Endocrine Pathology

Dave Chandra, DMD, PhD

OPTH 727

What words come to mind when you hear the word endocrine?

What organs will we talk about in this lecture?

- Pituitary
- Thyroid
- Parathyroid
- Adrenal

- Pancreas
  - Endocrine function… insulin
    - Dysfunction may lead to diabetes

Will talk about sex hormones in male/female reproductive pathology lectures.

Endocrine dysfunction… hypofunction vs hyperfunction

- Hypofunction – too little hormone produced
- Hyperfunction – too much hormone produced

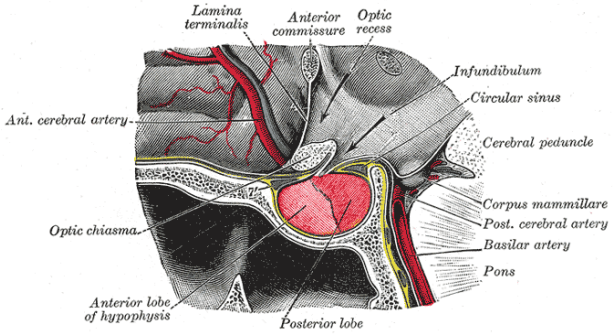
Primary dysfunction vs Secondary dysfunction

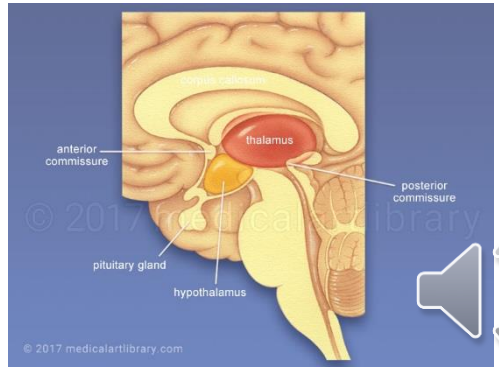
- *Primary dysfunction* – cause of glandular dysfunction is due to pathology originating in the same gland
  - Examples:
    - Neoplasia within the gland
    - Hyperplasia, hypoplasia
    - Destruction of the gland itself
      - Hashimoto's thyroiditis,
      - Surgical removal
- *Secondary dysfunction* – cause of glandular dysfunction is due to pathology outside the gland.
  - Examples:
    - Secondary hyperparathyroidism may be due to kidney failure
    - Secondary hypothyroidism may due to pituitary hypofunction

Pituitary

Pituitary (hypophysis) review

- Main regulatory gland of endocrine system (works hand in hand with hypothalamus, which it receives close neuronal control)
- Located at base of brain- attached to hypothalamus via pituitary stalk
- Pituitary is highly vascularized
  - Helps regulate endocrine feedback mechanisms
- Anterior pituitary produces
  - Growth hormone, prolactin, FSH, LH, ACTH, TSH
- Posterior pituitary produces
  - ADH (vasopressin), oxytocin





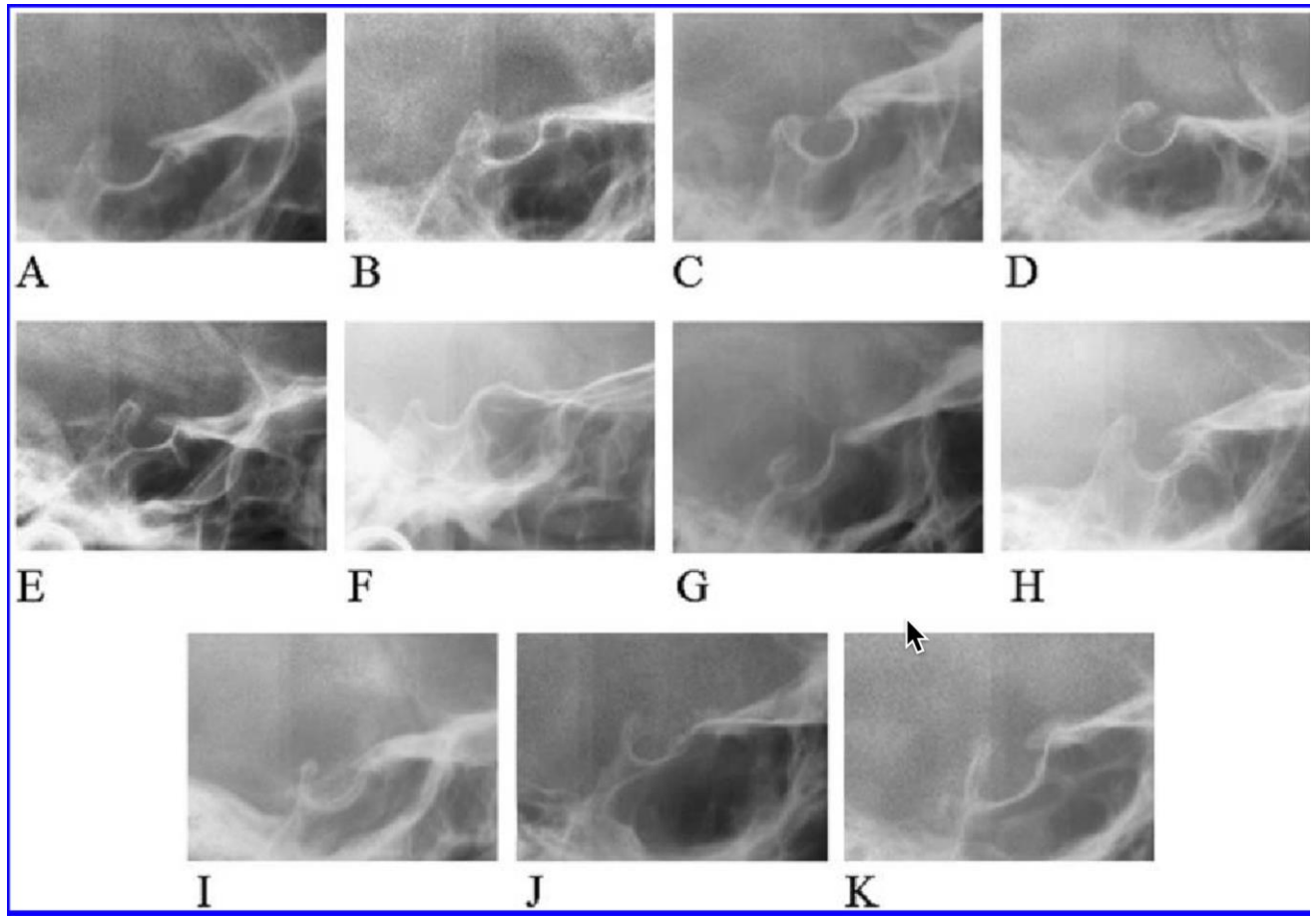
Pituitary adenoma is the main disease of the pituitary

