REFERENCES:
M. Maxie (ed), Pathology of Domestic Animals, 5th edition (2007), vol 3, Chapter 3

ENDOCRINE GLANDS:
- Pituitary gland
- Thyroid (follicular and parafollicular)
- Parathyroid
- Adrenal (cortex and medulla)
- Pancreatic islets
- Chemoreceptor organs (aortic and carotid bodies)
- Others: testis, ovary, placenta, kidney, thymus, pineal and G-I tract (DNES)

GENERAL:
- Endocrine glands, unlike those of other body systems, are scattered, achieve no physical continuity and have diverse embryological origins.
- Endocrine glands synthesize, store and release hormones directly into the bloodstream.
- They are sensing & signalling devices in extracellular fluid compartment (ECF) that help maintain homeostasis.
- Hormones interact with target organs / cells to elicit a biological response.
- Diseases of the endocrine system are common, particularly in small animal practice.
- Endocrine disorders are manifest by derangement of functions in target organs (eg alopecia with Cushing’s or hypothyroidism, seizures/coma caused by hyperinsulinism, bone fracture with hyperparathyroidism, etc).
- Various laboratory tests are available for clinical diagnosis and monitoring of endocrine dysfunction (eg CBC, serum chemistry, specific hormone assays, etc)

TYPES OF HORMONES:
1) Polypeptide Hormones (eg pituitary, pancreatic islets, parathyroid)
   - RER synthesis & stored in cytoplasm as secretory granules → release by fusion to plasma membrane.
   - Bind to target cell membrane receptors (eg GPCR’s) → response via intracellular signalling pathways.
2) Steroid Hormones (eg adrenal cortex, ovary, testis)
   - SER synthesis (little storage) from cholesterol, etc → continuous biosynthesis to maintain normal levels.
   - Penetrate plasma membrane and bind to target cell cytosolic receptors → move to nucleus and cause ↑ mRNA transcription → ↑ protein synthesis in target cells.
3) Catecholamines and Iodothyronine Hormones
   - Hormones derived from the amino acid tyrosine.
   - Catecholamines (epinephrine and norepinephrine from adrenal medulla) act like polypeptides and iodothyronines (thyroxine & triiodothyronine from follicular cells of thyroid) act like steroids.
MECHANISMS OF ENDOCRINE DISEASE

1) Hyperactivity

① Primary hyperfunction
   • autonomous hypersecretion of hormone due to tumor or hyperplasia of the gland (eg hyperthyroidism, some forms of hyperadrenocorticism).

② Secondary hyperfunction
   • a lesion in one organ (e.g. pituitary gland adenoma) secretes excess trophic hormone that leads to long-term stimulation and hypersecretion of hormones by the target organ (eg adrenal cortical hyperplasia with excess cortisol).

③ Hyperactivity secondary to diseases of other organs
   • hyperparathyroidism secondary to chronic renal disease or nutritional imbalance.

④ Hypersecretion of hormones or hormone-like substances by non-endocrine tumors
   • mostly peptides that are similar chemically and/or biologically to the native hormone (eg parathyroid hormone-related protein production by adenocarcinoma of apocrine glands of anal sacs in dogs, lymphoma in dogs and cats, and several others).

⑤ Iatrogenic syndromes of hormone excess
   • administration of hormones directly or indirectly influences the activity of target cells (eg corticosteroid administration causing iatrogenic Cushings disease)

2) Hypoactivity

① Primary Hypofunction
   • this is subnormal hormone secretion due to destruction of secretory cells, failure of development or genetic defect in biosynthesis (eg’s immune-mediated thyroiditis or adrenalitis, congenital dyshormonogenetic goiter).

② Secondary hypofunction
   • a destructive lesion in one organ (e.g. pituitary) interferes with the secretion of trophic hormone and results in hypofunction of the target gland (eg adrenal cortex, thyroid, gonads).

③ Endocrine dysfunction due to failure of target-cell response
   • alterations or defects in receptors on target cells make them less responsive to normal or increased amounts of hormone (eg insulin resistant diabetes mellitus, nephrogenic diabetes insipidus).

PITUITARY GLAND

STRUCTURE AND FUNCTION

• embryologic development – oropharyngeal ectoderm + diencephalic neuroectoderm – adenohypophysis (pars distalis, pars intermedia, pars tuberalis) and neurohypophysis (pars nervosa, infundibular stalk and median eminence/hypothalamus).
• anatomic location – in sphenoid bone (sella turcica + diaphragma sella).
ADENOHYPOPHYSIS

