# Endocrine Path Robbins Outline

PITUITARY (Goljan 488, Big Robbins 1156, Baby Robbins 561)

**Normal Function**

- Pituitary is divided in the Endodermal derived **adenohypophysis** (anterior pituitary) and the ectodermal derived **neurohypohpysis** (posterior pituitary)
- Hypothalamus sends signaling hormones through the portal vein to the anterior pituitary
    - Somatrophs = Growth Hormone, Stimulated by GHRH
    - Lactotrophs = Prolactin, Stimulated by
    - Corticotrophs = Corticotropins (ACTH), stimulated by CRH
    - Thyrotrophs = Thyroid Stimulating Hormone (TSH), stimulated by TRH
    - Gonadotrophs = Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)
- Hypothalamus has axonal projections from nuclei sent into the posterior pituitary
    - Oxytocin = uterine contractions
    - Vasopressin / ADH = water and sodium resorption in the kidney
- **Feedback inhibition** occurs at the level of the pituitary (from target organ secretion) and the level of the hypothalamus (from pituitary secretion and target organ secretion
- **Signaling Molecules** are either catecholamines, peptides, or steroids

ANTERIOR PITUITARY (Big Robbins 1158, Baby Robbins 562)

**Hyperpituitary**

- Causes
    - **Most Common** cause is a **Hyperfunctioning adenoma**
    - May be caused by secondary Hypothalamic Dysregulation, ↑stimulus from above
- Adenomas
    - **Prolactinoma**
        - **Most Common** functional pituitary adenoma
        - Is usually a **macroadenoma** (>10mm
        - Characterized by their **efficiency**, large adenomas = large dosage of Prolactin
        - ↑Prolactin = **amenorrhea**, galactorrhea, **loss of libido**, infertility
            - Absence of menses is an early sign in females
            - Large tumors develop in men and elderly women, symptoms are subtle
        - Morphology
            - **Sparsely granulated** acidophilic or chromophobic cells
            - Immunohistochemistry demonstrates Prolactin staining on Histo
        - ↑Prolactin may be normal
            - Pregnancy causes ↑ Prolactin
            - Dopamine antagonists (Seizure Drugs) ↑Prolactin
            - ↑Prolactin ≠ Prolactin Adenoma; you must see the tumor

- **Growth Hormone**
  - Second most common functional pituitary adenoma
  - ↑Growth hormone has two clinical presentations
    - **Gigantism**
      - Hypersecretion **prior to closure of epiphsyeal plates** (children)
      - Results in enlarged stature with disproportionate arms & legs
    - 
      - Hypersecretion **after closure of epiphyseal plates** (adults)
      - Enlargement of heads, hands, feet, jaw, tongue, and soft tissues


Acromegaly


Gigantism

  - Morphology
    - Composed of **densely granulated** cells which are **acidophilic** or chromophobic; immunohistochemistry is diagnostic
    - There may be sparsely granulated variants, called **fibrous bodies**
- **Corticotroph**
  - ↑ACTH results in Hypersecretion of cortisol from the adrenals
  - ↑Cortisol= Cushing's Syndrome, ↑Cortisol from Adenoma = **Cushing's Disease**
    - See below, Cushing's Comes up alot
  - Usually a microadenoma with basophilic cells, immune staining for ACTH
- **Gonadotroph** *(low-yield)*
  - Found in middle-age, men and women, but only when they cause neurologic sx
    - **Mass effect** compresses the optic chiasm, causing diplopia
- **Thyrotroph** *(low-yield)*
  - Rare (1%) Hypersecretion of TSH, rare cause of hyperthyroid
- **Nonfunctioning** *(low-yield)*
  - **Null** tumors = hormone absent, very rare
  - **Silent** tumors = have secretory granules, they just don't secrete anything

**Hypo**

- Requires **75% of pituitary** to be lost prior to symptom onset
- Causes
  - Tumors, masses
    - Cysts, Tumors, Carcinomas, all cause mass effect, compressing healthy pituitary
  - Pituitary surgery, radiation
    - Excision of tumor may take healthy adenoma
    - Radiation may cause the same problem
  - Apoplexy
    - Adenomas or cysts may have spontaneous hemorrhage end enlargement
  - Ischemic Necrosis, Sheehan
    - Hypoperfusion can cause ischemia, though it is generally well tolerated
    - **Sheehan** = postpartum DIC resulting in infarction of pituitary
    - Other causes of DIC can lead to infarction of pituitary

POSTERIOR PITUITARY (Big Robbins 1163, Baby Robbins 566)

**Hypo = Diabetes Insipidus**

- Caused by a **↓Secretion of ADH**
  - There is no syndrome of Oxytocin deficiency
- Inability to resorb water from kidneys, leading to water loss
  - Results in ↑Urination (**polyuria**), ↑Drinking (**polydypsia**), and **Hypernatremia**
  - **Diabetes Insipidus** is caused by the inability of pituitary to produce ADH
  - **Nephrogenic Diabetes Insipidus** is caused by inability of the kidney to respond to ADH
- Result of head trauma, tumors, inflammation, or surgery
  - Necrosis of the pituitary stalk

**Hyper = SIADH**

- Caused by **↑Secretion of ADH**
  - There is no syndrome of Oxytocin excess
- Causes **retention** of water from the kidneys
  - Results in ↑Water Retention and **Hyponatremia** (diluted)
  - Results in **Cerebral Edema** and Neurologic Dysfunction
- Caused by
  - **Malignant neoplasms** (such as small cell of the lung)
  - **Damage to hypothalamus** of any origin

SUPRASELLAR TUMORS

**Craniopharyngioma**

- Most common cause of hypopituitarism in kids
- Made from the **remnant of Rathke's pouch**
- Comes from above the sella, i.e. in the hypothalamus, and **crushes anterior pituitary**

| CLINICAL FINDINGS OF HORMONE DYSREGULATION | | |
|---|---|---|
| **Hormone/Cell** | **Deficiency** | **Excess** |
| Gonadotropin FSH/LH | Children have **delayed Puberty**<br>Women have **secondary Amenorrhea**<br>Men have impotence | |
| Growth Hormone (GH) | Children have growth delay, delayed bone fusion<br>Adults have hypoglycemia, ↓gluconeogenesis | Kids: **gigantism**, increased growth, long arms and legs<br>Adults: **acromegaly**, big hands, feet, facial structure |
| Thyroid Stimulating Hormone (TSH) | Secondary Hypothyroidism, ↓T3/T4 and TSH<br>Cold intolerance, Constipation, **Cretinism** (kids) or **myxedema** (adults) | Secondary Hyperthyroidism (rare), ↑T3/T4 and TSH<br>Heat intolerance, diarrhea, ↑appetite |
| Adrenocortiotropic Hormone (ACTH) | Hypoglycemia and decreased gluconeogenesis<br>Hyponatremia (mild SIADH) from loss of inhibition | Cushing's Syndrome, Hypercortisolism<br>Moon facies, periorbital edema, weight gain, humpback<br>Dexamethasone Test; if Cortisol ↓secondary, if ACTH ↑ primary tumor of adrenals |
| Prolactin | | Amenorrhea, Loss of Libido, Galactorrhea, Infertility |

THYROID GENERAL (Goljan 492, Big Robbins 1164, Baby Robbins 567)

**Normal Function**

- Hypothalamus releases TRH to Pituitary, Pituitary releases TSH
- TSH = formation of T3/T4 from colloid, iodine uptake, T3/T4 release
- T4 deiodinated to form T3 in periphery, T3 binds receptor 10 times affinity T4
- T3-TR binds hormone response elements in target cell = ↑metabolic activity

**Hyperthyroidism**

- Definition
  - Called **thyrotoxicosis**, usually synonymous with hyperthyroid
  - ↑Release of T3/T4 for any reason causes ↑Basal Metabolic Rate systemically
- Causes
  - **Primary** causes = adenomas, nodular goiters, hyperplasia (Graves); intrinsic
  - **Secondary** causes = pituitary adenomas /dysregulation, tertiary = hypothalamus
- Symptoms
  - Cardiac = ↑heart Rate and stroke volume**, tachycardia, palpitations**
  - Neuromuscular = **tremor**, figiditiness, hyperactivity, **emotionally labile**
  - Skin = dilated, warm, wet, flushed, trying to get rid of heat
  - GI = diarrhea, malabsorption
  - Occular= staring gaze, lid lag, note that buggy eyes is unique to Graves

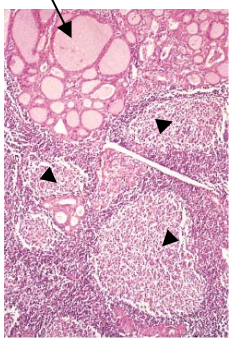
**Hypothyroidism**

- Definition
  - Inadequate production of T3/T4 for any reason
- Causes
  - **Primary** = destruction (Hashimotos, Iatrogenic) or iodine deficiency
    - ↑TSH (no response to signal, appropriate upregulation of signal)
  - **Secondary** = Pituitary or Hypothalamic deficiency
    - ↓TSH (not enough signal to stimulate Thyroid)
- Symptoms
  - **Cretinism**
    - Happens to babies and infants
    - Craniofacial abnormalities (wide eyes, weird faces)
    - Mental Retardation, physical retardation, failure to thrive
  - **Myxedema**
    - Periorbital edema, coarsening of facial features
    - Cardiomegaly, pericardial effusions
    - Hair loss
    - Accumulation of Mucopolysaccharide rich glycoproteins

THYROIDITIS (Big Robbins 1169, Baby Robbins 569)

Colloid surrounded by eosinophilic (pink) Hurthle Cells

## Hashimoto's Thyroditis



Large infiltrate with germinal centers (arrowheads) and deeply eosinophilic Hurthle cells surrounding colloid.

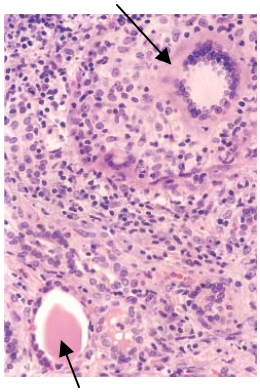
Pathogenesis
- **Autoimmune** disease with **Blocking TSH-Receptor antibodies**, as well as Thyroglobulin, Thyroid Peroxidase, and other Thyroid Proteins
  - Association with HLA-DR3 and HLA-DR5
- Replacement of thyroid parenchyma with **mononuclear infiltrate** and **fibrosis** (lymphocytes, macrophages, and plasma cells destroy the parenchyma)

Morphology
- Diffuse enlargement of the thyroid, with an intact capsule and with a paler parenchyma
- **Mononuclear Infiltrate** with fibrosis, formation of **germinal centers**
- **Hurthle Cells** = eosinophilic, granular cytoplasm in residual follicular cells

Clinical
- Generally affects **women** in their **40s-60s**, most common cause of hypothyroid
- Present with an **initial hyperthyroid** and then, as tissue is destroyed, **hypothyroid**
- Increased risk for other autoimmune disorders = Lupus, Endocrine Autoimmune

Giant Cell

## Subacute (Granulomatous) Thyroiditis also called de Quervain de *Quavain Rhymes with Pain*



Naked Colloid

Pathogenesis
- Caused by a **viral infection** or may be **post viral**
  - Coxsackievirus, Measles, Mumps, Adenovirus, Others
- Autoimmune disease (Females > males) with an association with HLA-B35

Morphology
- There is a variable enlargement of the gland that may be asymmetrical
- *Early disease* = follicular disruption and Neutrophilic infiltrate
- *Late Disease* = **mononuclear infiltrate**, **granulomas**, giant cells, and **naked colloid**

Clinical
- **Painful thyroditis** that may radiate to the jaw, throat or ears, especially on swallowing
- Thyroid inflammation = **hyperthyroid**, though it is transient
- If present, subsequent hypothyroid is limited, **recovery is the rule**
- Occurs between ages of **30-50, women > men**

## Subacute Painless Lymphocytic Thyroiditis *(gets left out of Goljan, Lippincott, and Robbins Review)*

- Thyroiditis that is often **post partum**, with the classic symptoms of thyrotoxicosis
- Causes a **hyperthyroidism** with **painless glandular enlargement** that is self limiting and may be followed by hypothyroidism in 50% of cases
- There is **no germinal centers** and **no clear antigen** determined

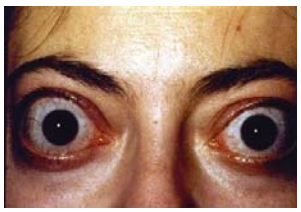
## Reidel's Thyroiditis

- A rare **fibrosing** process of **unknown origin** causing a replacement of thyroid by fibrosis
- Fibrosis may **invade capsule** and affect nearby structures (esophagus) mimicking carcinoma
- Causes **glandular atrophy** (firm and nonmovable mass) with **hypothyroid**

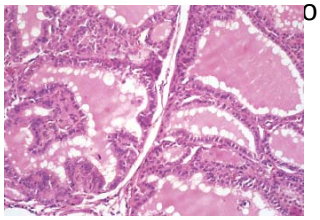
GRAVES (Big Robbins 1172, Baby Robbins 571)

**Graves Disease**

- Pathogenesis
  - **Autoimmune** with **Stimulating TSH-Receptor Antibodies**, most common Hyperthyroid
    - HLA-DR3 Association, IgG antibodies, Type II Hypersensitivity
  - Unlike the blocking and destruction of Hashimoto's, Graves causes overactivation of growth signals = **hyperthyroid**
  - Colloid gets used up, iodine is consumed, and there is an **elevated T3/T4** response with an **intact feedback** to the pituitary
  - The growth signal is from the antibodies


Exophthalmos

- Morphology
  - The gland is **symmetrically enlarged** with an **intact capsule** and soft parenchyma
  - There is hypertrophy and hyperplasia of the follicular cells, resulting in a columnar stacking into **papillary folds**
  - Increased Thyroid activity = **scant colloid** (it gets used up)
- Clinical
  - Affects **women > men**, especially in the **20s-40s** with an unknown inciting event
  - Triad of thyrotoxicosis, opthalmopathy, and dermopathy
    - **Thyrotoxicosis**
      - Diffuse hyperplasia of the thyroid
      - Hyperthyroidism = palpitations, afib, heat intolerance, flushed skin
    - **Opthalmopathy**
      - Retro-orbital lymphocytic infiltration leads to **exophthalmos** (buggy eyes)
    - **Dermopathy**
      - Scaly thickening of the skin, usually over the shins, **pretibial myxedema**


Columnar epithelia line the shrunken Colloid. Hyperplastic follicles invade the colloid). Active use of colloid results in scalloped appearance (white in the pink colloid)

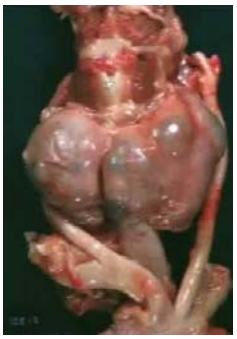
  - Labs
    - ↑T3/T4, ↓TSH, + TSH-IgG

GOITERS (Big Robbins 1173, Baby Robbins 573)

**Diffuse Nontoxic Goiter** (Simple)

- Pathogenesis
  - **Endemic Type** = **iodine deficient diet** like in the Mountainous regions of the world
    - ↓Iodine = ↓T3/T4 = ↑TSH to compensate; ↑TSH = Thyroid Enlargement
  - **Sporadic Type** = rare, consumptions of goitrogens (cabbage), puberty, pregnancy
    - Effectively ↓T3/T4 by preventing steps of iodination; path follows endemic
- Morphology
  - **Hyperplastic Stage** = symmetrically enlarged, scant cytoplasm, hyperplastic follicles
  - **Colloid Involution** = As supply = demand, colloid accumulates, follicles involute
- Clinical
  - **Generally Euthyroid** (they enlarge to compensate, and do it well)
  - **Mass Effect** into esophagus (dysphagia), trachea (breathing), and cosmetics

## Multinodular Goiter

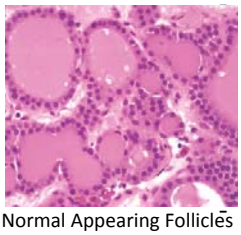

Multinodular Goiters are enlarged glands, but are euthyroid

- Pathogenesis
  - Repeated episodes of stimulation and involution of simple goiters
  - Most long-standing simple goiters become multinodular goiters
  - Represent extreme nodular growth, and are usually asymmetrical
- Morphology
  - Multilobulated, massive, asymmetrically enlarged glands
  - Follicular hyperplasia, scant colloid, involution of Simple is the same
  - These are just really **big, old, Possibly self-sustaining simple goiters**
- Clinical
  - Hyperfunctioning multinodular goiters = thyrotoxicosis
  - **Mass effects** are greater = esophagus, trachea, vena cava, cosmetics
  - Small subset can become **self-sustaining** leading to hyperthyroidism without the presentation of the Grave's triad, is a condition called **Plummer Syndrome**
  - Hyperfunctioning nodules appear **hot** on **radioiodine uptake**

NEOPLASMS OF THE THYROID (Big Robbins 1175, Baby Robbins 575)

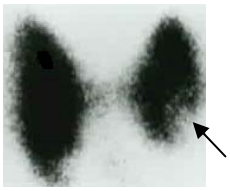
## Adenoma


Gross Image, Follicular Adenoma


Normal Appearing Follicles

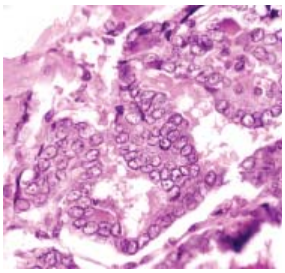
- Pathogenesis
  - **Nonfunctional Adenomas** = most common, little it known of pathogenesis
  - **Functional/Toxic Adenomas**
    - Somatic mutation of either the **TSH-Receptor** or **$G_s$ protein**
    - Causes ↑cAMP, T3/T4 production, and monoclonal growth selectivity
    - ↑T3/T4 leads to thyrotoxicosis, thus the name, "Toxic" adenomas
- Morphology
  - **Well-Demarcated**, **solitary lesion**, with **well-defined capsule** (unlike carcinoma)
  - Despite growth and compression, there is **no multinodularity** (unlike goiters)
  - Follicular Growth surrounding colloid, resembling normal parenchyma
  - There may be, sometimes, Hurthle Cells
- Clinical
  - These are **cold nodules** relative to adjacent thyroid (take up less radio-iodine)
  - Definitive diagnosis is based on capsular and histologic examination