- Tumor arises (theoretically) from a single cell
  - Pituitary is composed of many different secreting cells that produce different hormones
- Pituitary adenoma may
  - Increase production of a particular pituitary hormone. i.e. GH
    - Neoplastic cells are “functional”
  - Decrease production of a particular pituitary hormone
    - Neoplastic cells are “non-functional”. And neoplasm may crowd out cells that produce other hormones.
  - Increase production of one hormone, and decrease production of another pituitary hormone.
    - Neoplastic cells are functional and crowd out cells that produce other pituitary hormones
    - Example: a pituitary adenoma may be derived from cells that produce prolactin - maybe you will see an increase in prolactin and also see a decrease in GH, FSH, ACTH
- Pituitary adenoma may produce “mass effect”
  - Pressure on optic chiasm – may produce visual disturbances, and other symptoms of brain tumors – headache, etc.
- No two pituitary adenomas are alike
  - Need functional testing, i.e. measure various hormone levels
- As you would surmise, the clinical effects of a pituitary adenoma would be dependent on which hormones are overproduced/underproduced

You might be the first to recognize a pituitary adenoma…. Why?

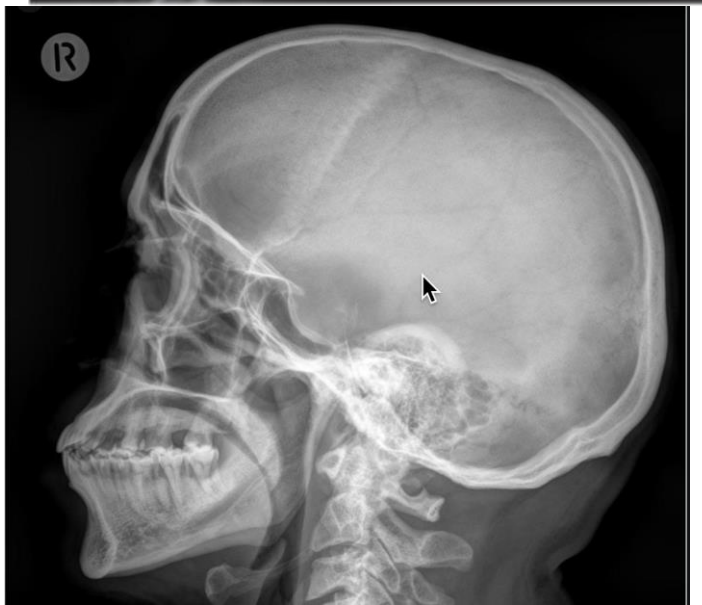
- Orthodontists often take lateral cephalograms (to assess malocclusion) – you may see an enlarged sella turcica (in which the pituitary is housed)
  - What is the significance of a large sella turcica?
    - An enlarged pituitary caused by a pitutary adenoma
    - Or. Could just be an ”empty sella” – no pathology associated
  - How do you distinguish? Advanced imaging- usually MRI
    - Neurologist or endocrinologist will also look for “mass effects” of possible tumor… i.e. vision disturbances

Examples of sella turcica that are within normal limits



Radiographic analysis examines size and angles of sella

Examples of enlarged sella



Pituitary Dwarfism is caused by abnormally low growth hormone (hypofunction).

- Dwarfism – abnormally short stature
  - Most causes of dwarfism are not due to pituitary dysfunction
    - Most cases of dwarfism due to a genetic disease- achondroplasia
- Pituitary dwarfism – due to low growth hormone
  - Causes? Pituitary adenoma or
  - Or… treatment of pituitary adenoma-
    - Radiotherapy or surgery (or infection/autoimmune disease) may destroy pituitary gland
- Main sign/symptom: short stature, as well as other pathology, which is dependent on which other hormone levels are affected.
- Treatment: hormone replacement therapy

Gigantism –due to increased secretion of growth hormone BEFORE puberty

- Usually due to pituitary adenoma
  - Present before puberty – before epiphyseal plates close
- Main sign/symptom: very tall stature (> 7ft), enlargement of facial soft tissues
- Treatment?
  - May remove the adenoma – surgery or radiation
  - May prescribe growth factor antagonists
- Prognosis. Usually shorter lifespan

- Treatment, prognosis, and other symptoms depend on many factors including which other hormone levels are affected by pituitary adenoma