<table>
<thead>
<tr>
<th>Cells</th>
<th>Hormones</th>
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<tr>
<td>Somatotrophs</td>
<td>Growth Hormone (GH)</td>
<td>[GH-RH + GH-RIH]</td>
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<tr>
<td>Lactotrophs</td>
<td>Prolactin (luteotropic hormone)</td>
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<td>Gonadotrophs</td>
<td>Luteinizing (LH) &amp; follicle stimulating hormone (FSH)</td>
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<td>Thyrotrophs</td>
<td>Thyroid Stimulating Hormone (TSH)</td>
<td>[T-RH]</td>
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<tr>
<td>Corticotrophs</td>
<td>Adrenocorticotropic Hormone (ACTH)</td>
<td>[C-RH]</td>
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- secretion is controlled by releasing hormones (RH), +/- release-inhibiting hormones (RIH), produced in hypothalamic neurons.
- RH and RIH are transported by axonal processes and released into a capillary plexus in the median eminence and from there to adenohypophysis, via the hypothalamic-hypophyseal portal system.
- interact with specific populations of trophic hormone-secreting cells in the adenohypophysis.
- negative feed-back (on hypothalmus and pituitary cells) is through blood concentration of the hormones of the target endocrine glands.

NEUROHYPOPHYSIS

Antidiuretic hormone (ADH = vasopressin) [from supraoptic nucleus]
Oxytocin [from paraventricular nucleus]

- hormones are produced by neurosecretory cells in the hypothalamus and are transported to pars nervosa by axonal processes which terminate on fenestrated capillaries from where the hormones are released into general circulation.

MALFORMATIONS

1) Adenohypophyseal Aplasia/Hypoplasia (for information only)
   - aplasia of the adenohypophysis is seen as a genetic defect in Guernsey & Jersey cattle; results in hypoplasia of target organs, cessation of fetal development after 7 months and prolonged gestation.
   - ingestion of the toxic plant Veratrum californicum by ewes in early pregnancy causes cranio-facial deformity and aplasia/hypoplasia of the fetal pituitary; results in hypoplasia of target organs and prolonged gestation, but the fetus will continue to grow.
   - prolonged gestation in both is due to hypoplasia of the adrenal cortex leading to inadequate cortisol secretion and failure of induction of 17-hydroxylase in placenta that converts progesterone to estrogen; estrogen surge stimulates uterine prostaglandin synthesis required for parturition.

2) Pituitary cysts
   ① Cysts resulting from failure of differentiation of oropharyngeal ectoderm of Rathke's pouch
      - progressively enlarging, multiloculated cyst in the sella turcica, leads to complete or partial absence of the adenohypophysis and compression of the neurohypophysis.
      - causes juvenile panhypopituitarism (pituitary dwarfism); occurs most frequently in German Shepherd dogs with a simple autosomal recessive mode of inheritance.
      - puppies are stunted (due to hyposomatotrophism), retain juvenile hair, become alopecic & hyperpigmented.
      - secondary endocrine dysfunctions due to atrophy of thyroids (hypothyroidism), adrenals (hypoadrenocorticism) and gonads.
      - large cysts may cause diabetes insipidus due to compression of the neurohypophysis.

   ② Other Cysts
      - cysts derived from the craniopharyngeal duct.

INFLAMMATION

1) Pituitary Abscesses
   - seen sporadically in ruminants and swine.
   - caused by bacteria (esp. A. pyogenes) or mycotic agents.
   - affected animals often show neurological signs due to local extension causing meningitis / encephalitis.

2) Infiltration of mononuclear inflammatory cells
   - in some viral and protozoan diseases as part of encephalitis or meningitis.
DIABETES INSIPIDUS

1) Hypophyseal form (= central diabetes insipidus)
   • seen with any lesion that interferes with ADH synthesis or secretion, eg neoplasms, granulomas, cysts or trauma that cause compression and/or destruction of the pars nervosa, infundibular stalk or supraoptic nucleus in the hypothalamus.

2) Nephrogenic form
   • hereditary defects in the ADH receptor or in the water channel (aquaporin-2) in the plasma membrane of collecting duct and distal tubular epithelial cells → cells fail to respond (ie no increased permeability to H₂O) to normal or elevated circulating ADH.

i) both forms of diabetes insipidus result in polyuria / polydipsia and urine of low osmolality even after water deprivation.
ii) administration of exogenous ADH will lead to a rapid increase in urine osmolality above that of plasma in the hypophyseal form, but not in the nephrogenic form.

HYPERPLASIA / NEOPLASIA
   • neoplasms may be functional, overproducing a specific trophic hormone that stimulates a target organ.
   • or they may be nonfunctional but destructive to adjacent structures causing panhypopituitarism, diabetes insipidus and neurologic disorders (eg CNS and/or cranial nerve dysfunction); ± metastatic.
   • adenomas and carcinomas are seen more commonly in adults; craniopharyngiomas seen more in young.
   • adenomas are distinguished from nodular hyperplasia by their larger size and presence of a capsule and compression of the adjacent tissue (note, sometimes there is a gradual transition between the two).

1) Adenomas of Pars Distalis
   1) ACTH-Secreting (Corticotroph) Adenoma
      • common in dogs and tumors are often small.
      • tumor cells stain immunohistochemically for ACTH.
      • secrete excess ACTH leading to bilateral hyperplasia of adrenal cortex (primarily zona fasciculata and zona reticularis), which secretes excess glucocorticoids, causing lesions in skin, muscle, lung, etc (ie one cause of Cushing's disease).

