Effect of corticosteroids on renal tubules
  - May predispose to uroliths
  - 33% have mild hypophosphatemia

Chemistry Profile & Urinalysis

- Electrolytes (mineralocorticoid activity)
  - Mild hypernatremia
  - Mild hypokalemia
- Dilute urine
  - Specific gravity < 1.020
- Proteinuria
  - 50% have mild proteinuria (UPCR < 5)
  - Secondary to hypertension and/or UTIs
- UTI
  - 50% have a UTI at time of diagnosis
  - Only 18% have pyuria/bacteruria
  - Dilute urine and anti-inflammatory effects of steroids are contributory factors

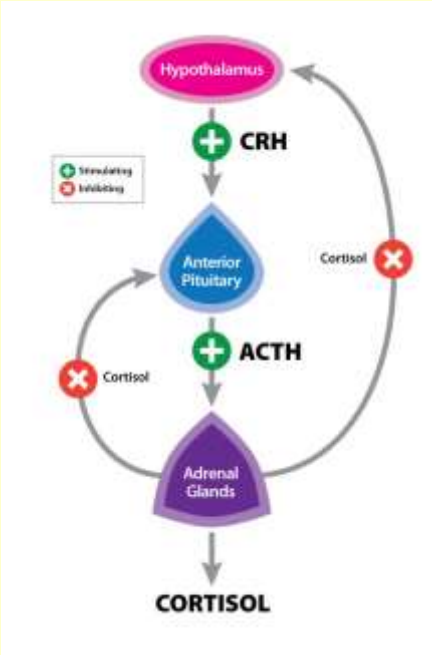
Urine Cortisol-to-Creatinine Ratio

- Home collected, free-catch, mid-stream, early morning urine (consider pooling samples from 2-3 days)
- Test sensitivity 75-100%
- Test specificity 20-25%
- Easy, low cost screening test to help rule out HAC (if negative and high suspicion evaluate other tests)



ACTH Stimulation Test

- Evaluation of adrenal capacity to secrete cortisol
- IV or IM 1 (monitoring) or 5 (diagnosis) µg/kg Cosyntropin (maximum 250 µg)
- Pre and 60 min post
- 80-85% sensitivity for PDH
- 57-63% sensitivity for AT
- 59-93% specificity for HAC
- Drug interference: glucocorticoids, progestogens, ketoconazole

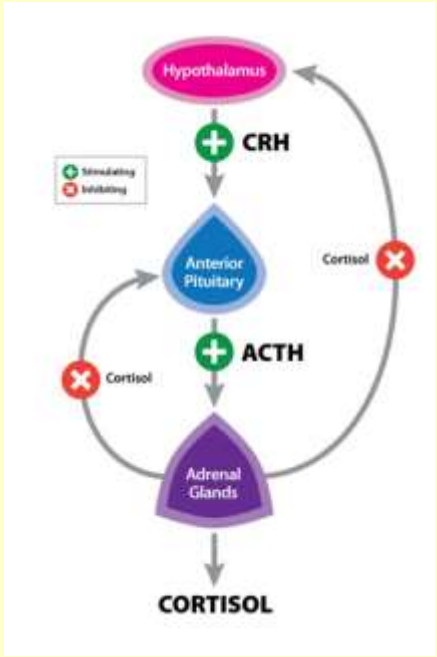


ACTH Stimulation Test

- Cortrosyn (cosyntropin)
  - Sterile lyophilized powder
  - Vials contain 0.25 mg (250 µg)
  - Reconstitute in 1 mL of 0.9% NaCl
  - Current cost ~$113 for 1 ml vial
  - Study showed that reconstituted solution frozen in plastic syringes (50 µg/syringe) is stable at -20C for at least 6 months
  - For diagnosis of HAC dose of 5 µg/kg recommended
  - For monitoring of treatment with lysodren and trilostane a dose of 1 µg/kg is sufficient
- Responses to synthetic ACTH gels are variable and therefore not recommended

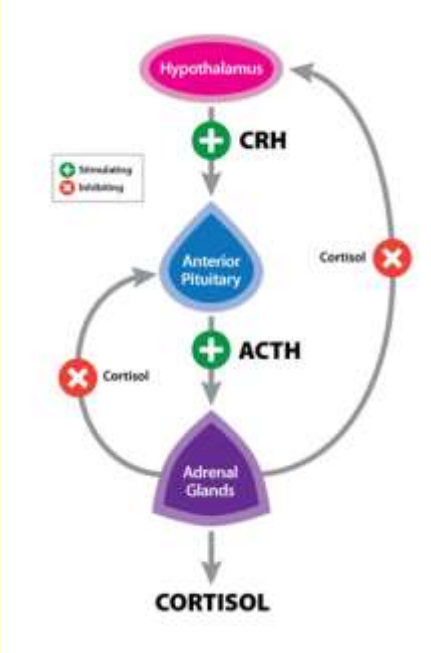
Low Dose Dexamethasone Suppression Test

- Evaluation of hypothalamic-pituitary-adrenal axis sensitivity to glucocorticoid negative feedback
- Dexamethasone 0.01 mg/kg IV
- Pre, 4-hr post, 8-hr post
- Normal dogs have suppression >50% of baseline and/or to < 1.4 µg/dL (40 nmol/L) lasting 24-48 hrs
- Lack of suppression at 8 hours has 85-100% sensitivity for HAC
- Lack of suppression at 8 hours has 44-73% specificity for HAC
- Suppression only at 4 hrs seen in 40-60% of dogs with PDH
- Drug interference: phenobarbital, phenytoin, rifampin, carbamazepine, barbituates (activate P450 3A4 and accelerate DXMS clearance)



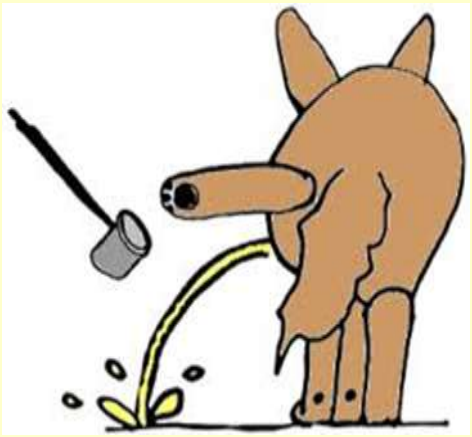
High Dose Dexamethasone Suppression Test

- Evaluation of hypothalamic-pituitary-adrenal axis sensitivity to glucocorticoid negative feedback at a 10X higher dose
- Dexamethasone 0.1 mg/kg IV
- Pre, 4-hr post, 8-hr post
- Suppression at either time has 75% sensitivity for PDH
- No suppression
  - Tumors of pars distalis
  - Adrenal tumors
  - Large pars intermedia tumors
  - Increased clearance of DXMS



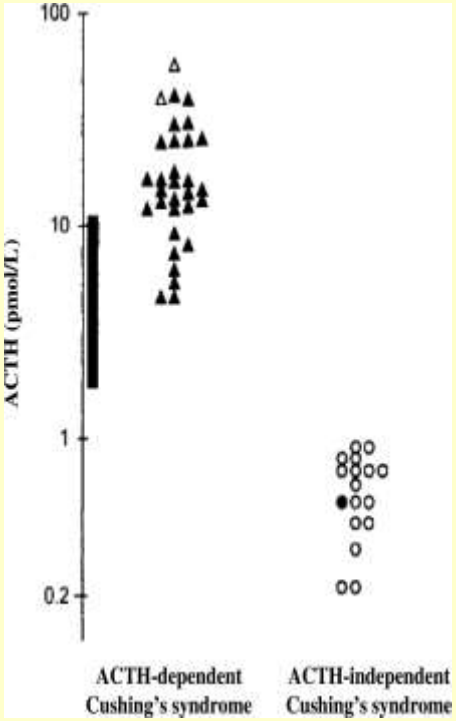
DXMS Suppression with UC-CR

- Owner collects urine for baseline UC-CR for two days
- Give 0.1 mg/kg DXMS PO q 6-8 hours for 3 doses
- Collect 3rd urine sample the following morning
- Sensitivity 70% for PDH = UC-CR <50% of mean of the two baseline samples