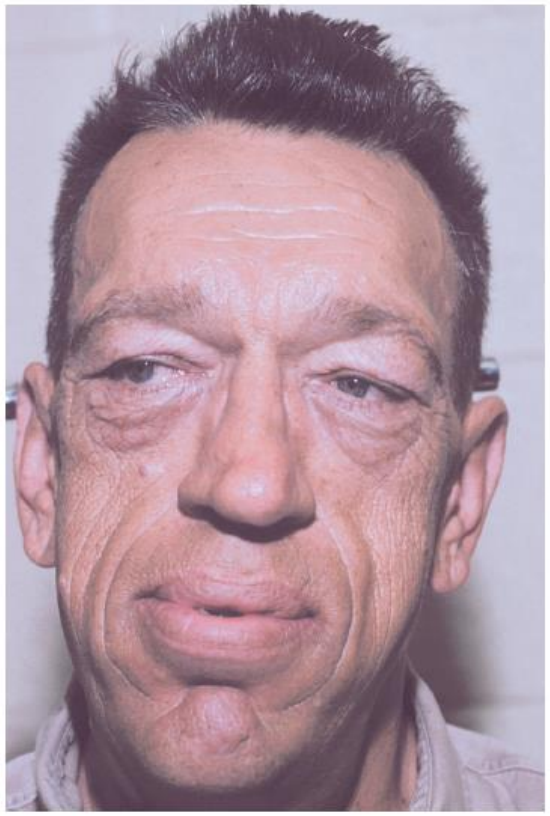
Acromegaly- due to increased secretion of growth hormone AFTER puberty

- Usually due to pituitary adenoma
  - Present after puberty – after epiphyseal plates close, therefore no increase in height, but increase in “membranous bones”
- Main sign/symptom: enlargement of jaws, skull, hands and feet.

- Treatment?
  - May remove the adenoma – surgery or radiation
  - May prescribe growth factor antagonists

- Treatment, prognosis, and other symptoms depend on many factors including which other hormone levels are affected by pituitary adenoma

Acromegaly



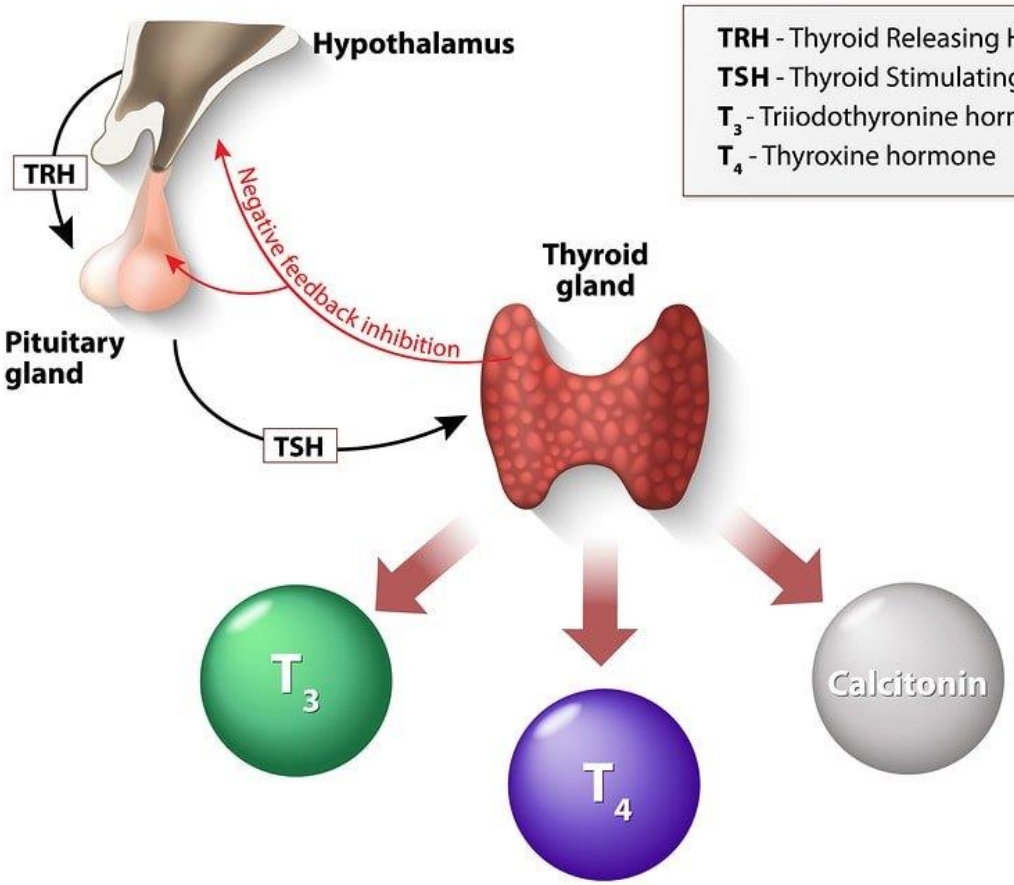
• **Fig. 17-20 Acromegaly.** This patient shows the typical coarse facial features. (Courtesy of Dr. William Bruce.)

• **Fig. 17-19 Acromegaly.** Enlargement of the bones of the hands. (Courtesy of Dr. William Bruce.)

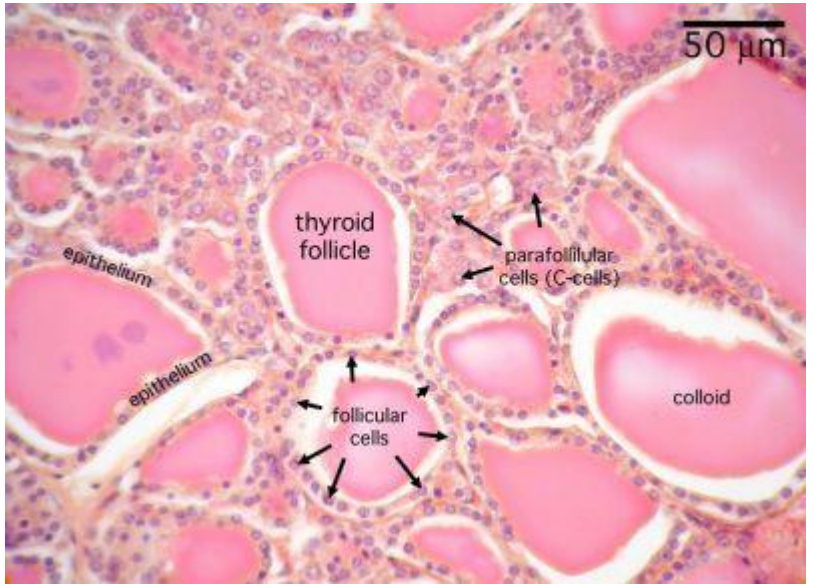
• **Fig. 17-21 Acromegaly.** This lateral skull film shows the dramatic degree of mandibular enlargement that may occur.