2) Nonfunctional (Hormonally-inactive or Chromophobe) Adenoma
   • primarily seen in dogs.
   • usually become large before causing clinical signs, ie compression atrophy / space occupying lesion.

3) Somatotroph Adenoma
   • rare; in humans, these tumors cause gigantism in the young and acromegaly in adults.

4) Adenomas of Lactotrophs, Gonadotrophs and Thyrotrophs
   • very rare; excess prolactin secretion has been reported in non-pregnant, lactating goats.
2) Hyperplasia and Adenoma of Pars Intermedia
   in dogs:
   • can be inactive (hypopituitarism / diabetes insipidus) or active (excess ACTH / Cushing's disease).

   in horses:
   • PPID (pituitary pars intermedia dysfunction) is common disease of horses and ponies over 15 years old.
   • pituitary is often large and compresses the adjacent neurohypophysis and hypothalamus; causing hirsutism
     (long hair coat and failure of seasonal shedding), altered carbohydrate metabolism (eg hyperglycemia),
     polyphagia, muscle atrophy / weakness, laminitis, intermittent hyperpyrexia, hyperhidrosis and PU/PD.
   • neoplastic (or hyperplastic) cells produce excess proopiomelanocortin (POMC) derived peptides; due to altered
     post-translational processing varying amounts of ACTH, CLIP, α-MSH, β-endorphin.

3) Craniopharyngioma
   • seen in younger animals (derived from epithelial remnants of the oropharyngeal ectoderm).
   • can be quite large, causing panhypopituitarism (and dwarfism when in young growing animals), diabetes
     insipidus and disturbances of CNS / cranial nerves.

4) Pituitary carcinoma
   • occurs in older dogs and cattle.
   • often inactive, but space occupying, leading to panhypopituitarism, diabetes insipidus, cranial nerve / CNS
     dysfunction, ± metastasis.

5) Metastatic tumors
   • tumors metastasizing to the pituitary are uncommon; can cause panhypopituitarism, etc.

ADRENAL CORTEX
STRUCTURE AND FUNCTION
• ~ 75% of the adrenal gland, produces over 50 different steroid hormones & essential for life.
• it is derived from mesoderm and consists of:

Zona glomerulosa - 15% (SALT):
• outermost zone produces mineralocorticoids, e.g. aldosterone which affect Na⁺ and K⁺ homeostasis through
  their effect on kidney and sweat glands.
• aldosterone causes retention of sodium, loss of potassium; sodium retention leads to expansion of extracellular
  fluid volume and increased blood pressure.
• it is controlled by the renin-angiotensin system and to a lesser extent by ACTH.
• the zone is necessary for regeneration of other 2 zones.

Zona fasciculata - 70% (SUGAR):
• middle zone produces glucocorticoids (controlled by ACTH levels); esp cortisol & corticosterone which affect
  glucose homeostasis by acting on carbohydrate (gluconeogenesis & use of glucose), protein (protein catabolic)
  and lipid (lipolytic) metabolism.
• the hormones cause hyperglycemia, increase glucose production and inhibit the action of insulin.
• also suppress inflammation, wound healing and immune response.

Zona reticularis - 15% (SEX):
• this innermost zone produces sex hormones, mainly androgens in both males & females.
DEVELOPMENTAL ANOMALIES & MISCELLANEOUS LESIONS (*for information only)

1) *Agenesis, unilateral or total* - unilateral occasionally seen in dogs; total (bilateral) is fatal in all species.
2) *Hypoplasia to maldevelopment of pituitary gland* - result of adenohypophyseal aplasia / hypoplasia.
3) *Accessory adrenal cortical tissue* - can be found around adrenal, kidney or testis (esp horses).
4) *Mineralization* - especially in adult cats and primates, occasionally in dogs.
5) *Amyloid deposition* - primarily in the zona fasciculata.
6) *Capsular sclerosis* - as a senile changes in cattle.
7) *Telangiectasis* - senile change in many species, especially near corticomedullary junction.

8) Hemorrhage (Waterhouse-Friderichsen syndrome) - esp in sepsis / toxemia.
   - also severe stress or trauma in neonates.

INFLAMMATION
- adrenalitis, often with necrosis, is usually due to bacterial localization during sepsis.
  1) Viruses - eg herpesvirus causing multi-focal necrosis; +/- intranuclear inclusion bodies.
  2) Bacteria - gram negatives (eg Actinobacillus, Salmonella) cause necro supplicative adrenalitis
     - mycobacteria causes granulomatous adrenalitis
  3) Fungi - dimorphic fungi (eg Histoplasma, Cryptococcus) cause granulomatous adrenalitis.
  4) Parasites - eg Toxoplasma

HYPOADRENOCORTICISM (ADDISON’S DISEASE)

Primary Hypoadrenocorticism
a) Bilateral idiopathic adrenal cortical atrophy:
   - occurs most frequently in young to middle-age female dogs; proposed to be autoimmune / hereditary.
   - destruction of all three cortical layers, often with infiltration of mononuclear inflammatory cells.
   - deficient production of all cortical hormones (note: deficiency of mineralocorticoids can be lethal!).

b) Bilateral destruction of adrenal glands
   - due to inflammation, infarction, hemorrhage, tumor (eg lymphoma).