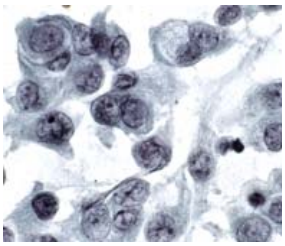
## Carcinoma Generalities


radioiodine scan with a "cold" region (adenoma or carcinoma)

- There are both genetic and environmental factors that cause carcinoma
- Subtypes include
  - Papillary = 75-80%, Ionizing Radiation
  - Follicular = 10-20%, RAS oncogene and PAX-8;PPARy1 translocation
  - Medullary = 5%, from C cells, overproduction of Calcitonin
  - Anaplastic = 5%, elderly, dreaded prognosis

## Papillary Carcinoma


Orphan Annie Nuclei

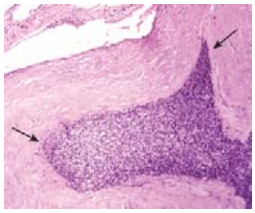

Eosinophilic Nuclear Inclusions of a needle aspiration biopsy

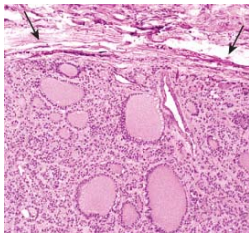
Pathogenesis
- **Most Common Primary Thyroid Tumor**, occurring in women, ages 20-50
- Caused by **ionizing radiation**

Morphology
- **Orphan-Annie Nuclei** are pathognomonic, even in absence of papillary structure
  - Hypochromatic, empty nuclei devoid of nucleoli
- **Psammoma Bodies** may be present = dystrophic calcification of tumor cells
- Eosinophilic Intranuclear Inclusions
- Papillary growth structure that may be **invasive to capsule**

Clinical
- **Singular Mass** moves freely and is **indistinguishable** from a benign lesion on physical exam
- 50% of cases of regional metastasis, distant metastasis is rare
- Prognosis is **excellent** (95% 10 year survival)

## Follicular Carcinoma


Minimal capsular invasion (arrows)


No capsular invasion of a follicular adenoma

- Pathogenesis
  - Common in areas of **iodine deficiency**, link to **multinodular goiters**
  - Female preponderance, usually occurring in the 40s-60s

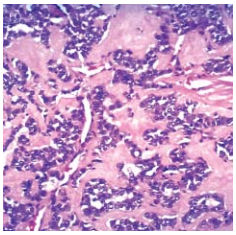
Morphology
- **Single Nodules** that may be minimally invasive or widely invasive
  - **Minimally Invasive**
    - Look like Adenomas, require extensive sampling to ensure benign
  - **Widely Invasive**
    - Extensive invasion into or through capsule, obvious diagnosis
    - Normal thyroid cells to anaplastic tissue; nothing like papillary

Clinical
- Spread **hematogenously** rather than lymphatically
- Minimally invasive have a high cure rate, widely invasive have a poor cure rate
- Most are **cold nodules**, though rare, well-defined thyroid lesions may be **hot**

## Anaplastic Carcinoma

- **Rare**, aggressive tumor of the **elderly,** particularly in areas of endemic goiter
- **Anaplastic** nuclei, poorly differentiated thyroid cells
  - May be spindle cells, large pleomorphic giant cells, or small cells (Neuroendocrine)
- **Dismal Prognosis** (weeks, not years)

**Medullary Carcinoma**


Amyloid Deposition around the tumor

- Pathogenesis
  - **Sporadic** cases account for 80% of medullary carcinomas
  - **Familial** cases are associated with MEN2A or MEN2B (See later)
  - Generated from **C-Cells** = **Calcitonin** production which leads to **amyloid deposition**

Morphology
  - Sporadic = single nodules with pentagonal/spindle cells with amyloid nearby
  - Familial = multiple, bilateral nodules with pentagonal/spindle cells with amyloid nearby

- Clinical
  - **Sporadic** = mass effect, hoarseness, dysphagia, hypocalcemia
  - **Familial** = found on screening, ↑Calcitonin, ↓Ca
  - Calcitonin = a hypocalcemia, tetany

CONGENITAL (Big Robbins 1183, Baby Robbins 579)

**Thyroglossal Duct/Cyst**

- The Thyroid descends from the mouth, leaving a trail that eventually is eliminated
- If that trail does not go away, there may be a **duct** or **cyst** left behind
- Present from birth, it may not be noticed until any age
- Up top (close to origin) = **sqaumous epithelium,** down low (close to thyroid) = **thyroid**
- May give rise to **infection/abscess** or **carcinoma**, though only rarely

| TSH, T3/T4 DIFFERENTIAL | | | |
|---|---|---|---|
| **Disease** | **TSH** | **T3/T4** | **Notes** |
| Hashimoto's | ↑ | ↓ | Antibodies |
| Grave's | ↓ | ↑ | Antibodies |
| Goiters | ↑ | ↓ | |
| "Primary" Hyperthyroid | ↓ | ↑ | Intrinsic, Feedback Intact |
| "Secondary" Hyperthyroid | ↑ | ↑ | ↑Signal, Normal response |
| "Primary" Hypothyroid | ↑ | ↓ | Intrinsic, Feedback Intact |
| "Secondary" Hypothyroid | ↓ | ↓ | ↓Signal, Normal response |

| RADIOACTIVE IODINE DIFFERENTIAL | | |
|---|---|---|
| **Disease** | **Iodine** | **Notes** |
| Follicular Adenomas | Hot | Resembles Normal |
| Simple Goiter, Graves Disease, Multinodular Goiters | Hot | Hyperplasia of Normal Tissue |
| Carcinomas | Cold | Dysplastic Tissue |

PARATHYROID (Goljan 502, Big Robbins 1183, Baby Robbins 579), *Organized for lecture*

**Calcium and Definitions**

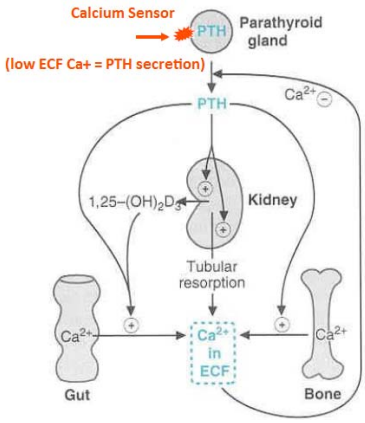
- **Generalities**
  - Most abundant mineral in the body, but is taken in only in the diet
  - 99% of total body calcium is found in bone, serving as a functional reservoir
  - Required for **bones**, **teeth**, **muscle contraction**, **enzyme activation**, **nerve impulses**
  - Because it is a second messenger, it must be regulated in a tight zone of "normal" range (normal is 8.7-10.4 mg/dL with about 50% of it bound to albumin)
- **Hypocalcemia**
  - Defined as $\downarrow [Ca]_{blood}$ = Low Blood Concentrations
    - Total body calcium is irrelevant, it's about how much is in the blood
  - Clinical Signs
    - Tetany, Muscle Spasms
    - Rickets, Bone Pain
- **Hypercalcemia**
  - Defined as $\uparrow [Ca]_{blood}$ = High Blood Concentrations
  - Precipitation of $CaPO_4$ (calcium phosphate) in tissues, leading to widespread organ dysfunction and damage
- **Calcium Pools**
  - Intracellular Calcium
    - Used as an **intracellular signal** (generally 2$^{nd}$ messenger)
    - Induces **enzyme activation** directly, or through action of channels
    - Allows for **muscle contractions** through interaction with Troponin-C
  - Calcium in blood and extracellular fluid
    - ~50% is bound to plasma proteins
    - $[Ca^{2+}]$ = 10,000 x [Free Intracellular Ca]
  - Bone Calcium
    - **Majority of total body calcium** is in bone
    - **99% is** unusable, tied up in the mineral phase
    - **1%** is usable, and is rapidly exchanged with extracellular calcium

**Overview of Regulation**

Calcium must be tightly regulated in narrow ranges. Elevations in calcium result in inhibition of PTH from the parathyroid gland through Calcium Sensing Receptors (CaSR). When Calcium levels fall, PTH synthesis and release is disinhibited. PTH works to increase Calcium and decrease phosphate by bringing in Calcium from the gut and bone, saving calcium in the kidney, and letting phosphate go in the kidney. It also upregulates activation of Vitamin D, which brings in calcium from the gut, bone, and kidneys. The absence of PTH/Vitamin D (in the presence of high calcium) is enough to maintain homeostasis. However, there is Calcitonin, a non-essential regulation hormone, which is activated when calcium levels get high, and acts to block the effects of PTH.

## Calcium Hormones

- **Parathyroid Hormone (PTH) –** "*PTH trashes Phosphate*"

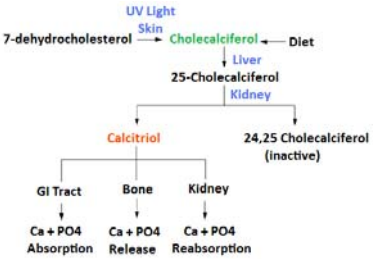



Secreted by
- Parathyroid glands

Regulated by
- **Calcium Levels; ↑[Ca] = ↓[PTH]**; small change in Ca = large changes PTH
- Vitamin D Levels; ↑[Vitamin D] = ↓[PTH]
- Phosphorous Levels; ↑[$PO_4$] = ↑[PTH]

Action
- Stimulates **1-α-hydroxylase** in the **kidney** producing **active 1,25-vitamin D** from 25,vitamin-D; upregulates expression of 1-α-hydroxylase
- **↑ Resorption Ca** from the kidney and **↑Excretion $PO_4$** in the kidney
- **↑Resorption Ca** and **$PO_4$** from bone
  - Goal is to increase Ca levels at the cost of generating Phosphate, which it eliminates through the kidney

- **1,25 vitamin D = 1,25 cholecalciferol = calcitriol**




Cholecalciferol = Inactive Vitamin D
25-Cholecalciferol = Storage Vitamin D
1,25-Cholecalciferol = Active Vitamin D
24,25-Cholecalciferol = Inactive Vitamin D

- Secreted by
  - Vitamin D made by the **skin** in response to **UV light** or **dietary intake**
  - 25,Vitamin D made in the **Liver** via 25-Hydroxylase = *storage form*
  - 1,25 Vitamin D (Active form) made in the **kidney** by 1-α-hydroxylase
- Regulated by
  - **↑PTH** (so ↓Ca) and **↓$PO_4$** stimulate 1-α-hydroxylase, and therefore stimulates *active* 1,25-Vitamin D formation
  - 24-α-hydroxylase converts 25-Vitamin D to the *inactive* 24,25-Vitamin D
  - Must have a **sufficient GFR** to make Calcitriol (↓levels in renal failure)
- Action
  - ↑$[Ca]_{blood}$ at the cost of everything else; **increases Blood Calcium**
  - ↑Ca and $PO_4$ from the GI tract, the Bone, and Resorption in Kidney

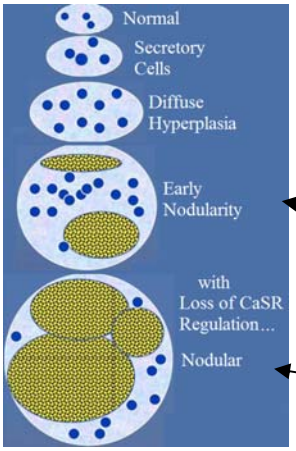
- **Calcitonin** ("Calci-tone-down")
  - Secreted By
    - Thyroid Gland, parafollicular cells, the **C cells** (C cells for Calcitonin)
    - The hormone that does the opposite of PTH is released by a nearby organ
  - Regulated By
    - Poorly understood, **↑Calcium Levels = ↑Calcitonin Levels**
  - Action
    - Exact **opposite of PTH** = **reduce blood calcium levels**
    - ↓Reabsorption of Ca in kidney; ↑Excretion into Urine
    - Inhibition of bone resorption
    - Thyroidectomy produces no abnormality in calcium regulation, while rare Calcitonin secreting tumors do produce hypercalcemia, its precise role is **unknown**, and probably **minor**

## Hypercalcemia Differentials

- **Hypercalcemia ≠ Hyperparathyroidism**, high calcium does not mean high PTH
  - Causes
    - If Patient is **Hospitalized or Sick → Hypercalcemia of Malignancy**
    - If Patient is **Generally Healthy → Primary Hyperparathyroidism**
    - There are other diseases in differential that you must at least consider
      - See "Hypercalcemic Evaluation", and the following info

99% of your hypercalcemia patients

- **High Calcium + High PTH** = *hypercalcemia caused by PTH*
  - Primary Hyperparathyroidism
    - Pathogenesis
      - Majority are **asymptomatic**, **middle aged** (>45), and **women**
      - ↑PTH secretion from a **hyperplasia** or **adenoma,** growth signal coming from within the parathyroid causing a growth of the parathyroid
    - Presentation and Labs
      - Osteoporosis, **Kidney Stones**, and years (chronic) hypercalcemia
      - ↑Serum Ca, ↑PTH, ↓$PO_4$, ↑Urine Ca
    - Treatment
      - **Surgical Removal** of Parathyroid Gland
      - **Calcimimetics** – turn on CaSR without actually being calcium
      - **Bisphosphonates** – ↓osteoclast activity = ↓bone turnover
    - Differentiate from
      - Secondary Hyperparathyroidism
        - Gland Hypertrophy from external growth signals
        - Caused by **Kidney Failure** (most common) / Vitamin D Deficiency
        - No Vit D= No ↑ Ca = Demand for ↑PTH = Hyperplasia
      - Tertiary Hyperparathyroidism
        - **Longstanding Secondary Hyperplasia** results in the development of **irreversible nodular growths** which are **autonomous for PTH secretion**

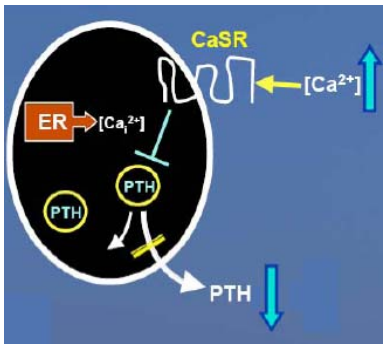


Modified image from our Renal Path Lectures

  - Familial Hypocalciuric Hypercalcemia (FHH)
    - **Autosomal Dominant** Mutation of the **Calcium Sensing Receptor (CaSR)** resulting in a new "set point"
    - "Normal" calcium levels for these patients is **greater than normal**, requiring higher than normal levels of Calcium to induce PTH release
    - Patients **generally tolerate** high calcium well; the only symptom is the **hypercalcemia** itself, an incidental finding on serum panel
    - Findings: **↑Blood Ca**, **↑** or **Normal PTH**, and **↓Urine Ca**
  - Medications
    - **Thiazides** (Hydrochlorothiazide) can worsen the hypercalcemia of primary hyperparathyroidism by decreasing urinary excretion of calcium
    - **Lithium** both **↓Urinary Excretion** of calcium, and **↑PTH Secretion**

- **<u>High Calcium + Low PTH</u> =** *Hypercalcemia not produced by the Parathyroid Gland (PTH)*
  - Hypercalcemia of Malignancy
    - **PTH-rp** (parathyroid related protein) is made by tumors, is structurally related to PTH, but has nothing to do with PTH feedback, which is still intact
      - Net result = PTH feedback inhibition (↓PTH), Unrestrained PTH-like activation (↑PTH-rp), resulting in hypercalcemia (↑Ca)
    - **Malignancy** – direct stimulation of osteoclasts to resorb bone
  - Granulomatous Disease = *Sarcoid and TB, for example*
    - **↑ Extra-renal** (active macrophages) 1-α-hydroxyalse = **↑↑↑**1,25 Vitamin D
    - Vitamin D does its normal thing, and ↑Ca
    - Ca feeds back on PTH, downregulating expression, so ↓PTH
  - Vitamin D intoxication
    - If you **buy** or **eat 25 vitamin D** you do the same thing as in granulomatous disease, just without the extra-renal 1-α-hydroxyalse
- **Milk Alkali Syndrome**
  - Caused by an overingestion of **calcium carbonate ingestion** (say, antacids like Tums)
  - The classic triad is seen: **Metabolic Alkalosis**, **Hypercalcemia**, and **Renal Insufficiency**

**<u>Calcium-Sensing Receptor</u>**



From our Renal Calcium Lecture

Essential in controlling the synthesis and secretion of PTH;

- **Activated by increased serum Calcium**
- **Activation leads to inhibition of PTH**
- Carries the "we've got enough calcium" signal

**Activating Mutations** (gain of function)

- Cause an **autosomal dominant hypocalcemia**
- Serum PTH is low, despite low calcium
- Always says "we've got enough calcium" even when we don't

**Inactivating Mutations** (loss of function)

- Cause an **autosomal recessive hypercalcemia**
- Serum PTH is high, despite the presence of high calcium
- Always says "we need more calcium" even when we don't

**<u>Hypercalcemia Evaluation</u>**

- Step 1: **Repeat Calcium, assess clinical data**
  - Be specific, include albumin or check ionized only
  - Check for medications (Thiazides, lithium) or for other diseases (chronic inflammation)
- Step 2: **Check PTH level**
  - Compare it to calcium levels, is it where it should be? Higher? Lower?
  - Use the Differential Section
- Step 3: **Check Urine Calcium** (really relevant only in ↑PTH and ↑Calcium differentials)
  - If Fractional Excretion of calcium is **less than 0.01** you have **FHH**
  - If Fractional Excretion of calcium is **more than 0.01** you have **Primary Hyperparathyroid**
- Step 4: **Check Vitamin D levels** → intoxication, macrophages/granulomatous, etc.
- Step 5: **Check an ECG** QT interval shortening leading to arrhythmias

PANCREAS - DIABETES (Big Robbins 1189, Baby Robbins 583, Goljan 514)

**Normal Insulin Function**

- Insulin is an **anabolic hormone** necessary for uptake of glucose and amino acids
- Causes glycogen storage, fat synthesis, and protein anabolism
- **Glucose** regulates insulin release
    - ↑Glucose = ↑Glucose into Pancreatic **β cells** via insulin independent GLUT2 channels
    - Glucose metabolism = ATP synthesis = **K+ channel inhibition** = depolarization
        - **Immediate phase** = insulin release (also caused by certain amino acids)
        - **Delayed phase**= insulin synthesis (only glucose does this)
- Insulin binds to its receptor, acts through MAPL and PI-3k pathways to activate its functions

**Type 1 Diabetes**

- Definition
    - Insulin dependent diabetes that results from autoimmune destruction of the β-islets
- Pathogenesis
    - **Autoimmune** disorder following viral infection in patients with genetic susceptibility
        - HLA-DR3 and HLA-DR4 haplotypes are greatest risk
    - CD4+ T cells induce macrophage and CD8 T cells to destroy pancreas - **cellular**
    - Autoantibodies are against the **glutamic acid decarboxylase (GAD)** protein
- Morphology
    - Pancreas is **shrunken**, with **absent or pale β-islets** with deposition of **amyloid**
    - Diabetic macrovascular and microvascular disease present (see later)
- Clinical
    - Usually occurs in the **first decade of life** though all ages groups are possible
    - Presents with **polyphagia** (eating) **polydypsia** (thirsty) and **polyuria** (need to pee) with weight loss despite the eating, and is usually considered "abrupt"
    - Initially, there is no loss of function = "honeymoon period"
    - Eventually, there is total loss of function, **hyperglycemia**, insulin dependence and a risk for **diabetic Ketoacidosis** ensues.