Thyroid

THYROID HORMONES



TRH - Thyroid Releasing Hormone
TSH - Thyroid Stimulating Hormone
T_3 - Triiodothyronine hormone
T_4 - Thyroxine hormone



Follicular cells – secrete T3 and T4
Parafollicular cells – secrete Calcitonin

Thyroid hormones (T3 and T4) regulate body temperature, metabolism and heart rate.

Calcitonin regulates calcium levels in blood – opposes the action of parathyroid hormone
Calcitonin reduces blood calcium levels

Thyroid dysfunction

In discussing thyroid pathology, The term "toxic" refers to overproduction of thyroid hormone

Hypothyroidism

- Too little T3/T4
  - Many possible causes. Many cases are idiopathic.
- Cretinism, myxedema, Hashimoto's disease are particular diseases associated with hypothyroidism.
- Most cases of hypothyroidism do not relate to any of the above.
- Worldwide, iodine deficiency is most common cause of hypothyroidism

Hyperthyroidism, aka thyrotoxicosis

- Too much T3/T4
- Graves disease, toxic multinodular goiter, toxic adenoma are particular diseases associated with hyperthyroidism.

"Goiter" – means enlargement of thyroid gland, can have many causes; some causing hyperthyroidism, some causing hypothyroidism.

Thyroid dysfunction

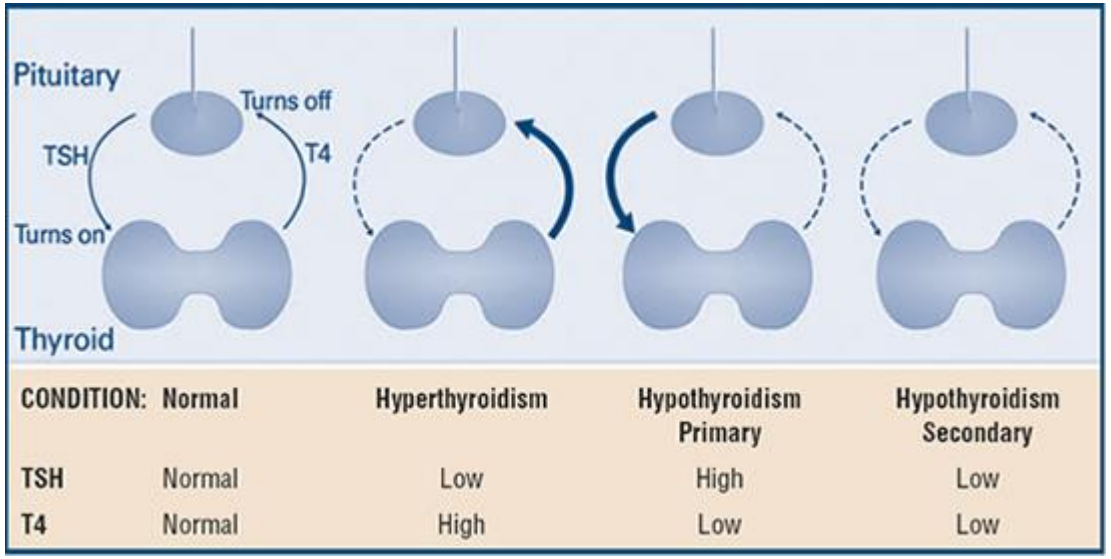
Hyperthyroidism is usually slow onset. One rare clinical situation is "thyroid storm" sudden exacerbation of hyperthyroidism that may be life threatening- may lead to heart failure

Hypothyroidism

- Symptoms:
  - Lethargy
  - Dry, coarse skin
  - Constipation
  - Reduced body temperature
  - Additional symptoms if found in kids
- Treatment. Thyroid hormone agonists

Hyperthyroidism,

- Symptoms
  - Weight loss despite increased appetite
  - Rapid heart rate
  - Excessive perspiration
  - Warm, smooth skin
  - Tremor
  - Some cases present with bulging of eyes (proptosis, exophthalmos)
- Treatment:
  - Thyroid removal (surgery),
  - Radioactive iodine therapy
  - Drugs that inhibit thyroid hormone production



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low

TSH and T4 levels are a “quick and dirty” way to assess thyroid function- if something is amiss, more advanced testing is indicated.

- Iodine uptake assays
- Serology, (anti-thyroid antibodies) etc.

High levels of T4 associated with hyperthyroidism:
If correspondingly low TSH… probably primary hyperthyroid
If correspoindingly high TSH… probably secondary hyperthyroid (which is rare)

Most cases of thyroid dysfunction <u>are primary, not secondary</u>

Graves' Disease – common cause of hyperthyroidism

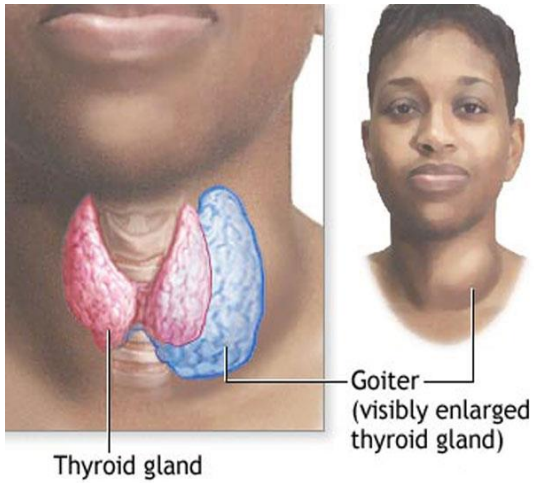
- Etiology: auto-antibodies to TSH receptors on thyroid follicular cells
  - These antibodies are receptor agonists, meaning that they stimulate thyroid cells to secrete more thyroid hormone