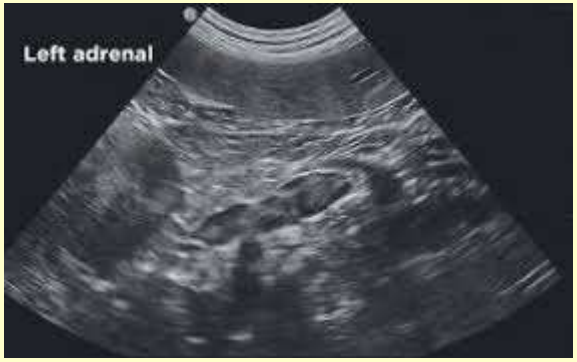
Endogenous ACTH

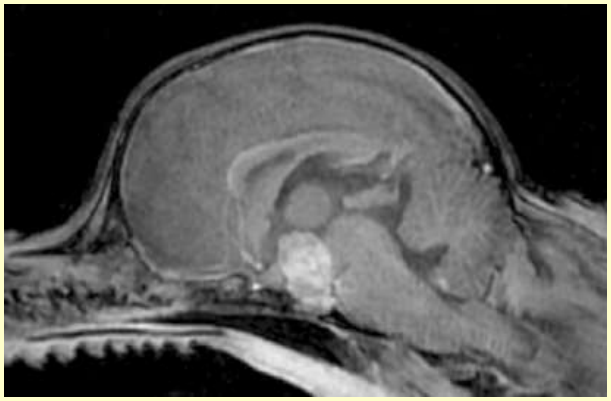
- eACTH < 10 pg/mL consistent with ATs
- eACTH > 15 pg/mL consistent with PDH
- ACTH binds to glass – use plastic or silicon-coated glass EDTA tubes
- Tubes should be prechilled and centrifuged within 15 minutes, transferred to plastic tubes and frozen immediately
- Protease inhibitor aprotinin improves stability of eACTH however can artifactually decrease ACTH in ChLIAs
- 80% sensitivity in differentiation of PDH and ATs



Imaging

- Abdominal Ultrasonography
  - Hepatomegaly –steroid hepatopathy (FNA)
  - PDH—bilateral adrenal enlargement
  - AT—one large, one small
- CT/MRI
  - Pituitary tumors
    - Macroadenomas (if > 0.8 cm vertical height candidate for RadTx)
  - Adrenal tumors (also assess vascular invasion)



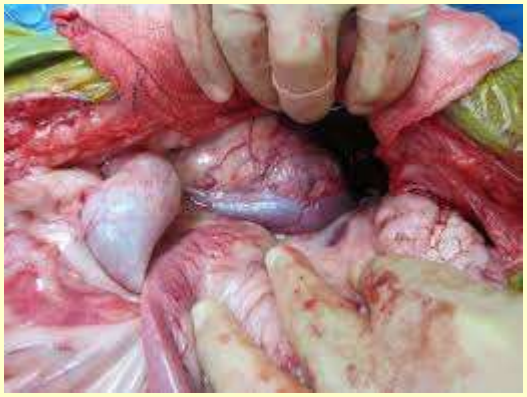


"To Treat or Not To Treat"

- Severity of clinical signs
- Owner's commitment
  - Close monitoring required
  - Multiple rechecks needed
  - Financial considerations
- Goal to improve quality of life and reduce complications related to disease

Adrenalectomy

- Remove adrenal tumor
  - Curative if non-metastatic, non-invasive
  - Surgery is technically challenging
  - Potential for life-threatening complications
    - Hemorrhage
    - Addisonian crisis
    - 25% mortality



Eastcott referrals UK; this adrenal is invading into vena cava

Hypophysectomy

- Transsphenoidal hypophysectomy
- Remove pituitary tumor
- Complications may include
  - Central DI
  - Hypernatremia
  - KCS
  - Secondary hypothyroidism

Pituitary Irradiation

- Reduce size of pituitary tumor
  - Consider if tumor > 8-10 mm at greatest vertical height
- Improve neurologic signs
- May not reverse adrenal hyperplasia

Lysodren (Mitotane; o,p'DDD)

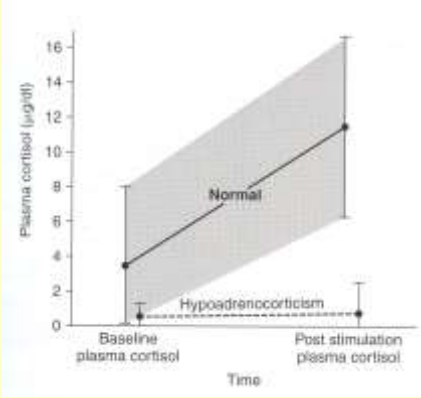
- Chlorinated hydrocarbon
- Binds to reactive acyl chloride intermediates in adrenal cortex
  - Selective necrosis of zona fasciculata and zona reticularis
- Good responses in 85% of dogs with PDH
- 6-10% of treated dogs develop adrenocortical insufficiency

Lysodren (Mitotane, o,p'DDD)

- Induction
  - 20-25 mg/kg q 12 hours
  - Twice daily owner should feed ½ of a meal and monitor appetite
    - Good appetite – give Lysodren with remainder of meal
    - Decreased appetite – do not give Lysodren
  - In addition to appetite monitor for signs of decreased water consumption, vomiting, diarrhea, muscle tremors and lethargy – if any of these occur do not give Lysodren and contact DVM and/or give prednisolone ("antidote")

Lysodren (Mitotane, o,p'DDD)

- Induction monitoring: clinical signs & ACTH stimulation test, Na/K levels
  - Bloodwork after ~8 days of treatment (sooner if decreased drinking/appetite, tremors or lethargy occur)
  - Goal of both pre- and post- cortisol level between 1-5 µg/dL
  - Higher levels → continue induction another 3-5 days and recheck ACTH stimulation
  - Cortisol < 1 µg/dL stop treatment and recheck ACTH stim in 2 weeks, if clinical give prednisolone
  - ↓Na or ↑K stop Lysodren, check aldosterone levels (pre and 30 min post ACTH), if low aldosterone and/or clinical start on Percorten-V or Florinef

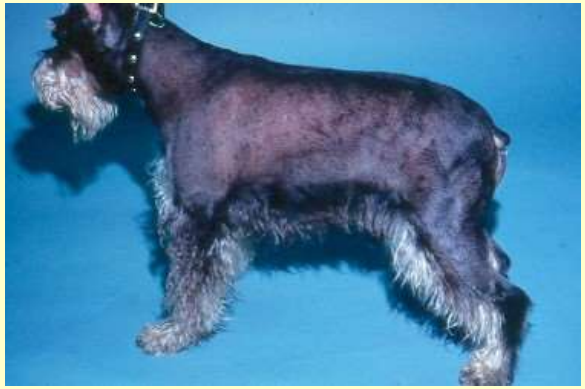


Lysodren (Mitotane, o,p'DDD)

- Maintenance
  - ~25 mg/kg twice weekly
  - Repeat ACTH Stimulation tests + Na/K levels at one, three and six months and every 3 months thereafter
  - If cortisol > 5 µg/dL and/or > 2-fold increase increase Lysodren dose and recheck in one month or sooner if any clinical signs of glucocorticoid deficiency
  - If cortisol < 1 µg/dL, stop Lysodren and recheck ACTH stimulation test in 2 weeks, if clinical give prednisolone 0.2 mg/kg; if restart Lysodren reduce dose by 50% and recheck in one month