Secondary Hypoadrenocorticism
- with ACTH deficiency see trophic atrophy of only the inner two zones; thus mineralocorticoids are
  minimally affected and generally no electrolyte imbalances.

a) Destructive pituitary lesions
   - damage to the pituitary, including corticotrophs, results in deficiency of ACTH.

b) Iatrogenic
   - the most common cause of secondary hypoadrenocorticism is iatrogenic; seen following the sudden
     withdrawal of synthetic glucocorticoids treatment after prolonged usage.

Clinical Signs / Lesions
- mainly seen in dogs; see lethargy, stress intolerance, bradycardia (note specific ECG changes), anorexia,
  vomiting and diarrhea (non-specific gastroenteritis), leading to dehydration / emaciation.
- can present with acute circulatory failure, ie cardiogenic / hypovolemic shock.
- laboratory tests show electrolyte imbalance (hyponatremia & hyperkalemia) - hallmark of Addisons.
- in addition, there may be hypoglycemia, hemoconcentration and a low plasma cortisol which does not respond
  to ACTH administration.
- in long-standing cases, the skin may be hyperpigmented due to an excess of pituitary ACTH / MSH that
  develops due to lack of negative feed-back.
ADRENAL CORTICAL HYPERPLASIA / NEOPLASIA

1) Diffuse hyperplasia:
   - cortex is uniformly enlarged due to increased inner two zones in response to ACTH from pituitary (adenoma or idiopathic).
   - produces excess glucocorticoids.

2) Nodular hyperplasia:
   - seen in old horses, dogs, cats; may be functional.
   - the nodules are often multiple, bilateral and yellow.

3) Cortical adenomas:
   - especially old dogs (often functional).
   - sometimes difficult to distinguish from nodular hyperplasia (generally larger and encapsulated).

4) Cortical carcinoma:
   - rare; old dogs (may be functional).
   - often bilateral and may invade vena cava.

HYPERADRENOCORTICISM (Cushing's disease)
   - relatively common in old dogs, less so in horses but rare in other animals.

   1 Primary hyperadrenocorticism (10-15%):
      - cortical neoplasm, especially adenoma.

   2 Secondary hyperadrenocorticism (80%):
      - bilateral cortical hyperplasia due to ↑ ACTH from pituitary tumor (Pituitary Dependent Hyperadrenocorticism).
      - idiopathic cortical hyperplasia / altered negative feedback set-point (esp Poodles).

   3 Iatrogenic (pharmacological) hyperadrenocorticism (5-10%):
      - over administration of glucocorticoids.

Clinical Signs / Lesions
   - due to combined gluconeogenic, lipolytic, protein catabolic & anti-inflammatory / immunosuppressive effects of corticosteroids.
   - polyuria / polydipsia - due to ↑ GFR &/or interfer with ADH secretion or action.
   - polyphagia - by direct affect of excess cortisol on satiety center.
   - hepatomegaly - “steroid hepatopathy” due to ↑ glycogen in hepatocytes.
   - pendulous abdomen - muscle atrophy / weakness due to protein catabolism and hepatomegaly.
   - skin lesions (90% of cases) - dermal atrophy, bilateral symmetric alopecia, delayed wound healing, etc.
   - dystrophic mineralization - esp skin; +/- lung, muscle, stomach (catabolism alters collagen/elastin).
   - bacterial infections of skin, urinary tract, etc - increased susceptibility due to immunosuppressive effects.
   - others: hypercoagulability, eosinopenia and lymphopenia / lymphoid involution.
ADRENAL MEDULLA

STRUCTURE AND FUNCTION
- derived from neuroectoderm / neural crest; medulla occupies up to 25% of volume of adrenal gland.
- composed of pheochromocytes (chromaffin cells) and a few ganglion cells.
- produces catecholamine hormones (epinephrine and norepinephrine) from tyrosine.
- most common and significant lesion is pheochromocytoma.

HYPERPLASIA / NEOPLASIA
1) Diffuse or nodular hyperplasia:
   - this is a nonencapsulated proliferation of chromaffin cells.
   - it often precedes pheochromocytoma and thyroid C cell tumors in bulls.

2) Pheochromocytoma:
   - it occurs mainly in dogs & cattle.
   - the tumor is often large and encapsulated but may invade the vena cava and metastasize extensively.
   - rarely functional, if so can cause tachycardia, edema and cardiac hypertrophy.
   - the application of potassium dichromate or iodate (eg Zenker's solution) to a freshly cut surface of a pheochromocytoma will give a dark-brown coloration in 5-20 minutes.

