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Thyroid Embryology

- Forms from floor of pharynx (epithelial cells)

24-28 Day Old Embryo

Thyroid Anatomy

- Two lobes (left, right)
- Isthmus: thin band of tissue between lobes
- Sometimes pyramidal lobe above isthmus

- Blood supply: superior and inferior thyroid arteries
- Superior thyroid: 1st branch external carotid artery
- Inferior thyroid: Thyrocervical trunk (off subclavian)

Thyroid Gland

Jason Ryan, MD, MPH

Thyroid Anatomy

- Foramen Cecum
- (end of median sulcus)

- Descends into neck
- Initially maintains connection to tongue
- Thyroglossal duct
- Disappears later in development
- Two remnants of duct in child/adult
- Foramen cecum in tongue
- Pyramidal lobe of thyroid

Thyroid Anatomy

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24-28 Day Old Embryo

- Blood supply: superior and inferior thyroid arteries
- Superior thyroid: 1st branch external carotid artery
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- Descends into neck
- Initially maintains connection to tongue
- Thyroglossal duct
- Disappears later in development
- Two remnants of duct in child/adult
- Foramen cecum in tongue
- Pyramidal lobe of thyroid
**Thyroglobulin**
- Large protein
- Produced by thyroid follicular cells
- Contains numerous tyrosine molecules

**Thyroid Hormones**
- Two hormones: T3 and T4
- Synthesized from tyrosine and iodine

**Thyroid Histology**
- Thyroid gland contains “follicles”
- Filled with colloid (protein material)
- Single layer of epithelial cells lines each follicle
- “Follicular cells”
- Hormone synthesized by follicular cells

**Ectopic Thyroid**
- Functioning thyroid tissue outside of gland
- Most common location is base of tongue
- Presents as a mass in the tongue
- Commonly detected during increased demand for hormones
- Puberty and pregnancy
- May be the only functioning thyroid tissue
- May under-produce thyroid hormone → hypothyroidism
- ↑ TSH → growth of ectopic tissue

**Thyroglobulin**
- Large protein
- Produced by thyroid follicular cells
- Contains numerous tyrosine molecules
Iodine

- **Iodine** = I (chemical element, atomic number 53)
- **Iodide** = iodide bound to another atom
  - "Iodide salt" with negative charge (I\(^{-}\))
  - Potassium iodide = KI
  - Plasma iodine exists as iodide salt
- For thyroid hormone, iodide in our diet needs to be:
  - Taken up by follicular cells
  - Oxidized to I\(_2\) (undergo "oxidation")
  - Added to organic/carbon structures ("organification")
Amiodarone
- Class III antiarrhythmic drug
- Commonly used in atrial fibrillation
- Contains iodine
- Can cause hypothyroidism via excess iodine
- Wolff-Chaikoff Effect

Wolff-Chaikoff Effect
- Excessive iodide in diet could lead to hyperthyroidism
- Thyroid protects itself via Wolff-Chaikoff Effect
- Organification inhibited by ↑ iodide
  - Less synthesis of MIT/DIT

Thyroid Hormones
- T4 is major hormone produced by thyroid gland
  - >90% of thyroid hormone produced is T4
  - T3 more potent hormone
  - T4 is a "prohormone" for T3
  - 5' deiodinase converts T4 → T3
  - Most conversion occurs in peripheral tissues

Hormone Synthesis

Hyperthyroid Medications
- Propylthiouracil (PTU)
  - Inhibits TPO: ↓ T3/T4 from thyroid gland
  - Inhibits 5'-deiodinase: ↓ T4 to T3 conversion peripherally
- Methimazole
  - Inhibits TPO
- Propranolol
  - Beta blocker
  - Weak inhibitor of 5'-deiodinase
  - Excellent drug in thyrotoxicosis
  - Blocks catecholamines and T4-T3 conversion

PTU and Methimazole are both "thioamides"

Hyperthyroidism
- Excessive T3/T4 in plasma
- Adaptive mechanism of peripheral tissues

Thyroid Peroxidase
- Multifunctional enzyme
- Catalyzes:
  - Oxidation of iodide
  - Organification of iodine into MIT/DIT
  - Coupling of MIT/DIT into T3/T4
- TPO antibodies common in autoimmune thyroid disease

Iodide
– thyroglobulin
– TPO
– MIT/DIT
– T3
– T4

TPO
Thyroid Peroxidase
- Multifunctional enzyme
- Catalyzes:
  - Oxidation of iodide
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- TPO antibodies common in autoimmune thyroid disease
**Thyroid Hormone Receptor**
- Family of nuclear receptors
- Hormone-activated transcription factors
- Modulate gene expression

**TBG**
- Thyroxine-Binding Globulin
  - Most plasma thyroid hormone is T4
  - Thyroid hormones poorly soluble in water
  - Most T4 is bound to TBG
    - Some with transthyretin and albumin
    - TBG present in small amount but has high affinity
    - TBG produced in liver
  - Key point:
    - Less TBG → less available T4/T3 to tissues

**Radioactive Iodine**
- I\(^{131}\) is an isotope of iodine
  - Has 53 protons like elemental iodine
  - Extra neutrons
  - Emits radiation (\(\beta\)-decay)
  - Exposure → radioactive iodine in thyroid gland
    - Competes with elemental iodine for uptake
    - Will concentrate in thyroid gland
    - Small dose: Used for imaging
    - Large dose: Destroys thyroid tissue
  - Used as therapy for hyperthyroidism

**TBG**
- Thyroxine-Binding Globulin
  - Estrogen raises TBG levels
  - Modifies TBG molecules
  - Slows clearance from plasma
  - Pregnancy, OCP users
    - Will raise total T4 levels
  - Liver failure lowers TBG levels
    - Less production of protein
    - Can lower total T4 levels

**Amiodarone**
- Mimics T4
  - Inhibits 5’-deiodinase
  - ↑T3 → ↑TSH from pituitary gland
  - TSH rises after start of therapy then normalizes

**Thyroid Hormone Receptor**
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### Effects of Thyroid Hormone

- Major regulator of **metabolic activity** and **growth**
- Glucose, lipid metabolism
- Cardiac function
- Bone growth
- CNS development

### Thyroid Hormone

#### Metabolic Effects

- ↑ Carbohydrate Metabolism
- ↑ glycogenolysis, gluconeogenesis
- ↑ Fat Metabolism
- ↑ lipolysis
- ↑ concentrations of cholesterol, triglycerides
- ↑ low-density lipoprotein receptors in liver (↓ LDL)
- ↑ cholesterol secretion in bile
- Hypothyroid patients: ↑ cholesterol
- Hyperthyroid patients: **hyperglycemia**

#### Cardiac Effects

- ↑ CO/HR/SV/contractility
- ↑ β1 receptors in heart
- Hyperthyroid patients: **Tachycardia**

#### Metabolic Effects

- ↑ basal metabolic rate
- Basal rate of energy use per time
- Amount of energy burned if you slept all day
- ↑ Na/K ATPase pumps
  - More pumps = more ATP consumed
  - ↑ oxygen demand to replenish ATP
  - ↑ respiratory rate
  - ↑ body temperature
- Hyperthyroid patients: **weight loss**

#### CNS and Bone effects

- TH required for normal bone growth/CNS maturation
- Childhood hypothyroidism → **cretinism**
- Stunted growth
- Intellectual disability
- Causes
  - Iodine deficiency
  - Thyroid dysgenesis
  - Inborn errors of hormone synthesis (dys hormonogenesis)
  - TPO most common
- Most common **treatable** cause intellectual disability
- Most babies appear normal
- Maternal T3/T4 crosses placenta
- Newborn screening programs
  - Measure T4 or TSH from heel-stick blood specimens
Thyroid Hormone

- Intellectual disability
- Coarse facial features
- Short stature
- Umbilical hernia
- Enlarged tongue

Thyroid Hormone Regulation

- Serum T4/T3 level sensed by hypothalamus
- Releases thyroid stimulating hormone (TSH)

- TSH (thyrotropin) released by anterior pituitary
- Binds to receptors on follicular cells
- Activates cAMP/PKA 2nd messenger system
- ↑ T3/T4 release
  - ↑ rate of proteolysis of thyroglobulin
  - Leads to rapid release of more T3/T4
  - Also stimulates thyroid cell growth, TG synthesis

Pregnancy

- Multiple effects on thyroid hormone production
  - Rise in total plasma T4/T3 levels
  - Rise in TBG levels (estrogen)
  - hCG stimulates thyroid (same alpha unit as TSH)
  - Raises free T4 → lower TSH

Thyroid Panel

- Four standard measurements to assess thyroid

<table>
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<tr>
<th>Test</th>
<th>Normal Value</th>
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<tr>
<td>TSH</td>
<td>0.4 to 5.0 mIU/L</td>
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<tr>
<td>Total T4</td>
<td>60 to 145 nmol/L</td>
</tr>
<tr>
<td>Total T3</td>
<td>1.1 to 3 nmol/L</td>
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<tr>
<td>Free T4</td>
<td>0.01-0.03 nmol/L</td>
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Note:
- T4 = T3
- Total T4 ↔ Free T4 (most bound to TBG)

Calcitonin

- Hormone produced by thyroid
- Synthesized by parafollicular cells (C-cells)
Calcitonin

- Lowers serum **calcium**
  - Suppresses resorption of bone; inhibits osteoclasts
  - Inhibits renal reabsorption of calcium, phosphorus
  - Increased calcium in urine
- Probably minor role in calcium handling in humans
- Used as pharmacologic therapy for **hypercalcemia**
**Myxedema**
Thyroid dermopathy

- **Non-pitting** edema of the skin from hypothyroidism
- Hyaluronic acid deposits in dermis
- Draws water out → swelling
- Usually facial/periorbital swelling
- Pretibial myxedema
- Special form of myxedema over shin
- Seen in Graves' disease (hyperthyroidism)
- Myxedema coma = coma from hypothyroidism
**Hypothyroid Myopathy**
- Muscle symptoms common in hypothyroid
- Weakness, cramps, myalgias
- ↑ serum creatine kinase (CK) common (up to 90%)

**Thyroid Replacement**
- Levothyroxine (Synthroid): synthetic T4
- Liothyronine (Cytomel): synthetic T3
- Levothyroxine preferred
  - T3 absorbed from intestines rapidly
  - Can cause mild hyperthyroidism symptoms
  - Tachycardia, tremor
  - Also, T4 converted to T3
- Titrate dose until TSH is normal