Lysodren (Mitotane, o,p'DDD)

- Anticipated responses
  - PU/PD improve quickly
  - Polyphagia improves quickly
  - Hair regrowth and other clinical signs improve over months
    - Note – initial hair regrowth may differ in color and/or texture from normal coat ("puppylike")
- Stress or illness
  - Consider giving prednisolone $\geq$ 0.2 mg/kg

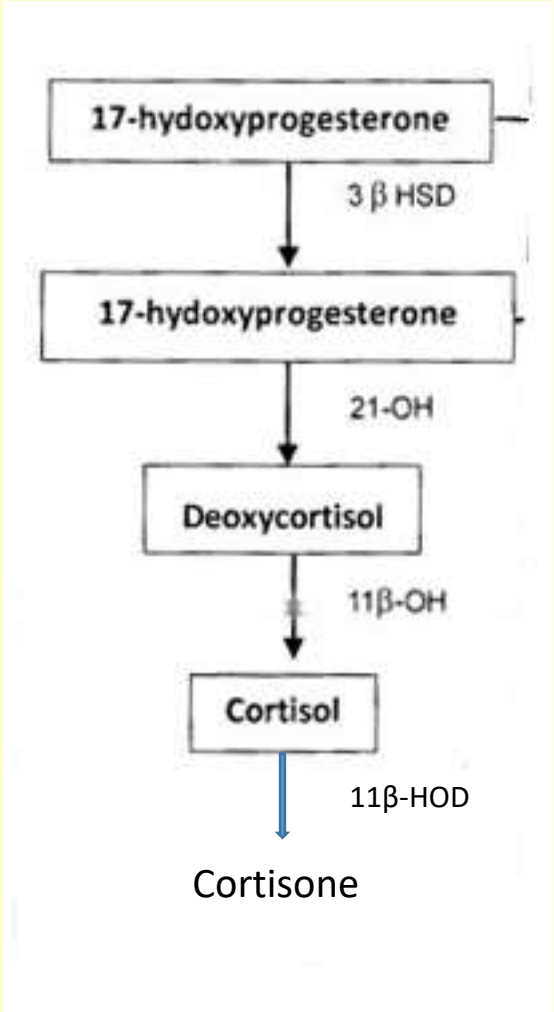


Lysodren for purposeful destruction of adrenal cortex

- May destroy adrenal tumors
- May be easier to manage hypoadrenocorticism than hyperadrenocorticism
- Administer Lysodren at 25 mg/kg q 8 hrs for 25 days
- Also give prednisolone at 0.1 mg/kg q 12 hrs for 25 days, then taper to 0.1 mg/kg q 48 hrs unless clinical signs of hypocortisolism (anorexia, tremors, lethargy)
- After 3 days start on mineralocorticoids (Florinef or percorten-V) and monitor electrolytes to adjust doses
- Monitor ACTH stimulation test – may need further treatment with Lysodren initially or if relapses

Trilostane

- Synthetic steroid analogue
- Inhibits adrenal 3-β-hydroxysteroid dehydrogenase (3 β-HSD) ± 11- β-hydroxylase and 11- β-hydroxysteroid dehydrogenase
- Better absorption with food
- Peak concentration 1.7-3.8 hr
- Cortisol levels back to baseline within 12 hr (activity < 12 hr in some dogs with HAC)
- Metabolite ketotrilostane has increased potency



Trilostane

- Compounded forms not recommended (variable potency of 39-152.6% in one study)
- Available sizes: 5, 10, 30, 60, 120 mg
- Wide variation in dose required to achieve clinical control of HAC (0.42-50 mg/kg BW PO daily)
  - Once daily dosing range 0.8-50 mg/kg q 24 hr
  - Twice daily dosing range 0.21-9.05 mg/kg q 12 hr
  - One report of 5.6% of dogs (10/180) needing q 8 hr
- Low risk of adrenal necrosis (including zona glomerulosa) – thought to be due to high ACTH
- SE's: mild electrolyte abnormalities, anorexia, vomiting, diarrhea, lethargy

Trilostane

- Pre-treatment
  - Water consumption and appetite
- Initial treatment
  - Feed ½ of meal (appetite ok?)
  - Give 0.5-1 mg/kg q *12 hours with rest of meal
  - Stop if loss of appetite, change in drinking, tremors, lethargy
- Recheck in 10-14 days (sooner if any concerns)
  - How has patient been acting?
  - ACTH stimulation test & Na/K – start at 4-6 hrs after morning dose
    - Cortisol < 1 µg/dL stop trilostane and recheck in 2 wks (if > 1 µg/dL in 2 weeks restart at 50% lower dose)
    - Cortisol > 1 µg/dL continue treatment and recheck in 1 mo

* Manufacturer recommends 2.2 mg/kg PO q 24 hr

Trilostane

- One month recheck
  - How is patient doing?
  - ACTH response test – start test at 4-6 hrs after giving am dose
    - Cortisol pre- and post- of 1-5 µg/dL is ideal
    - Cortisol pre- or post < 1 µg/dL stop treatment, check Na/K, recheck in 2 weeks and if cortisol > 1 µg/dL restart at 25-50% lower dose and recheck in another 2 weeks
    - Cortisol > 9 µg/dL post ACTH and clinical signs of HAC still present increase dose by 25% and recheck in 2 weeks
- When clinical signs resolved and/or cortisol levels 1-5 µg/dL recheck again in 1 month, 3 months and every 3 months thereafter

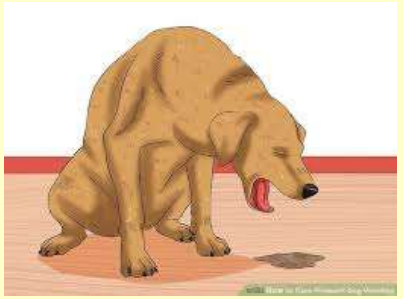
Trilostane-alternative monitoring protocols

- *"Most important considerations are clinical response and avoiding hypoadrenocorticism"*
- Correlation between clinical response and results of ACTH stimulation testing is controversial/unclear
  - Many dogs "look better on paper" than "in real life"
  - Testing at different times post-dosing → significant differences; cortisol levels are lowest 2-4 h after dosing
  - Recommended times for ACTH stim testing has varied (2-6h, 3-4h, 3 h, 2-4h, 8-12h)
  - Many different recommendations for optimal post-ACTH target concentrations from as low as 20 to < 250 nmol/L

Trilostane-alternative monitoring protocols

- *Most important considerations are clinical response and avoiding hypoadrenocorticism*
- Above goal can be achieved by evaluation of clinical response (recommend using a questionnaire for owners to complete at each visit) and evaluating cortisol level pre-trilostane ("peak") ± cortisol levels 3-hour post-trilostane ("trough").
- If cortisol level is low (<1 µg/dL or < 30 nmol/L) should stop treatment, check electrolytes and when levels increase restart trilostane at a lower dose

Trilostane



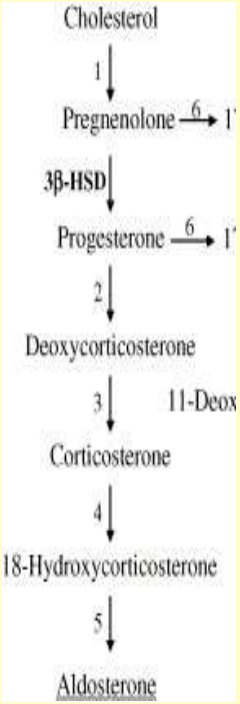
- Side effects
  - vomiting, diarrhea, lethargy, weakness
  - Stop treatment and check Na/K and ACTH stimulation test (aldosterone levels best checked pre and 30-minutes post-ACTH)
- Effectiveness
  - 70-90% of treated patients favorable response
    - Decrease in PU/PD, less ravenous appetite, hair regrowth, improved endurance; improved liver values
  - “Paper values” may show more improvement than patient
    - Likely due to short half-life of trilostane
  - Several physiologic abnormalities have not been shown to improve in trilostane treated dogs