**Type 2 Diabetes**

- Definition
    - Insulin independent diabetes that results from pancreatic "burn out"
- Pathogenesis
    - **Insulin Resistance**
        - Decreased ability for tissue to respond to presence of insulin
            - Downregulation of receptor, dephosphorylation, decreased signals
            - The pancreas must increase production to meet resistance
        - Strong link to **obesity**

    - **Beta-Cell Dysfunction**
        - Continual production of massive insulin leads to burnout
        - Pancreas does not produce insulin in sufficient amounts, despite a hyperglycemia and insulin resistance
        - ↓Insulin production, ↓islet size
- Morphology
    - Start of the disease = normal pancreas
    - Late disease = shrunken, fibrotic pancreas without β-islets
- Clinical
    - Patients are generally **older,** are **obese**, and had symptoms of encroaching diabetes
    - These patients suffer **nonketotic hyperosmolar coma** (opposed to DKA)
    - Treat with oral medications, though may digress to insulin dependence

**Complications of Diabetes**

- **Macrovascular Changes**
    - Increased atherosclerosis and increased risk for stroke, MI, extremity gangrene
    - Occurs in the medium to large arteries
        - Hyaline arteriosclerosis is more profound in diabetes than in patients without
- **Microvascular Changes**
    - Affects arterioles and capillaries, causes Nephropathy, Neuropathy, and Retinopathy
    - Underlying cause is **thickened basement membranes**
        - 3 Mechanisms (at least
            - Nonenzymatic Glycation
                - Amino acids of hemoglobin glycate to excess glucose ($HbA_{1C}$)
                - **Irreversible** transition to **Advanced Glycation End products (AGEs)**
                - Causes protein cross-linking, trapping of lipoproteins in vascular walls
            - Alternate Glucose Pathways
                - Certain tissues do not require insulin for glucose to enter the cell
                - ↑[Glucose] = new pathways, **Glucose → Sorbitol → Fructose**
                - ↑ Osmotic load = water entering = swelling and damage
            - Protein Kinase C
                - ↑Glucose = de novo synthesis of DAG (activates PKC) and PKC itself
                - ↑Intracellular signaling for things like **VEGF** (angiogenesis of retina) or **PAI-1** (reduced fibrinolysis and increased risk for thrombus
- **Neuropathy**
    - Caused by microvascular channels
    - **Distal extremities** lose sensation and motor
    - **Autonomic Dysfunction** causes loss of bladder control and impotence
    - This ↑ risk of infections, ulcers, and is generally inconvenient for the patient

- **Nephropathy**
  - Renal failure is a common cause of death; the kidneys are almost always involved in DM
    - Diabetes is the leading cause of renal failure in the United States
  - Glomerular effects = **fibrosis**, Kimmelstiel-Wilson Nodules, **progressive proteinuria**
    - Microalbuminuria → Macroalbuminuria → Hypertension → Overt Failure
  - Vascular effects = arteriosclerosis and decreased renal perfusion
  - Infection = ↑risk for Pyelonephritis
- **Retinopathy**
  - Proliferative = angiogenesis, new vessels in retina, causes blindness
    - 4th leading cause of acquired blindness
  - Nonproliferative = edema, hemorrhage, no new vessels, damaging but not blinding
  - ↑risk for cataracts and glaucoma (through the Sorbitol pathway)

**Metabolic Complications**

- Classic triad = polyphagia, polydypsia, polyuria
- **Diabetic Ketoacidosis**
  - Occurs in Type I Diabetics, sugar usually ~600-1000 (a super shit ton)
  - ↓Insulin + ↑Glucagon = **Ketone Body Formation** (butyric and acetoacetic)
  - Can cause life threatening **metabolic acidosis**
  - Treat with fluids, insulin (slowly), watch for hypokalemia
- **Nonketotic Hyperosmolar Ketoacidosis**
  - Occurs in Type II diabetics, sugar usually ~400-600
  - Type II Diabetes + Dehydration = hyperosmolar fluid state
  - Enough insulin to prevent Ketoacidosis, not enough to prevent hyperglycemia

| COMPARISON OF TYPE 1 AND TYPE 2 DIABETES | | |
|---|---|---|
| **Characteristic** | **Type I** | **Type II** |
| Named | Insulin Dependent Diabetes Mellitus (IDDM) | Non-Insulin Dependent Diabetes Mellitus (NIDDM) |
| Age | Childhood (<20 years) | Adult (>30 years) |
| Onset | Rapid | Insidious |
| Weight | Thin to Normal | Obese |
| Genetics | HLA-DR3, HLA-DR4 Haplotypes<br>Family history uncommon | Family History Common, no HLA haplotypes<br>African American and Native American at risk |
| Pathogenesis | Cell mediated autoimmune destruction of β-islets = an absence of insulin production<br>Trigger suspected to be a viral mimicry | Insulin resistance followed by β-Cell dysfunction<br>Need more insulin, Pancreas meets it, then burns out<br>↓Insulin Receptor, Insulin Pathway Alterations |
| Clinical Findings | Polyuria, Polydypsia, Polyphagia and Weight loss, usually in kids<br>Nephropathy, Retinopathy, Neuropathy, Cardiovasculr → Accelerated Athero- and Aterio-sclerosis | Recurrent Blurry Vision (retinopathy)<br>Recurrent Infections (Candida, Bacteria)<br>Nephropathy, Retinopathy, Neuropathy, Cardiovascular → Accelerated Athero- and Aterio-sclerosis |
| Metabolic Derangement | DKA – hyperglycemia, coma, ketone bodies (butyric and acetoacetic), sugar > 600 | HNKC – hyperglycemia, coma, without Ketoacidosis, sugars in the 400-600 |
| Treatment | Insulin | Weight loss (upregulates Insulin receptor synthesis)<br>Oral Hyperglycemics (See pharm) |

Modified Goljan table, page 516 of edition 2

PANCREATIC NEOPLASMS (Big Robbins 1205, Baby Robbins 591)

**Insulinoma**

- **Most common pancreatic neoplasm** is the **β-Cell Insulin Secreting Subtype**
    - May cause hypoglycemia (check for C-peptide to ensure endogenous production)
    - Attacks are alleviated by carbohydrate ingestion
- Composed of (usually) singular, yellow-tan masses with well differentiated β-cells
    - β-Cell granules are present on EM and Immunohistochemistry
- Differential against β-cell hyperplasia, as seen in baby's of diabetic mothers

**Gastrinoma (Zollinger-Ellison Syndrome)**

- Encountered this in the GI block
- **Gastrin Secreting Tumor** causes **multiple intractable ulcers** of the stomach and duodenum
- Gastrinomas can occur in the stomach, in the duodenum, or in the pancreas
- Gastrinomas are usually (60%) malignant

**Others**

- Glucagonoma = α-cell tumor, peri/post menopausal women, ↑glucagon levels, anemia
- Somatostatinoma = δ-cells, cholelithiasis, steatorrhea, hypochlorydia, ↑somatostatin levels
- VIPoma = watery diarrhea, association with neural crest tumors
- Pancreatic Carcinoid Tumors = serotonin producing tumor of the pancreas

ADRENAL CORTEX (Goljan 507, Big Robbins 1207, Baby Robbins 593

**Normal Function**

- Adrenal cortex makes 3 hormones, which means 6 disease states (↑ or ↓ in each of the 3)
    - Zona Glomerulosa makes Aldosterone, which resorbs $H_2O$ & Na while excreting K
    - Zona Fasiculata makes Glucocorticoids (Cortisol), regulating sugar metabolism
    - Zona Reticularis makes Androgens (Testosterone), regulating sexual maturation

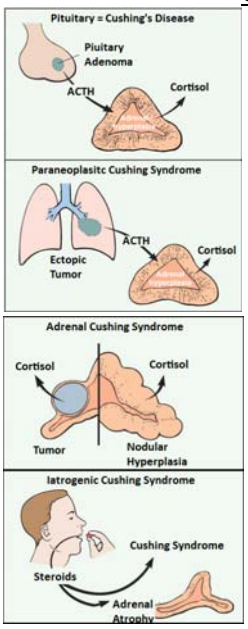
GFR, Salt Sugar Sex,
"It gets better as it goes deeper"

**Image of Normal Signalling**

- Do not memorize for pathology
- Review to look back and realize why some pathways shunt into others
- Most useful for 21-Hydroxylase Deficiency and androgenital syndromes

**Hypercortisolism = Too much Cortisol = Cushing's Syndrome**

- Causes



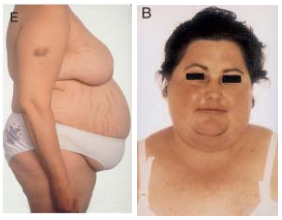

  - **Exogenous Administration** (doctor's give too much), this is the most common cause
    - Administration of glucocorticoids is sometimes necessary; too much = iatrogenic
  - **Caused by the Adrenals** such as an adenoma or carcinoma
    - Autonomous cortisol-secreting adenomas, carcinomas, + hyperplasia account for 20% of endogenous Cushing's Syndrome
    - Independent of corticotrophin; unilateral neoplasms cause **atrophy** of the contralateral gland as corticotrophin from anterior pituitary is downregulated
      - ↑Cortisol = ↓ACTH = ↓Size of Normal Gland b/c Neoplastic Gland = ↑Cortisol
  - **Caused by the Pituitary** such as a Corticotroph adenoma, called **Cushing's Disease**
    - Hypersecretion of corticotrophin found in young life, usually in females
    - Anterior Pituitary adenoma accounts for 70-80% of Cushing's Syndrome
    - ACTH levels are elevated, **bilateral enlargement** of adrenal cortex
  - **Caused by something else** such as ectopic nonendocrine tumors
    - Accounts for 10% of Cushing's Syndrome
    - Associated with **small cell** in the lung, **Carcinoid tumors** (both secrete ACTH)
    - Even tumors that secrete **corticotrophin-releasing hormone (CRH)**
    - Adrenals are **bilaterally hypertrophied** as ACTH is the growth signal

- Clinical Features of Cushing's Syndrome

Page 512 of Goljan's Rapid Review that shows a patient with severe Cushings

  - **Truncal Obesity**, **Moon Facies, Buffalo Hump** are chronic, and are classic triad
  - Weakness comes from selective atrophy of fast-twitch muscle fibers
  - **Glucose Intolerance** as glucocorticoids induce gluconeogenesis, antagonizing insulin
  - **Osteoporosis** and **Wound Healing Delay** are a result of the catabolic effects of cortisol

- Laboratory Diagnosis



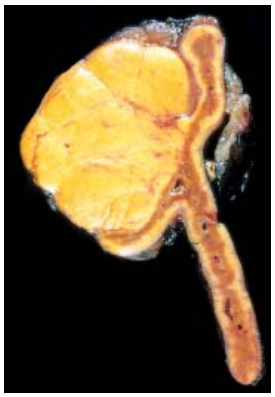
Truncal Obesity and Moon Facies shown in a snipit from MD Consult. Buffalo hump is not present, though rounded face is

  - Image of the adrenals, an image of the pituitary, and a dexamethasone test
  - Adrenals –
    - Unilateral enlargement = primary (in the adrenal) tumor
    - Bilateral enlargement = everything else
  - Pituitary
    - Enlargement = adenoma (pituitary), Cushing's Disease
    - No enlargement = look for something else
  - Dexamethasone test (Dexamethasone is a glucocorticoid, which should feedback)
    - ↓ACTH with test = intact pituitary feedback
    - ↓Cortisol with test = hypercortisolism is under non-neoplastic control

| | Pituitary Cushing's | Adrenal Cushings | Ectopic Cushings | Iatrogenic Cushings |
|---|---|---|---|---|
| Serum Cortisol | ↑ | ↑ | ↑ | ↓ |
| Urine Cortisol | ↑ | ↑ | ↑ | ↓ |
| Low-Dose Dexamethasone | Cortisol Not Suppressed | Cortisol Not Suppressed | Cortisol Not Suppressed | N/A |
| High-Dose Dexamethasone | Cortisol Suppressed | Cortisol Not Suppressed | Cortisol Not Suppressed | N/A |
| Plasma ACTH | Normal to ↑ | ↓ | ↑↑↑↑ | ↓ |

**Hyperaldosteronism = Too much Aldosterone**

- Primary
  - Is an **autonomous secretion** of aldosterone
  - **Conn Syndrome**
    - Most common cause of primary hyperaldosteronism (80%)
    - Is a solitary, unilateral neoplasm secreting aldosterone
    - Eosinophilic, PAS-reactive, laminated cytoplasmic inclusions = **Spironolactone bodies**
  - **Idiopathic Hyperaldosteronism**
    - Genetic overactivity of the Aldosterone Synthase gene
  - **Glucocorticoid-Remediable Hyperaldosteronism**
    - Chimeric fusion between 11-β-Hydroxylase and Aldosterone Synthase
    - When ACTH activates 11-β-Hydroxylase, it also activates Aldosterone
    - Treatment with Glucocorticoids feedsback, ↓ACTH, ↓Aldosterone

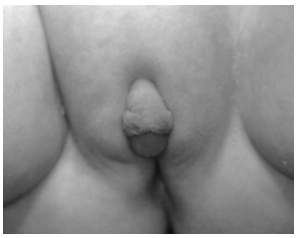


Adrenal Cortical Adenoma. Yellow, encapsulated, solitary mass. May represent any layer of the adrenal cortex, I just happen to show it here.

- Secondary
  - Anything that **induces renin transcription**, activating renin-angiotensin axis, leading to a secondary ↑ in aldosterone
  - Caused by Decreased renal perfusion, aka **decreased blood flow**
    - CHF or Pregnancy (sequestration of blood on the venous side)
    - Renal Artery Stenosis (↓renal perfusion pressure)
- Clinical
  - **Hypertension** and **Hypokalemia**
    - Aldosterone ↑resorption of Na at the cost of K, so potassium is lost (hypo K) while Na, which means $H_2O$, is retained, and expands vascular volume (hypertension)

**Androgenital Syndromes** = Hyper-Androgen Syndromes

- Definition
  - ↑Androgen production leading to **virilization** of female genitalia (ambiguous) or **precocious puberty** in males
- Neoplasms
  - Androgen-secreting tumors are more likely to be **carcinomas** than adenomas
- Congenital Adrenal Hypertrophy
  - **Enzyme deficiencies** in the pathway for glucocorticoids shunt precursors down the androgen line, condition called **Congenital Adrenal Hyperplasia**
    - Deficiency in any of the **Hydrolases** (see image on page 17)
    - **21-Hydroxylase Deficiency** is the most common (80%)
    - **All** are autosomal recessive disorders
  - Activation of cortisol synthesis by ACTH actually results in activation of androgens
    - No cortisol is made, so there is no inhibition of ACTH, so ACTH increases, leading to an ↑in adrenal growth signal (from ACTH) and hyperplasia



Virilization of female genitalia to ambiguous maybe-penis looking structure. High index of suspicion for Congeital Adrenal Hypertrophy, usually 21-Hyrdoxylase Deficiency

- **Complete Deficiency**
  - Salt-wasting syndrome caused by complete absence of 21-Hydroxylase
  - Neither Cortisol nor Aldosterone can be secreted
    - No aldosterone = no Na resorption = no fluid resorption
  - All hormones go down Androgen route
    - Female virilization at birth
    - Requires exogenous mineral and glucocorticoids supplementation
  - ↑ACTH (not enough cortisol made), ↑Androgen (stimulus actually goes here), and Bilateral hyperplasia of cortex (from ACTH stimulus)
- **Incomplete Deficiency**
  - Virilization without Salt-Wasting because some hydroxylase is intact
  - ↑ACTH (not enough cortisol made), ↑Androgen (stimulus actually goes here), and Bilateral hyperplasia of cortex (from ACTH stimulus)
  - Exogenous administration may or may not be required
- **Nonclassic**
  - Asymptomatic, and rare

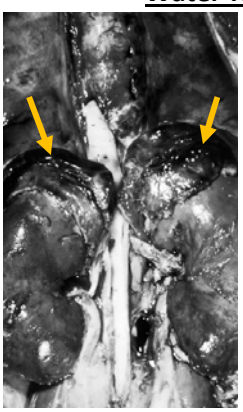
Cortisol = Glucocorticoids
Aldosterone = Mineralcorticoids

ADRENAL INSUFFICIENCY (Big Robbins 1212, Baby Robbins 596)