3) Neuroblastomas & Ganglioneuromas:
   - rare; occur in young animals.

4) Metastatic Tumors:
   - malignant tumors (esp lymphomas & mammary carcinomas) may metastasize to the adrenal medulla.

THYROID GLAND

STRUCTURE AND FUNCTION
- the thyroid is the largest endocrine organ &is usually bilobed (its morphology and location vary with species).
- it consists of follicles containing colloid; follicular cells (thyrocytes) trap iodine and synthesize thyroglobulin (from tyrosine, CHO, etc.) but the final assembly of the hormones (thyroxine $T_4$ & triiodothyronine $T_3$) occurs extracellularly in the colloid.
- both hormones are formed by the combination of monoiodotyrosine (MIT) and diiodotyrosine (DIT), ie MIT + DIT $\rightarrow$ $T_3$ or DIT + DIT $\rightarrow$ $T_4$.
- secretion of $T_3$ and $T_4$ into circulation follows phagocytosis of colloid by follicular cells, cleavage of the hormone from thyroglobulin and its diffusion into adjacent capillaries.
- secretion controlled by thyroid stimulating hormone (TSH) & T-RH.
- $T_4$ and $T_3$ act like steroid hormones, but they act on virtually all cells of the body.
- they regulate growth and differentiation, as well as rate of metabolism of lipids, proteins and carbohydrates leading to a general increase in the basal metabolic rate.
- in certain diseases, $T_4$ is preferentially monodeiodinated to "reverse" $T_3$ which is inactive (ie mechanism to attenuate the metabolic effects of $T_4$).
- evaluation of thyroid is through determination of the levels of serum cholesterol, blood $T_4$ & $T_3$, TSH Stimulation Test, and followed, if necessary, a biopsy of the caudal portion (ie avoid parathyroid glands).
DEVELOPMENTAL ANOMALIES (for information only)

1) Aplasia and Hypoplasia
   • rare.

2) Accessory Thyroid Tissue
   • common in dogs; can be located anywhere from the larynx to the diaphragm but is most often in the fat around the base of the heart (can become neoplastic).

3) Thyroglossal duct cysts
   • seen in dogs & pigs; the cysts are located in the ventral neck region and can become neoplastic.

DEGENERATIVE & INFLAMMATORY CHANGES

1) Lymphocytic (Immune-mediated) Thyroiditis:
   • seen mostly in dogs; affected dogs may or may not develop clinical hypothyroidism.
   • similar to Hashimoto's disease of humans, ie autoantibodies to thyroglobulin and other colloid Ag’s.
   • thyroid shows multifocal to diffuse infiltrates of lymphocytes, plasma cells and macrophages and later replacement fibrosis; colloid is vacuolated and may contain cellular debris mixed with inflammatory cells.

2) Idiopathic Follicular Atrophy ("Collapse"):
   • also a cause of hypothyroidism in dogs.
   • characterized by progressive loss of follicular epithelium and replacement by adipose tissue with minimal inflammatory response.

3) Mineralization, lipofuscinosis, corpora amylaceae & amyloidosis
   • incidental senile changes.

HYPOTHYROIDISM

• seen in all species; but most common in dogs.
• can be due to: idiopathic follicular collapse, lymphocytic thyroiditis, bilateral nonfunctional tumors, chronic pituitary lesions (compression/destruction) or severe (prolonged) iodine deficiency.

Clinical Signs / Lesions
• reduction in basal metabolic rate manifested as: lethargy, weight gain, muscular weakness, slow reflexes
• skin lesions (see derm path): bilateral symmetric alopecia (telogen hairs), hyperpigmentation ± myxedema.
• reproductive abnormalities - eg lack of libido, infertility, etc.
• joint pain and effusion.
• hypercholesterolemia can result atherosclerosis and hepatic / glomerular / corneal lipidosis.
• clinical pathology tests - low T4 / T3, normocytic normochromic anemia & high serum cholesterol.
HYPERPLASIA (GOITER)

- goiter is the non-neoplastic, noninflammatory enlargement of thyroid gland due to increased TSH secretion; resulting from inadequate thyroxine synthesis and decreased blood levels of T₄ and T₃.
- the four major pathogenetic mechanisms include:
  ① iodine deficient diet
  ② excess dietary iodine
  ③ goitrogenic compounds interfering with thyroxinogenesis (e.g., Brassica plants)
  ④ genetic enzyme defects in hormone synthesis
- the morphologic types of goiter in animals include:

  ① Diffuse Hyperplastic Goiter:
  - more common in young animals born to dams on iodine deficient diet or excess iodide (e.g., dry seaweed fed to pregnant mares) or dams fed goitrogenic substances.
  - marked enlargement of glands due to follicular cell hyperplasia within irregular follicles having lightly eosinophilic & vacuolated colloid.