Trilostane

- Physiologic abnormalities that have not been shown to improve in trilostane treated dogs
  - Hypertension persists long-term
    - Renin activity increases with trilostane
  - Proteinuria persists in many patients
  - Hypercoagulativity (based on measurement of thromboelastographic assays) does not improve
  - Adrenal size increases over time

Aldosterone levels in dogs treated for HAC

- Dogs treated for HAC often have decrease in aldosterone secretory reserve
- Na^{2+} and K^{+} levels do not predict aldosterone reserve
- Evaluate aldosterone reserve by measuring levels pre-ACTH and 30 min post-ACTH (5 µg/kg IV)
  - 49% of trilostane-treated dogs have decreased reserve
  - 78% of lysodren-treated dogs have decreased reserve
    - Only 6-10% of dogs treated with lysodren have clinical signs of Addison's



Ketoconazole for HAC

- Antifungal: inhibits conversion of lanosterol to ergosterol
- High doses: inhibit 17-20 desmolase and 11-hydroxylase
- Decreases serum levels of cortisol and testosterone when given at 10-15 mg/kg PO q 12 hrs
- For treatment of HAC
  - Week 1: give 5 mg/kg PO q 12 hr
  - Week 2-3: give 10 mg/kg PO q 12 hr
  - Day 21: check ACTH stim
    - Pre & post cortisols 1-5 µg/dL: continue current dose
    - Cortisols > 5 µg/dL: increase dose to 15 mg/kg PO q 12 hr
      - Retest in 14 days
        - Pre and post cortisols 1-5 µg/dL: continue current dose
        - Cortisols > 5 µg/dL: increase dose to 20 mg/kg PO q 12 hr
          - Restest in 14 days…
- SEs: may cause anorexia, vomiting, hepatotoxicity

L-Deprenyl (Anipryl, seligiline) for treatment of HAC

- First FDA approved treatment for K9 HAC
- Monoamine oxidase B inhibitor: inhibits degradation of dopamine in brain → increases in dopamine decrease ACTH production by pituitary pars intermedia
- 10-20% of dogs with PDH have tumors of pars intermedia
- Give 1 mg/kg once daily for 30 days, if no improvement increase dose to 2 mg/kg
- Monitoring is based on clinical signs – rarely changes in cortisol levels or other laboratory tests
- Metabolized to amphetamine and methamphetamine: changes in dog's activity levels may be due to these metabolites
- SE's: vomiting, diarrhea, pytalism

Bromocriptine for treatment of HAC in dogs

- Dopamine agonist—may decrease ACTH production by pituitary pars intermedia
- One study showed improvement in 1/47 dogs treated with it

“Atypical Cushing’s Syndrome”

- Clinical signs of HAC however cortisol levels within normal ranges in all tests
- One theory is affected animals have adrenal overproduction of progesterone and other sex hormones
- May be caused by high levels of FSH and LH in neutered pets →hyperplasia or tumors of zona reticularis
- ACVIM Consensus Panel in 2013 reports lack of evidence for a role of sex hormones

Iatrogenic Hypercortisolism in dogs

- Clinical signs identical to “spontaneous” HAC
- ACTH stimulation test: suppression of pre- and post-ACTH cortisol levels
- Recovery of adrenal function may take 3-12 months
- If develop signs of hypocortisolism (weakness, anorexia, hypotension, muscle tremors) supplement with physiologic doses (prednisolone 0.1-0.2 mg/kg /day) with gradual taper

“Rocky Ryan”

- 10 yr old MC Boston Terrier
- Chief concerns: hair loss and PU/PD
- Previous history: has been on phenobarbital for 7 years for control of seizures, has 1-2 short seizures per year; current dose is 10 mg/kg PO q 12 hr
- PE: panting, HR 140/min, RT 100.4 F, thinning of hair coat—trunk, rear legs, abdomen, slightly pot-bellied, moderate hepatomegaly, some loss of muscle mass
- 10 kg BW

“Rocky Ryan”

- Baseline bloodwork
  - PCV 42%; WBC 11,200; platelets 350,000
    - 8,800 neutrophils; 1,400 monocytes; 800 lymphocytes, 200 eosinophils
  - ALT 2100 IU/L; ALP 3800 IU/L; GGT 16 U/L; Bilirubin 0.3 mg/dL; BUN 5 mg/dL; Creatinine 1.1 mg/dL; cholesterol 585 mg/dL; triglycerides 195 mg/dL; total protein 7.1 g/dL; albumin 3.4 g/dL; globulin 3.6 g/dL; Na 145 mmol/L, K 4.7 mmol/L; chloride 111 mmol/L
  - Urinalysis: Sp. Gr. 1.013, normal sediment
  - PB level: 140 µmol/L (therapeutic range 70-170)

“Rocky Ryan”

- ACTH response test
  - Cortisol pre: 8.9 µg/dL (normal 2-6)
  - Cortisol post: 27 µg/dL (normal 6-18)
- HDDST
  - Cortisol pre: 7.8 µg/dL (normal 2-6)
  - Cortisol post: 4.7 ug/dL (normal < 1.4 µg/dL)
- Abdominal ultrasound
  - Enlarged liver
  - Bilateral enlargement of adrenal glands

“Rocky Ryan”

- Baseline water consumption: average 110 ml/kg/day
- Started on Lysodren 250 mg/kg PO q 12 hrs
- Day 10: owners report no changes in appetite or drinking
- ACTH stimulation test
  - Cortisol Pre: 7.7 µg/dL (normal 2-6)
  - Cortisol Post: 21.0 µg/dL (desired range 2-6)
- Continued Lysodren 250 mg/kg PO for 7 more days: owners report no changes in appetite or drinking

“Rocky Ryan”

- ACTH Stimulation test (now 17 days on TX)
  - Cortisol pre: 9.0 µg/dL (normal 2-6)
  - Cortisol post: 19.9 µg/dL (desired 2-6)
- Increased Lysodren dose to 375 mg PO q 12 hrs
- Rechecked 5 days later: owners report no changes in appetite or water drinking
- ACTH Stimulation test (now 22 days on TX, last 5 at higher dose)
  - Cortisol pre: 8.8 µg/dL (normal 2-6)
  - Cortisol post: 17.2 µg/dL (desired 2-6)

“Rocky Ryan”

- Recheck Day 28: owners report no change in appetite or water drinking
- ACTH Stimulation test
  - Cortisol pre 8.2 µg/dL (normal 2-6)
  - Cortisol post 17.9 µg/dL (desired 2-6)
- Drug interference? Phenobarbital may induce faster metabolism of Lysodren)
- Stopped Lysodren
- Added KBr 10 mg/kg q 12 hrs
- After two 2 wks started decreasing PB
  - Day 14-21: 75 mg q 12 hr
  - Day 22-28: 50 mg q 12 hr
  - Day 29- 35: 25 mg q 12 hr
  - Day 36-42: 25 mg q 24

“Rocky Ryan”

- Recheck Day 42 after starting KBr: owners report no seizures, initially sleepier than normal however now back to normal
  - KBr level: 18 mmol/L (therapeutic range 10-20)
- Stopped phenobarbital at day 42 after starting KBr
- Day 49: Restarted Lysodren at 250 mg PO q 12 hrs
- Day 58: owners report decrease in appetite, did not give Lysodren this am
  - Na/K: 140/4.4
  - ACTH Stimulation test
    - Cortisol Pre: 4.8 µg/dL (normal 2-6)
    - Cortisol Post: 7.8 µg/dL (desired 2-6)

“Rocky Ryan”