**Primary Acute Adrenocortical Insufficiency**

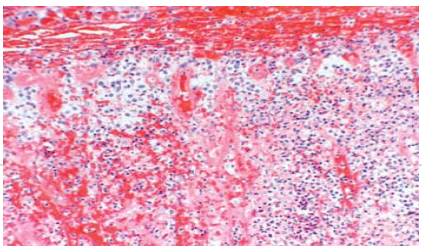
- Any lesion of the adrenal cortex that causes **↓Corticosteroid Production**
- Caused by alteration in glucocorticoids supply or demand
  - **Sudden removal of glucocorticoids**
    - Exogenous administration caused adrenal atrophy, suddenly removing them means there is neither exogenous nor endogenous production
  - **Sudden increase in glucocorticoids demand**
    - Failure to increase dosage in patients with long-standing disease with an increased need for glucocorticoids (stressor)
  - **Massive Destruction** in a normal patient
    - See next heading

**Water-House Friderichsen Syndrome**



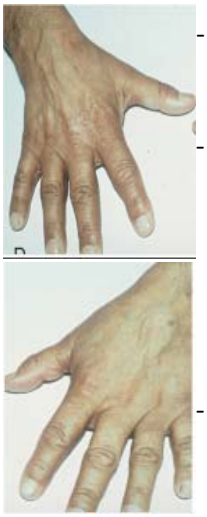
Darkly Hemorrhagic Adrenal Glands in a child

- Rare, catastrophic destruction of the adrenal cortex caused by **meningococcal septicemia**
  - Causes a rapid hypotension, DIC, Purpura, and **adrenal hemorrhage**
- Common in kids, but can occur at any age
- Causes a **massive, bilateral adrenal hemorrhage** beginning in the medulla
- Clinical course is abrupt (because the patient dies) if not caught and treated immediately



Hemorrhagic Cortex with loss of architecture

## Primary Adrenocortical Insufficiency = Addison's Disease



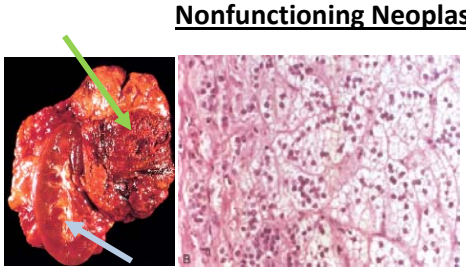
Hyperpigmentation before (top, dark) and after (bottom, lighter) glucocorticoid treatment

- Definition
  - Problem within the adrenal gland that makes it so the cortex cannot produce any hormones, requiring 90% of the adrenal glands to be nonfunctioning or destroyed
- Causes and morphology
  - **Autoimmune** adrenalitis accounts for 90% of Primary Insufficiency
    - May be isolated, part of Autoimmune Polyendocrinopathy Syndrome (APS) type 1 or Type 2.
  - **Infection** either from Candida/Histoplasma (normal) or Kaposi Sarcoma (AIDs)
  - **Metastatic Neoplasms** are rare, though metastasis from breast and lung are possible
  - **Rare genetic disorders** such as Adreonleukodystrophy (neuro block)
- Clinical Manifestations
  - No matter how much signal there is, the adrenals cannot produce glucocorticoids
    - ↓Cortisol and therefore ↑ACTH due to lack of feedback
      - ACTH is made from a molecule that also makes melanin, so ↑Melanin
      - **Hyperpigmentation of the skin** caused by Melanin, byproduct of ACTH synthesis
      - Exacerbates hypotension; cortisol required for catecholamine vasoconstriction
      - **Fasting Hypoglycemia**, cortisol utilized in mobilization of energy stores
    - ↓ Aldosterone
      - **Hypotension**, Hyponatremia, **Hyperkalemia** (no effects of aldosterone)
      - If complete, there is a "salt wasting" syndrome as before
  - All factors lead to hypotension, fatigue, weakness, and hyperpigmentation
- Treatment = Exogenous cortical hormones

## Secondary Adrenal Insufficiency

- Caused by either a **pituitary** or **hypothalamic** dysregulation resulting in ↓ACTH secretion
- Labs
  - Since aldosterone is free from ACTH regulation, **aldo levels are normal**
  - ↓ACTH = ↓Cortisol, with a deficient feedback to activate more ACTH
- Clinical (differential from primary)
  - No salt wasting, so normal tension, sodium, and potassium
  - No overload of ACTH, so no hyperpigmentation
  - Still symptoms of glucocorticoid deficiency
- Treatment = Exogenous cortisol only

## Nonfunctioning Neoplasms *(not really that important, but they are in Robbins)*



Adrenal tumor (green arrow) dwarfs the kidney (blue arrow). Histo shows normal cells against carcinoma

| NONFUNCTIONING NEOPLASMS | |
|---|---|
| **Adenomas** | **Carcinomas** |
| Poorly encapsulated, yellow-orange lesions that lie within cortex or protrude into medulla or through the supracapsular region | **Highly Malignant Neoplasms** that are often large when discovered. Predominantly yellow with significant invasion and even metastasis |
| Larger lesions may be hemorrhagic or cystic | Lesions may be hemorrhagic or cystic |
| **Adjacent tissue is normal** opposed to the functioning adenomas seen before | Can vary in degree of dysplasia, but are **more likely to be functional** than adenomas |

ADRENAL MEDULLA (Big Robbins 1218, Baby Robbins 599)

**Pheochromocytoma**

- Definition
  - Tumor of the adrenal gland that is functioning for the release of catecholamines
- Pathogenesis = Rule of 10s
  - 10% arise in association with other neoplastic syndromes
    - Von Hippel Lindau, MEN 2A, Neurofibromatosis Type 2, Sturge Webber
  - 10% Are **extra-adrenal** occurring in the carotid body
  - 10% of **nonfamilial** are **bilateral** (70% of familial are bilateral)
  - 10% are malignant, though associated HTN is fatal in "benign tumors"
  - 10% Arise in childhood
- Morphology
  - Pale gray or brown on cut surface
  - Tumors are usually very vascular
  - Tumors are generally **well-differentiated**
- Clinical Features
  - Catecholamine release results in **Hypertension**
    - Abrupt elevation in BP associated with tachycardia, palpitations, sweating
    - **Pulsatile** release of catecholamines may cause **episodic** headaches, vision disturbances, tremor, abdominal pain
  - May cause **heart failure**, **stroke**, or **MI**

**Extra-Adrenal Paragangliomas** *(in Baby Robbins but never comes up anywhere else)*

- Pheochromocytomas that occur outside the adrenal glands are called paragangliomas
- Common in the carotid body where they are called chemodectomas
- Occur in the teens and can be multicentric (10%) and can be malignant (50%)
- These are small, well differentiated tumors arranged in nests or cords of Neuroendocrine cells

**Multiple Endocrine Neoplasia Syndrome Type 1 = Wermer Syndrome**

- Caused by a mutation in the MEN gene, coding from **menin**
- Causes the "3 P's"
  - **Parathyroid Hyperplasia**/Adenoma
  - **Pancreatic Hyperplasia**/Adenoma, usually of the islets, usually of β-cells or Gastrin
  - **Pituitary Adenomas** which are usually Prolactinomas
- Presents with features of hyper-whatever-is-hyperplastic (Zollinger-Ellison, Hypoglycemia, Hypercalcemia, Amenorrhea)

**Multiple Endocrine Neoplasia Syndrome Type 2**

- Caused by a mutation in the **RET oncogene**
- **MEN2A** = Pheochromocytoma + Thyroid + Parathyroid (
- **MEN2B** = Pheochromocytoma + Thyroid + Neural Tumors

PENIS (Selection Starting at Big Robbins 1035, Baby Robbins 514) – *all of the penis gets 3 questions, max.*

**Congenital Disorders** (notice nothing is in bold)

- Improper "zipping" of the phallus can lead to either dorsal or ventral urethral openings, termed hypospadias and epispadias, respectively.
- Phimosis is an abnormally small orifice in the prepuce, predisposing to infection, inflammation, and carcinoma

**Benign Neoplasms = Condyloma Acuminata**

- **HPV** strains **6 and 11** induce **genital warts** just as they do in the female genital tract
- It is a sexually transmitted disease, if seen in a child, expect child abuse
- Refer to dermopathy, but there is a hyperkeratosis on top of a rapidly proliferating keratinized sqaumous epithelium

**Sqaumous Cell Carcinoma of the Penis**

- Occurs almost exclusively in **uncircumcised males** who are **coinfected with HPV 16/18**
- It is simply a sqaumous cell carcinoma that occurs on the penis
  - Dysplasia→Anaplasia→ Carcinoma in Situ→Invasion → Metastasis
  - **Bowen's Disease** and Bowen Dysplasia represent premalignant dysplasia, aka they are just carcinoma in situ!
- Presents as an ulcerative plaque on the shaft of the penis
  - Look for **Keratin Pearls** and sqaumous hyerplasia

TESTES AND EPIDIDYMIS (Big Robbins 1037, Baby Robbins 517)

**Congenital Abnormalities**

- **Cryptochordism**
  - Failure of the testes to descend fully, apparent at about 1 year of age
  - Usually unilateral (75%) there may be regressive changes in the contralateral testes
  - The undescended testes represents **↑Risk of Sterility, Hernias,** and **Neoplasms**
  - Surgical correction (orchiopexy) fixes sterility risk, uncertain if it fixes neoplasm risk
- **Regressive change**
  - **Atrophy** of the testes, decreased germ cell development, thickened hyaline, and a preservation of Leydig cells and their testosterone production
  - Associated with Cryptochordism and primary gene defects like Kleinfelter's

## Testicular Torsion

- Testes descend through inguinal canal and are dangling, rather than being attached
- **Torsion** occurs when the testes twirls about the spermatic cord, causing vascular strangulation
- This is a **medical emergency** as the ischemic testes will not spontaneous untwist and will die
- If a patient has one torsion, there is increased risk of torsion on the contralateral side
    - Both get tacked down to the wall when the first torsion is repaired

## Infertility

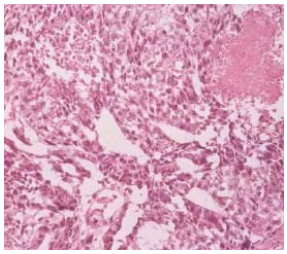
- **Pregonadal** = Pituitary Dysfunction = ↓FSH = ↓testosterone / ↓sertoli cell stimulation
    - Sperm do not get made because the signal never comes from above
- **Gonadal** = broken testes, such as in Kleinfelter's, Agenesis, or Destruction from Radiation
    - Sperm do not get made because the testes cannot respond to the signal
- **Post-Gonadal** = can be congenital (atresia) or acquired (vasectomy or gonorrhea)
    - Sperm is being made, it just cannot be released

GERM CELL TUMORS

## Seminoma


- The **most common** singular germ cell tumor, and most likely to occur on its own
- It is a **bulky, white tumor** that is **well circumscribed** without hemorrhage or necrosis
- It does **not form glands**, though has abundant **seminoma cells** surrounded by a **lymphocytic infiltrate**, minor fibrosis forming lobules, and even the presence of **granulomas**
    - Granulomas, while characteristic for seminoma, are not pathognomonic
- Most seminomas are curable with resection and radiotherapy

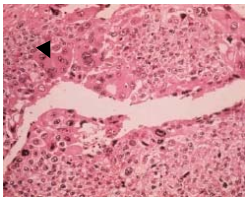
## Embryonal Carcinoma



Highly anaplastic, strongly pleomorphic embryonal cells

- An **aggressive**, **rapidly growing** tumor that is often diagnosed **small**
- These are **poorly circumscribed**, white, and often hemorrhagic
- They carry a **primitive appearance** (embryonal tissue, mesenchyme)
- They are very aggressive, metastasizing to the lymph
- They can produce any marker, since they can turn into any other carcinoma

## Choriocarcinoma



Admixed trophoblasts and a giant cell (arrowhead)

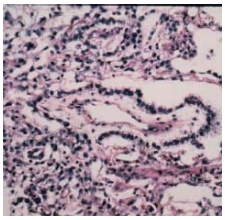
- Very rare in its pure form, this is the same tumor that arises from the placenta
- It is very hemorrhagic composed of **syncytialtrophoblasts admixed with cytotrophoblasts**
- Like the placenta, **hCG levels** will rise, and bizarre cells are often apparent next to normal tissue. Choriocarcinoma secretes human Chorionic Gonadotropin

## Teratomas

In a male, assume teratomas are malignant. In females, assume teratomas are benign

- Constituting 10-15% of call germ cell tumors, teratomas are composed of **2 or more germ layers**, and **does not secrete any marker**
- These can have teeth, hair, skin, etc
- **Malignancy is diagnosed** based on the **level of maturity**; in the testes, they are **always immature** and **always malignant**

## Yolk Sac Tumors / Endodermal Sinus Tumors

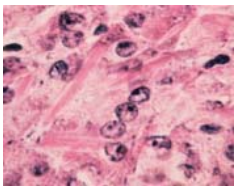


Schiller-Duval Body

- Lowest yield tumor, these are common and have good prognosis in kids < 3 years of age
- They may have **Schiller-Duval Bodies** (cuboidal cells and flat cells)
- The presence of a yolk sac tumor does not alter the diagnosis nor prognosis
- Secretes **Alpha-Feto-Protein (AFP)**

STROMAL TUMORS

## Leydig Cell Tumors



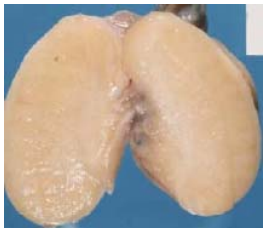
Crystalloids of Reincke

- **Leydig cells** are the cells that elaborate testosterone in the seminiferous tubules
- A Leydig cell tumor produces nothing but Leydig cells, which cause a **hyperandrogen syndrome,** which = precocious puberty.
- There may be a mass of Leydig cells with **crystalloids of Reincke** spread throughout

## Sertoli Cells

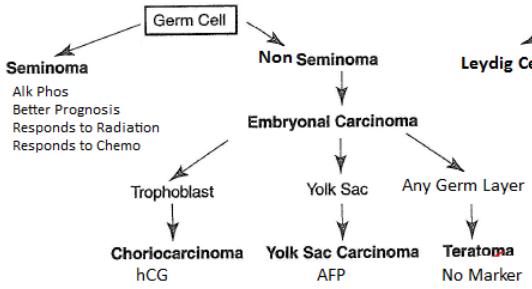
- Lowest yield tumor of this section
- May elaborate testosterone or estrogens, but not enough to cause any symptoms
- They do not make sperm well, and may crowd out good sperm-makers

## Lymphoma



Replaced by lymphoma, no discernable mass can be seen, it has insinuated itself everywhere

- Tumors of old men, which usually are not primary testicular tumors
- **Large**, **white** tumor that invades the tissue, pushing it around, melding with it
  - **Poorly Defined**, **Poorly Encapsulated**, **Poorly Demarcated** white tumor
- This is either a primary lymphoma or a metastasis from somewhere else




Note: Choriocarcinoma secretes human Chorionic Gonadotropin.

Diagram of possible Testicular Tumors. Sertoli intentionally left out.

# Endocrine Path Robbins Outline

BREAST (Goljan 477, Big Robbins 1112, Baby Robbins 551) *Images of subtypes occur throughout*

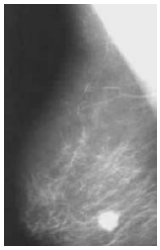
**Developmental Disorders**

- **Milkline Remnants** = "third nipple" that may give rise to extra nipples or breast tissue from the axilla to the perineum. This tissue can undergo hyperplasia during pregnancy or become cancer
- **Congenital Inversion** = a deformity present at birth that might lead an observer to conclude there is invasive carcinoma underneath
- **Reduction** or **Augmentation** are the "boob jobs" that alter breast size or reconstruct tissue
    - Surgery involves the insertion of saline or silicone implants
    - These may rupture causing granulomatous inflammation

**Clinical Presentations of Breast Disease (all disease, not just cancer)**

- **Pain**
    - Most common breast symptom in general, associated with cancer in only 2% of cases
- **Palpable Mass**
    - Second most common breast symptom overall
    - May be adenomas, carcinomas, or cysts
        - ↑ Age = ↓Risk of Mass but ↑Risk that the mass is a Carcinoma
        - Cysts may be aspirated, essentially removing them, "curing" the mass

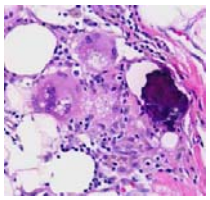
**Nipple Discharge**

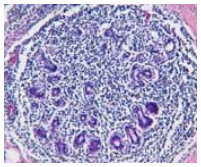

Calcification on mammography.

- Normal discharge may be caused by **lactation**, **Prolactinoma**, and **suckling** (oxytocin)
- Bloody discharge = intraductal papilloma (benign) or ductal carcinoma (malignant)
- Purulent discharge is a sign of infection/acute mastitis, usually Staph Aureus

- **Mammography**
    - Mammograms (<1.2cm) can pick up a lesion prior to palpation (2.4cm)
    - "something" is found in 2% of screened women
        - 30% of the time, it is a carcinoma, usually at the ductal carcinoma in situ stage
        - Cannot distinguish between malignant and non malignant (cyst, calcification)
    - Screening usually begins around 40 unless there is familial risk

**Inflammations**

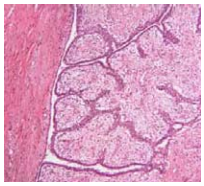

Fat Necrosis. Adipose on the left, inflammation, and large purple nodule (calcification)


Mastitis. Inflammatory infiltrate surrounding atrophic ducts.