  ② Colloid goiter:
  - represents involutionary phase of hyperplastic goiter (i.e., recovery following correction of the problem in diffuse hyperplastic goiter).
  - the gland now contains macrofollicles with densely eosinophilic colloid and is less vascularized than diffuse hyperplastic goiter.

  ③ Congenital dyshormonogenetic goiter (inherited goiter):
  - autosomal recessive disorder in some breeds of sheep, goats, and cattle; rare in dogs and cats (more common in children).
  - result of genetic impairment of thyroglobulin synthesis; T₄ & T₃ levels are low even though iodine uptake and turnover are increased.
  - affected animals have subnormal growth rate, sparse haircoat, myxedema, weakness, and sluggish behavior (most die shortly after birth).
  - thyroid lobes are symmetrically enlarged at birth.

THYROID HYPERPLASIA / NEOPLASIA

1) Multifocal Nodular Hyperplasia
   - an idiopathic usually incidental lesion in old animals; except cats where it may be functional.
   - the gland is moderately enlarged and contains multiple, irregular, non-encapsulated nodules.

2) Follicular Cell Adenoma
   - may be functional and are more common in cats than in dogs and horses.
   - adenomas usually single, encapsulated, nodular or cystic masses.

3) Follicular Cell Carcinoma:
   - carcinomas are more common in dogs (+/- functional), especially beagles, boxers, golden retrievers.
   - they often invade local tissues (to become “fixed” in position) and metastasize early to the lungs via the thyroid vein before regional lymph nodes.
   - may also arise in accessory thyroid tissues (i.e., mediastinum or heart base regions).
HYPERTHYROIDISM
- mostly in aged cats with multifocal nodular hyperplasia, adenomas or carcinomas of follicular cells.

Clinical Signs / Lesions
- restlessness, increased activity and weight loss in spite of voracious appetite (polyphagia).
- polydipsia & polyuria.
- may be cervical swelling, coughing and dyspnea due to the enlarged gland.
- long term hyperthyroidism can cause left ventricular hypertrophy in cats (can look like HCM)

THYROID C (PARAFOLLICULAR) CELLS

STRUCTURE AND FUNCTION
- C cells are found between follicles or follicular cells and are derived from neural crest cells.
- secretory granules contain calcitonin (CT), an emergency hormone, which protects against hypercalcemia by:
  ① inhibit bone resorption
  ② diuresis of Ca^{2+}

THYROID C CELL HYPERPLASIA / NEOPLASIA [for information only]

1) Thyroid C Cell Hyperplasia: diffuse or nodular (nodules lack a capsule).
2) Thyroid C Cell Adenoma: encapsulated nodule(s) and compression of surrounding tissue.
3) Thyroid C Cell Carcinoma: metastasis is common.
   - all 3 conditions seen in aged bulls; may be due to excessive dietary calcium for bulls on cow rations;
     ie prolonged stimulation of C cells.

PARATHYROID GLANDS

STRUCTURE AND FUNCTION
- morphology, number and location of parathyroid glands vary greatly with species.
- two pairs (most species), and each is composed of a single type of secretory cells (chief cells) which changes appearance depending on the stage of synthetic and secretory activities (ie oxyphil cells are aged chief cells).

Parathyroid Hormone (PTH)
- principal hormone involved in minute-to-minute, fine regulation of blood calcium (unlike calcitonin)
- PTH level is controlled by direct feedback control system based on [Ca^{2+}/Ph] in the blood
- protects against hypocalcemia by: ① increasing intestinal absorption of calcium (with Vit D₃)
  ② stimulating bone resorption of calcium (via osteoclasts / osteocytes)
  ③ enhancing renal tubular reabsorption of calcium

Vitamin D₃ (1,25-dihydroxycholecalciferol)
- synthesized in the skin and/or ingested in an inactive form.
- has to be metabolized, first in the liver and then kidney to the active form.
- involved in calcium regulation and acts by:
  i) increasing intestinal absorption of Ca^{2+} & Ph (to ensure sufficient ions for mineralization of bone matrix).
  ii) increases renal reabsorption of Ca^{2+} (in association with PTH).
Calcium
• calcium is involved in key roles in several biologic processes, eg: blood coagulation, muscle contraction, neural excitability, enzyme activity, hormone release, membrane permeability, mineral of bone, etc.
• PTH and CT act in concert to keep \([\text{Ca}^{2+}]\) in the ECF within narrow limits (good health depends on the precise control of calcium levels in the blood and body fluids).

MISCELLANEOUS CONDITIONS (for information only)

1) Parathyroid cysts
• occur frequently in dogs and are usually incidental.
• embryonic developmental remnants of the duct connecting the parathyroid and thymic primordia.
• differentiate from ultimobranchial or thyroglossal duct cysts, branchial cysts and salivary mucoceles

HYPOPARATHYROIDISM
1) Lymphocytic parathyroiditis
• occurs in adult dogs (rare), particularly in smaller breeds such as schnauzers and terriers.
• believed to be immune-mediated and causes hypoparathyroidism

2) Parturient Paresis (Milk Fever)
• occurs in cows fed a high calcium diet before parturition, ie cows have increased calcitonin secretion and parathyroids are inactive (ie calcium homeostasis is overly dependant on intestinal absorption).
• then at onset of lactation (esp with frequent concurrent anorexia / GI stasis) there is a delayed response of the parathyroids to the sudden significant calcium loss in the milk.
• cows develop progressive hypocalcemia, hypophosphatemia and paresis with the onset of lactation.