**Hypothyroidism**
- Metabolism SPEEDS UP
- Hyperactivity
- Heat intolerance
- Weight loss with increased appetite
- Diarrhea
- Hyperreflexia
- Warm, moist skin
- Fine hair
- Tachycardia (atrial fibrillation)

**Thyroid Storm**
- Life-threatening hyperthyroidism (thyrotoxicosis)
- Usually precipitated by acute event
  - Patient with pre-existing hyperthyroid disease
  - Graves’ or toxic multinodular goiter
  - Surgery, trauma, infection
  - Massive catecholamine surge
  - Fever, delirium
  - Tachycardia with death from arrhythmia
  - Hyperglycemia (catecholamines/thyroid hormone)
  - Hypercalcemia (bone turnover)

**Goiter**
- Enlarged thyroid
- High TSH, inability to produce T3/T4
- Thyroid stimulating antibodies (Graves’)

**Hyperthyroidism**
- Hypothyroidism is a well-described cause ↓Na
- High levels of ADH (SIADH)
- May lead to confusion

**Hyponatremia**
- Hypothyroidism is a well-described cause ↓Na
- High levels of ADH (SIADH)
- May lead to confusion

**Hypothyroid Myopathy**
- Muscle symptoms common in hypothyroid
- Weakness, cramps, myalgias
- ↑ serum creatine kinase (CK) common (up to 90%)
Hyperthyroidism

- Graves' disease (#1 cause)
- Toxic multinodular goiter
- Amiodarone
- Iodine load
- Early thyroiditis

Reverse T3

- Isomer of T3 also derived from T4
- Level usually parallels T4
- Low T4 → Low rT3
- One special use: Euthyroid sick syndrome
  - Critically ill patients → low TSH → Low T3/T4
  - Can look like central hypothyroidism
  - rT3 rises in critical illness (impaired clearance)
  - Critically ill patient with low TSH/T4/T3
    - Check rT3
    - Low → central hypothyroidism
    - High → sick euthyroid syndrome

Lab Findings

- Best initial test is TSH
- Most disorders are primary disease
  - Disorder of the thyroid gland
  - TSH is opposite thyroid hormone
  - Hypothyroidism = ↑ TSH with low T3/T4
  - Hyperthyroidism = ↓ TSH with high T3/T4

Lab Findings

- Central hyper/hypo thyroid disease
  - Low TSH and low T3/T4; High TSH and high T3/T4
  - Rare disorders of the pituitary, hypothalamus
  - Usually hypothalamic-pituitary tumors
  - Tumors block secretion TRH/TSH (hypothyroidism)
  - Rarely a TSHoma can secrete TSH (hyperthyroidism)
  - Pituitary resistance to thyroid hormone (hyperthyroidism)

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**Graves' Disease**

- Autoimmune disease
- Thyroid stimulating antibodies produced
- Symptoms of hyperthyroidism occur

**Graves' Disease**

- Exophthalmos (bulging eyes)
- Proptosis (protrusion of eye) and periorbital edema
- Usually no ocular symptoms
- Pretibial myxedema (shins)
- T-cell lymphocyte activation of fibroblasts
- Fibroblasts contain TSH receptor
- Stimulation → secretion of glycosaminoglycans
  - Hydrophilic substances, mostly hyaluronic acid
  - Draws in water → swelling

**Graves' Disease**

- Diagnosis:
  - Usually hyperthyroid labs plus exophthalmos
  - Can measure TSH receptor antibodies
  - “Thyroid stimulating immunoglobulins”
- Treatment
  - Symptoms: beta blockers, thionamides
  - Drugs often started in preparation for definitive therapy
  - Radioactive iodine ablation or surgery

**Thionamides**

- Methimazole
  - Inhibits thyroid peroxidase (TPO)
  - Organification of iodine
  - Coupling of MIT/DIT
- Propylthiouracil (PTU)
  - Inhibits TPO
  - Also inhibits 5’-deiodinase
  - Blunts peripheral conversion T4→T3

**Thionamides**

- Skin rash (common)
- Agranulocytosis
  - Rare drop in WBC
  - May present as fever, infection after starting drug
  - WBC improves with stopping drug
  - Aplastic anemia cases reported
- Hepatotoxicity
**Thyroid Storm**

**Treatment**
- Propranolol
  - Beta blocker
  - Blocks T4 → T3 conversion
- Thionamides (PTU, Methimazole)
  - SSKI (saturated solution of potassium iodide)
    - Iodide load → shuts down T4 production
    - Wolff-Chaikoff effect
- Steroids
  - Reduce T4 → T3 conversion
  - Suppress auto-immune damage
  - Treat possible concomitant adrenal insufficiency

---

**Radioactive Iodine Uptake**

- Important test for thyroid nodules
- Administration of I^{131} (lower dose than ablation)
- Contraindicated in pregnancy/breast feeding
- "Hot" nodule
  - Takes up I^{131}
  - Not-cancerous
- "Cold" nodule
  - Chance of cancer (~5%)
  - Often biopsied (Fine-needle aspiration)

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**Graves' Ophthalmopathy**

- Sometimes worsens despite treating hyperthyroidism
- Can cause irritation, excessive tearing, pain
- Symptoms often worse by cold air, wind, bright lights
- Severe inflammation treatments:
  - Steroids
  - Radiation
  - Surgery

---

**Toxic Adenomas**

- Nodules in thyroid that function independently
  - Usually contain mutated TSH receptor
  - Do not respond to TSH
  - One nodule: Toxic adenoma
  - Multiple: Toxic multinodular goiter
- Findings:
  - Palpable nodule
  - Hyperthyroidism symptoms/labs
- Treatment: Radioactive iodine or surgery

---

**Jod-Basedow Phenomenon**

- Iodine-induced hyperthyroidism
  - Often occurs in regions of iodine deficiency
- Often occurs in patients with toxic adenomas
  - Drugs administered with high iodine content
  - Expectorants (potassium iodide)
  - CT contrast dye
  - Amiodarone

---
**Goitrogens**

- Substances that inhibit thyroid hormone production
- Most common is iodine
- **Lithium** (inhibits release of thyroid hormone)
- Certain foods (cassava and millet)
Iatrogenic Hypothyroidism

- Thyroid surgery
  - Often done for Graves’ or malignancy
- Radioiodine therapy
  - I131 administered orally as solution or capsule
  - Beta-emissions → tissue damage
  - Ablation of thyroid function over weeks
- Neck radiation
  - Hodgkin’s lymphoma
  - Head and neck cancer

Thyroid Hormone

CNS and Bone effects

- Intellectual impairment
- Coarse facial features
- Short stature
- Umbilical hernia
- Enlarged tongue

Congenital Hypothyroidism

- TH required for normal bone growth/CNS maturation
- Childhood hypothyroidism → cretinism
- Causes
  - Iodine deficiency
  - Thyroid dysgenesis
  - Inborn errors of hormone synthesis (dyshormonogenesis)
  - TPO most common

Thyroid Hormone

CNS and Bone effects

- Most common treatable cause intellectual disability
- Newborn screening programs
  - Measure T4 or TSH from heel-stick blood specimens

Iodine Excess Inhibits 5’-diodinase
Hypothyroidism
Wolff-Chaikoff Hypothyroidism
↓T4→T3
Hypothyroidism
Iodine Load Thyroiditis
Hyperthyroidism
Always check TSH before starting amiodarone

Amiodarone

- Can cause hypothyroidism
- Excess iodine → Wolff-Chaikoff Effect
  - Suppression of thyroid hormone synthesis
  - Normal patients “escape” in few weeks
  - Pre-existing subclinical thyroid disease → “failure to escape”
- Also mimics T4
  - Inhibits 5’-diodinase

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  - Inhibits 5’-diodinase
Lymphocytic Thyroiditis

- Painless Thyroiditis
  - Variant of Hashimoto’s
  - Lymphocytic infiltration of thyroid gland
  - Transient hyperthyroidism
    - Can look like Graves’ without eye/skin findings
    - Serum thyroid stimulating immunoglobulins not elevated
  - Followed sometimes by hypothyroidism
    - Can look like Hashimoto’s
  - Usually self-limited (weeks)

Riedel’s Thyroiditis

- Fibroblast activation/proliferation
- Fibrous tissue (collagen) deposition in thyroid
- “Rock hard” thyroid
- Often extends beyond the thyroid
  - Parathyroid glands → hypoparathyroidism
  - Recurrent laryngeal nerves → hoarseness
  - Trachea compression → difficulty breathing
  - Associated with IgG4 plasma cells
    - May be an “IgG4-related disease” (autoimmune pancreatitis)
    - IgG4 plasma cells identified in biopsy specimens
  - Parathyroid glands → hypoparathyroidism
  - Recurrent laryngeal nerves → hoarseness
  - Trachea compression → difficulty breathing
  - Associated with IgG4 plasma cells
    - May be an “IgG4-related disease” (autoimmune pancreatitis)
    - IgG4 plasma cells identified in biopsy specimens

Subacute Thyroiditis

de Quervain’s/granulomatous thyroiditis

- Granulomatous inflammation of thyroid
- Occurs in young females
- Tender, enlarged thyroid gland
- Hyperthyroid → euthyroid → hypothyroid
- Treatment:
  - Anti-inflammatories (aspirin, NSAIDs, steroids)
  - Thyroid symptoms usually mild (no treatment)
  - Usually resolves in few weeks

Hashimoto’s Thyroiditis

Chronic Autoimmune Thyroiditis

- Most common cause of hypothyroidism (non-diet)
- Lymphocytes infiltrate thyroid gland
  - Autimmune disorder (T-cell attack thyroid, B cell activation)
  - HLA-DR3, HLA-DR5 and others
- Antibodies produced
  - Anti-TPO
  - Anti-thyroglobulin
- Histology:
  - Massive lymphocytic infiltrate (germinal centers)
  - Hurthle cells (enlarged eosinophilic follicular cells)

Hashimoto’s Thyroiditis

Chronic Autoimmune Thyroiditis

- Primarily occurs in women
- Enlarged non-tender thyroid gland
- Gradual loss of thyroid function → symptoms
- Symptoms/labs of hypothyroidism
- Treatment: thyroid hormone replacement
- Increased risk of Non Hodgkin B cell lymphoma

Lymphocytic Thyroiditis

- Variant of Hashimoto’s
- Lymphocytic infiltration of thyroid gland
- Transient hyperthyroidism
  - Can look like Graves’ without eye/skin findings
  - Serum thyroid stimulating immunoglobulins not elevated
- Followed sometimes by hypothyroidism
  - Can look like Hashimoto’s
  - Usually self-limited (weeks)
Thyroid Cancer