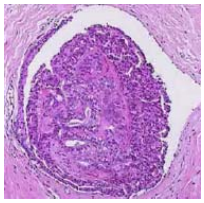
- **Acute Mastitis**
    - Infection of the nipple, usually following breast feeding (which is rough on nipples)
    - Commonly caused by Staph Aureus, cleared with antibiotics, can return to suckling
- **Fat Necrosis**
    - Following **trauma** to the breast, surgery, or radiation
    - Causes fibrosis and **dystrophic calcifications** that appear as cancer on mammography
    - Can also be palpated (like a neoplastic mass) and may cause nipple retraction
- **Mammary Duct Ectasia** *(lowest yield)*
    - Non bacterial infection
    - Presents as a poorly defined mass with viscous secretions and nipple retraction
        - May look like cancer
    - Caused by blockage, dilation, and inflammation of the mammary ducts

# Endocrine Path Robbins Outline

## Benign Breast Tumors


Firboadenoma. Fibrous tissue on the left, Adenoma on the right

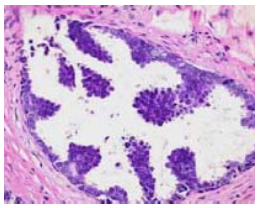
- **Fibroadenoma** (fibro = fibrous, adenoma = gland)
  - Most common benign tumor of the female breast, occurring during reproductive years
  - It is a **well-circumscribed** discrete, **painless** mass of **stromal tissue** (epithelia and CT)
  - **↑in size during pregnancy**, but involutes and calcifies at menopause
  - Is a benign, common positive finding on mammography, though may cause mass effect
- **Phyllodes Tumors** (malignant variant of Fibroadenoma)
  - Usually presenting as **palpable masses** in the elderly (**50s-70s**) made of **stromal tissue**
  - They are most often benign, but may be malignant, seeding the blood to the lungs
  - The **epithelial component overgrows**, forming slits and groves (**leaf-like pattern**)


Intraductal Papilloma Papillary growth within the duct

- **Adenoma**
  - Generally well differentiated, well-demarcated, benign tumor of glandular elements
    - Tubular Adenoma = Regular Tubules resembling **resting** lobule
    - Lactating Adenoma = Tubulo-acinar structures with pronounced secretory changes, seen in pregnancy and lactation. These tumors may be self-sustaining
- **Intraductal Papilloma**
  - Discrete, benign papillary tumor arising in a mammary duct, usually **unilateral**
    - There is periductal inflammation and sclerosis/fibrosis
    - There is usually a **bloody nipple discharge** (differentiate from invasive ductal)

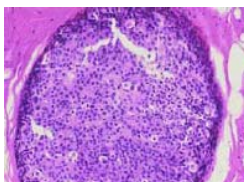
CARCINOMA OF THE BREAST (Big Robbins 1129, Baby Robbins 552)

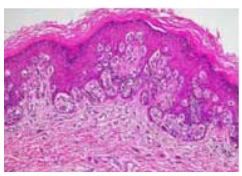
## Incidence and Epidemiology


Intraductal Carcinoma in Situ with growth into the lumen, basement membrane is intact

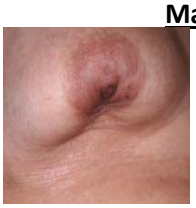
Generalities
- Breast cancer = number 1 nonskin cancer, and number 1 nonskin cancer killer in women
- A woman who lives to 90 has a 1/8 chance of developing breast cancer

Risk Factors
- **Exposure to estrogen**
  - Age of menarche; early menarche = ↑Risk
  - First live birth; nullipara (no babies delivered) = ↑Risk
  - First-Degree Relatives; Genetic/Unknown mechanisms, Mom or sister = ↑ Risk
  - Post Menopausal Administration; replacement therapy = ↑Risk
  - Obesity/Cirrhosis; ↓metabolism of estrogen = ↑ Risk
- Race = Whites (7%) worse than blacks (5%) worse than Asian/Hispanic (4%)
- Toxins = radiation (treatment of cancer or the A bomb), smoking, or alcohol
- **Genetics**
  - Germ line mutations account for about 10%
    - **BRCA1** (breast in women) and **BRCA2** (colon and breast in men)
    - **ERB2** is a prognostic marker for ↑risk of carcinogenesis and malignancy
  - Autosomal-Dominant Tumor-Suppressor Loss-of-Function Mutations
    - CHEK2, **p53** (Li-Fraumeni Syndrome), others
  - 70% are idiopathic familial breast cancer


Intraductal Carcinoma in Situ with a filled lumen, but the basement membrane is still intact


Paget's Disease, Dark nuclei with clear cytoplasm within the epidermis

## Major Prognostic and Predictive Factors


Nipple Retraction

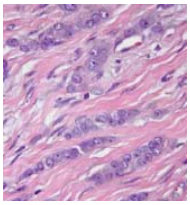

Paget's Disease

- **Invasive vs Carcinoma in Situ** –
  - In situ tumors have not penetrated the basement membrane, and cannot metastasize
  - In situ tumors, once they seed or penetrate basement membrane, are Invasive
  - **Invasive worse than In situ**
- **Distant Metastasis** *(M of TMN, Most Important For Staging)****
  - Worse prognostic marker, cure is unlikely, though remission is possible
  - There are no valves in central veins, so spread can be to lungs, bone, brain, adrenals, liver, kidney, etc.
  - Fortunately, with screening, few women present with distant metastasis
- **Lymph Node Status** *(N of TMN, Second Most Important for Staging)****
  - Outer Quadrant Tumors (Most of the Breast) drains into the **axillary nodes**
    - Where most palpable lesions are first identified, NOT primary lesion
  - Inner Quadrant Tumors (Some of the Breast) drains into the **internal mammary nodes**
  - **Sentinel Nodes** are biopsied or traced
    - Negative Sentinel nodes yields a better prognosis
    - Negative sentinel nodes may avoid radical mastectomy

| STAGE | DEFINITION | 10 yr survival |
|---|---|---|
| Stage 0 | Carcinoma in situ | 99% |
| Stage I | < 2 cm | 75% |
| Stage II | 2-5 cm, OR axillary node positive | 50% |
| Stage IIIa | > 5 cm, or fixed nodes | 27% |
| Stage IIIb | Ca spread to chest wall or skin or spread to internal mammary nodes | |
| Stage IV | Distant metastases | < 10% |

- **Tumor Size** *(T of TMN, Least important for Staging)****
  - If < 1cm (detectable only by mammography) generally have no lymph involvement and a prognosis similar to women without a mass
  - If >2cm (detectable by palpation) lymph nodes are generally involved and prognosis falls

## "Minor" Prognostic and Predictive Factors (not all in Robbins included here)


Invasive Lobular carcinoma, bland cells all lined up, one after the other

- **Estrogen Receptor (ER)** and **Progesterone Receptors** (**PR**)***
  - Positivity is generally the rule, and offers a target for hormone therapy
  - Response to hormonal therapy ↑ with the more receptors there are
- **Her2/Neu aka ERB-B2*****
  - The presence of this RTK conveys a worse prognosis
  - Visualized with FISH or Immunohistochemistry
  - Offers a target for use of **Herceptin/Trastuzumab**
- **Mitotic Figures** and **DNA Count**
  - ↑ Proliferation = ↑Risk for mutation and loss of cell cycle regulation = poor marker
  - ↑ or ↓ in DNA count = abnormal cells = poor marker
- **Histologic Subtypes** (what our lecture was on, and is a small table on Baby Robbins 553)
  - This is a chart on the next page, adapted from Goljan page 482

## Fibrocystic Change (Image) versus Invasive Carcinoma (See CD)


- Most common finding in a mass of a breast = Fibrocystic change > Normal Breast > Carcinoma
- **Nonproliferative Fibrocystic Change** carries **no risk** of carcinoma
  - Fibrosis, Cysts, Apocrine Metaplasia, Adenosis, Apocrine Metaplasia
- **Proliferative Changes** carry **increased risk** for carcinoma
  - **Atypical** ductal or lobular hyperplasia, Papillomas
- Carcinoma is usually **singular, unilateral** without changes in menstrual cycle
- Fibrocystic changes is usually **multiple, bilateral** with changes in menstrual cycle

MALE BREAST

**Gynecomastia**

- Enlargement of the male breast, and indicator of **↑Estrogens and/or ↓Androgens**
- Found either as a side effect of drugs, in **cirrhotic liver disease**, Kleinfelter's, or puberty
- Benign proliferation of both epithelial and stromal components of breast tissue

**Carcinoma**

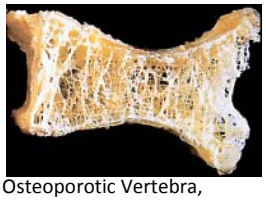
- Extremely rare, almost requiring the BRCA2 mutation (male breasts do not grow and involute as do females breasts during reproductive cycles)
- Same histologic variants, generally a poorer prognosis because reduced breast tissue allows chest wall or thorax invasion more easily; matched per stage, life expectancy is the same

| TYPES OF BREAST CANCER | |
|---|---|
| **Types** | **Characteristic** |
| NONINVASIVE | |
| Ductal Carcinoma In Situ (DICS) | Nonpalpable masses that come in variable forms: **Cribiform** (Sieve-like) and **Comedo** (necrotic center)<br>Have not penetrated the basement membrane, but are full thickness of dysplastic **ductal cells**<br>Commonly contain microcalcifications and 1/3rd will eventually invade |
| Lobular Carcinoma In Situ | Nonpalpable, if found, virtually always an incidental finding while looking for something else<br>**Lobules** are distended with bland neoplastic cells<br>1/3rd of these tumors will invade, and there is ↑risk for the same carcinoma in the opposite breast |
| INVASIVE | |
| Invasive (Infiltrating) Ductal Carcinoma | These are **ductal tumors** that have penetrated the basement membrane and are termed infiltrative<br>This is the **most invasive** cancer with the **worst prognosis**<br>They are stellate-shaped, sometimes with a **stellate scar** in the center of the tumor<br>**Desmoplasia** is the result of reactive fibroplasias and are **hormonally dependent** |
| Ductal Carcinoma, Tubular Subtype | Develops in the **terminal ductules** resembling a the ductules of a resting (non-secreting) lobule<br>With one, there is increased risk of carcinoma on the opposite side, better prognosis than Invasive Ductal |
| Ductal Carcinoma, Mucinous Subtype | Usually occurs in the **elderly** , better prognosis than Invasive Ductal<br>Neoplastic cells are surrounded by extracellular **mucin**, making the cells away from blood vessels |
| Ductal Carcinoma, Medullary Subtype | **BRCA1** Mutation associated<br>Bulky, soft tumor with large cells and lymphoid infiltrate, better prognosis than Invasive Ductal |
| Invasive (Infiltrating) Lobular Carcinoma | Invasive carcinoma composed of uniform cells resembling those of lobular carcinoma in situ<br>20% occur bilaterally, constituting 10% of all carcinomas<br>Tumor cells that are bland lining up in single file |
| Paget's Disease of the Nipple | Extension of DCIS into lactiferous ducts and skin of the nipple producing a **scaly rash** of the nipple<br>There may or may not be **nipple retraction**, but somewhere underneath Paget's is a primary tumor<br>Large pale-staining cells within the epidermis of the nipple, called **Paget's Cells** which are **intra-epidermal** |
| Inflammatory Carcinoma | When **tumor emboli block lymphatics** it causes local lymphedema – its already in the lymph!<br>Presents with dimpling of the skin, like an orange, called **peau d'orange**<br>Bears an extremely poor prognosis, and is usually the most invasive, worst tumor **= invasive ductal** |
| Other benign and malignant neoplasms are presented in lecture, with images | |

BONE (Big Robbins 1282, Baby Robbins 634, Goljan 522)

**Osteoporosis** – *most common bone disease in the US*

Normal Vertebrae, thick Trebecula



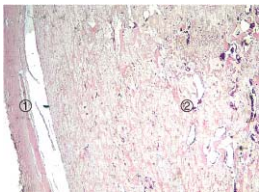
Osteoporotic Vertebra, Shrunken with a loss of Trebecula (flimsy)

- Definition
  - Reduction in bone mass owing to small but incremental losses occurring with the constant turnover of bone (osteoclasts are winning over osteoblasts)
- Pathogenesis
  - **Osteoblasts** build bone, **Osteoclasts** clear bone
  - Things that stimulate osteoblasts, stimulate the building of bone
    - Physical activity (impact on bones)
    - Estrogen stimulation
    - Requires that calcium and genes be sufficiently present to mineralize bone
    - Reach a **peak bone mass** sometime during late childhood, from there, its downhill
  - Things that stimulate osteoclasts stimulate the clearing or loss of bone
    - ↓Estrogen = ↑IL-1, IL-6, and TNF-$\alpha$ = ↑RANK cytokine = ↑Osteoclast Activity
      - Menopause is a big deal with bone loss, women are at increased risk
    - Decreased physical activity and a sedentary life style with age
- Morphology
  - The entire skeletal system is involved
  - Cortex and Trabeculae are thinned, Haversian System is widened
  - Residual bone is of normal composition
- Clinical

Risk factors are being Female, Post Menopause, Being Old, Having Cushings, and a Lack of Exercise

  - **Women > Men,** usually occurring some time after menopause (**senile osteoporosis**)
  - Microfractures cause pain while loss of bone causes shrinking
  - **↑ Risk of Fractures** in the wrist, hip, and vertebrae; "Pathologic Fractures"
    - Remains asymptomatic and undetectable until a bone breaks
- Treatment
  - Calcium + Estrogen can maintain bone, but with ↑risk of Breast Cancer with Estrogen

**Osteopetrosis**




(1) Normal Cortex with (2) Spongiosa filling the medulla, where there should be hematopoietic stem cells

A disease of **too much bone** caused by a genetic defect that **inhibits osteoclasts**

Osteoblast activity lays down mineralized bone into the marrow, essentially eliminating it

- Extramedullary hematopoiesis must occur (in the spleen) leading to organomegaly
- Pancytopenia causes **anemia** and **risk for infections**

Bone is **brittle** and easily broken, like a piece of chalk (**chalk stick fracture**)

- Most often cause of postpartum mortality

Bone is continually made

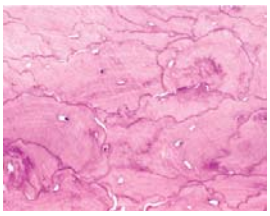
- May appear as a tumor, causing **intracranial deficits** or **compression syndromes**

**Achondrosis**

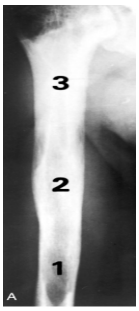
**Autosomal dominant** gain-of-function mutation in **fibroblast growth receptor** causing premature fuston at the growth plate resulting in normal head, normal spine, but **short arms and legs**.

**Paget Disease (Osteitis Deformans)** *Board Favorite according to Kaplan*

- Pathogenesis
  - Infection with a **parvovirus** may lead to inflammatory processes
  - Occurs in three phases
    - *Osteolytic Phase* – carving out a giant whole in the bone
    - *Mixed Phase* – radical, uncontrolled rebuilding of bone which the clasts carved out
    - *Sclerotic / Quiescent* – bone is mostly sclerotic, and no bone cell activity is noted
  - The result is a **gain in bone mass** though it is unfortunately unstable


Mosaic pattern of lamellar bone development in Paget's Disease

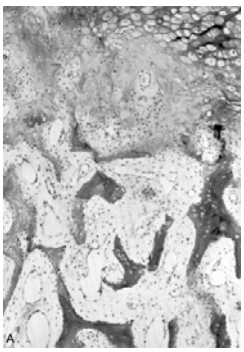
- Morphology
  - Bones are **enlarged**, but are structurally unsound, lending to fracture's
  - The **mosaic pattern** of lamellar bone is classic for Paget's Disease
    - Cement lines should all be going the same way, but here they go every which way



Paget's of the humerus. 1 shows the osteolytic stage, 2 the mixed, and 3 the quiescent stage

- Clinical
  - Diagnosed on an X-ray and lab findings
    - X ray = enlarged, thick bone with a thickened Trebecula and cortex (sclerosis, 3)
    - X ray = empty, hollow bones, near the sclerotic bone (Osteolytic phase, 1)
    - X ray = multiple stages of the same disease in the same bone (image)
    - Lab findings = ↑Alk Phos (usually a marker for Biliary Dz but it can also be bone)
  - ↑ Risk for fractures and compression syndromes (Cranial Nerve Palsy)
  - **Lion-Like Faces** (growth of the bones in the head, "**hat/shoes don't fit anymore**")

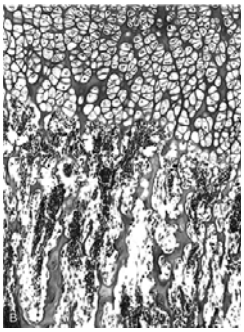
**Rickets and Osteomalacia** *"Silly Osteomalacia, Rickets are for kids!"*



Ricket's Bone

Definition
- Osteopenia caused by insufficient Vitamin D

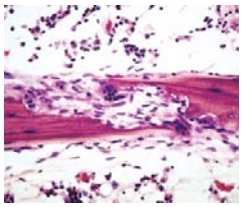
Pathogenesis
- Vitamin D is made first in the sun, then converted in the liver, and finally activated in the kidney by 1-α-hydroxylase to 1,25-CholeCalciferol
- If there is insufficient dietary intake or sunlight exposure, there is a ↓ Vitamin D
  - ↓ Vitamin D = Hypocalcemia = activation of PTH
    - PTH = Bone resorption (loss of bone), Phosphate Excretion (impaired remineralization of bone) and ↑Vitamin D (which is good)
- It is the **resorption of bone** combined with **impaired remineralization of bone** that causes disease


Normal bone

Morphology (basically nothing for Osteomalacia, but a whole lot for kids)
- There is a loss of the cartilage alignment at the epiphyseal plates (Rickets)
- There will be a bowing of the joints (Rickets)
- Classic **Pigeon Breast Deformity** from the bending in of ribs, **Harrison's groove** from the pulling in of the diaphragm, and **square head features** are classic of Rickets
- The most classic appearance in Osteomalacia is **Osteopenia** predisposing patients for fractures since in adults, there is no growth of bone anymore

Clinical
- Essentially the same for any Osteopenia

**Hyperparathyroidism**


osteoclasts boring into the trebecula

Either primary or secondary, calcium is resorbed from bone, producing **osteitis fibrosis cystic**
- Unabated osteoclasts activity predisposes to microfracture, hemorrhage, and cyst formation around fibrosis from healing wounds

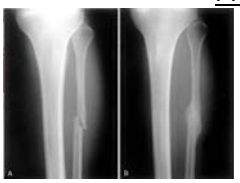
Constant fracture causes the influx of **giant cells** with **fibrosis** or reparative changes
- ↑Vascularity, Hemorrhage, and Presence of Cells is called a **brown tumor**
- See Hyperparathyroid Section for more information on Parathyroid Diseases

**Renal Osteodystrophy**

- Chronic renal failure leads to an increase in osteoclastic activity
  - Lack of vitamin D = ↓ Calcium = ↑PTH = ↑Osteoclasts
  - Metabolic Acidosis from renal failure = ↑Osteoclastic Activity
- Deposition of **Calcium** and **Aluminum** (iatrogenic, dialysis) into other organs common
- Also the presence of **amyloid** in the bones

**Fractures**

- Generally the result of significant trauma, they can be exacerbated by bone degeneration
- **Well-Aligned**, **Incomplete** (Greenstick), and **Closed** (intact skin) heal well and rapidly
- **Comminuted** (Crushed bone) or **compound** (open skin) heal poorly and slowly
- Process
  - Organization of the hematoma into a **procallous**
  - Reactive mesenchymal cells turn the procallous into a **firboconnective callous**
  - Eventually ossification results in a **osseous callous**
  - The callous is remodeled just as normal bone is until it is repaired


Fracture and Callous

**Pyogenic Osteomyelitis**

General: Staph Aureus
Sickle Cell: Salmonella
Sexual: Neisseria
Spinal Cord: TB

- Infection of the bone, presenting as a **febrile** infection with **pain**, tenderness, and heat
- Caused by a hematogenous spread or direct inoculation (biopsy, Intraosseous Access)
- Most common in everyone is **staph aureus,** Most common in sickle cell is **salmonella**
- X-ray changes are minimal to start, but may cause abscess and loss of bone, ↑risk for fractures

**Tuberculous Osteomyelitis**

- Tuberculosis gets into the skeletal system and forms destructive necrotizing granulomas
- When it is in the spine (low lumbar spine), it is called **Pott's Disease**

**Osteogenesis Imperfecta** = Brittle Bone Disease, "Mr Glass Disease"

- Autosomal Dominant defect in the **synthesis of collagen type I**
- **Pathological fractures** at and following birth, **blue sclera, deafness**
- Commonly confused with child abuse
- Fractures of the ossicles can lead to **hearing abnormalities**

There are multiple types. *Know Type 1 is as described, and that Type 2 recessive and fatal.*

Note: FEMALE PATHOLOGY / STDS, was not included in the original series. We just didn't have enough time given the Shelf, Boards, and our own studying. Instead, we added this Kaplan Overview of the material, rather than reading all of Robbins to write up an Outline.