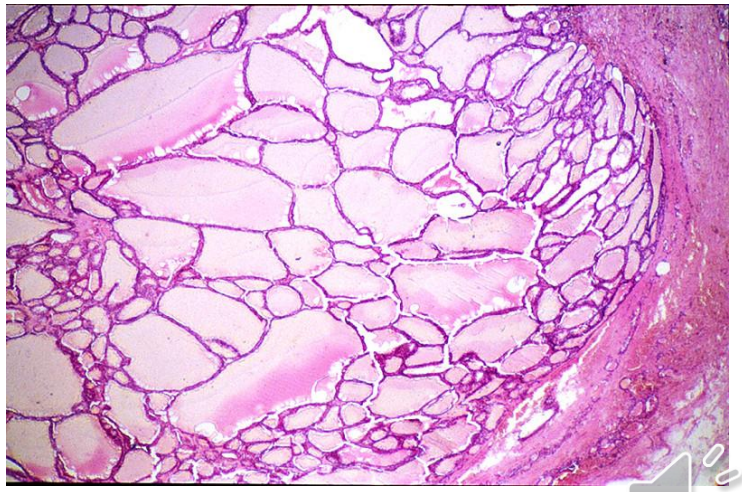
• **Fig. 17-26 Hyperthyroidism.** The prominent eyes are characteristic of the exophthalmos associated with Graves disease.

- Symptoms of hyperthyroidism
- Tx: radioactive iodine
  - Iodine is uptaken into follicular cells. Radioactivity kills thyroid follicles
  - Surgery

Toxic multinodular goiter

- Cause? follicular hyperplasia/adenoma – (difficult to discern between adenoma and hyperplasia)
  - End result: too many thyroid nodules
    - Thyroid enlargement (goiter)
    - If nodules produce thyroid hormone, then considered “toxic” – symptoms will be similar to Graves disease (see previous slide)
- Tx- removal of thyroid
  - Lobectomy
  - Thyroidectomy
  - Subsequent administration of synthetic thyroid hormones

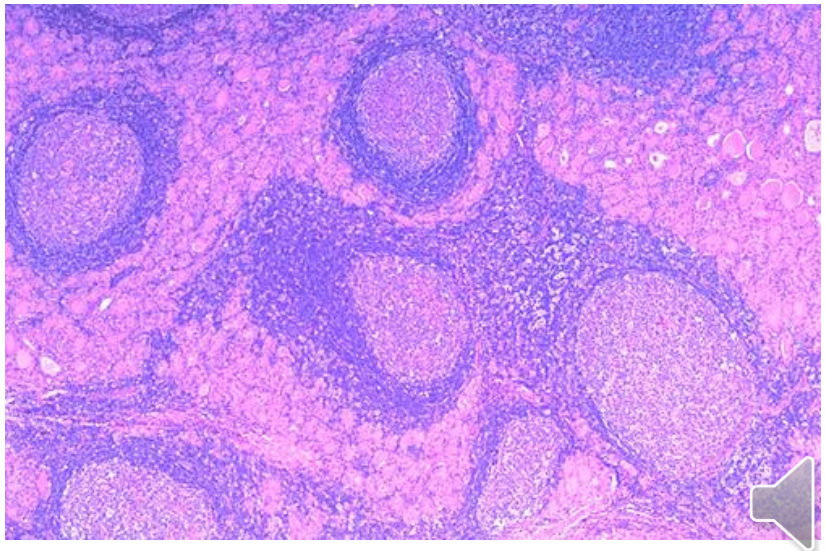




Note: non-toxic goiter may also be removed- not on exam – just FYI

Hashimoto’s thyroiditis (Hashimoto’s disease)

- Autoimmune destruction of thyroid gland
  - Lymphocytic/lymphoid invasion, may increase size of thyroid
    - This increased size may also lead to goiter.
- Treatment: removal and/or hormone analogs



Other hypothyroid diseases

- Cretinism- severe hypothyroid in infancy
  - May be due to maternal thyroid insufficiency
  - Malnutrition (low iodine in diet)
- Accumulation of glycosaminoglycan ground substance leads to tissue edema and “enlargement” of tissues
  - Edema is in addition to other symptoms of hypothyroid
- May have dental ramifications… delayed eruption

- Myxedema is a term used to signify a severe hypothyroidism; adults, children. Usage differs.

• **Fig. 17-22 Hypothyroidism. A,** The facial appearance of this 9-year-old child is due to the accumulation of tissue edema secondary to severe hypothyroidism. **B,** Same patient after 1 year of thyroid hormone replacement therapy. Note the eruption of the maxillary permanent teeth.