Jason Ryan, MD, MPH

General Principles
- Thyroid cancer usually no hyper/hypo symptoms
- Often presents as nodule
- Differential is benign adenoma versus cancer
- Biopsy done by **fine needle aspiration**

Follicular Adenoma
- Common cause of thyroid nodules
- Benign proliferation of follicles
- Normal follicular tissue seen on biopsy
- Completely surrounded by fibrous capsule
- **FNA cannot distinguish between adenomas/cancer**
  - Cannot see entire capsule
  - Follicular carcinoma has similar histology by FNA
  - FNA follicular pathology followed over time
  - Growth, suspicious new findings → surgery

Radioactive Iodine Uptake
- Small oral dose I$^{131}$ given to patient
- Scintillation camera → image of thyroid
- Normal: diffuse, even uptake
- Diffuse high uptake: Graves’
- Diffuse low uptake: Hashimoto’s
- Multiple areas of high uptake: nodular goiter
- Single "hot" nodule: adenoma
- Single "cold" nodule: Possible cancer
  - Most cancers do not make hormone
  - About 10% cold nodules are malignant

Thyroid Imaging
- Ultrasound
  - Some characteristics suggest cancer
  - Borders, vascularity, calcifications

Thyroid Cancer
- Papillary
- Follicular
- Medullary
- Anaplastic

Follicular Adenoma
- Common cause of thyroid nodules
- Benign proliferation of follicles
- Normal follicular tissue seen on biopsy
- Completely surrounded by fibrous capsule
- **FNA cannot distinguish between adenomas/cancer**
  - Cannot see entire capsule
  - Follicular carcinoma has similar histology by FNA
  - FNA follicular pathology followed over time
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Papillary Carcinoma

- Most common form thyroid cancer (~80%)
- Increased risk with prior radiation exposure
  - Childhood chest radiation for mediastinal malignancy or acne
  - Survivors of atomic bomb detonation (Japan)
  - Nuclear power plant accidents (Chernobyl)
- Presents as thyroid nodule
  - Sometimes seen on chest/neck imaging (CT/MRI)
  - Diagnosis made after fine needle aspiration (FNA)
- Excellent prognosis
  - Treated with surgery plus radioactive iodine ablation

Psammoma Bodies

- Calcifications with an layered pattern
- Seen in other neoplasms but only papillary for thyroid

Papillary Carcinoma

- Three key pathology findings:
  - Psammoma bodies
  - Nuclear grooves
  - Orphan Annie's Eye Nuclei
- Diagnosis made by nuclear findings

Nuclear Grooves

- Empty-appearing nuclei

Orphan Annie's Eyes

- Empty-appearing nuclei
Anaplastic Carcinoma

- Occurs in elderly
- Highly malignant - invades local tissues
- Dysphagia (esophagus)
- Hoarseness (recurrent laryngeal nerve)
- Dyspnea (trachea)
- Don't confuse with Riedel's ("rock hard" thyroid/young pt)
- Poor prognosis
- Pathology: Undifferentiated cells
  - No papilla, follicles, or amyloid

MEN Syndromes

- Gene mutations that run in families
- Cause multiple endocrine tumors
- MEN 2A and 2B associated with medullary carcinoma
  - Caused by RET oncogene mutation
  - Some patients have elective thyroidectomy

Follicular Carcinoma

- Similar to follicular adenoma
- Breaks through ("invades") fibrous capsule
- FNA cannot distinguish between adenomas/cancer
- Follicular pathology followed over time
  - Growth, suspicious new findings → surgery

Medullary Carcinoma

- Cancer of parafollicular cells (C cells)
- Produces calcitonin
  - Lowers serum calcium
  - Normally minimal effect on calcium levels
  - Used for monitoring
- Amyloid deposits in thyroid
  - Amyloid = protein deposits
  - Calcitonin = peptide
  - Appearance of amyloid on biopsy

Follicular Carcinoma

- Possible hematogenous metastasis
- Treatment:
  - Thyroidectomy
  - I131 to ablate any remaining tissue or metastasis

Anaplastic Carcinoma

- Occurs in elderly
- Highly malignant - invades local tissues
- Dysphagia (esophagus)
- Hearseness (recurrent laryngeal nerve)
- Dyspnea (trachea)
- Don't confuse with Riedel's ("rock hard" thyroid/young pt)
- Poor prognosis
- Pathology: Undifferentiated cells
  - No papilla, follicles, or amyloid
Adrenal Glands

Cortex and Medulla
- Cortex: Three groups of hormones
  - Mineralocorticoids (aldosterone)
  - Glucocorticoids (cortisol)
  - Androgens (testosterone)
  - Derived from mesoderm
- Medulla
  - Epinephrine and norepinephrine
  - Sympathetic nervous system control
  - Derived from neural crest

Mineralocorticoids
- Most important is aldosterone
- Key effects on kidney function
- Release controlled by RAA system
- Renin-angiotensin-aldosterone
- Increase Na+ /Water resorption
- Promote K+ /H+ excretion

Signal Transmission

Adrenal Glands
- Located above kidneys
- Arteries: Suprarenal arteries
  - Left and right
  - Superior, inferior, middle
-Veins:
  - Left adrenal → renal vein → IVC
  - Right adrenal → IVC
**Cortisol**

- Major glucocorticoid
- Synthesized by adrenal cortex
- Binds to intracellular receptors (cytosol)
  - Glucocorticoid receptor (GR)
- Translocates to nucleus
- Activates/suppresses gene transcription

**Cortisol Binding Globulin**

- Cortisol poorly soluble in plasma
- Most (>90%) serum cortisol bound to CBG
- Levels ↑ estrogen

**Adrenal Androgens**

- Small contribution to androgen production in males
- ~50% androgens for females
- Clinical relevance: congenital adrenal hyperplasia
  - Over/underproduction → abnormal sexual development
- Production stimulated by ACTH (like cortisol)

**Pituitary-Adrenal Axis**

- Controls cortisol secretion
- Hypothalamus: CRH
  - Corticotropin releasing hormone
  - Paraventricular nucleus (PVN)
- Anterior pituitary: ACTH
  - Adrenocorticotropic hormone
  - Acts on adrenal gland
  - cAMP/PKA 2nd messenger
- Adrenal: Cortisol

**Circadian Rhythms**

- Serum cortisol highest early morning (about 6 AM)
  - 10 to 20 mcg/dL
- Lowest one hour after sleep onset
  - Less than 5 mcg/dL
- Testing rarely done with single blood test

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Cortisol Effects

- Enhanced effects of glucagon, epinephrine
- Leads to insulin resistance
- Long term steroid use: diabetes

Cortisol Effects

- Activation of lipolysis in adipocytes
  - $\uparrow$ free fatty acids
  - $\uparrow$ total cholesterol, $\uparrow$ triglycerides
  - Stimulate adipocyte growth
  - Key effect: fat deposition

Cortisol Effects

- Inactivate NF-κB
  - Key inflammatory transcription factor
  - Mediates response to TNF-α
  - Controls synthesis inflammatory mediators
  - COX-2, PLA2, Lipoxygenase

Cortisol Effects

- More glucose produced by liver
  - $\uparrow$ synthesis of glucose 6-phosphatase, PEPCK
  - $\uparrow$ gluconeogenesis
  - Less glucose taken up peripherally (muscle, fat)
  - Net results: $\uparrow$ serum glucose
  - More glycogen storage in liver
  - $\uparrow$ synthesis of glycogen synthase

Corticosteroid Drugs

- Cortisone
- Prednisone
- Methylprednisolone
- Triamcinolone
- Betamethasone
- Hydrocortisone
- Dexamethasone

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Cortisol
Effects
- Muscle atrophy
- Skin effects
  - Blunted epidermal cell division in skin
  - ↓ collagen, inhibition of fibroblasts
  - Net effects: Thin skin, easy bruising, striae
- Bones: Inhibits osteoblasts
  - Steroids → osteopenia and osteoporosis

Zones of the Adrenal Glands

Zona Glomerulosa
3-β-hydroxysteroid Dehydrogenase

Aldosterone
Cortico
terone

11-deoxycorticosterone

Pregnenolone
Progesterone

Zona Medulla

Aldosterone
Synthase

Aldosterone
Cortico
terone

11-deoxycorticosterone

Pregnenolone
Progesterone

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Ketoconazole

- Antifungal
- Blocks ergosterol synthesis in fungi
- Potent inhibitor of 17,20 lyase
  - Key side effect: gynecomastia
- Also inhibits 17-alpha hydroxylase, desmolase
  - Blocks cortisol synthesis
- Can be used to treat Cushing’s syndrome
CAH
Congenital Adrenal Hyperplasia

- Loss of one of the four enzymes for cortisol synthesis
  - 21-α hydroxylase
  - 11-β hydroxylase
  - 17-α hydroxylase
  - 3-β hydroxysteroid dehydrogenase

CAH

- Enzyme deficiency syndrome
- Can cause ↑ production of other hormones
  - Mineralocorticoids
  - Androgens

Calcium
Cholesterol
Aldosterone
Cortisol
Androgens

ACTH

CAH
Congenital Adrenal Hyperplasia

- All result in low cortisol
- Stimulates ACTH release

Low Cortisol
Signs/Symptoms

- Hypoglycemia
- Nausea/vomiting
**Hydroxylase Deficiency**

- **Cholesterol**
- **Aldosterone**
- **Cortisol**
- **Androgens**

**ACTH Effects**

- High ACTH can cause **skin hyperpigmentation**
- Melanocyte stimulating hormone (MSH)
- Common precursor protein in pituitary with ACTH
- ↑ melanin synthesis

**Ambiguous Genitalia**

- Females (XX) with excess androgen exposure
- Males (XY) with deficient androgen exposure

**Androgens**

- Depend on chromosomal sex of child (XX/XY)
- Excess androgens
  - Female (XX): Ambiguous genitalia
  - Male (XY): Precocious (early) puberty
- Androgen deficiency
  - Female (XX): Normal genitalia
  - Male (XY): Female or ambiguous genitalia

**Aldosterone**

- **Deficiency**
  - Na loss → water loss
  - Hypovolemia → shock
  - Hyperkalemia
  - ↑ renin
- **Excess**
  - Na retention
  - Hypertension
  - Hypokalemia
  - ↓ renin

**Androgens**

- Signs/Symptoms
  - Depend on chromosomal sex of child (XX/XY)
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**21-α Hydroxylase Deficiency**