VULVA

**Condyloma Acuminata**

- Occurs in males and females, and are **genital warts**
    - Verrucous wart-like lesion occur on the vulva, perineum, and vagina
- Caused by **HPV** serotypes 6 and 11
    - The nuclei are crinkled and surrounded by a halo
    - **Koliocytosis** of the epidermal cells

**Third Nipple**

- Benign tumor that **occurs along milk lines**
    - Looks like an intraductal papilloma of the breast

**Extramammary Paget's Disease of the Vulva**

- Usually is on the labia majora
- There will be a **crusting, Erythmatous rash,** with an **intra-epidermal spread** of a tumor
    - It is **not associated** with underlying malignancy
    - This is in direct opposition to the Paget's Disease of Breast where there is almost AWLAYS an underlying tumor

VAGINA

**Vaginal Adenosis**

- "Glands in the Vagina"
    - Vagina should be non-keratinized stratified sqaumous epithelium
    - If you see glands, it is Vaginal Adenosis
- Develops in women who were exposed to **DES in utero**
    - **DES** is an old anti-abortion medication (which didn't work AND caused teratogenicity)
- ↑Risk for **adenocarcinoma** of the Vagina
    - **Clear Cell Adenocarcinoma** is the real useful link to DES

**Embryonal Rhabdomyosarcoma** (Butriyodes)

- Occurs in **infants** or **children** with a **grape-like tumor mass** coming out of the vaginal orifice
- This is a **Rhabdo-myo-sarcoma**
    - A tumor of **skeletal muscle** that stains with **desmin, actin**, and **vimentin**
    - Tumor is elongating and has cross-striations just like muscle

PELVIS

**Pelvic Inflammatory Disease**

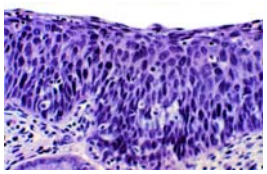
- This is a sequella of an **infection** causing **pelvic pain**
  - Commonly **Neisseria** or **Chlamydia**
    - Neisseria Gonorrhea = chocolate agar, nonmotile, gram negative coccus
    - Chlamydia Trachomatis = obligate intrallcellular organism, gram negative rod
    - Trhicomonas Vaginallis = flagellated protozoan, usually does not cause PID
- Can **ascend to fallopian tube** called "**salpingitis**"
  - Causing lateralization of pain to one side
  - This is an infection, which can cause an abscess in the fallopian tube
    - Fistula formation is possible
  - This is an infection, with subsequent inflammation, which can lead to **scarring**
    - Scarring can produce **infertility** or narrow the lumen causing **ectopic pregnancy**
    - Fertilization occurs at the ampula, ectopic pregnancies occur at ampula
- Can enter the peritoneum
  - Firstly causes peritonitis (rebound tenderness) or **adhesions**
    - Adhesions can cause GI obstruction
  - Can secondly cause an odd sequella of ascending fibrotic strings to the liver
    - Called **Fitz-Hughes-Curtis** disease
    - A "Violin String Lesion"

TUMORS

- Incidence
  - Endometrial > Ovarian > Cervical
- Mortality
  - Ovarian > Endometrial > Cervical
    - We detect cervical carcinoma in situ with pap smears, so identify it, and remove it

**Cervical Cancer**

- Effectively induced by **HPV strains 16 and 18**
  - Brings with it its own proteins **E6 inhibits p53** and **E7 inhibits Rb**
  - Allows unrestrained growth through the first checkpoint
- Morphology
  - **Pap Smears** identify this tumor in its early stages
  - Dysplasia → Carcinoma In Situ → Cervical Cancer takes 20 years
    - Dysplasia = abnormal cells
    - Carcinoma In Situ = The entire thickness is cancer without invasion
    - Invasion = breaking through of the basement membrane
  - Look for the typical signs of cancer (invasion, dark cells, ↑N:C ratio, anaplasia)


Carcinoma In Situ

UTERUS

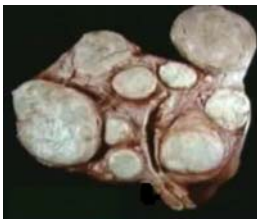
**Endometritis**

- Is defined as an **inflammation of the endometrium**
    - Look for **plasma cells** in the wall of the endometrium; pathognomonic
- **Intrauterine Device** use (IUD) predisposes for Endometritis
    - **Actinomyces** grows on IUD

**Endometriosis**

- Presence of the **endometrial glands stroma outside the uterus**
    - Effects women in their reproductive age
    - Goes to any organ, but most often occurs on the ovary, with pouch of douglas, fallopian tubes, and peritoneum going in close behind
- You will see red-brown lesions called **chocolate cysts** (hemolyzed blood)
    - Each month the ectopic endometrium responds to hormones
    - It grows, then dies, and bleeds
    - Instead of exiting through the vagina, it just resorbed
- Causes **severe menstrual pain** and can cause pain during intercourse or defectation

**Leiomyomas** (Fibroids)


Multiple, white/tan trebeculated lesions on all surfaces of the uterus

- These are **benign tumors** of **smooth muscle**
- They grow during reproductive years and shrink after menopause
- They are **large, white/tan**, **trebeculated** structures with a **whirling pattern**
- Can be serosal (palpable from abdominal palpation), intramural, or submucosal
- More common in **African Americans**.
- Causes infertility, vaginal bleeding, and pain, but can be easily resected
- Malignant Variant = Leiomyosarcoma
    - Spread hematogenously
    - Has the same presentation and description of fibroids, but metastasizes

**Endometrial Carcinoma**

- Most commonly presents as **post menopausal vaginal bleeding**
- Risk factors are caused by **increased exposure to estrogen**
    - HTN, Diabetes, Nulliparid Uterus, Early Menarche, Late Menopause
    - Estrogen causes endometrial hyperplasia
    - Women who use **estrogen replacement therapy** or **tamoxifen** for breast cancer are inducing endometrial hyperplasia, predisposing to carcinoma
- Don't forget about Lynch Syndrome (HNPCC) from GI tract that causes multiple tumors everywhere
- Depth of invasion (if no mets) upon diagnosis has the strongest prediction of prognosis

OVARY

**Polycystic Ovarian Disease**

- Effects **young women** early in their reproductive life
    - Presents with **amenorrhea, hirutism,** and **obesity**
- Not really sure of the cause, but we do know that there is a increase in FSH and LH that leads to an overproduction of testosterone
- It is a **bilateral disease** that produces **benign follicular cysts**
- Treatment is hormone therapy

**Ovarian Tumors**

- Epithelium
    - **Cystadenomas**
        - Are benign large cystic tumors
        - Benign tumors have **one or two** cystic spaces, which is usually **smooth** without nodules, masses, or papillary structures
        - The lining cells could either be **serous** (produces watery fluid) or **mucinous** (which produce mucous)
    - **Cystadenocarcinoma**
        - Are malignant MASSIVE cystic tumors (125 lbs big)
        - Malignant tumors have **multiple cystic spaces** (complex and multiloculated) with **solid nodular areas** and **papillary regions**
        - ↑ Risk with BRCA-1 and Lynch Syndrome
        - Tumor marker of choice is **CA-125**
        - Spreads by **seeding**
- Ovary
    - **Teratoma**
        - Is assumed to be **mature** and **benign** in a female
        - Occur in young women, are usually unilateral, well circumscribed, and removable
        - Consists of **all three germ cell layers** (ectoderm, mesoderm, and endoderm)
            - If there is a presence of thyroid tissue it is called **Stroma Ovarii**
    - **Dysgerminomas**
        - Refer to seminomas, they are the same thing as in males
        - Responds to radiotherapy
    - Yolk Sac
        - Produces **AFP**
        - Same as male pathology
    - Chorio
        - Produce **B-HCG**
        - Same as male pathology

- Stroma
    - **Ovarian Fribroma**
        - These are a **solid white, unilateral** adnexal mass
        - There is an increased risk of Meeg Syndrome with a pleural effusion in addition to ascites and the fibrous stroma of the ovary
        - Is larger than the normal ovary, but not as large as, say, the cyst tumors
        - Can release **hormones** and **steroids** (estrogens)
    - **Granulosa Cell Tumor**
        - Granulosa Cells produce **estrogen**
        - If prepubertal, then there is **precocious puberty**
        - If postpubertal, then there is a risk for **abnormal menses**
        - If post menopause, then there is a risk for **endometrial carcinoma**
        - Granulosa cells form the **follicle** around the released ovary
    - **Sertoli-Leydig**
        - Sertoli-Leydig cells produce **androgens**
        - Causes a **virilization** of baby, if mom is pregnant
            - Virilization cannot happen in the adult female (hirsutism maybe)
            - If ↑androgens circulating with a female embryo → virilization
    - **Krukenburg Tumor**
        - Metastasized signet ring cell of the stomach

GESTATIONAL = COMPLETE VS PARTIAL MOLES

**Complete Moles**

- An egg **without a nucleus** is fertilized by a **normal sperm**
- A complete mole has a completely normal set of chromosomes (**46,XX**)
- There is **no fetal tissue** and instead there is a **grape like mass**
- Small risk of transformation to **choriocarcinoma**

**Partial Moles**

- A **normal egg** is fertilized by **two sperm** resulting in **triploidy** (usually)
- There **is fetal tissue** and no grape-like mass
- There is **no risk of cancer**

NUTRITION/ENVIRONMENTAL was a self study we just didn't get to at all. Instead, we included it in the rapid review sheets at the end.

| THYROID | | |
|---|---|---|
| **Disease** | **Disturbance** | **Notes/Character/Path** |
| Hashimoto's Thyroditis | Thyroditis | **Autoimmune** disorder with **Anti-Thyroglobulin** and **Anti-Peroxidase Antibodies**<br>**Lymphocytic Infiltrate** with formation of multiple **Germinal Centers**, Fibrosis<br>Hurthle Cells may be present, and are pathognomonic; Hashimotos Hurthle<br>Affects **women** in their **40s-60s**, with an initial hyperthyroid followed by hypothyroid |
| Subacute Thyroditis (Granulomatous) | Thyroditis | **Postviral** (Coxsackie, Adenovirus) **autoimmune** destruction of thyroid (women > men)<br>Mononuclear Infiltrate, **Granulomas**, **Giant Cells**, and **Naked Colloid**<br>**Painful thyroid mass** with a **self-limited** hyperthyroid → hypothyroid → normal flow |
| Subacute Lymphocytic Thyroditis (Painless) | Thyroditis | **Postpartum** thyroiditis that causes **painless enlargement** and **hyperthyroidism**<br>Hypothyroid follows in 50% of the cases<br>There is **no germinal center** and **no clear antigen** identified |
| Riedel Thyroditis | Thyroditis | Rare, poorly understood **fibrosing** thyroiditis → glandular atrophy and **hypothyroid**<br>May invade locally, causes stricture or fibrosis of nearby structures |
| Graves | Auto | **Autoimmune** disorder with **TSH-Receptor Stimulating IgG** (activates TSH-R)<br>Causes **thyrotoxicosis**, **follicular hyperplasia**, **opthalmopathy**, **dermopathy**<br>IgG activates receptors, so **↑T3/T4**, **↓TSH** → heat intolerance, exophthalmos<br>Demonstrates **scant colloid** (it gets used), and a **symmetrically enlarged** thyroid with **intact capsule** and **papillary fold** |
| Diffuse Nontoxic Goiter | Goiter | *Endemic* = **iodine deficient diet =** ↓T3/T4 and compensatory ↑TSH<br>*Sporadic* = **iatrogenic T3/T4 deficiency**, cabbage, puberty, pregnancy<br>**Hyperplastic Stage =** Symmetrically enlarged, scant cytoplasm, hyperplastic follicles<br>**Colloid Involution** = ↑Colloid, recession of hyperplastic follicles<br>Generally euthyroid, though may cause a mass effect |
| Multinodular Goiter | Goiter | Continued Hyperplasia and Involution of Simple Goiters = Multinodular Goiters<br>May be **nontoxic** (just big and ugly), or rarely **toxic** (self-sustaining, T3/T4 producing)<br>**Plummer Syndrome** = thyrotoxicosis from Multinodular Goiter, it is late and rare |
| Adenoma | Neoplasm | **Functional Adenomas** have mutation in **TSH-R** or **$G_s$** protein that = "always on"<br>Well-demarcated with a **well-defined capsule** (no invasion)<br>May cause mass effect, but there is **no multinodularity**<br>"**Cold**" nodules on radio-iodine administration, they are **benign** |
| Papillary Carcinoma | Neoplasm | **Most common carcinoma** of the thyroid, caused by **ionizable radiation**<br>Demonstrates **Orphan-Annie Nuclei**, Psammoma Bodies, and Nuclear Inclusions<br>Singular Mass, **excellent prognosis**, papillary architecture not required |
| Follicular Carcinoma | Neoplasm | Link to **multinodular goiters** and **iodine deficiency** (all three are linked)<br>Spread **hematogenously** rather than **lymphatically**<br>Most are cold nodules, though well differentiated may be hot<br>Distinguishing adenoma (no capsular invasion) from carcinoma (invasion) is difficult |
| Medullary Carcinoma | Neoplasm | From **C Cells** that produce **Calcitonin** = Hypo-Ca and **Amyloid Production**<br>*Familial Type*= multinodular, **MEN2A** and **MEN2B** association<br>*Sporadic Type* = **singular, mass effect** |
| Anaplastic Carcinoma | Neoplasm | Poorly differentiated tumor of the **elderly**, particularly of endemic goiter patients<br>**Dismal prognosis** related to significant anaplasia and metastasis |
| Thyroglossal Duct | Congenital | Duct is remnant of **thyroid descent**; may become infected or develop carcinoma;<br>Near the start (the mouth) = sqaumous, Near the end (the thyroid) = thyroid |
| Hyperthyroid | Heat Intolerance, High Basal Metabolic Rate, ↑GI motility, eventual seizure (thyroid storm) | |
| Hypothyroid | Cold intolerance, low basal metabolic rate, cretinism (children), myxedema (Adult), weight gain | |
| Screening | Look for **TSH**, **T3/T4**, **antibodies**, and see which is erroneously elevated | |
| Cretinism | Babies, mental defects, growth retardation, craniofacial abnormalities, **severe mental retardation** | |
| Myxedema | Periorbital edema, Cardiomegaly, Pericardial Effusions, Hair loss | |
| **CALCIUM HORMONES** | | |

| Hormone | Effect on Kidney | Effect on Bone | Effect on GI | Notes |
|---|---|---|---|---|
| PTH | ↑Ca resorption<br>↑$PO_4$ Excretion<br>↑1-α-hydroxylase | ↑Ca Resorption<br>↑$PO_4$ Resorption | ↑Ca Absorption<br>↑$PO_4$ Absorption | Minute by minute regulation, maintains calcium levels and gets rid of phosphorous |
| Vitamin D | ↑Ca Resorption<br>↑$PO_4$ Resorption | ↑Ca Resorption<br>↑$PO_4$ Resorption | ↑Ca Absorption<br>↑$PO_4$ Absorption | Increases levels of phosphorous and calcium. Lost in renal failure |
| Calcitonin | ↑Ca Excretion<br>↑$PO_4$ Resorption<br>0 Enzyme Effects | ↓Ca Resorption<br>↓$PO_4$ Resorption | ↓Ca Absorption<br>↓$PO_4$ Absorption | Opposes PTH at every organ level, though is nonessential |