3) Other causes include:
• destruction of the parathyroids by neoplasms, accidental removal during thyroid surgery or long-term hypercalcemia from ingestion of calcinogenic plants like *Cestrum diurnum.*
HYPERPARATHYROIDISM

a) Primary Hyperparathyroidism
• due to parathyroid adenomas (older dogs; usually single, encapsulated & functional) or parathyroid carcinomas.
• functional tumors produce excess PTH in spite of negative feedback by increased blood calcium; will see atrophy of the other parathyroid glands.
• clinical signs of hypercalcemia, PU/PD, weakening of bones (ie fibrous osteodystrophy - see below).

b) Secondary Hyperparathyroidism
① Secondary to Nutritional Imbalances
• condition seen in all species but especially cats, dogs, horses, nonhuman primates, birds and reptiles.
• response to excess dietary phosphorus and normal or low calcium and low Vit D₃.
• horses on high-grain (eg all-bran) / poor quality roughage diet; dogs and cats on all-meat diets.
② Secondary to Renal Disease
• the condition is seen mainly in dogs and cats.
• response to hypocalcemia resulting from: progressive hyperphosphatemia due to ↓GFR and impaired activation of Vit D₃ (effect on Ca²⁺ absorption in intestine & Ca²⁺ reabsorption in kidney).
• in both nutritional and renal secondary hyperparathyroidism, prolonged hypocalcemia leads to:
  i) hypertrophy & hyperplasia of chief cells, resulting in bilateral enlargement (hyperplasia) of parathyroids.
  ii) excess PTH causes excessive bone resorption and marked proliferation of fibroblasts and unmineralized osteoid throughout the body (hence the term generalized fibrous osteodystrophy - bones of the skull become swollen but are soft and pliable, hence "big head" in horses and "rubber jaws" in dogs & cats).

c) Humoral Hypercalcemia of Malignancy (= pseudohyperparathyroidism)
• a type of paraneoplastic syndrome.
• caused by the secretion of humoral factors (eg PTH-related protein which mimics the action of PTH) from tumor cells, which act to cause hypercalcemia and hypophosphatemia.
• two main examples are adenocarcinoma of apocrine glands of anal sac mainly in dogs, and lymphosarcoma in dogs and cats.

PANCREATIC ISLETS

STRUCTURE AND FUNCTION
• “Islets of Langerhans” are small clusters of endocrine cells which are scattered throughout the exocrine acinar pancreas; with 4 main cell types:
  Alpha cells (~20%)
  • produce glucagon which causes an increase [glucose] in ECF by target cell catabolism (esp glycogenolysis and gluconeogenesis in the liver and some lipolysis in adipose tissue).
  Beta cells (~60-70%)
  • produce insulin which causes a decrease [glucose] in ECF by increased membrane transport of glucose (+ other nutrients and ions) in most cells, but especially in liver, adipose and muscle tissues.
  • note, a few tissues don’t require insulin for glucose transport (eg lens, nerve, kidney, blood vessels), so with persistent hyperglycemia there is a tendency for increased intracellular glucose in these tissues.
  • insulin has direct effects on CHO, protein & fat metabolism; ie promotes target cell anabolism / storage.
  • insulin and glucagon act in concert to maintain [glucose] in the ECF within relatively narrow limits.
  Delta cells (~5%)
  • produce somatostatin which inhibits release of insulin, glucagon and gastro-intestinal peptides.
  F or PP cells (~10%)
  • make pancreatic polypeptide → inhibits intestinal motility & stimulates secretion of gastric/intestinal enzymes.
DIABETES MELLITUS

1 Type I diabetes mellitus
- see destruction of beta cells with progressive and eventual complete loss of insulin secretion.
- sudden onset of clinical signs due to abrupt loss of insulin secretion; require insulin from the time of diagnosis (ie insulin-dependent diabetes mellitus).

2 Type II diabetes mellitus
- characterized by insulin resistance and/or dysfunction of beta cells (gradual loss of insulin secretion as beta cells are destroyed slowly); insulin may be high, low or normal but is unable to overcome insulin resistance in the peripheral tissues.
- if identified early in the disease, animals may have mild hyperglycemia and be easily controlled with small doses of insulin (ie non-insulin-dependent diabetes mellitus); however over time these develop into insulin-dependent diabetes mellitus.

3 Secondary diabetes mellitus
- reflects antagonism in peripheral tissues between insulin and other hormones; progesterone (eg diestrus/pseudopregnant bitch), glucagon (with glucagonomas), growth hormone (from pituitary tumors) and glucocorticoids (eg endogenous from Cushings or exogenous from iatrogenic).