- ACTH
- Cholesterol
- Aldosterone
- Cortisol
- Androgens

**21-α Hydroxylase Deficiency**

- ↑ ACTH
- Cholesterol
- Aldosterone
- Cortisol
- Androgens
### 21-α Hydroxylase Deficiency
- Classic cause of CAH (90% of CAH)
- Low cortisol symptoms
- Low mineralocorticoid symptoms
- Excess androgen symptoms
  - Girls (XX): ambiguous genitalia
  - Boys (XY): precocious puberty (early onset)
- Variable symptoms based on enzyme levels
  - Classic form: 0 to 2% normal enzyme activity
  - Non-classic forms: 20-50% normal enzyme activity

### 11-β Hydroxylase Deficiency
- Similar to 21-α hydroxylase deficiency
- Low cortisol symptoms
- Girls: ambiguous genitalia
- Boys: precocious puberty
- One exception: ↑ mineralocorticoid activity
  - ↑ 11-deoxycorticosterone (weak mineralocorticoid)
  - Hypertension
  - Hypokalemia

### 17-α Hydroxylase Deficiency
- Cytochrome P450c17 enzyme (CYP17A1)
- Found in adrenal glands and gonads
- Catalyzes two reactions
  - 17-hydroxylase
  - 17,20 lyase

### 21-α Hydroxylase Deficiency
<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic, Salt-losing</td>
<td>Nausea/Vomiting</td>
</tr>
<tr>
<td></td>
<td>Volume depletion</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>7 to 14 days</td>
</tr>
<tr>
<td>Milder Forms</td>
<td>Females: Ambiguous genitalia</td>
</tr>
<tr>
<td></td>
<td>Males: Precocious puberty</td>
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</tbody>
</table>
CAH Screening
• Some states screen with newborn blood testing
• Measure level of 17-Hydroxyprogesterone
• Elevated level in 21-α hydroxylase deficiency (most common)

Disorders of Sex Development
Ambiguous Genitalia
46, XX 46, XY
Excess Androgens
Often CAH
Lack of androgens
Synthesis/Effect
Rarely due to CAH

17-α Hydroxylase Deficiency
• Females (XX):
  • Normal at birth
  • Primary amenorrhea at puberty
  • Theca cells lack of androgens \(\rightarrow\) ↓ estradiol
  • Often diagnosed at puberty
  • XX female fails to develop
  • XY phenotypic female or male fails to develop
  • Hypertension, low K+ identified

17-α Hydroxylase Deficiency
• Males (XY):
  • Female or ambiguous external genitalia
  • Absent uterus/fallopian tubes (Sertoli cells \(\rightarrow\) MIH)
  • Undescended testes

17-α Hydroxylase Deficiency
• Low cortisol
• Excess mineralocorticoids: HTN, ↓K+
• Low androgens
  • CYP17A1 : adrenal gland and gonads

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3-β Hydroxysteroid Dehydrogenase Deficiency
\(\uparrow\) ACTH

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• Low androgens
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CAH Screening
• Some states screen with newborn blood testing
• Measure level of 17-Hydroxyprogesterone
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CAH Treatment

- Many forms treated with glucocorticoids
- Replenishes cortisol
- Lowers ACTH
- Stops overproduction of other hormones
- Can also use mineralocorticoids (fludrocortisone)
Cushing’s Syndrome

**Excess Cortisol Effects**

- Stimulation of adipocytes → growth
- Progressive central obesity
- Face, neck, trunk, abdomen
- “Moon face”
- “Buffalo hump”
- Fat mound at base of back of neck

**Cortisol alters GnRH release → ↓ FSH, LH**

- Menstrual irregularities in women
  - Abnormal cycles (80%)
  - Oligomenorrhea (~30%)
  - Amenorrhea (~30%)
- Hirsutism of face in women
- Males: Erectile dysfunction

**Hypertension**

**Hyperglycemia**

**Diabetes (insulin resistance)**

**Immune suppression**

- Risk of infections, especially opportunistic

**Cushing’s Syndrome**

- Syndrome of clinical features due to excess cortisol
- Most common cause: corticosteroid medication
- Often prescribed for inflammatory conditions
  - e.g., daily prednisone for lupus
- Cushing’s disease: Pituitary ACTH-secreting tumor
  - One cause of Cushing’s syndrome

**Adrenal Disorders**

- Excess cortisol
- Insufficient cortisol
- Excess mineralocorticoids
- Tumors

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**Adrenal Disorders**

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- Hyperglycemia
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- Risk of infections, especially opportunistic
**Cushing’s Syndrome**

**Causes**
- ACTH-independent (↓ACTH)
  - Glucocorticoid therapy
  - Adrenal adenoma
- ACTH-dependent (↑ACTH)
  - Cushing’s disease (pituitary ACTH secreting tumor)
  - Ectopic ACTH (small cell lung cancer)
  - ↑ACTH \(\rightarrow\) adrenal hyperplasia \(\rightarrow\) cortisol

**Skin Changes**
- Thinning of skin
- Easy bruising
- Striae: Stretch marks
  - Purple lines on skin
  - Fragile skin stretches over trunk, breasts, abdomen
  - Thin skin cannot hide venous blood in dermis
  - Commonly occur on sides and lower abdomen

**Cushing’s Syndrome**

**Diagnosis**
- Low dose dexamethasone suppression test
  - 1mg dexamethasone (“low dose”) administered at bedtime
  - Suppresses normal pituitary ACTH release
  - Morning blood test
  - Cortisol level should be low (suppressed)
  - Cortisol remains high in Cushing’s syndrome
  - Adenomas, tumors do not suppress cortisol production

- 24-hour urine free cortisol
  - Integrates cortisol level over time
  - Salivary cortisol
  - No cortisol binding globulin in saliva
  - Free cortisol level measured at night (should be low)

- Measuring plasma cortisol difficult
  - Circadian rhythm → high levels in AM
  - Most cortisol bound to CBG
  - CBG levels can affect serum measurement

- Special note: skin hyperpigmentation
  - Can occur in ACTH-dependent Cushing’s syndrome
  - Caused by ↑ACTH not cortisol
  - ↑ACTH \(\rightarrow\) ↑MSH

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Adrenal Insufficiency

Symptoms
• Loss of cortisol
  • Weakness, fatigue
  • Weight loss
• Postural hypotension
  • Nausea, abdominal pain, diarrhea
  • Hypoglycemia
• Loss of aldosterone
  • Potassium retention → hyperkalemia
  • H+ retention → acidosis
  • Sodium loss in urine → hypovolemia

Cushing’s Syndrome

Diagnosis
• Step 1: Establish Cushing’s syndrome
• Step 2: Establish cause
• Key test is serum ACTH level

<table>
<thead>
<tr>
<th>ACTH-Dependent Causes (High ACTH)</th>
<th>ACTH-Independent Causes (Low ACTH)</th>
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<tr>
<td>Cushing’s disease</td>
<td>Steroid therapy</td>
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<tr>
<td>Ectopic ACTH</td>
<td>Adrenal adenoma</td>
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Cushing’s Syndrome

Treatment
• Surgery
  • Removal of adenoma (adrenal gland, pituitary)
  • Removal of lung tumor
  • Ketoconazole

Ketoconazole

• Antifungal
  • Blocks ergosterol synthesis in fungi
  • Also blocks 1st step in cortisol synthesis
    • Desmolase (side chain cleavage)
    • Can be used to treat Cushing’s syndrome
  • Also potent inhibitor androgen synthesis
    • Key side effect: gynecomastia

High Dose Dexamethasone

• Low dose testing (1mg)
  • Used to establish diagnosis of Cushing’s syndrome
• High dose dexamethasone test (8mg)
  • Differentiate causes of high ACTH Cushing’s syndrome
  • Will suppress cortisol in pituitary adenomas (↑ set point)
  • Will not suppress cortisol from ACTH tumors

AM Cortisol After Dexamethasone

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<tr>
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  • Sodium loss in urine → hypovolemia
**Waterhouse-Friderichsen Syndrome**
- Rare cause of acute adrenal insufficiency
- Caused by acute hemorrhage into adrenal glands
- Associated with meningococcemia
- Clinical scenario:
  - Patient with bacterial meningitis
  - Acute onset of shock

**Addison's Hyperpigmentation**
- Generalized hyperpigmentation
- Most obvious in sun-exposed areas
  - Face, neck, backs of hands
- Also areas of friction/pressure
  - Elbows, knees, knuckles,
- May occur in palmar creases
- Classic scenario:
  - GI symptoms (nausea, pain)
  - Darkening skin

**Adrenal Crisis**
- Acute adrenal insufficiency
- Abrupt loss of cortisol and aldosterone
- Main manifestation is shock
- Hypoglycemia
- Other symptoms: nausea, vomiting, fatigue, confusion
- Often when acute adrenal function cannot be met
  - Infection, surgery, trauma in patient with adrenal insufficiency
  - Patients on chronic steroids
  - "Stress dose steroids" for prevention

**Addison's Disease**
- Common Causes
  - Autoimmune adrenalitis
    - Antibody and cell-mediated disorder
    - Antibodies to 21-hydroxylase commonly seen
    - Atrophy of adrenal gland
    - Loss of cortex
    - Medulla is spared
  - Infections
    - Tuberculosis
    - Fungal (histoplasmosis, cryptococcus)
    - CMV
  - Rare: tumor metastasis especially lung

**Metastasis from Lung Cancer**
- Adrenals
  - Usually found on imaging without symptoms
- Brain
  - Headache, neuro deficits, seizures
- Bone
  - Pathologic fractures
- Liver
  - Hepatomegaly, jaundice

**ACTH Effects**
- ACTH is high in primary adrenal insufficiency
- This leads to skin hyperpigmentation
- Melanocyte stimulating hormone (MSH) shares common precursor protein in pituitary with ACTH
- ↑ melanin synthesis

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Primary Aldosteronism
Mineralocorticoid Excess
• Hypertension, classically at a young age
• Hypokalemia
• Weakness, muscle cramps
• Unreliable finding → many cases with normal K+
• Metabolic alkalosis

Adrenal Insufficiency
Diagnostic Tests
• 8 AM serum cortisol
  • Levels should be highest at this time
  • Low level indicates disease
• Serum ACTH
  • High ACTH with low cortisol = primary disease
  • Low ACTH with low cortisol = secondary disease

Adrenal Insufficiency
Important Points
• No skin findings
• ACTH is not elevated
• No hyperkalemia
• Aldosterone not effected