| CALCIUM DISEASES | | | |
|---|---|---|---|
| **Disease** | **Pathogenesis/Presentations** | **Lab Findings** | **Critical Test** |
| Primary Hyperparathyroidism | Adenoma/Tumor/Neoplastic growth within the parathyroid gland creating an autonomous production of PTH without regulation of feedback | ↑Ca ↑PTH | PTH |
| FHH | Autosomal Dominant mutation of CaSR resulting in a new set point, requires higher than normal levels of calcium to stimulate CaSR to inhibit PTH; PTH levels are up | ↑Ca ↑PTH | ↓ Urine Calcium Clearance, Ca/Cr |
| Medications | HCTZ and Lithium prevent urine excretion of calcium, similar picture to PHH = ↓Urine Ca, ↑Blood Ca | ↑Ca ↑PTH | ↓ Urine Calcium Clearance, Ca/Cr |
| Hypercalcemia of Malignancy | *Metastasis* = bone destruction and release<br>*PTH-rp* = solid tumors elaborating PTH-like hormone | ↑Ca ↓PTH | PTH-rp, X-ray for bone lesions |
| Granulomatous Diseases | *Macrophages* activate 1-α-Hydroxylase causing upregulation of | ↑Ca ↓PTH | Vitamin D |
| Vitamin D Toxicity | Ingestion of supplementation increases amount of active cholecalciferol | ↑Ca ↓PTH | Vitamin D |
| Milk Alkali | Calcium Carbonate (tums) ingestion in massive quantities | ↑Ca ↓PTH | |
| Hypoparathyroid | Surgically induced, part of **DiGeorge Syndrome**, or associated with gene mutations and **Candida** infections. Presents with tetany, cramps, spasms, prolonged QT, and psychosis | ↓Ca ↓PTH | |

| PARATHYROID DYSREGULATION PRESENTATION | | |
|---|---|---|
| **Disease** | | **Lab Findings** |
| Asymptomatic Hyperparathyroidism | The serum calcium is up, but there are no presenting symptoms. This is usually found on routine blood draw in the early stage of disease | ↑Ca and ↑PTH if primary<br>↑Ca and ↓PTH if outside gland |
| Symptomatic Hyperparathyroidism | with "painful bones" (**osteitis fibrosa cystic**a), "renal stones" (**Kidney Stones** most common presentation), "abdominal groans" (**constipation**, nausea, ulcers), "psychic moans" (weakness, fatigue, depression, lethargy, s**eizures**) | ↑Blood and Urine Calcium<br>↑Calcium in organs (calcinosis)<br>↓Phosphate |
| Secondary Hyperparathyroidism | Most commonly the result of **renal failure** (cannot make 1,25-Vitamin D if the kidneys are dead). | ↓Ca and ↑PTH, despite ↓Vit D |
| Hypoparathyroidism | Neuromuscular dysfunction = **tetany**, cramps, stridor<br>Mental Status changes = **psychosis**<br>Cardiac Conduction defects = **QT prolongation** | ↓Ca ↓PTH ↓Vit D |
| Pseudohypo-parathyroidism | PTH is made, but the kidneys do not respond. It is as if there is no PTH (thus pseudo) even though there is a lot of PTH. That means the calcium is low, phosphate is high | |

| PITUITARY | | |
|---|---|---|
| **Disease** | **Location** | **Characteristics** |
| Prolactinoma | Anterior | **Most common anterior pituitary adenoma**, usually forming a macroadenoma<br>↑Prolactin causes **amenorrhea**, **loss of libido**, **infertility**, and **galactorrhea**<br>Sparsely granulated acidophilic cells staining for Prolactin on immunohistochemistry<br>Women caught earlier than men (no menses usually worrisome for a woman) |
| Growth Hormone Adenoma | Anterior | Second most common adenoma of the anterior pituitary, usually microadenoma<br>If prior to closure of epiphyseal plate result is **gigantism** (really tall with long arms/legs)<br>If after closure of epiphyseal plate result is **acromegaly** (large hands, feet, face) |
| Cushing's Disease | Anterior | Corticotroph Adenoma of Ant Pituitary releasing ACTH = ↑cortisol release from adrenals<br>**Cushing's Syndrome** is an ↑cortisol NOT from an adenoma, **Cushing's Disease** is Ant Pit<br>See Cushing's Syndrome for many more details in the adrenal section |
| Nonfunctioning Adenoma | Anterior | Comes in **null** tumors, which are rare, and there is no hormone<br>Comes in **silent** tumors, where the granules are there, they just do no release |
| Apoplexy | Anterior | Abrupt hemorrhage into a cyst or adenoma of the anterior pituitary, causes ischemia or mass effect |
| Ischemic Necrosis (Sheehan Syndrome) | Anterior | Symptoms are not present until 75% of pituitary is lost<br>During pregnancy, anterior pituitary enlarges but the vasculature does NOT<br>**Sheehan Syndrome** is a **post-partum** DIC syndrome that causes hypotension and necrosis |
| Diabetes Insipidus | Posterior | **Inability** to produce **ADH** (central) or to respond to ADH (nephrogenic)<br>Polyuria, Polydypsia, hemoconcentration, causing a **hypernatremia** |
| SIADH | Posterior | **Too much ADH** results in water retention = **hypertension** and **hyponatremia**<br>Results in cerebral edema and neurologic dysfunction<br>Caused by Malignant neoplasms and damage to hypothalamus |
| Craniopharyngioma | Hypothal | Most common cause of hypopituitarism in kids<br>Formed from **remnant of Rathke's pouch** causing **mass effect** and bitemporal hemianopsia |

| COMPARISON OF TYPE 1 AND TYPE 2 DIABETES | | |
|---|---|---|
| **Characteristic** | **Type I** | **Type II** |
| Named | Insulin Dependent Diabetes Mellitus (IDDM) | Non-Insulin Dependent Diabetes Mellitus (NIDDM) |
| Age | Childhood (<20 years) | Adult (>30 years) |
| Onset | Rapid | Insidious |
| Weight | Thin to Normal | Obese |
| Genetics | HLA-DR3, HLA-DR4 Haplotype<br>Family history uncommon | Family History Common, no HLA haplotype<br>African American and Native American at risk |
| Pathogenesis | Autoimmune destruction of β-islets<br>No insulin production<br>Trigger suspected to be a viral mimicry | Insulin resistance followed by β-Cell dysfunction<br>Need more insulin, Pancreas meets it, then burns out<br>↓Insulin Receptor, Insulin Pathway Alterations |
| Clinical Findings | Polyuria, Polydypsia, Polyphagia and Weight loss, usually in kids<br>Nephropathy, Retinopathy, Neuropathy, Cardiovascular | Recurrent Blurry Vision (retinopathy)<br>Recurrent Infections (Candida, Bacteria)<br>Nephropathy, Retinopathy, Neuropathy, Cardiovascular |
| Metabolic Derangement | DKA – hyperglycemia, coma, ketone bodies (butyric and acetoacetic), sugar > 600 | HNKC – hyperglycemia, coma, without Ketoacidosis, sugars in the 400-600 |
| Treatment | Insulin | Weight loss (upregulates Insulin receptor synthesis)<br>Oral Hyperglycemic (See pharm) |

| ADRENAL CORTEX | |
|---|---|
| **Disease** | **Character** |
| Androgenital Syndrome | Most commonly caused by **21-Hydroxylase deficiency**, though can be 18β- or 11β-Hydroxylase<br>Shunting to testosterone causes **virilization** of female genitalia and precocious puberty in males<br>May be severe (salt wasting, no aldo or cortisol), moderate (virilization without wasting), more mild |
| Primary Hyperaldosterone (Conn Syndrome) | Most commonly caused by a primary adenoma, **Conn Syndrome**, containing **Spironolactone Bodies**<br>Autonomous production of **aldosterone** without activating renin-angiotensin-aldosterone axis<br>Causes **Hypertension** (salt and water retention) and **Hypokalemia** (trades K out for Na back in) |
| Secondary Hyperaldosterone | Stimulation of renin secretion, thereby inducing aldosterone production; ↑Renin is difference from Conn's<br>Renal artery stenosis, **↓Renal Perfusion** from **CHF or Shock**<br>Causes **Hypertension** (salt and water retention) and **Hypokalemia** (trades K out for Na back in) |
| Hypercortisol (Cushing's) | Multiple causes: **Iatrogenic** (most common), Primary Adenoma of Adrenals, Primary Adenoma of the Pituitary (**Cushing's Disease**), or extra-adrenal nonendocrine paraneoplastic tumors<br>**Truncal Obesity, Moon Facies, Buffalo Hump**, Weakness, **Glucose Intolerance**, Wound Healing Delay<br>Types differentiated based on the Dexamethasone Test, Pituitary Imaging, and Adrenal Imaging |
| Primary Hypocortisol (Addison's) | Destruction of the adrenals: infection, metastasis, **autoimmune** (90%), or Adreonleukodystrophy<br>ACTH signal is not broken (enhanced, actually), but no cortisol is made<br>**Hyperpigmentation** (↑ACTH), **Hypotension** (↓catecholamine action), **Hyperkalemia** (↓Aldosterone) |
| Secondary Hypocortisol | Deficiency of ACTH production, ↓ACTH and ↓Cortisol, **no hyperpigmentation**<br>Aldo levels normal, **no hypotension** and **no hyperkalemia** |
| Waterhouse-Friderichsen Syndrome | Caused by **meningococcal septicemia** or other bacterial infections/DIC (especially kids)<br>Causes **massive, bilateral adrenal apoplexy** (hemorrhage) that is catastrophic to function of adrenals<br>Clinical course is abrupt (fatal) if underlying infection not treated and hormones replaced |
| **ADRENAL MEDULLA** | |
| **Disease** | **Character** |
| Pheochromocytoma | **Neural Crest** derived **Chromaffin Cell** tumor of the adrenal medulla; secretes **catecholamines**<br>Paroxysmal (Pulsatile) activation of Norepi = **hypertension**, **tachycardia**, **palpitations**, **sweating**, **anxiety**<br>Found in kids and adults ages 30-50, is also part of the MEN2 syndrome<br>Rule of 10s = 10% Extra-Adrenal, 10%Bilateral, 10%Malignant, 10%Kids, 10%Familial |
| Extra-Adrenal Pheochromocytoma | Pheochromocytomas that are not part of the adrenal glands, *very low yield, but in Robbins*<br>Same symptoms, same path, different location, such as **carotid body** |
| Neuroblastoma | See Neuro |
| MEN 1 | Mutation of the **MEN** gene for **menin,** presenting with the 3 Ps = **Parathyroid Hyperplasia**/Neoplasm, **Pancreatic Hyperplasia**/Neoplasm, and **Pituitary Adenomas** usually Prolactinomas<br>Presents with whatever hormone is elevated (Hypercalcemia:PTH, Zollinger-Ellison:Gastrin) |
| MEN 2A | Mutation of the **RET oncogene**<br>**Medullary carcinoma** (Calcitonin) of the thryroid, **pheochromocytoma** and **parathyroid hyperplasia** |
| MEN 2B | Mutation of the **RET oncogene**<br>**Medullary carcinoma** (Calcitonin) of the thyroid, **pheochromocytoma** and **neuroblastomas** |
| To keep these straight, think of it as MEN1 and MEN2. MEN1 is MEN gene with the 3Ps. MEN 2 is the medullary carcinoma, pheo, and something else. MEN2A is parathyroid ("2 Ps") and MEN2A is neuroblastomas ("1 P"). Just realize that "P" is not always the same P (different Ps in MEN1 to MEN2A/MEN2B | |

| TYPES OF CUSHINGS AND LAB VALUES | | | | |
|---|---|---|---|---|
| | **Pituitary Cushing's** | **Adrenal Cushings** | **Ectopic Cushings** | **Iatrogenic Cushings** |
| Serum Cortisol | ↑ | ↑ | ↑ | ↓ |
| Urine Cortisol | ↑ | ↑ | ↑ | ↓ |
| Low-Dose Dexamethasone | Cortisol Not Suppressed | Cortisol Not Suppressed | Cortisol Not Suppressed | N/A |
| High-Dose Dexamethasone | Cortisol Suppressed | Cortisol Not Suppressed | Cortisol Not Suppressed | N/A |
| Plasma ACTH | Normal to ↑ | ↓ | ↑↑↑↑ | ↓ |

| MALE PATHOLOGY | |
|---|---|
| **Disease** | **Character** |
| PENIS | |
| Epispadias | Urethral opening on the dorsal surface of the penis (*epi*, on top of) |
| Hypospadias | Urethral opening on the ventral surface of the penis (*hypo*, below), this is **more common** |
| Balantitis | Inflammation of the glans, usually a result of poor hygiene and lack of circumcision |
| Genital Warts | Called, Condyloma Acuminatum, **Genital Warts** are caused by **HPV 6** and **11**, if in kids, assume **abuse** |
| Sqaumous Cell Carcinoma | **Same as anywhere else**, with keratin pearls, nests of sqaumous cells<br>Result of Bowen or Bowenoid Disease, generally rare in the United States except in **HPV 16/18** infections |
| TESTES | |
| Variocele | Dilated tortuous veins in the spermatic cords, feel like a "bag of worms," potential for infertility |
| Hydrocele | Fluid within the Tunica Vaginalis, caused by a persistent processus vaginalis |
| Spermatocele | Dilated portion of the spermatic cord filled with sperm |
| Epididymitis | Pain in the posterior of the testes. This does not necessarily have to be caused by bacteria<br>**Acute < 35** = STD, either Neisseria Gonorrhea or Chlamydia Trachomatis<br>**Acute > 35** = E. Coli or Pseudomonas, possibly from GI tract<br>**Chronic** = TB, often with Caseating Granulomas |
| Orchitis | Most commonly associated with **Mumps Infection** (Orchitis + Parotitis) in unimmunized individuals.<br>Risk for infertility (and the neural sequella or mumps, obvi) |
| Testicular Torsion | Testes twist inside scrotum, **strangulating vasculature**, representing a medical emergency; PAINFUL<br>Must surgical adhere the testes to wall, contralateral has ↑risk of torsion, tack that one down too |
| Cryptochordism | **Failure of the testes to descend**, bearing an **increased risk of carcinoma,** hernia, and infertility<br>May be surgically repaired, if not, infertility is almost a certain; unknown if surgery prevents carcinoma |
| TESTICULAR CARCINOMA | |
| Seminoma | **Placental Alkaline Phosphatase** elevated. All other tumors are called nonseminomas<br>Seminoma vs Nonseminoma: Seminoma = **Late metastasis, Radio responsive, Chemo responsive**<br>Most common testicular mass in **ages 15-35** and carries an **excellent prognosis**<br>Large, bulky, white tumor that is well-demarcated and separated from the rest of the testes without bleeding<br>Micro = tumor cells with **delicate fibrosis**, **lymphocytic infiltrate**, and maybe a **giant cell** |
| Embryonal Carcinoma | Since it can turn into chorio, yolk, or teratoma, any serum factors can be elevated, it is nonspecific<br>A low-yield tumor, it occurs in 20s and 30s as a bulky mass with areas of **hemorrhage** and **necrosis**<br>Under the microscope there are **primitive, embryonal cells** without differentiation |
| Choriocarcinoma | More mature form of embryonal carcinoma, **β-hCG**<br>Board Favorite since it is the **most malignant, spreading quickly** through the blood, and **dividing rapidly**<br>On gross, since it spreads quickly, the tumor may be small in the testes, look for metastasis<br>Look for **syncytialtrophoblasts** next to **cytotrophoblasts** (simply "trophoblast" might be enough in vignette) |
| Yolk Sac Tumor or Endodermal Sinus | More mature form of embryonal carcinoma, **α-Feto-Protein**<br>This is the most common tumor of **children**, but it can occur in adults, but tends to be mixed<br>Under the microscope there are **Schiller-Duval Bodies** (attempts at yolk sac) which are pathognomonic |
| Teratoma | More mature form of embryonal carcinoma, **No Serum marker**<br>Teratomas can be mature or immature, in **males**, we assume the teratoma is **immature and malignant**<br>Under the scope, you look for **all 3 germ layers** (ecto, endo, and mesoderm) |
| Mixed | Most commonly there is a mix of any of the tumors listed above. |
| Leydig Cell Tumors | Leydig cells make **androgens** (hard to see in a male) and **estrogens** (gynecomastia)<br>Occurs in the 20-50s (adults), coming in with painless intratesticular mass, and is usually benign<br>If it occurs in a male child, they will have **precocious puberty** |
| Testicular Lymphoma | Most common presentation of a **painless mass** in an **elderly male** (non-Hodgkin's Lymphoma)<br>Bulky white testes; the tumor will merge and insinuate through the stroma, difficult to differentiate |
| All carcinomas are **painless masses** in the testes. Risk factors involve essentially any of the diseases listed above, as they cause inflammation and proliferation. **Cryptochordism** and **Testicular Dysgenesis** (testicular feminization) are the major risk factors. Note that we **never biopsy the testes**. If you think its cancer, take the testes out (orchiectomy), biopsying the tumor just helps it spread! | |

| TESTICULAR TUMOR REVIEW | | | | |
|---|---|---|---|---|
| **Tumor** | **Marker** | **Age** | **Prognosis** | **Histo** |
| Seminoma | Alkaline Phosphatase | 15-35, common | Excellent | Fibrosis, Tumor and Giant Cells / Granulomas |
| Embryonal | Any | 15-35, rare | Poor | Primitive Cells |
| Choriocarcinoma | hCG | 20-50, adults | Poorest | Trophoblasts |
| Yolk Sac Tumor | AFP | 5-15, Kids | Poor | Schiller-Duval Bodies |
| Teratoma | None | 20-50, adults | Good | 3 Germ Layers or Products |
| Leydig Cell | Estrogen, Androgens | 5-50, Kids and adults | Excellent | Leydig cells |
| Lymphoma | | 60+, elderly or older | Poor | Tumor insinuating through stroma |