Thyroid cancers

- Papillary thyroid carcinoma
  - Most common
- Follicular carcinoma

- Medullary thyroid carcinoma
  - Carcinoma of parafollicular cells that produce calcitonin
  - Associated with Multiple Endocrine Neoplasia Syndromes (see later slide)
- Anaplastic thyroid carcinoma

Parathyroid

Parathyroid dysfunction

- Parathyroid glands:
  - 4 very small glands located behind thyroid gland in 4 corners that release parathyroid hormone (PTH)
  - Parathyroid hormone elevates serum calcium levels (remember: calcitonin reduces serum calcium levels).
    - PTH elevates serum calcium levels via mechanisms in kidney and bone
      - Promotes release of calcium from the bones into serum
    - NOTE: High serum calcium levels may be due to many causes – metastatic bone cancers, other endocrine disturbances, idiopathic,

- Hyperparathyroidism--- too much PTH
  - Causes can be Primary or Secondary
- Hypoparathyroidism ---- too little PTH

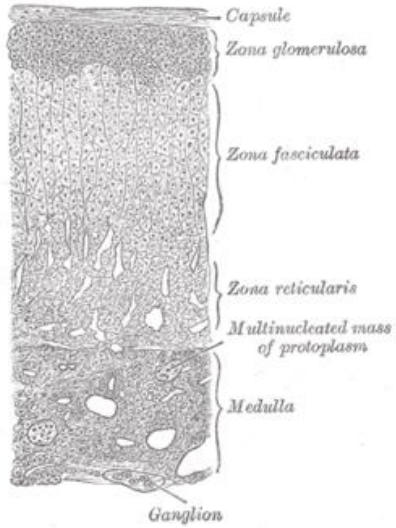
Hyperparathyroidism vs Hypoparathyroidism

- Main causes
  - Primary- parathyroid adenoma or hyperplasia is most common
    - Produces hypercalcemia
  - Secondary – renal failure is most common cause
    - Vitamin D is activated in kidney
      - Kidney failure leads to inability to activate Vit D
      - Active Vit D is required to absorb calcium
        - Lower blood calcium levels stimulate PTH glands
    - May or may not produce hypercalcemia
- Symptoms-
  - "Bones"
    - Osteoporosis – excess removal of calcium from bone
    - Other bone lesions- central giant cell granulomas – jaws may be affected- leading to enlargement
  - "Stones"
    - Increased susceptibility to kidney stones (nephrolithiasis)
  - "Moans"
    - Psychiatric symptoms of depression, anxiety, fatigue
  - Groans
    - Abdominal pains caused by peptic ulcers

- Main causes
  - Autoimmune disease
  - Inadvertent removal of parathyroid glands during thyroid surgery
- Symptoms: hypocalcemia
  - If severe
    - Seizures
    - Muscle spasms/convulsions (tetany)
      - Skeletal or cardiac muscle
    - Confusion

Adrenal

Adrenal glands



- Glands sit on top of kidneys
- Gland has 4 layers
  - Outermost- Zona glomerulosa- secretes aldosterone (mineralocorticoid)
    - Conn Syndrome- primary hyperaldosteronemia – usually due to adrenal adenoma
      - Patients have weakness and hypertension
  - Zona fasciculata – secretes cortisol (glucocorticoid)- critical for stress response
    - Cushing's Disease/Syndrome – too much cortisol (see subsequent slides)
  - Zona reticularis – secretes sex hormones (precursors)

  cortex
  - Medulla- secretes epinephrine upon stimulation
    - Pheochromocytoma – produces secondary hypertenstion – that cannot be managed by medications
      - May be part of Multiple Endocrine Neoplasia syndromes (see later slides)

Hypercortisolism – Cushing's Syndrome

- Too much cortisol may be due to many reasons:
  - Long term use of prednisone and other steroid medications- MOST COMMON CAUSE
    - Steroids treat a variety of auto-immune /inflammatory diseases
  - Adrenal tumor
  - Pituitary adenoma secretes excess ACTH
    - Hypercortisolism due to pituitary adenoma – Cushing's Disease

- Symptoms:
  - Weight gain
    - Accumulation of fat in upper back and face ("moon facies")
  - Mood changes – depression, irritability
  - Acne
  - Hypertension, excess body hair (hirsutism)
  - Easy bruising- poor wound healing

• **Fig. 17-33 Cushing Syndrome.** The rounded facial features ("moon facies") of this patient are due to the abnormal deposition of fat, which is induced by excess corticosteroid hormone. (Courtesy of Dr. George Blozis.)

Hypoadrenocorticism – Addison's Disease

- Insufficient production of adrenal cortex hormones, i.e. aldosterone, cortisol, etc
- Causes:
  - Autoimmune destruction is most common cause
  - Other causes include: infections usually in immune compromised, and less often due to tumors or pituitary dysfunction
- Symptoms:
  - Generalized hyperpigmentation (bronzing) of skin (and oral mucosa)
  - Hypotension due to hyponatremia
  - Weakness
  - Craving for salt, GI upset, nausea
  - Weight loss

Addisonian (Adrenal) Crisis

- Hypoadrenocorticism (Addison's disease) is usually slow onset
- Addisonian crisis is a life threatening situation
  - Usually occurs in patients with adrenal insufficiency… they could have…
    - 1) Addison's disease
    - 2) For patients on long term corticosteroids, ACTH production is severely dimished
      - Patient on long term steroids cannot make their own cortisol anymore
  - What happens in Addisonian crisis?
    - Stressful event – like a dental procedure – patient may not have the capacity to produce enough adrenal hormones
      - Leads to rapid hypotension (hyponatremia) --- SHOCK, hyperkalemia, high fever
- Take home point (for the next 40 years). Be careful when treating patients on long term steroids. Why?
  - Delayed wound healing
  - Altered stress response may precipitate Addisonian crisis