2° Adrenal Insufficiency
• Most common cause: glucocorticoid therapy
• Chronic suppression ACTH release
• Leads to adrenal atrophy over time
• Sudden discontinuation → hypoadrenalism

2° Adrenal Insufficiency
• Basis for “weaning” off steroids
• Slow discontinuation over time
• Basis for “stress dose steroids”
  • Patients on chronic steroids with infection, trauma, surgery
  • Risk of adrenal crisis
  • High dose of glucocorticoids administered

Primary Aldosteronism
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Adrenal Insufficiency
Diagnostic Tests
• ACTH stimulation test ("cosyntropin stim test")
  • Exogenous ACTH administered
  • Cortisol should rise 30-60 minutes later
  • Failure to rise = primary adrenal insufficiency
  • Normal rise = secondary disorder

Adrenal Insufficiency
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Primary Aldosteronism

**Most common causes**
- Bilateral idiopathic hyperaldosteronism (~60%)
- Aldosterone-producing adenoma (~30%)
  - Sometimes called Conn’s syndrome

**Diagnosis**
- Abdominal imaging for adrenal nodules/tumors
- **Adrenal vein sampling**
  - Differentiates unilateral vs. bilateral disease
  - Measure PAC and PRA in each vein

**Treatment**
- Surgical adrenalectomy
- Adenomas
- Unilateral hyperplasia
- **Spironolactone**
  - Drug of choice
  - Potassium-sparing diuretic
  - Blocks aldosterone effects

**Primary Aldosteronism**

**Diagnosis**
- Plasma aldosterone concentration (PAC)
- **Plasma renin activity (PRA)**
  - Plasma incubated
  - Renin cleaves angiotensinogen in plasma
  - Angiotensin I produced measured by assay
  - ↓PRA and ↑PAC = Primary aldosteronism
  - ↑PRA and ↑PAC = Secondary aldosteronism
  - Renal artery stenosis, CHF, low volume

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**Licorice**

- Contains glycyrrhetinic acid (a steroid)
  - Weak mineralocorticoid effect
  - Inhibits renal 11-beta-hydroxysteroid dehydrogenase
  - Large amounts → Hypertension, hypokalemia
  - Plasma aldosterone level low

**Pheochromocytoma**

- Catecholamine-secreting tumor
  - Secretes epinephrine, norepinephrine, dopamine
  - **Chromaffin cells** of adrenal medulla
  - Derivatives of neural crest
Pheochromocytoma

Treatment
• Definitive therapy: Surgery
• Pre-operative management:
  • Phenoxybenzamine (irreversible α-blocker)
  • Non-selective beta blockers (propranolol)

Diagnosis
• Metanephrines often measured for diagnosis
  • Metanephrine and normetanephrine
  • 24-hour urine collection or plasma
  • Older test: 24-hour urine collection of VMA

Clinical presentation
• Classically episodic symptoms
• Hypertension
• Headaches
• Palpitations
• Sweating
• Pallor (pale skin)

Monoamine Oxidase (MAO)
Catechol-O-methyltransferase (COMT)

Dopamine
MAO
COMT
MAO
COMT
MAO
COMT
MAO
COMT

Epinephrine
Homovanillic Acid (HVA)
Vanillylmandelic acid (VMA)

Noradrenaline
Normetanephrine
Metanephrine

Pheochromocytoma

Dopamine
Catechol-O-methyltransferase (COMT)

Epinephrine
Vanillylmandelic acid (VMA)

Dihydroxymandelic Acid
Paraganglioma
- Catecholamine-secreting tumor
- Arise from sympathetic ganglia (extraadrenal)
- Similar clinical presentation to pheochromocytoma

MIBG
Metaiodobenzylguanidine
- Chemical analog of norepinephrine
- Diagnosis of pheochromocytoma & neuroblastoma
- Concentrated in sympathetic tissues
- Labeled with radioactive iodine ($^{131}$I)
- Will concentrate in tumors → emit radiation
- Special note: thyroid gland must be protected
- Non-radioactive iodine
- Will be taken up by thyroid instead

Neuroblastoma
- Tumor of primitive sympathetic ganglion cells
- Also derived from neural crest cells
- Can arise anywhere in sympathetic nervous system
  - Adrenal gland most common (40 percent)
  - Abdominal (25 percent)
  - Thoracic (15 percent)
- Almost always occurs in children
  - 3rd most common childhood cancer (leukemia, brain tumors)
  - Most common extracranial tumor

Neuroblastoma
- Symptoms related to tumor mass effect
  - Commonly present as abdominal pain
- Can synthesize catecholamines
  - Rarely cause symptoms like pheochromocytoma
  - Urinary HVA/VMA levels used for diagnosis
- Rare feature: Opsoclonus-myoclonus-ataxia (OMA)
  - Rare paraneoplastic syndrome
  - Rapid eye movements, rhythmic jerking, ataxia
  - Half of OMA patients have a neuroblastoma

Neuroblastoma
- Diverse range of disease progression
  - Key risk factor: Age at diagnosis
  - Infants with disseminated disease often cured
  - Children over 18 months often die despite therapy
  - Younger age = better prognosis
- N-myc
  - Proto-oncogene
  - Amplified/overexpressed in some tumors
  - Associated with poor prognosis

Adrenal Adenomas
- Often discovered on abdominal imaging
  - "Adrenal incidentaloma"
- Concern for malignancy and/or functioning adenoma
Adrenal Adenomas

- May secrete cortisol or aldosterone
- Common functional tests
  - 24 hour urine metanephrines (pheochromocytoma)
  - 24 hour urine free cortisol (Cushing’s)
  - Low dose dexamethasone suppression (Cushing’s)
  - Serum PRA/aldosterone (aldosteronism)
- Often followed for growth over time (non-functional)
- Large (>5cm) often removed
Endocrine Pancreas

Insulin
- Protein hormone
- Synthesized by beta cells
- Synthesized as preproinsulin
  - Made by ribosomes of rough endoplasmic reticulum
- Preproinsulin cleaved to proinsulin
  - Transferred to Golgi apparatus
- Packaged into secretory granules
  - Proinsulin cleaved to insulin and C-peptide in granules

Insulin Structure
- Alpha chain
- Beta chain
- Disulfide bridges
- C-peptide
  - "Connecting" peptide
  - Long half-life
  - Indicator insulin production

Insulin Release
- Produced in response to: glucose, amino acids

Pancreatic Islets
Islets of Langerhans
- Millions of islets found in pancreatic tissue
- Endocrine portion of pancreas
- Beta cells: Insulin
  - Most abundant cell type
  - Centrally located
- Alpha cells: Glucagon
- Delta cells: Somatostatin
- Alpha/delta cells: Outer islet

Pancreatic Islets
- Alpha chain
- Beta chain
- Disulfide bridges
- C-peptide

Glucose
Amino Acid

Endocrine Pancreas
Jason Ryan, MD, MPH

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Glucose
Amino Acid
**Insulin Release**
- Production inhibited by epinephrine
  - Beta-2 receptors: ↑ insulin
  - Alpha-2 receptors: ↓ insulin release
  - Alpha effect is dominant effect in pancreas
  - Fight or flight response → ↑ plasma glucose

**Glucokinase**
- Beta cell enzyme
  - 1st step of glycolysis
  - Found in liver and pancreas
  - Induced by insulin
  - Insulin promotes transcription
    - High Km (rate varies with glucose)
    - High Vm (can convert lots of glucose)

**GLUT-2 Transporter**
- Bidirectional glucose transporter
  - Found in liver, kidney, beta cells
  - Liver, kidney: Gluconeogenesis
  - Beta cells: Glucose in/out based on plasma levels
  - Also found in intestine, other tissues

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**Insulin Receptor**
- Tetramer
  - Two α units
  - Two β units
  - Disulfide bonds
  - Step 1: Insulin Binding
    - Activates "Tyrosine Kinase" domains within receptor complex
    - "Tyrosine Kinase Receptor"

**Insulin Receptor**
- Step 2: Tyrosine Phosphorylation
  - Receptor phosphorylates itself
  - "Autophosphorylation"
**RAS/MAP Kinase Pathway**

- Insulin receptor can activate RAS
- G protein
- RAS can activate many growth pathways
  - Raf
  - MEK (mitogen-activated extracellular kinase)
  - MAP (mitogen-activated protein)
- Modify cell growth and gene expression

**GLUT-4 Transporter**

- Stored in vesicles in cells, especially muscle
- Insulin → PIK3 pathway → GLUT-4 Activation
- Major mechanism for increased glucose uptake
- Important muscle/fat
- Insulin exposure → GLUT-4 on surface

**PIK3 Pathway**

- Phosphatidylinositol 3–kinase Pathway
  - Catalyzes many intracellular processes
  - Glycogen formation
  - Fatty acid synthesis
  - GLUT-4 glucose transporter

**RAS/ MAP Kinase Pathway**

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**Insulin Receptor**

**Key Points**
- Tetramer of α/β subunits with disulfide bridges
  - α: extracellular
  - β: transmembrane
- Insulin binding → **tyrosine kinase** activity
- Autophosphorylation of tyrosine residues
- PI3K Pathway → **GLUT-4 glucose transporter**
- RAS/MAP Kinase Pathway: growth/gene transcription

**Insulin Dependent Organs**

- Muscle and fat
  - Use GLUT-4 for glucose uptake
  - Depend on insulin (no insulin = no GLUT-4)

**Insulin Independent Organs**

- Brain and RBCs
  - Use GLUT-1 for glucose uptake
  - Not dependent on insulin
  - Takes up glucose when available
  - RBCs: No mitochondria (depend on glycolysis)
  - Brain: No fatty acid metabolism (glucose/ketones)
- Liver, kidney, intestines
  - Also insulin independent (GLUT-2)
- Other organs: nerves, lens

**Insulin Effects**

- **Fatty acid synthesis**
  - Activates acetyl-CoA carboxylase
- **Protein synthesis**
  - Stimulates entry of amino acids into cells → protein synthesis
  - Important for muscle growth
- Key side effect insulin therapy: weight gain

**Hormone Sensitive Lipase**

- Removes fatty acids from TAG in adipocytes
- Inhibited by **insulin**
- Activated by **glucagon** and **epinephrine**
Glucagon

- Protein hormone
- Single polypeptide chain
- Synthesized by alpha cells
- Opposes actions of insulin
- Main stimulus release: low plasma glucose

Glucagon Receptor

- G-protein receptor
- Activates adenylyl cyclase
- Increases cAMP
- Activates protein kinase A (PKA)