In dogs:
- diabetes mellitus is a common endocrinopathy of dogs (1:200); female dogs are more frequently affected than males and almost all cases are clinically like type I diabetes of humans.
- can be associated with the following lesions:
  1. destruction of islets concurrently with exocrine pancreatic tissue, eg pancreatic necrosis syndrome, infiltrating tumor, etc.
  2. aplasia / hypoplasia of pancreatic islets, alone or with generalized (exocrine) pancreatic hypoplasia
  3. immune destruction of beta cells which may be idiopathic, autoimmune (autoreactive T lymphocytes or autoantibodies) or secondary to isletitis

In cats:
- diabetes mellitus also relatively common in cats; most cases resemble type II diabetes.
- can be associated with the following lesions:
  1. amyloidosis of islets in cats (similar to primates/human form); accumulation of amyloid eventually interferes with insulin secretion and function.
  2. severe vacuolation of islet cells; thought to be response to long term overstimulation (“exhaustion”) because of insulin resistance.

Clinical Signs and Lesions
- hyperglycaemia and glycosuria - due to decreased insulin or insulin resistance.
- polyuria / polydysia - polyuria due to glucosuria / osmotic diuresis with compensatory polydypsia.
- polyphagia - increased food consumption due to affect on satiety center.
- weight loss - due to glucosuria & generalized ↑ catabolism.
- weakness - due to ↓ tissue/muscle glucose, protein catabolism ± polyneuropathy.
- hepatic lipidosis - reduced insulin-dependant glucose uptake by cells leads to increased lipolysis in adipose tissue → excess fat acids presented to the liver → impaired movement through hepatocytes.
- recurrent infections - due to ↓ leukocyte kinetics and ↑ glucose substrate eg emphysematosus cystitis.
- cataracts - in dogs with hyperglycemia the normal anaerobic pathway in lens becomes saturated and the excess is shunted to the polyol (sugar alcohol) pathway → accumulation of osmotically active sorbitol in lens + depletion of reduced glutathione → hydroptic degeneration & oxidative damage of lens cells.
- vascular damage - eg, causes glomerulo-sclerosis and retinopathy; these are less common in animals.
- neuropathies - peripheral demyelinating neuropathies are less common in animals; occasionally in cats.
NEOPLASIA OF PANCREATIC ISLETS
- not common; when occur, malignant variety is more frequent.
- not all tumors are functional.
- although most tumors appear to secrete multiple hormones, one hormone is usually dominant and most often, it is insulin (ie insulinomas).

1) Beta cell neoplasms = Insulinomas
- mostly seen in adult dogs & ferrets.
- often functional, producing excess insulin (insulinomas).
- adenomas are encapsulated whereas carcinomas are larger and may metastasize.
- clinical signs of functional tumors are related to severe hypoglycemia, ie weakness, fatigue after vigorous exercise, ataxia, mental confusion and periodic convulsive seizures.
- CNS signs occur because glucose uptake in the CNS is by diffusion, and is low during hypoglycemia (note: CNS depends primarily on metabolism of glucose for energy).
- diagnosis of an insulinoma is established by detecting high serum insulin, low blood glucose and one or more nodules in the pancreas (cell type can be confirmed by immunohistochemistry).

2) Non-beta cell neoplasms:
   Ø Glucagonomas
   - rare; have been reported in dogs.
   - produce excess glucagon; causing secondary diabetes mellitus and occasionally crusting of footpads and muzzle area (skin lesions called necrolytic migratory erythema or superficial necrolytic dermatitis or hepatocutaneous syndrome).
   Ù Gastrinomas
   - rare; have been reported in dogs and cats.
   - arise from ectopic amine precursor uptake decarboxylase (APUD) cells in the pancreas
   - they produce excess gastrin which causes ulceration of the gastrointestinal mucosa (Zollinger-Ellison syndrome).

CHEMORECEPTOR ORGANS
STRUCTURE AND FUNCTION
- also called nonchromaffin paraganglia.
- located at several sites in the body (eg aortic bodies, carotid body, some cranial nerves, etc).
- are sensitive barometers of change in blood CO₂, pH, & O₂, aids in regulating respiration and circulation.

NEOPLASMS
- tumors also called chemodectomas or non-chromaffin paragangliomas.
- seen mainly in dogs, especially in brachycephalic breeds.
- mainly from the aortic or carotid bodies (tumors of both bodies may occur together).

1) Aortic Body Adenomas / Carcinomas
- in animals more common than carotid body tumors (reverse in humans).
- usually cause heart failure due to space-occupying nature in the pericardium; do not usually secrete hormones.
- common cause of "heart-base tumor" and should be differentiated from a tumor of ectopic thyroid.

2) Carotid Body Adenomas / Carcinomas
- located near the bifurcation of the common carotid artery.
- may interfere with swallowing and blood flow.