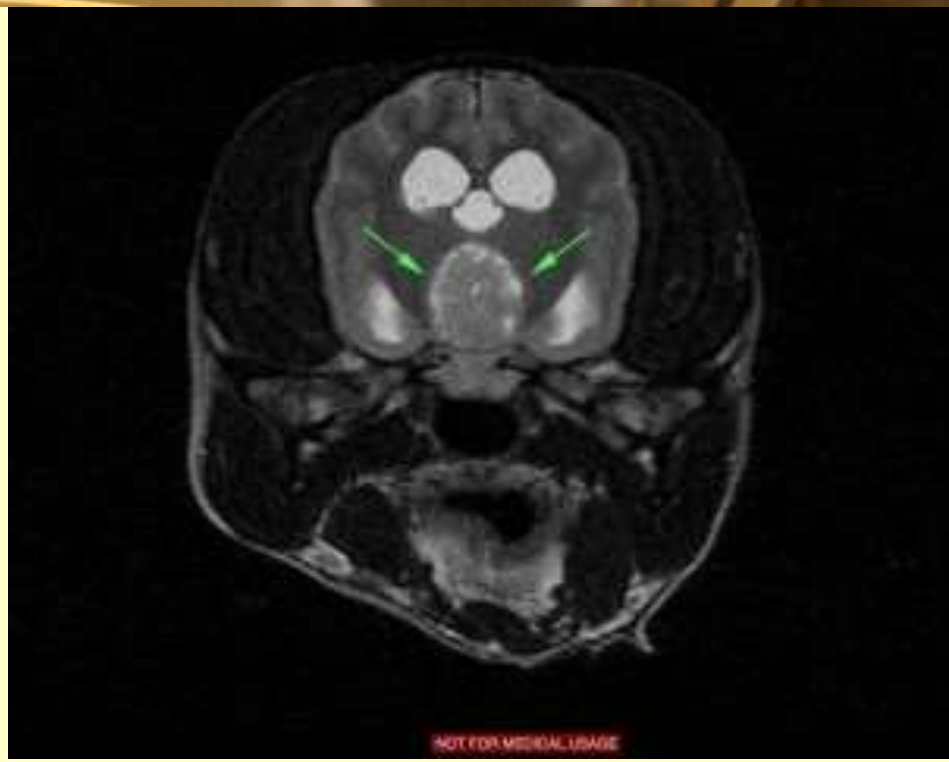
- Started on maintenance of 250 mg every Monday and Thursday
- Recheck 30 days later: owners report less panting and decreased water drinking
- Na/K = 141/3.9
- ACTH Stimulation test
  - Cortisol pre: 5.1 µg/dL (normal 2-6)
  - Cortisol post: 7.4 µg/dL (desired 2-6)
- Continued 250 mg every Monday and Thursday
- Rechecked 60 days later (3 months on maintenance): owners report continued improvement with hair regrowth

“Rocky Ryan”

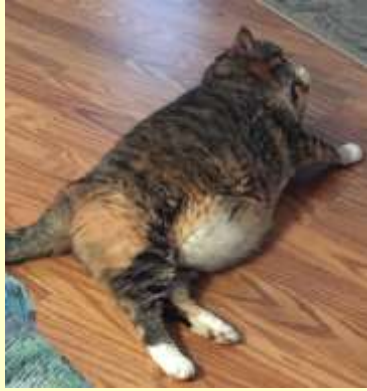
- ACTH stimulation test
  - Cortisol pre: 3.3 µg/dL (normal 2-6)
  - Cortisol post: 4.1 ug/dL (desired 2-6)
- Recheck two months later (now 5 months on maintenance): owners report that dog is having behavioral changes: circling, standing in corners, snapping at them when they pick him up
- ACTH Stimulation test
  - Cortisol pre: 2.7 µg/dL (normal 2-6)
  - Cortsol post: 4.3 µg/dL (desired 2-6)

“Rocky Ryan”

- MRI of head
  - 2 cm macroadenoma of pituitary
- Radiation treatment recommended



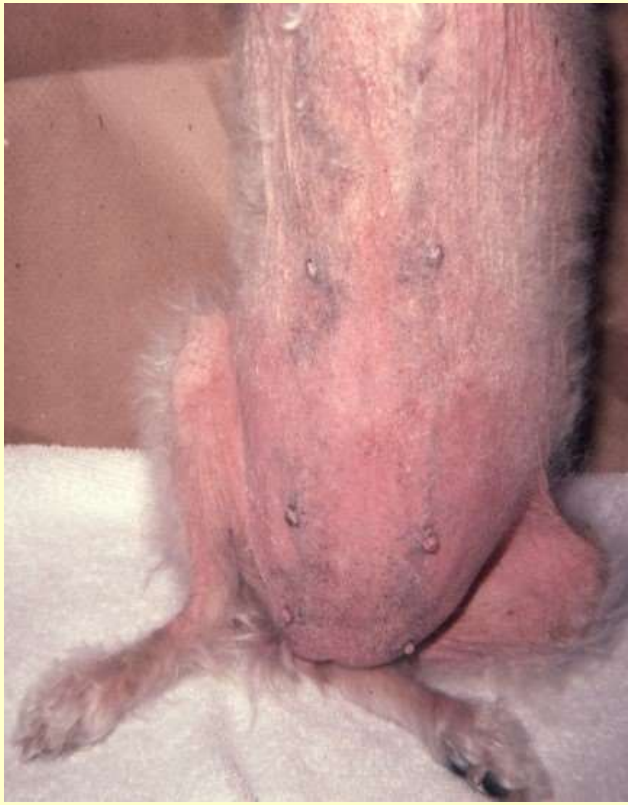
Feline Hypercortisolism



- Spontaneous hypercortisolism is rare in cats
  - 80% PDH
  - 20% adrenal tumors
- Clinical signs: PU/PD, polyphagia, weight loss, lethargy, weakness, alopecia, reduced grooming, coarse hair coat, curled ear tips, decrased appetite, thin skin, fragile skin, pot-bellied appearance, vomiting, diarrhea
- 90% pre-diabetic or diabetic
- Laboratory findings may be normal for non-diabetics (do not have a CI-ALP isoenzyne)

Feline Hypercortisolism

- Cutaneous changes
  - Alopecia
  - Thin skin
  - Skin fragility
  - Easy bruising
  - Recurrent abscesses
  - Comedones
  - Seborrhea
  - Reduced self-grooming
  - Coarse haircoat
  - Hyperpigmentation
  - Curled ear tips



Feline Hypercortisolism

- Diagnosis of HAC
  - Dexamethasone suppression test
    - 20% of normal cats do not show suppression with 0.01 mg/kg
    - 0.1 mg/kg with 0 and 8 hour post DXMS serum samples
  - ACTH response tests
    - HAC and non-HAC cats with DM have similar results
- Differentiation of PDH and AT
  - "mega" HDDST: 1 mg/kg with 0 and 8 hr post DXMS samples
  - UC-CR: two baseline morning urine samples then give DXMS 0.1 mg/kg q 8 hrs for 3 doses and following am collect urine for 3rd UC-CR (suppression to <50% = PDH)
  - Imaging (ultrasonography, CT scan, MRI)

Feline Hypercortisolism

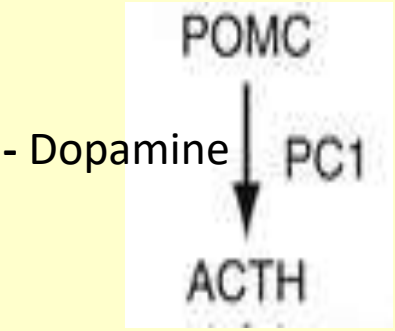
- Treatment of HAC
  - Trilostane – has been reported as effective (5 cases)
  - Lysodren – not effective
  - Metyrapone (blocks adrenal conversion of 11-doxycortisol to cortisol) – reported effective in 3/5 cats with PDH
  - Adrenalectomy
- Further reading: Chapter 11 in Canine and Feline Endocrinology 4th edition