Insulin Effects

- Na⁺ retention
  - Increases Na⁺ resorption in the nephron
- Lowers potassium
  - Enhanced activity of Na-K-ATPase pump in skeletal muscle
  - Insulin plus glucose used in treatment of hyperkalemia
- Inhibits glucagon release

Glucagon

- Increases liver (not muscle) glycogen breakdown
  - Raises blood glucose level
  - Increases gluconeogenesis

Glucagon

- Increases amino acid uptake in liver
  - More carbon skeletons for glucose via gluconeogenesis
  - Plasma amino acid levels fall
  - Activates lipolysis via hormone sensitive lipase

Glucagon Receptor

- Glucagon receptors mostly in liver
  - Many activated processes occur in liver
  - Breakdown of glycogen to raise plasma glucose
  - Gluconeogenesis
  - Most other tissues have lower density than liver
  - Not found in skeletal muscle
### Hypoglycemia

- Unconscious patient with hypoglycemia
- Treatment:
  - #1: IV dextrose
  - #2: Intramuscular glucagon
- Useful when IV access cannot be established
- Raises plasma glucose level

### Beta Blocker Overdose

- Causes bradycardia and hypotension
- Drug of choice: **Glucagon**
  - Activates adenylyl cyclase
  - Different site from beta-adrenergic agents
  - Raises cAMP \( \rightarrow \) myocyte calcium
  - Same mechanism as beta stimulation (via Gs proteins)

### Insulinoma

- Rare, pancreatic islet-cell tumor
- Occurs in adults (median age ~50 years)
- Key feature: fasting hypoglycemia
  - Insulin levels remain elevated when fasting
- "Neuroglycopenic symptoms"
  - Confusion, odd behavior
  - Sympathetic activation from low glucose
  - Palpitations, diaphoresis, tremor

### Fasting Hypoglycemia

- Differential diagnosis
  - Exogenous insulin
  - Oral hypoglycemics (sulfonylureas \( \rightarrow \) insulin)
  - Insulinoma

<table>
<thead>
<tr>
<th></th>
<th>Exogenous Insulin</th>
<th>Insulinoma</th>
<th>Oral Hypoglycemics</th>
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<tbody>
<tr>
<td>Insulin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C-peptide</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Hypoglycemic Agent Screen</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

### Glucagonoma

- Rare pancreatic tumors
- Excess glucagon secretion
- Leads to glucose intolerance
  - Elevated fasting glucose levels
  - Rare to develop DKA (insulin function intact)
MEN Syndromes
• Multiple endocrine neoplasia
• Rare inherited disorders
• Numerous endocrine tumors
• **MEN Type 1**: Insulinomas/glucagonomas
  • 3 P’s: Pituitary, Parathyroid, and Pancreas
  • Mutations of **MEN1** tumor suppressor gene

Glucagonoma
• **Weight loss**
  • Liver gluconeogenesis
  • Consumption of proteins/amino acids
• **Necrolytic migratory erythema**
  • Red, blistering rash
  • Itchy, painful
  • Fluctuates in severity
  • Genitals, buttocks, groin
  • Key clinical scenario: new diabetes and rash

Glucagonoma
• Diagnosis: ↑ plasma glucagon level
• Treatment: **somatostatin analogs** (octreotide)
  • Inhibit glucagon secretion
  • Improves symptoms

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Diabetes

Hemoglobin A1C

• Small fraction of hemoglobin is “glycated”
• Glucose combines with alpha/beta chains
• Subfraction HbA1c used in diabetes
• Non-enzymatic glycation of beta-chains
• Occurs at amino-terminal valines

Diabetes Diagnosis

• Symptoms
  • Symptoms plus glucose >200mg/dl = diabetes
  • Asymptomatic
    • Fasting blood glucose level (no food for 8 hours)

<table>
<thead>
<tr>
<th>State</th>
<th>Fasting plasma glucose</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100mg/dl</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>100 to 125mg/dl</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt;=126mg/dl</td>
</tr>
</tbody>
</table>

Terminology

• Diabetes Mellitus
  • Mellitus = sweet
  • Common disorder of blood glucose
• Diabetes insipidus
  • Insipid = lacking flavor
  • Rare disorder of low ADH activity
• Both can cause polyuria, polydipsia
• Completely different mechanisms

Diabetes Symptoms

• Often asymptomatic
  • “Silent killer”
  • Often no symptoms until complications develop
  • Basis for screening
• Classic hyperglycemia symptoms
  • Polyuria (osmotic diuresis from glucose)
  • Polydipsia (thirst to replace lost fluids)

Diabetes

Jason Ryan, MD, MPH

Chronic disorder of elevated blood glucose levels
• Caused by:
  • Insufficient insulin
  • Insufficient response to insulin (“insulin resistance”)
  • Both
Diabetic Ketoacidosis (DKA)

- Life-threatening complication of diabetes
- More common type 1
- Common initial presentation type 1
- Often precipitated by infection/trauma
- Can occur when type 1 diabetic skips insulin therapy

Type 1 Diabetes

- Mostly a childhood disorder
- Bimodal distribution
- Peak at 4-6 years
- 2nd peak 10 to 14 years of age
- Often presents with symptomatic hyperglycemia
  - Polyuria
  - Polydipsia
  - Glucose in urine
- Treatment: Insulin
**Diabetic Ketoacidosis**

**Treatment**
- **Insulin**
  - Lowers blood glucose levels
  - Shifts potassium into cells
- **IV fluids**
  - Treats dehydration

**Clinical Presentation**
- Arrhythmias (hyperkalemia)
- Cerebral edema
- Mechanism poorly understood
- Common cause of death in children with DKA

**Phosphate**
- Risk of hypophosphatemia
  - Acidosis → shifts phosphate to extracellular fluid
  - Phosphaturia caused by osmotic diuresis
  - Loss of ATP
    - Muscle weakness (respiratory failure)
    - Heart failure (↓ contractility)

**Mucormycosis**
- Fungal infection
- Caused by *Rhizopus* sp. and *Mucor* sp.
- Classically starts in sinuses
- Spreads to adjacent structures
- Thrives in high glucose, ketoacidosis conditions
- Classic complication of DKA
  - Patient with DKA
  - Fever, headache, eye pain

**Diabetic Ketoacidosis**

**Clinical Presentation**
- Abdominal pain/nausea/vomiting
- Dehydration
- Hyperglycemia
- Hyperkalemia
- Elevated plasma/urine ketones
- Glucose in urine
- Anion gap metabolic acidosis
  - Kussmaul breathing: deep, labored breathing
  - Hyperventilation to blow off CO2 and raise pH
  - Fruity smell on breath

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  - Fever, headache, eye pain
Diabetic Ketoacidosis

Treatment
- Careful monitoring potassium
  - Total body potassium is low despite hyperkalemia
  - Insulin shifts into cells → can lead to hypokalemia
  - Usually need to administer potassium
- Careful monitoring glucose
  - Continue insulin until acidosis resolves
  - Often add glucose while insulin infusion continues

Type 2 Diabetes

Risk Factors
- Major risk factor: Obesity
  - Central or abdominal obesity carries greatest risk
  - Intra-abdominal (visceral) fat > subcutaneous fat
  - Visceral fat breakdown less inhibited by insulin
  - More lipolysis → more free fatty acids
  - Decreased glucose transport into cells
  - "Apple shape" worse than "pear shape"
  - Apple shape due to increased visceral adipose tissue
  - More subcutaneous adipose tissue in pear shape
  - Weight loss improves glucose levels

Type 2 Diabetes

Risk Factors
- Family history
  - Strong genetic component (more than type I)
  - Any first degree relative with T2DM: ↑ 2-3x risk
- Insulin resistance
  - Muscles, adipose tissue, liver
  - Reduced response to insulin → hyperglycemia
  - Pancreas responds with ↑ insulin
  - Eventually pancreas can fail → ↓ insulin

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Type 2 Diabetes

Risk Factors
- Most common form of diabetes
  - Common in adults
  - Prevalence is rising
  - Also becoming more common among children

Type 2 Diabetes

Risk Factors
- Insulin resistance
  - Muscle, adipose tissue, liver
  - Reduced response to insulin → hyperglycemia
  - Pancreas responds with ↑ insulin
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Diabetic Complications

- Chronic hyperglycemia → complications
  - Cardiac disease
  - Renal failure
  - Neuropathy
  - Blindness
- Two key underlying mechanisms
  - Non-enzymatic glycation
  - Sorbitol accumulation

Acanthosis Nigricans

- Hyperpigmented plaques on skin
- Intertriginous sites (folds)
- Classically neck and axillae
- Associated with insulin resistance
  - Often seen obesity, diabetes
  - Rarely associated with malignancy
  - Gastric adenocarcinoma most common

HHS - Hyperglycemic Hyperosmolar Syndrome

- Life-threatening complication of diabetes
- More common type 2
- High glucose → diuresis
  - Markedly elevated glucose (can be >1000)
- Severe dehydration
- Different from DKA
  - Few or no ketone bodies (insulin present)
  - Usually no acidosis
  - Very high serum osmolarity → CNS dysfunction

Type 2 Diabetes

- Histology
  - Classic finding is amyloid in pancreatic islets
  - Amylin peptide normally made by beta cells
    - Precise function not known
    - Packaged and secreted with insulin
    - Pramlintide: amylin analog used for diabetes treatment
- Type 2 Diabetes
  - Classical finding is amyloid in pancreatic islets
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    - Packaged and secreted with insulin
    - Pramlintide: amylin analog used for diabetes treatment
  - Accrulates in islets in patients with type 2 diabetes

Insulin Resistance Mechanism

- Reason for insulin resistance not known
- Many data suggest insulin receptor abnormalities
- Fatty acids may activate serine-threonine kinases
  - Phosphorylate amino acids on beta chain of insulin receptors
  - Inhibiting tyrosine phosphorylation
- TNF-α may be synthesized by adipocytes
  - TNF-α can activate serine-threonine kinases

Serine

Threonine
Proteinuria in Diabetics

- Annual screening for albumin in urine
- Evidence of protein is indication for ACE-inhibitor
- ACEi shown to reduce progression to ESRD
- Potential mechanism is dilation of efferent arteriole
- Reduction in hyperfiltration

Renal Arterioles

- Hyaline arteriosclerosis
  - Thickening of arterioles
  - Also seen in HTN
  - Can result from AGEs
  - Crosslinking of collagen
  - Commonly occurs in kidneys of diabetics
  - Can involve afferent AND efferent arteriole
  - Afferent arteriole: Ischemia
  - Efferent arteriole: Hyperfiltration
  - Efferent arteriosclerosis rarely seen except in diabetes