Remaining diseases

- Multiple Endocrine Neoplasia Syndrome
- Diabetes Mellitus
- Diabetes Insipidus

Multiple Endocrine Neoplasia Syndromes

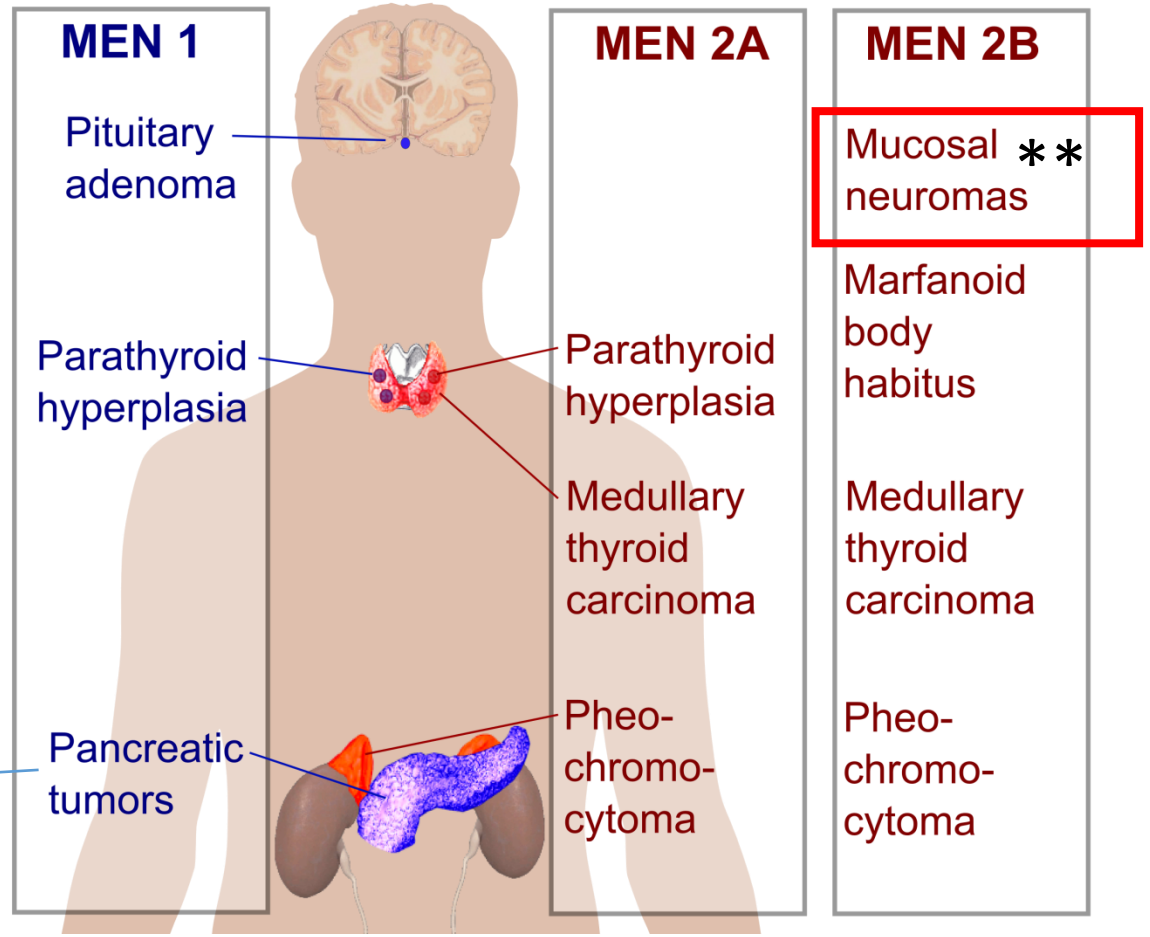
- What are they?
  - A group of genetic conditions characterized by:
    - Tumors of endocrine tissues

- Which are the main entities?
  - MEN Type 1 - mutation in MEN1 gene
  - MEN Type 2A - mutation in RET proto-oncogene
  - MEN Type 2B (MEN Type 3) - mutation in RET proto-oncogene

- Etiology – genetic
- Incidence… very rare ~1:200,000

Will not ask you the specific genes associated with different MEN types, but could be board questions.

Differences between the MEN types



Not pancreatic cancer

Of these: MEN Type 2B is most rare - but the only one with oral manifestations

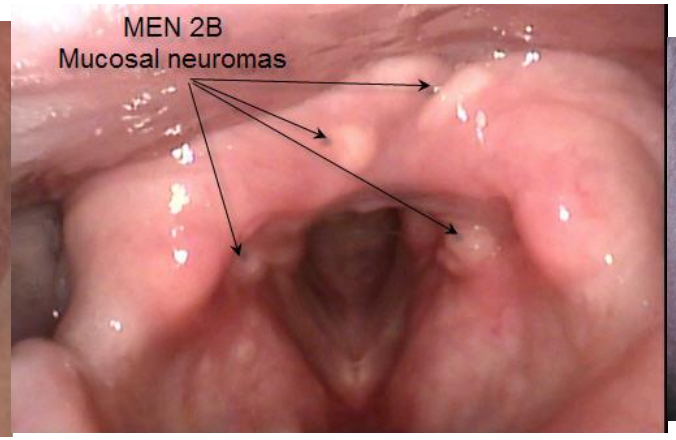
MEN Type 2B

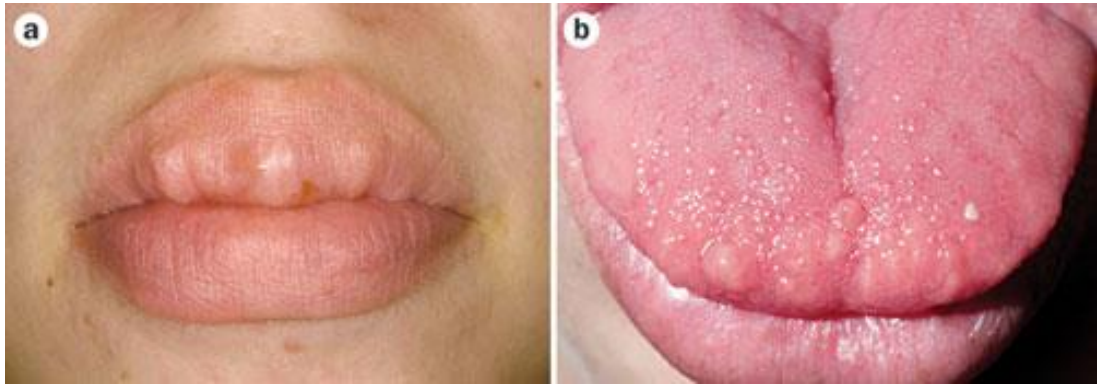
- Very serious condition –
  - Average age of death = 21
  - **Most** develop medullary thyroid carcinoma at young age
    - MTC has a very poor prognosis
    - Early detection is critical
      - Prophylactic thyroidectomy (hopefully before the age of 1)
      - Otherwise MTC silently develops early in life and metastizes by adolescence
  - Can also develop pheochromocytomas (50%)
    - Adrenal gland adenomas – secrete catecholamines
      - Can result in profuse sweating, diarrhea, headaches, flushing, heart palpitations and severe hypertension
      - Can result in life threatening hypertensive crisis – esp during surgery with general anesthesia