Pituitary Pars Intermedia Dysfunction (PPID) Equine Cushing's Disease

- Affected horses typically >15 yrs
- Ponies and Morgans ↑ risk
- Clinical signs
  - HIRSUITISM
    - Long, curly hair, lighter color
    - Delayed/incomplete spring shed
  - Chronic laminitis/foot abscesses
  - Muscle atrophy/wasting/"pot-bellied"
  - Dullness/lethargy/blindness
  - PU/PD
  - Hyperhidrosis
  - Infertility
  - Opportunistic infections

Pituitary Pars Intermedia Dysfunction (PPID) Equine Cushing's Disease

- Decreased pars intermedia dopamine levels (some 88% below normal)
  - Degeneration of dopamine-secreting neurons
- Loss of dopaminergic regulation
- Hyperplasia of pars intermedia
- Excess ACTH production
  →Adrenocortical hyperplasia
  →increased cortisol and androgens
- Poorly responsive to negative feedback from corticosteroids



Pituitary Pars Intermedia Dysfunction (PPID) Equine Cushing's Disease

- Screening tests
  - Neutrophilia and lymphopenia
  - Hyperglycemia
    - 30% have insulin resistance and hyperinsulinemia (not specific for PPID, hyperinsulinemia also with EMS and obesity)
  - Hypertriglyceridemia
  - Increased liver enzymes
  - High fecal egg count

PPID Diagnosis: ACVIM Equine Endocrinology Group Recommendations

- For EARLY PPID: TRH Stimulation Test with measurement of ACTH
  - Pituitary adenoma cells lack receptor specificity and are responsive to TRH
  - TRH compounded by Wedgewood Pharmacy as “Protirelin”
  - No grain for 12 hrs before testing (hay is ok)
  - Test during mid-Nov to mid-July (DX values not established for late summer/early fall)
  - Pre-plasma collected in EDTA tube
  - Inject 1 mg TRH IV for horses > 250 kg; 0.5 mg IV for ponies and horses <250 kg
    - SE’s may include coughing, Flehmen response, yawning
  - Collect EDTA blood samples at exactly 10 minutes after injection for ACTH measurements (cooled tubes, centrifuge asap)

PPID Diagnosis: ACVIM Equine Endocrinology Group Recommendations

- For Moderate to Advanced PPID: Resting ACTH concentrations
  - 65-90% sensitivity
  - EDTA tubes – plastic or coated glass
  - Keep tubes cool at all times
  - Centrifuge asap and separate plasma before shipping or freezing (plastic tubes)
  - If results are equivocal do TRH stimulation test (with measurement of ACTH levels)

Interpretation of ACTH levels for PPID Diagnosis

Mid-November to Mid-July (Recommended time)

	Negative	Equivocal	Positive
Resting ACTH	< 30 pg/mL	30-50 pg/mL	> 50 pg/mL
10 min post TRH	< 110 pg/mL	110-200 pg/mL	> 200 pg/mL

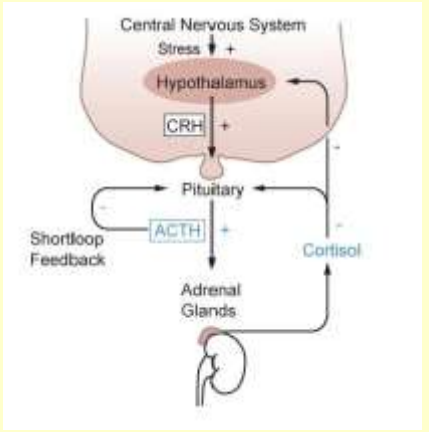
Mid-July to Mid-November (Fall) – Not enough data for recommendations regarding TRH responses

	Negative	Equivocal	Positive
Resting ACTH	< 50 pg/mL	50-100 pg/mL	>100 pg/mL

Pituitary Pars Intermedia Dysfunction (PPID) Equine Cushing's Disease

- Previous "Gold standard test" = Overnight DST
  - Collect pre/baseline blood sample
  - Inject 20 mg DXMS IM (DexSP or Azium)
  - Collect 2nd blood sample 19 hrs later
  - Minimum decrease in cortisol if horse has PPID
  - **THIS TEST HAS LOST "BEST TEST" STATUS and is now classified as "potentially supportive"**
  - False positives in fall months (85% of horses and 95% of ponies have higher cortisol levels in fall)

Pituitary Pars Intermedia Dysfunction (PPID) Equine Cushing's Disease



- Potentially supportive tests
  - Overnight DST
  - MRI of pituitary (enlarged pars intermedia)
- No longer recommended tests
  - Oral domperidone challenge
  - Combined DST/TRH test with cortisol measurements
- Not appropriate for PPID diagnosis
  - ACTH stimulation test
  - Resting cortisol
  - Diurnal cortisol rhythm (normally higher in am than night however stress, disease and old age can affect)
  - TRH stimulation test with cortisol measurement

PPID: Treatment

- Pergolide (Prascend; Boehringer Ingelheim Vetmedica, Inc)
  - Long-acting dopaminergic agonist
  - Obtain baseline Dx tests (ACTH ± TRH stim ACTH)
  - Give ~2 µg/kg PO q 24 hr (1.0 mg for 500 kg horse; 0.5 mg for 250 kg pony)
  - SE anorexia: stop and restart when eating at lower dose for several days or divide dose q 12 hr
  - After 30 days can recheck resting ACTH levels ± TRH stim; some may need higher doses (one study reported effective range 1.7-5.5 µg/kg/d)
  - May take 2 months to see clinical improvement
  - 85% of owners report improved clinical signs

PPID: Treatment

- Pergolide (Prascend; Boehringer Ingelheim Vetmedica, Inc)
  - Early signs of improvement (one month)
    - Improved attitude/performance/increased activity
    - Decreased PU/PD
    - Normal sweating
    - Improvement in glucose and insulin dynamics
  - Longer-term responses (1-12 months)
    - Improved shedding
    - Increase in muscle mass
    - Less “pot-bellied”
    - Fewer infections
    - Less laminitis

PPID: Cyproheptadine

- Seratonin antagonist
- 0.25 mg/kg PO q 24 hr
- Less effective than pergolide
  - 28% favorable response to cyprohetadine vs 85% favorable to pergolide)
- Sometimes used in combination with pergolide (high dopamine with low serotonin may synergistically inhibit ACTH secretion)

PPID: Supportive Care

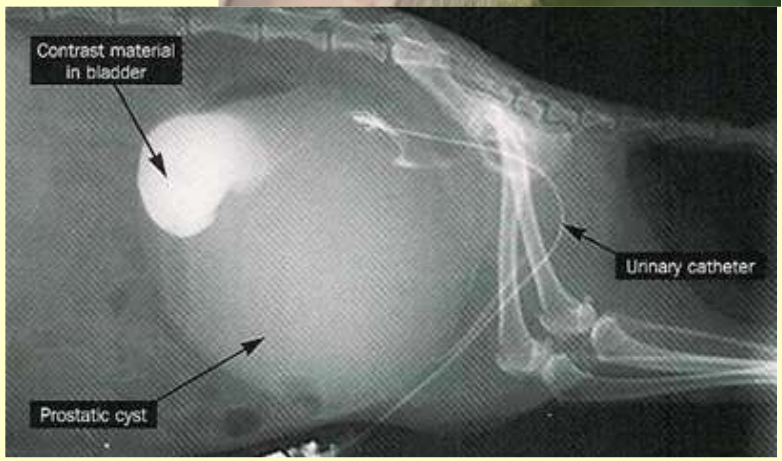
- Husbandry—frequent bedding changes
- Body clipping
- Shade available
- Frequent bathing/hosing with cold water
- Diligence in monitoring for infections
  - Rectal temperatures
- Regular hoof care
- Regular dental care
- Restrict sugars (avoid lush pasture and sweet feeds)
- Monitor fecal oval counts → control parasites