Non-enzymatic Glycation

- Glucose added to amino groups on proteins
- No enzyme required
- Driven by high glucose levels
- Leads to crosslinked proteins
- "Advanced glycosylation end products" (AGEs)

Diabetic Kidney Disease

- AGEs → damage to glomerulus and arterioles
- Leads to end stage kidney disease in many diabetics

Atherosclerosis

- AGEs trap LDL in large vessels → atherosclerosis
- Coronary artery disease
  - Angina, myocardial infarction
- Stroke/TIA
- Peripheral vascular disease
  - Claudication
  - Arterial ulcers
  - Poor wound healing
  - Gangrene

Diabetic Kidney Disease

Diabetic Microangiopathy

- AGEs

Renal Failure

Hyperfiltration

Albuminuria

Diabetic Kidney Disease

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Glomerular Basement Membranes

- AGEs $\rightarrow$ diffuse baseline membrane thickening
- Visible on electron microscopy
- Can lead to mesangial proliferation in glomeruli
- End result is glomerulosclerosis

Kimmelstiel-Wilson Nodules

- Hallmark of nodular sclerosis of diabetes
- Pathognomonic of diabetic kidney disease

Glomerulosclerosis

- Diffuse glomerulosclerosis
  - Deposits of proteins (collagen IV)
  - Diffuse on basement membranes of glomeruli capillary loops
  - Mesangial cell proliferation
  - Also occurs with aging and hypertension
  - If severe $\rightarrow$ nephrotic syndrome
- Nodular glomerulosclerosis
  - Nodules form in periphery of glomerulus in mesangium
  - Rarely occurs except in diabetes
  - Can lead to fibrosis/scarring of entire kidney

Sorbitol Accumulation

Polyol Pathway

- Little activity at physiologic glucose levels
- Chronic hyperglycemia can lead to $\uparrow$ sorbitol
- Sorbitol is osmotic agent
- Draws in fluid $\rightarrow$ osmotic damage
- Likely involved in many diabetic complications
  - Cataracts
  - Neuropathy

Cataracts

- Sorbitol accumulates in lens
- $\uparrow$ osmolarity
- Fluid into lens
- Opacification over time
**Diabetic Retinopathy**

- Findings
  - Microaneurysms, Hemorrhages
  - Loss of pericytes
  - Excavates
  - Leakage proteins, lipids
  - Cotton-wool spots
  - Nerve infarctions
  - Occlusion of precapillary arterioles
  - Vessel proliferation (*proliferative retinopathy*)
    - Retinal ischemia → new vessel growth
    - "Neovascularization"

- Prevention: Regular foot exams

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**Diabetic Foot Disease**

- Neuropathy + ischemia can lead to:
  - Ulcers
  - Infection
  - Amputation
  - Made worse by poor wound healing from PVD

- Prevention: Regular foot exams

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**Neuropathy**

- Sorbitol can accumulate in Schwann cells
  - Myelinating cells of peripheral nerves
  - Osmotic damage → neuropathy

- Classically causes "stocking-glove" sensory loss
  - Longest axons affected most
  - Often feet/legs
  - Worse distally; better proximally
  - Loss of vibration sense, proprioception
  - Impairment of pain, light touch, temperature
  - Autonomic neuropathy
    - Postural hypotension
    - Delayed gastric emptying

**Diabetes Complications**

- Atherosclerosis
- Diabetic Kidney Disease
- Retinopathy
- Neuropathy

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<tr>
<th>Blausen gallery 2014</th>
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**Diabetic Retinopathy**

- Can cause blindness among diabetics
- Multiple factors likely involved:
  - Capillary basement membrane thickening (AGEs)
  - Hyaline arteriosclerosis
- Pericyte degeneration
  - Cells that wrap capillaries
  - Evidence of sorbitol accumulation
  - Microaneurysms
  - Rupture → hemorrhage
  - Annual screening for prevention

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  - Worse distally; better proximally
  - Loss of vibration sense, proprioception
  - Impairment of pain, light touch, temperature
  - Autonomic neuropathy
    - Postural hypotension
    - Delayed gastric emptying
## Type 1 versus Type 2

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Insulin

Type 1 and Type 2

- Type 1 diabetes treated mainly with insulin
- Type 2 diabetes: oral or SQ drugs +/- insulin
  - Initial stages: Oral and/or SQ drugs
  - Advanced disease: Insulin

Insulin Hexamers

- Insulin forms hexamers in the body
  - Six insulin molecules linked
  - Stable structure
  - Insulin usually administered subcutaneously
  - Activity related to speed of absorption
    - Insulin hexamers → slower onset of action
    - Insulin monomers → faster onset of action

Rapid Acting Insulin

- Modified human insulin
- Contain insulin with modified amino acids
- **Reduced hexamer/polymer formation**
- Rapid absorption, faster action, shorter duration
  - Onset: 15 minutes
  - Peak: 1 hour
  - Duration: 2 to 4 hours
- Often used **pre-meal**

Insulin

- Many different types available for diabetes therapy
- All vary by **time to peak** and **duration of action**
- Also vary by peak effect

- Rapid Acting Insulin
- Regular Insulin
- NPH Insulin
- Detemir
- Glargine

- Fast Peak: Short Duration
- Slow Peak: Long Duration

Insulin

- Jason Ryan, MD, MPH

- Jason Ryan, MD, MPH

- Isaac Yonemoto /Wikipedia
Regular Insulin

- Synthetic analog of human insulin
- Made by recombinant DNA techniques
- Onset: 30 minutes
- Peak: 2 to 3 hours
- Duration: 3 to 6 hours

NPH Insulin

- Regular insulin combined with neutral protamine
- Slows absorption
- Peak: 4-8 hours
- Duration: 12-16 hours

Regular Insulin

- Commonly used in hospitalized patients
  - Blood sugar elevations common with infection/surgery
  - Sliding scale dose given based on finger stick blood sugar
  - “Regular insulin sliding scale”
  - Only type of insulin that is given IV
  - IV regular insulin used in DKA/HHS
  - Used to treat hyperkalemia
    - Given IV with glucose to prevent hypoglycemia

Regular Insulin

- Made by recombinant DNA techniques
- Onset: 30 minutes
- Peak: 2 to 3 hours
- Duration: 3 to 6 hours

Insulin

- Insulin with modified amino acid structure
- Soluble in acidic solution for dosing
- Precipitates at body pH after SQ injection
- Insulin molecules slowly dissolve from crystals
- Low, continuous level of insulin
- Onset: 1–1.5 hours
- Duration: 11–24 hours
- Often given once daily

Glargine

- Insulin with modified amino acid structure
- Soluble in acidic solution for dosing
- Precipitates at body pH after SQ injection
- Insulin molecules slowly dissolve from crystals
- Low, continuous level of insulin
- Onset: 1–1.5 hours
- Duration: 11–24 hours
- Often given once daily
**Hypoglycemia**

- Major side effect of all insulin regimens
- Tremor, palpitations, sweating, anxiety
- If severe: seizure, coma
- Always check blood sugar in unconscious patients
- Dosages, frequency adjusted to avoid low glucose

**Insulin Analogs**

- Do not contain human insulin molecules
- Modified insulin structure
  - Rapid acting, Detemir, Glargine
  - Regular insulin, NPH
  - Contain human insulin molecules
  - Regular: made by recombinant techniques
  - NPH: Regular added to neutral protamine to slow absorption

**Insulin**

- Rapid-acting
  - Pre-meal
- Regular
  - Sliding scale
  - IV for treatment of DKA, hyperkalemia
- NPH, Glargine, Detemir
  - Often given as background therapy

**Detemir**

- Insulin with fatty acid side chain added
- Slow rate of absorption
  - Aggregation in subcutaneous tissue
  - Also binds reversibly to albumin
- Onset: 1–2 hours
- Duration: > 12 hours
  - Usually given once or twice daily
  - May cause less weight gain

**Insulin**

- Rapid-acting
- Pre-meal
- Regular
  - Sliding scale
  - IV for treatment of DKA, hyperkalemia
- NPH, Glargine, Detemir
  - Often given as background therapy
Weight Gain

- Occurs in most patients on insulin
- Insulin promotes fatty acid and protein synthesis
Treatment of Diabetes

Type 1 and Type 2

- Type 1 diabetes treated mainly with insulin
- Type 2 diabetes: oral or SQ drugs +/- insulin
  - Initial stages: Oral and/or SQ drugs
  - Advanced disease: Insulin

Hemoglobin A1C

- Used to monitor therapy
- Too high = ↑ complications
- Too low = Risk of hypoglycemia
- Goal of ≤7.0% often used in many patients

Lifestyle Modifications

- Newly diagnosed type 2 diabetes
  - Weight loss, exercise improve glucose levels
  - First line treatment usually lifestyle modification
    - Usually a 3-6 month trial if initial A1c not markedly ↑

Oral/SQ Antidiabetic Agents

- Biguanides (Metformin)
- Sulfonylureas/Meglitinides
- Glitazones
- Glucosidase Inhibitors
- Amylin Analogs
- GLP-1 Analogs
- DPP-4 Inhibitors
- SGLT2 inhibitors

Biguanides

- Metformin
  - Oral therapy
  - Exact mechanism unknown
  - Primary effect: ↓ hepatic glucose production
    - Inhibits gluconeogenesis
Biguanides
Metformin

- **Lactic Acidosis**
  - Almost always occurs associated with:
    - Renal insufficiency
    - Liver disease or alcohol abuse
    - Acute heart failure
    - Hypoxia
    - Serious acute illness
  - Metformin not used in patients with low GFR
  - Often "held" when patients acutely ill
  - Also held during IV contrast tests

- **Biguanides**
  - **Metformin**
    - Rarely can cause **lactic acidosis**
      - Exact mechanism unclear/controversial
      - Metformin can increase conversion of glucose to lactate
      - Beneficial for lowering glucose levels
      - Too much \( \rightarrow \) lactic acidosis
      - Can be life threatening

- **Biguanides**
  - **Metformin**
    - **Other effects**
      - Reduced glucose absorption from GI tract
      - Direct stimulation of glycolysis in tissues \( \rightarrow \) glucose uptake
      - Reduced glucagon levels
    - Leads to \( \uparrow \) **insulin effect** (insulin sensitivity)
      - Insulin levels fall slightly on therapy