| BONE PATHOLOGY | |
|---|---|
| **Disease** | **Character** |
| Osteoporosis | Generally an age related event, osteoclasts start winning over osteoblasts, and bone denisty ↓ with age<br>**Worse in women** than in men, caused by a **deficiency in estrogen**<br>Humans reach a **peak bone mass** (genes) then slowly lose bone throughout their life (↓Trebecula Strength)<br>There is an ↑risk of fractures with age, especially at the **hip, wrist** and **vertebrae**<br>Treat them with exercise, calcium, and Vitamin D; generally, we do not want to give estrogen supplements |
| Osteopetrosis | ↑Osteoblast activity without osteoclasts activity = overproduction of bone<br>Crowds out the hematopoietic cells causing **anemia** and **pancytopenia** (↑ risk of infection) with **extramedullary Hematopoiesis** resulting in splenomegaly<br>Thick bone, bone growths, pathologic fractures (**chalk stick**) and compression syndromes (CN palsies) |
| Paget's Disease | Caused by an infection with **parvovirus** (at least suspected)<br>Causes a presentation of mixed phases: Osteolytic, Osteoblastic, and Sclerosis<br>There is a **gain of bone mass** that remains **unstable** (↑Fractures) characterized by **mosaic pattern** on histology, **↑Alk Phos** on labs, and multiple pases of development on Xray; *"Hat doesn't fit anymore"* |
| Rickets<br>*Vit D Def in Kids* | Caused by a **Vitamin D Deficiency** either from ↓exposure to sunlight or insufficient dietary administration<br>Causes a defect in the formation and elongation of bones<br>Results in **Pigeon Chest**, **Harrison's Groove**, **Bow Leggedness**, and **Osteopenia** |
| Osteomalacia<br>*Vit D Def in Adults* | Same as Rickets, may look like Osteoporosis, and must be differentiated (↑Vitamin D cures Osteomalacia)<br>Bones are already formed, so they just get **Osteopenia** and risk for fractures |
| Hyperparathyroid | Either primary or secondary, ↑PTH = ↑Osteoclasts, leaving giant "holes" in the bone<br>"Holes" can hemorrhage, form fibrosis or a cyst (**osteitis fibrosis cysitca**) = "Super Osteoperosis"<br>Increased Vascularity, hemorrhage, and giant cells may give rise to a **"brown tumor**" (nonneoplastic) |
| Renal Osteodystrophy | The result of **end stage renal disease**, causing a **lactic acidosis** and a **secondary hyperparathyroidism**<br>In addition to Osteopenia and renal failure, there is deposition of **calcium**, **aluminum** and **amyloid** |
| Fractures | Well-Aligned, **Closed** (intact skin), **incomplete** (Greenstick) fractures heal well<br>Poorly-Aligned, **Compound** (broken skin), **Comminuted** (crushed or fragmented) fractures heal poorly |
| Pyogenic Osteomyelitis | Infection of the bone, usually hematogenous spread, though can be direct administration (fracture)<br>**Salmonella** in **Sickle Cell, Neisseria** if Sexually Active, **Staph Aureus** in everyone else (FA has longer list) |
| Tuberculous Osteomyelitis | Granulomas and caseous necrosis occurring in TB infected patients within the bone<br>When it's in the spine it's called **Pott's Disease** (not to be confused with Pott's Tumor, another block) |
| Osteogenesis Imperfecta | Defect in the synthesis of **collagen Type I;** Disease Type 1 is **Dominant,** Type II is **recessive** and **fatal**<br>Presents with **pathological fractures** at birth and following, **blue sclera** and **deafness** |
| Achondrosis | Autosomal Dominant defect of proliferation of cartilage at the growth plate; overactivation of growth factor<br>Normal Head, Normal Spine, Short Arms and Legs; most common form of **dwarfism** |

There is more to the bone chapter, but the Lecture Objectives held us at what is here. Oddly, we did not go into bone tumors or some of the diseases in the Bone section of the Bone and Joint chapter. That information is included for your Board/Shelf study on the last pages of these quick-review charts.

| STDs | |
|---|---|
| **BUG** | **Character** |
| Candida Albicans | A **yeast** with **pseduohyphae**, common in patients with **Diabetes** or who are on **Antibiotics**<br>It causes a **white vaginal discharge** and is treated with fluconazole |
| Chlamydia Trachomatis | The "Clap" is the **most common STD** overall in women. Starting in the vagina, it can ascend into the cervix, uterus, fallopian tubes, ovaries, and then go either **peritoneal** or to the **liver** (Fitz-Heuz-Curtis)<br>A common cause of **PID**, it can result in infertility, fibrosis of the fallopian tube (ectopic), or pain<br>It is an intracellular obligate that may form granulomas (only saw this in Lippincott's Qbank) |
| Neisseria Gonorrhea | An STD that often coinfects with Chlamydia, Gonorrhea is a **gram negative dipplococcus**<br>This presents with conditions and locations similar to Chlamydia, only it can also cause **septic arthritis**<br>Must be grown on a **chocolate agar** with **antibiotics** to prevent the growth of other organisms |
| Gardnerella Vaginalis | This is a **gram negative rod** that produces **bacterial vaginosis** (a malodorous vaginal discharge)<br>The organisms adhere to sqaumous cells producing **"clue cells,"** treated with Metrondiazole |
| Haemophilus Ducreyi | "You do cry with ducreyi." This is a **painful ulcerative lesion** caused by a gram negative rod<br>Differentiate this from a primary syphilitc lesion that is a **painless ulcerative lesion** |
| Human Papilloma Virus | Strains **6 and 11 cause Genital Warts** = verrucous, cauliflower-like lesions, generally on the external vulva<br>Strains **16 and 18 cause Squamous cell Carcinoma** = E6 inhibits p53, E7 inhibits Rb |
| Treponema Pallidum *(Syphilis)* | Stage 1: **Early Presentation** is a **painless chancre** somewhere on the genitalia<br>Stage 2: **Intermediate** is a **macuolapular rash** on the skin, palms, soles, that are all contagious<br>Stage 3: **Late** stage is a degeneration of **neural function** called Tabes Dorsalis<br>Screened for using the VDRL (can be false positive in Lupus), but is simply treated with **Penicillin** |
| Trichomonas Vaginals | This **flagellated protozoan** produces a **green, frothy discharge** after causing vaginitis, urethritis, or cervicitis<br>It is treated with **metronidazole**, but **both partners** must be treated to avoid bounce-back sharing |
| E Coli | Most common cause of **urethral infections,** spread from colon |
| Staph Aureus | Most common cause of **acute mastitis**, not really an STD (though it could be!), associated with breast feeding |
| Neisseria Meningococcus | Septicemia causes Waterhouse-Freidrischsen syndrome, or however you spell it<br>Neisseria Meningitis is spread by transmission of bodily fluids (kissing, sharing drinks) |

| FEMALE PATHOLOGY | | |
|---|---|---|
| **Disease** | **Where** | **What** |
| Condyloma Acuminatum | Vulva | **HPV** strains **6 and 11** cause warty, verrucous lesions, usually on the outside of the vulva<br>These are commonly described as **white plaque-like lesions** |
| Bartholin Gland Cyst | Vulva | Submucosal glands that secrete lubricant can become infected (Staph, Chlamydia) and obstructed, leading to the formation of **cysts** which are often painful and noticeable |
| Extramammary Paget Disease | Vulva | This is the presence of **pale-staining tumor cells within the intraepidermis**<br>Unlike Paget's disease of the breast, there is **no underlying tumor** |
| Vaginal Adenosis & Adenocarcinoma | Vagina | Vagina is normally a stratified non-keratinized sqaumous epithelium without glands<br>Exposure to **DES** while **in utero** can cause a **glandular tumor** in the adult woman |
| Embryonal Rhadomyosarcoma | Vagina | A **grape-like lesion** occurring in the anterior vagina, commonly presenting in **children**<br>Is a rhabdo**myo**sarcoma so stains positive for **vimentin, desmin,** and **actin** |
| Pelvic Inflammatory Disease | Pelvis, Uterus, Fallopian | Caused most commonly by **Neisseria Gonorrhea** or by **Chlamydia Trachomatis**<br>Causes **pelvic pain** at any time in cycle, can lead to **salpingitis** (inflammation of fallopian tube)<br>Can result in **infertility** or **ectopic pregnancy** from tubal scarring, or "violin string adhesions" |
| Cervical Carcinoma | Cervix | Graded from Low Grade Dysplasia (CIN) to carcinoma in situ (CINIII) through microinvasion to metastasis, this is simply a **epithelial tumor of the cervix** caused by **HPV strains 16 and 18**<br>Risk of infection increases with **multiple sexual partners** and **early onset of intercourse**<br>**Invasion =** hysterectomy, **Microinvasion or sooner** = no treatment needed, but should monitor |
| Endometritis | | This is simply **inflammation of the endometrium.** Look for **plasma cells** in the myometrium<br>IUDs predispose to infection by **Actinomyces** |
| Endometrisosis | Uterus | The presence of **uterine tissue** that is **outside the uterus**<br>Causes **pain** or **hemorrhage,** especially during menses (estrogen caused development of this)<br>May present as a **chocolate ovary** when present on the ovary, replacing the ovary with glands |

| | | |
|---|---|---|
| Leiomyoma (fibroids) | Uterus | These are **white, trebeculated**, often multiple growths of the uterus<br>They are **not premalignant**, can be palpated if subserosal, but can be painful and multiple<br>Common in African American population |
| Leiomyosacroma | Uterus | Same as Leiomyoma, only now it is a full blown cancer, look for markers of smooth muscle such as **desmin**, and **actin**, ensuring that skin/melanin (S-100), Ovarian (CA125), and GI (CEA) are neg. |
| Adenomyosis | Uterus | Finding **glands** and **stroma** of the uterus **within the myometrium**. While they are u**sually asymptomatic** (50% of hysterectomies have them), Dysmenorrhea, Pain, and Bleeding are possible, usually immediately preceding or following the menstrual cycle |
| Endometrial Carcinoma | Uterus | Presents as **postmenopausal bleeding** (usually a female in their 50s-60s with bleeding)<br>Risk factors include **exposure to high-dose estrogen** (nulliparity, obesity, tamoxifen, estrogen replacement therapy though "the pill" doesn't count) |
| Polycystic Ovarian Disease | Uterus | Originally, it is characterized by **amenorrhea, hirsutism and obesity**<br>Now it characterizes ↑androgens, persistent anovulation and **subcapsular cysts**<br>The increased levels of estrogens put them at risk for endometriosis and adenocarcinoma<br>If cut open, the ovaries would be **bilaterally composed of cysts** |
| Kruckenburg Tumors | Ovary | **Metastasis** from the **gastric mucosa,** generally demonstrating **signet cell rings**<br>It is just a special form of metastasis that happens to occur and happens to be common |
| Epithelial Ovarian Tumors | | |
| Cystadenoma | **Benign tumor** presenting as a **single smooth cystic space** without nodularity or papillary structures<br>The lining can be **serous** (producing water) or **mucinous** (producing mucous) | |
| Cystadenocarcinoma | **Malignant tumor** presenting as **multicystic spaces** with **nodularity** and **papillary structures**<br>↑Risk with BRCA-1 and Lynch Syndrome (HNPCC), use **CA-125** marker, and spreads by **seeding** | |
| Ovarian Germ Cell Tumors | | |
| Teratoma | Same as in males, except **Teratomas in females are usually mature and benign** | |
| Dysgerminoma | Same as Seminomas in Males | |
| Yolks Sac | Same as in males, produces **AFP** | |
| Choriocarcinoma | Same as in males, produces **hCG** | |
| Ovarian Sex-Cord Stromal Tumors | | |
| Ovarian Fibroma | Presents with ascites and a **unilateral** adnexal mass that is generally **solid and white**<br>It is benign, generally **resembling normal ovarian** stroma surrounded by collagen (the "fibr" part)<br>An increased risk of **pleural effusions** is present (think ascites→ pleural effusion) | |
| Granulosa Cell Tumor | Hormonally active, Granulosa Cell Tumors secrete **estrogens** (causes endometrial hyperplasia)<br>Display **haphazard orientation about a degenerative space** (sort of a "rosette pattern") | |
| Sertoli-Leydig | Presents with **androgen production** (hirsutism, deepened voice) and an ovarian mass<br>Generally affect younger women, causing amenorrhea, ↓ breast development, and ↑hip fat | |
| Metastatic | | |
| Placenta | | |
| Hydatidifrom Mole | **Complete** moles = **Diploidy** = **normal sperm** (23X) + **absent egg** (0) = 23,x that then goes on to double the sperm contribution (46,XX), and has **large grape-like structures** <u>without</u> fetal parts<br>**Incomplete** moles = **triploidy** = 2 normal sperm (23x) + normal egg (23,X) = (69,XXX). This presents as **grape-like structures** <u>with</u> fetal parts | |
| Placenta Accreta | Pieces of the placenta imbed in the endometrium and cannot be delivered, causing hemorrhage<br>Find a firm **nodular** piece of the placenta imbedded in the **myometrium** during a D&C after delivery<br>This presents as a **painless bleeding** post-delivery | |
| Placenta Previa | The embryo implants **near to the os**, producing a small amount of blood in **any semester** | |
| Abruption Placentae | This is the only one that has a **painful bleeding** and occurs in the **3rd trimester**<br>It is caused by a **premature separation** (picture a tearing to attribute pain) of the placenta<br>Produces **scant bright red bleeding** and is often fatal | |
| Preeclampsia | **Hypertension**, **Proteinuria**, and **Edema** in a pregnant female. Risk for **seizures** (eclampsia)and **DIC**<br>Delivery of the baby is generally curative<br>Caused by the **infarction of the placenta** (why that leads to preeclampsia, I am not quite sure) | |

| ENVIRONMENTAL AND NUTRITIONAL SELF STUDY | | |
|---|---|---|
| **Nutrient** | **Disease** | **What it Looks Like** |
| General Calories | Marasmus | Usually in children **<1 year of age** (babies that need nursing that aren't getting it)<br>Total **wasting away** as a result of complete absence of all calories |
| Proteins | Kwashiorkor | Usually in children **>1 year of age**, calories are ok, but protein is lacking<br>Abdominal distension as body consumes abdominal muscles for nitrogen<br>White Streaks in hair and skin |
| WATER SOLUBLE | | |
| Vitamin B1, Thiamine | Beri-Beri<br>Weirnicke's<br>Korsakoff's | Peripheral Neuropathy, commonly seen in alcoholics<br>Cerebellar Dysfunction, Ataxia, Unstable Gait, Reversible<br>Memory Confabulation, Irreversible |
| Vitamin B2 | | Usually not deficient since it is added to bread and cereal in the united states<br>Deficiency = cheliosis (skin fissures), glossitis, and corenal vascularization |
| Vitamin B3, Niacin | Pellagra | The 3 D's of B3 Deficiency **Dementia, Dermatitis, Diarrhea** |
| Vitamin B6, Pyridoxine | | Associated with general malnutrition and with Tuberculosis medications<br>Too little causes **seizures** (failure to generate GABA) |
| Vitamin B12 | Megaloblastic Anemia "Plus" | Supplies deplete over the course of a decade (**pernicious anemia** or **vegans**)<br>Causes a **megaloblastic anemia** and **DCMLS degeneration** (proprioception and vibration) |
| Vitamin C | Scurvy | Vitamin C required as a cofactor for the Hydroxylation of Proline in collagen synthesis<br>Abnormal collagen = **bleeding gums**, **teeth falling out**, bone pain, joint pain |
| Folate Deficiency | Megaloblastic Anemia | Short-lived supply of folate depleted in alcoholics<br>Causes **megaloblastic anemia** without the neurologic symptoms of B12 |
| FAT SOLUBLE | | |
| Vitamin A | Night-Blindness | Retinoic Acid compounds are all similar and collectively called "Vitamin A"<br>Deficiency leads to **Night-Blindness**<br>Too much can lead to alopecia and bone changes; it is **HIGHLY teratogenic** |
| Vitamin D | Rickets | Vitamin D is required for calcium absorption from the gut See Rickets and Osteomalacia<br>Hypervitaminosis causes stunted growth, nephrocalcinosis, and hypercalciuria |
| Vitamin E | None | There is no disease associated with hyper or hypo vitamin E |
| Vitamin K | Bleeding Diathesis | Found in leafy greens, absent in alcoholics; its like the patient is overdosing on warfarin<br>Required for gamma-carboxylation of factors 2,5,7,9,10<br>No K = ↑PT and ↑PTT (Intrinsic and Extrinsic) but a normal bleeding time (Platelets normal) |

| MALIGNANT TUMORS OF BONE (not on the Tulane Endocrine Exam) | | |
|---|---|---|
| **Tumor** | **M/B** | **Characteristics** |
| Osteosarcoma | Mal | Malignant tumor of the **metaphysic** that is closely associated with **Retinoblastoma Mutations**<br>Most common tumor of bone exluding multiple myeloma, and usually occurs **around the knee**<br>Look for **periosteal lifting** (called **Codman's Angle**) and a **Sunburst Pattern** on X-ray<br>Can be secondary to Paget's Disease or Osteomyelitis, but Retinoblastoma is key |
| Chondrosarcoma | Mal | A low-yield tumor forming from **cartilage** found in **girdle bones** with malignant **chondrocytes** |
| Ewing's Sarcoma | Mal | Occurs in **young kids** and is the result of a **11:22 translocation** (11+22 = 33, Patrick Ewing's number)<br>Causes a duplication of the periosteal layers, called **onion-skinning** occurring usually in the **diaphysis**<br>Look for **Homer-Wright Pseudorosettes**, lymphocyte looking cells lining up in circles |
| Giant Cell Tumor | Ben | Causes a **soap-bubble lesion** within the **epiphysis** of adults |
| Osteoma | Ben | Tumors of the **jaw and face** associated with a variant of **Familial Polyposis Syndrome** = Gardner's |
| Osteochondroma | Ben | **Most common benign** bone tumor occurring in the **metaphysic** resulting in a growth plate that is **covered in cartilage.** Can degrade into a **chondrosarcoma**. |
| Enchondroma | Ben | A **benign cartilaginous** tumor found in the **hands and feet** that is usually **asymptomatic** |
| Mal = Malignant Ben = Benign, This is not an exhaustive list, but should do more than enough to cover you | | |

This material is NOT included in your Endocrine Tulane Exam, but, given the proximity to the Shelf, we thought this might be helpful in studying for that as well. Check out First Aid 2009 page 360. Benign tumors of Bone are not included because they are often not asked.