Why is it important to talk about MEN Type 2B?

- Characterized by mucosal neuromas
  - Usually **the first sign** of this disease
    - **Usually present in infancy**
  - Pediatric dentists must be aware
    - Remember… the worst sequelae of MEN Type 2B is development of medullary thyroid carcinoma… therefore, the earlier the patient is diagnosed… the earlier prophylactic (preventative) thyroidectomy can take place
  - Soft, painless nodules mostly on lips and anterior tongue
    - Can be seen on buccal mucosa, gingiva and palate

What do the oral mucosal neuromas look like in MEN Type 2B?





Diabetes Mellitus

Remember, insulin is secreted in response to high blood sugar

- Common disorder of carbohydrate metabolism
  - Basic problem is either lack of insulin, or tissue resistance to effects of insulin
    - Main result is persistently high blood sugar (hyperglycemia)
  - Can affect dental treatment.
    - Implant placement requires robust wound healing response. Wound healing is compromised in uncontrolled diabetics.
- Unknown cause
- Serious cause of morbidity and mortality in USA
  - ~ 8% of population, ~26 million people have diabetes
- Two general types
  - Type I - complete (or near complete) lack of insulin production
  - Type II – Resistance of target tissues to the effects of insulin and sometimes inadequate insulin production
- Diabetes Type I in the past was characterized as “insulin dependent” or “juvenile onset”, Type II was characterized as “insulin-independent” or “adult onset”. This is mostly true… however…
  - Type I diabetes can have an adult onset (~5% of Type 1 diabetics develop disease after age 30)
  - Type II diabetes sometimes has an early onset… possibly due to increasing childhood obesity
  - Type II diabetics often need to take insulin.

Type I diabetes mellitus

- Cause: autoimmune destruction of Beta islet cells in the pancreas
  - But the cause of autoimmune attack is unknown
- Symptomology is usually much more serious (see next page) than type II.
  - More difficult to control blood sugar levels
    - Insulin injections much more regimented
    - Constant monitoring of blood sugar levels.

Type II diabetes mellitus

- Far more prevalent
  - Type 2 is ~ 10 -20 times more common than Type 1
- Unknown cause… risk factors include:
  - Genetic predisposition
  - Obesity, poor diet
- Managed by:
  - Medications
    - Metformin – decreases blood sugar by suppressing liver glucose production
  - Diet modifications
  - Some insulin

Symptoms of persistently high glucose levels

- Polyphagia – persistent hunger
  - With weight loss
- Polyuria – frequent urination
  - High blood glucose leads to high osmolarity which leads to increased urine production
  - Frequent urination
  - Leads to serious dehydration
- Polydypsia – persistent thirst
  - Due to frequent urination.
- Blurred vision
- Confusion/stupor
- Fatigue
- Many others.

Blood glucose levels are normally between 80-120 mg/dL

These symptoms occur when blood glucose is greater than ~300

- Type I diabetics suffer from these symptoms frequently because it can be difficult to control their diabetes. Type II diabetics may suffer from these symptoms until they are diagnosed… then usually they are better controlled (diet/exercise/medicine and perhaps some insulin).

- “Insulin shock” may result from too much insulin administered and subsequent hypoglycemia- may lead to coma

Long term complications of diabetes

- Most complications of diabetes are due to vascular diseases –
  - Usually small vessels – microangiopathy – arterioles (arteriolosclerosis) and capillaries
    - Vessels get thicker and weaker – mechanism largely unknown
  - This produces ischemia – and tissue death
    - Kidney damage
      - 20% of patients with kidney failure are diabetics
    - Retinopathy/blindness
    - Brain damage
      - Silent stroke
    - Increased infections – gangrene – necrosis of limbs
    - Poor wound healing
      - Poorly controlled diabetes – dental implants contraindicated
        - At SOD, no implants if HbA1C levels greater than 7.5 (see next slide)
- Diabetic neuropathy
  - Peripheral nerve damage – tingling numbness of extremities
- Diabetes is risk factor for hypertension and atheroma

HbA1c is a measure of long term blood glucose levels

A1C	Blood glucose level
%	mg/dl
6	126
6.5	140
7	154
7.5	169
8	183
8.5	197
9	212
9.5	226
10	240

Normal – below 5.7
Pre-diabetes 5.7-6.4
Diabetes 6.5 and above

“uncontrolled diabetes”- A1C > 9
“well controlled diabetes”- A1C < 7.5

A well-controlled diabetic can bring A1C levels below 6.5

Diabetes Insipidus

- Nothing to do with blood sugar
- Disease of posterior pituitary or hypothalamus
  - Many causes, idiopathic, tumors,
- Etiology: lack of ADH (antidiuretic hormone, aka vasopressin)
  - ADH promotes reabsorption of water from kidney tubules
  - Therefore lack of ADH, will lead to excess urine formation
  - This will lead to polyuria (frequent urination) and polydipsia (extreme thirst and water consumption)
    - Called “diabetes” because polyuria and polydipsia is similar to diabetes mellitus