Adrenocortical Disease in Ferrets

- 2nd most common tumor = adrenocortical zona reticularis adenoma
- Excess secretion of estradiol, 17-hydroxyprogesterone, androsteindione
- Tumors may invade vena cava

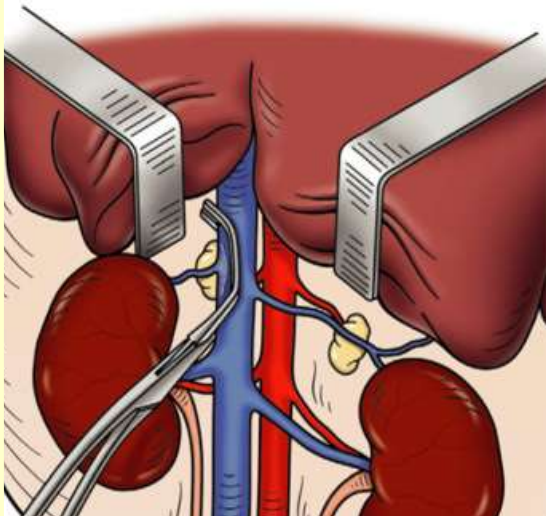
Adrenocortical Disease in Ferrets

- Clinical signs: hair loss, stranguria (from prostatomegaly), enlarged vulva, pancytopenia possible (estradiol →BM suppression)
- Diagnosis
  - Abdominal ultrasonography
    - Enlarged adrenals
  - Ferret Hormone Panel (UT)
    - Increases in estradiol, 17-hydroxyprogesterone and/or androsteindione



Adrenocortical Disease in Ferrets

- Treatment
  - Deslorein (Suprelorelin F = 4.7 mg implants)
    - GnRH agonist – initial stimulation then down regulation of sex hormone production
    - Improvement seen 4-6 weeks
    - Duration 10-20 months
    - TREATMENT OF CHOICE
  - Lupron (Leuprolide)
    - GnRH agonist given by injection
    - Duration ~ 1 month
  - Adrenalectomy
    - Potentially curative
    - Technically challenging, higher mortality



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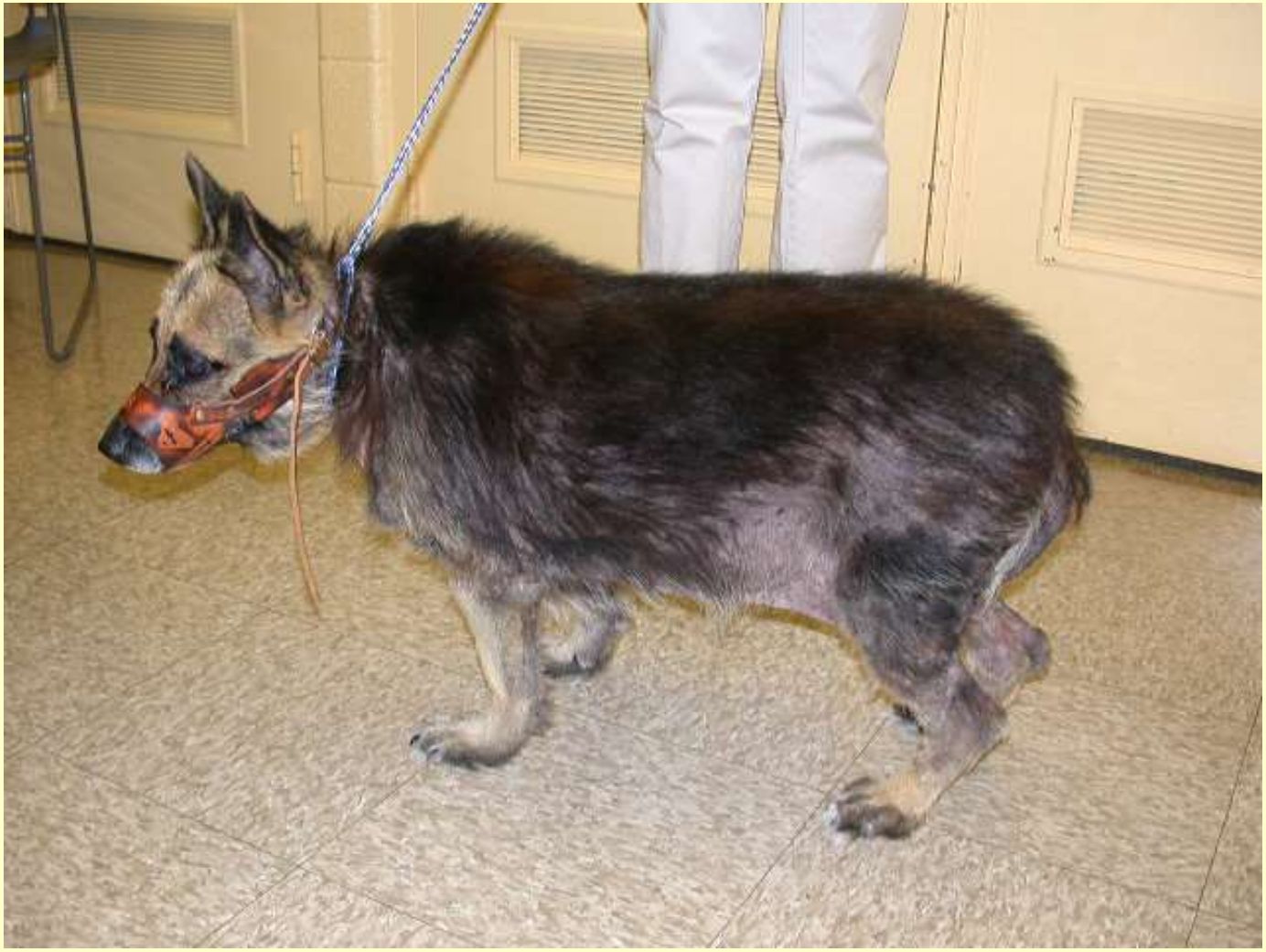
Pituitary Dwarfism



Pituitary Dwarfism

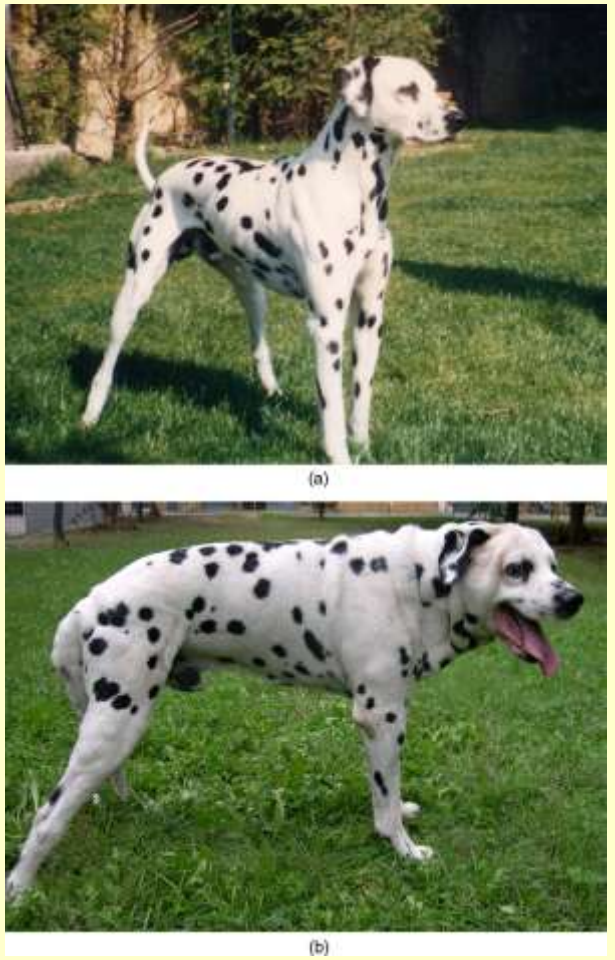
- German shepherd dogs & Karelian Bear dogs predisposed
  - Autosomal recessive
  - Persistent cysts of Rathke's pouch compress pituitary gland ↓ growth hormone, ↓ TSH, may ↓ FSH, LH & ACTH

Pituitary Dwarfism

- Proportionate dwarfs
- Retain puppy coat and teeth; over time develop alopecia and secondary infections
- Diagnose with history, examination, radiographs show persistence of growth plates in bones, CT or MRI to find pituitary cyst, pituitary function tests
- Treat secondary infections, thyroid supplementation if concurrent hypothyroidism

Acromegaly

- Hypersecretion of growth hormone
  - Underlying Causes
    - Pituitary tumor (somatroph)
    - GHRH producing tumor
    - Progesterone therapy
      - Promotes GH secretion
- Clinical signs
  - Thick folded skin, thick haircoat
  - Inspiratory stridor, broadening of limbs, ribcage, prognathism
  - Polyphagia, polydipsia, weight gain
- Diabetes mellitus
  - GH promotes insulin resistence



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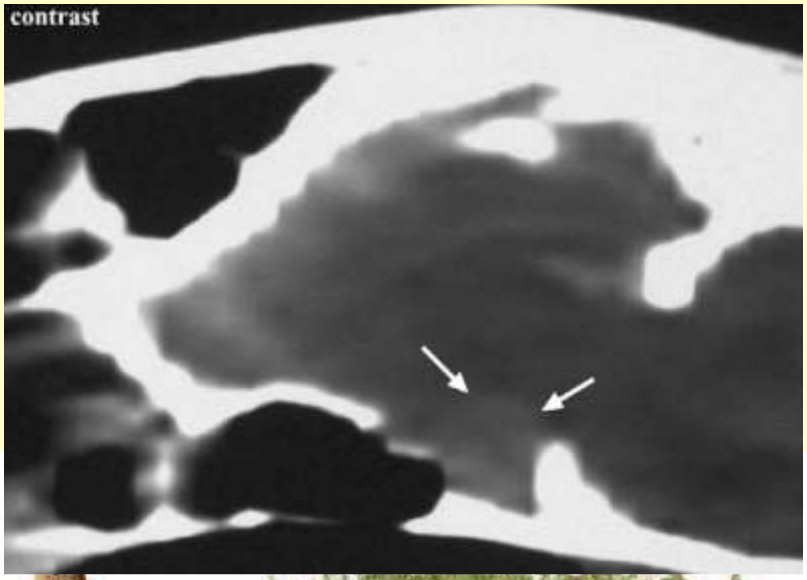
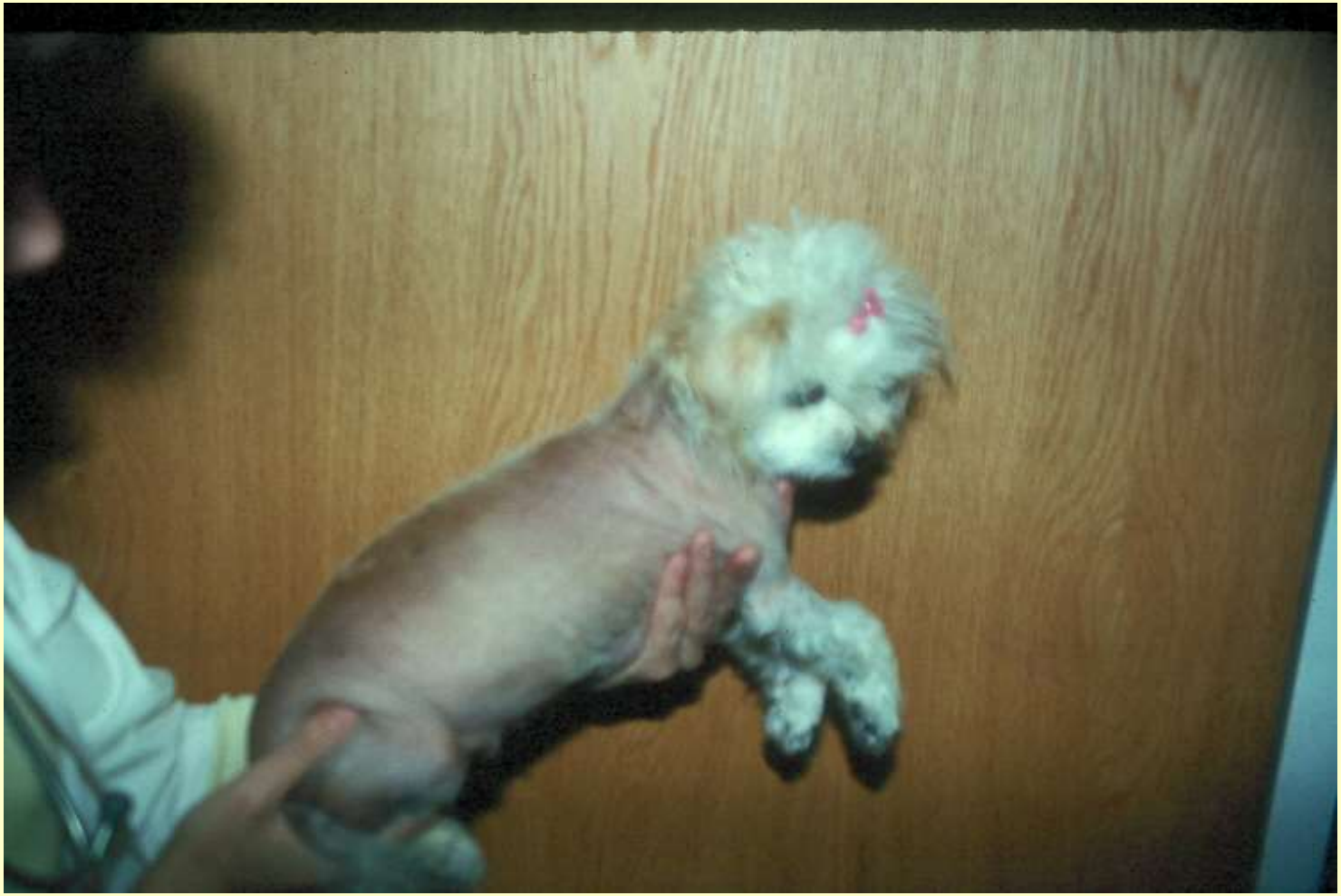
Acromegaly

- Diagnosis
  - History & clinical signs
  - Laboratory findings: ↑ PCV, hyperglycemia, ↑ liver enzymes, ↑ BUN, ↑ TP
  - Radiographs/ultrasound: organomegaly
  - Increased levels of GH and Insulin-like growth factor-1
  - CT/MRI: pituitary tumor
- Treatment
  - Discontinue progesterones, OHE
  - Control diabetes if present
  - Hypophysectomy
  - Pituitary radiation therapy
  - Somatostatin analogs (have not worked well in dogs/cats)



Sex Hormone Imbalances



Hyperestrogenism

- Causes
  - Sertoli cell (most common in cryptochid dogs)
  - Ovarian cysts
- Clinical signs
  - Symmetrical alopecia
  - Variable pigmentation
  - Seborrhea
  - Nipple enlargement/ feminization
  - Testicular tumor
- Diagnosis
  - Estrogen levels
  - Ultrasonography
- Treatment
  - neuter