- **Biguanides**
  - **Metformin**
    - Usually 1st line in type 2 diabetes
      - Associated with weight loss
      - Rarely causes hypoglycemia (unlike insulin/sulfonylureas)
    - Does not depend on beta cells
      - Can be given to patients with advanced diabetes

- **Biguanides**
  - **Metformin**
    - **Lowers serum free fatty acids**
      - ↓ substrates for gluconeogenesis
      - ↓ triglycerides
      - Small ↓ LDL
      - Small ↑ HDL

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      - ↓ triglycerides
      - Small ↓ LDL
      - Small ↑ HDL
**Meglitinides**

- Repaglinide, Nateglinide
- Oral therapy
- Different chemical structure from sulfonylureas
- Similar mechanism
  - Close K⁺ channels in beta cells → ↑ insulin secretion
- Short acting
- Given prior to meals
- Major side effect is hypoglycemia
- No sulfur → can be used in sulfa allergy

**Sulfonylureas**

- Oral drugs
- Each generation more potent
- ↓ dosage used → ↓ side effects
- First generation
  - Tolbutamide, Chlorpropamide, Tolazamide
- Second generation
  - Glyburide, glipizide
- 3rd generation: Glimepiride

**Adverse Effects**

- Hypoglycemia is the most common side effect
- Glucagon levels fall (unclear mechanism)
- May occur with exercise or skipping meals

**Sulfonylureas**

- Can also cause weight gain
  - More insulin release
  - Insulin causes weight gain

**Meglitinides**

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**Sulfonylureas**

- Bind to sulfonylurea receptor in pancreas
- Associated with ATP-dependent K⁺ channel in beta cells
- Sulfonylureas close K⁺ channels in beta cells
- Changes resting potential
- Results in depolarization (Ca influx)
- More sensitive to glucose/amino acids
- ↑ insulin release (“insulin secretagogues”)
Thiazolidinediones (TZDs)
Pioglitazone, Rosiglitazone
- Oral therapy
- Decreases insulin resistance

Thiazolidinediones
Potential mechanisms
- GLUT-4
  - Glucose transporter
  - Transcription upregulated
- Adiponectin
  - Adipocyte secretory protein
  - ↑ Insulin sensitivity via several mechanisms
  - Signaling may lead to improved glucose levels
- Antagonism of TNF alpha insulin resistance
  - TNF-α levels fall

Thiazolidinediones
Adverse Effects
- Weight gain
  - May cause proliferation of adipocytes
  - Also lead to fluid retention
- Risk of hepatotoxicity
  - Troglitazone removed from market due to liver failure

Thiazolidinediones
(Pioglitazone, Rosiglitazone)
- Act on PPAR-γ receptors
  - Nuclear receptor
  - Highest levels in adipose tissue
  - Also found in muscle, liver, other tissues
  - Modulate expression of genes
  - TZDs bind PPAR-gamma
  - TZD-PPAR bind retinoid X receptors (RXR)
  - Complex modifies gene transcription

NOTE: Fibrates activate PPAR-α
Lower triglycerides

Glucosidase Inhibitors
Acarbose, Miglitol, Voglibose
- Competitive inhibitors of intestinal α-glucosidases
  - Sucrase, maltase, glucoamylase, dextranase
  - Enzymes of brush border of intestinal cells
  - Hydrolyze starches, oligosaccharides, disaccharides
  - Slows absorption of glucose
  - Less absorption upper small intestine
  - More in distal small intestine

Edema
- Occurs in ~5% patients
- Due to PPAR-γ effects in nephron → ↑ Na retention
- Risk of pulmonary edema
- Not used in patients with advanced heart failure

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- Oral therapy
- Decreases insulin resistance

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DPP-4 Inhibitors

- Sitagliptin, Linagliptin
- DPP-4: Dipeptidyl peptidase 4
- Enzyme expressed on many cells
- Inhibits release of GIP and GLP-1
- Inhibition → ↑ GLP-1
- Oral drugs, once a day
- Side effects: Infections
- Reports of urinary and respiratory infections

GLP-1 Analogs

- Exenatide, Liraglutide
- Exenatide: Usually given SQ prior to meals
- Once weekly version available
- Liraglutide: SQ once daily
- GI side effects: nausea, vomiting, diarrhea

Amylin Analogs

- Pramlintide
- Amylin: protein stored in beta cells
- Co-secreted with insulin
- Several effects (mechanisms poorly understood)
  - Suppresses glucagon release
  - Delays gastric emptying
  - Reduces appetite
  - Allows insulin to work more effectively

Incretins

- Hormones that ↑ insulin secretion
- GIP (glucose-dependent insulinotropic peptide)
  - Produced by K cells of small intestine
  - Stimulates insulin release (similar to GIP)
  - Also blunts glucagon release, slows gastric emptying
  - Oral glucose metabolized faster than IV glucose

Amylin Analogs

- Pramlintide
  - Given SQ with meals
  - Always given with insulin (type 1 or type 2)
  - Hypoglycemia may result → need to ↓ insulin dose
  - Can also cause nausea

Glucosidase Inhibitors

- Acarbose, Miglitol, Voglibose
  - Taken orally before meals
  - Less spike in glucose after meals
  - Lowers mean glucose level → lowers A1c
  - Less insulin used ("insulin sparing")
  - Main side effect: GI upset
    - Flatulence
    - Diarrhea

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SGLT2 Inhibitors
Canagliflozin, Dapagliflozin

- SGLT2
  - Expressed in proximal tubule
  - Reabsorbs ~90% percent filtered glucose
  - Inhibition → loss of glucose in urine
    - Lowers glucose levels
    - Also causes mild osmotic diuresis

Proximal Tubule

SGLT2 Inhibitors
Canagliflozin, Dapagliflozin

- Oral drugs taken once daily
- Lead to mild weight loss
- May improve outcomes in heart failure
- Adverse effects
  - Vulvovaginal candidiasis
  - UTIs
- Not recommended with advanced renal disease

Diabetes Therapy
Helpful Tips

- Renal failure: Avoid metformin (lactic acidosis)
- Advanced heart failure
  - Avoid TZDs (fluid retention)
  - Avoid metformin (lactic acidosis)
- Insulin generally safe with any comorbidity

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Reproductive Hormones

SHBG
Sex Hormone Binding Globulins
- Glycoproteins
- Produced by the liver
- Binds androgens more than estrogens

A > E
Estrogen Amplification

- Free hormones → clinical effects
- ↑ SHBG → ↓ free androgens and estrogens
  - More effect on androgens
  - ↑ ratio estrogens to androgens
- "Amplification" of estrogen effects

Cirrhosis

- ↑ estrogen effects
  - Gynecomastia
  - Spider nevi
  - Palmar erythema
  - Testicular atrophy
  - Impotence
- ↑ SHBG → ↑ estrogen effects
- Clinical features of Testosterogens/androgens

Puberty

- FSH and LH are low before puberty
- Rise at puberty in boys and girls

GNRH

Gonadotropin-releasing hormone

- Peptide produced by hypothalamus
- Released in pulses ("pulsatile")
  - Frequency and amplitude of pulses varies
  - Changes effect release of LH/FSH from pituitary

Reproductive Hormones

- Hypothalamus: GnRH
- Pituitary:
  - Follicle stimulating hormone
  - Luteinizing Hormone
- Testes/Ovaries
  - Androgens/estrogens

Cirrhosis

- ↑ estrogen effects
- Gynecomastia
- Spider nevi
- Palmar erythema
- Testicular atrophy
- Impotence
- Altered metabolism/excretion → ↑ estrogen
- ↑ SHBG → ↑ estrogen effects
- Clinical features of ↑estrogens/↓androgens

SHBG

Sex Hormone Binding Globulins

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Estrogen Amplification

- Free hormones → clinical effects
- ↑ SHBG → ↓ free androgens and estrogens
  - More effect on androgens
  - ↑ ratio estrogens to androgens
- "Amplification" of estrogen effects

Gonadotropin-releasing hormone

- Peptide produced by hypothalamus
- Released in pulses ("pulsatile")
  - Frequency and amplitude of pulses varies
  - Changes effect release of LH/FSH from pituitary

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Gonadotropin-releasing hormone

- Peptide produced by hypothalamus
- Released in pulses ("pulsatile")
  - Frequency and amplitude of pulses varies
  - Changes effect release of LH/FSH from pituitary
Kallmann Syndrome

- Absence of GnRH secretion from hypothalamus
- Impaired migration of GnRH neurons from origin in olfactory bulb to hypothalamus
- Almost always occurs in males (5:1 ratio)
- Key features: hypogonadism and anosmia
- Low GnRH/FSH/LH/Testosterone
- Delayed puberty
- Small testes

Leuprolide

- GnRH agonists
  - Derived from GnRH
  - D-amino acid substitution for native L-amino acid
  - Resistant to degradation
  - ↑ half-life → occupies receptors for prolonged period of time

Leuprolide

- Uses
  - Pulsatile (rarely done)
  - Stimulation of LH/FSH release
  - Administered by infusion pump
  - Dose varies about every 90 minutes
  - Used to create LH surge for ovulation (infertility)

Leuprolide

- Initial binding can stimulate LH/FSH release
- Chronic treatment → ↓ LH/FSH
- Down-regulation of GnRH receptor
- Pituitary desensitization
- Suppresses ovarian follicular growth and ovulation
- Low levels of estradiol and progesterone
  - Similar to menopause

GnRH

- Gonadotropin-releasing hormone
- Gq protein system with IP3 second messenger
- PIP2 = Phosphatidylinositol bisphosphate
- IP3 = Inositol trisphosphate
- DAG = Diacylglycerol

Eak435s /Wikipedia
Pituitary Reproductive Hormones

- LH, FSH
- Proteins
- LH, FSH, TSH and HCG are "heterodimers"
  - Dimer = two molecules; hetero = different
- Two chains: α and β
- Same α, different β

Pituitary Hormones

- All have a **cAMP second messenger system**
- ATP → cAMP → Effects
Male Reproductive Hormones

Estradiol

- Testosterone also converted to estradiol
- Occurs in adipose tissue and Leydig cells
- Enzyme: Aromatase
- Some testosterone effects mediated by estradiol

Testosterone

Aromatase

Estradiol (17β-estradiol)

Finasteride

- 5-α reductase inhibited by finasteride
- Used for treatment of prostatic hyperplasia
- Also used to treat hair loss in men

Testosterone

Dihydrotestosterone (DHT)

5-α reductase

Finasteride

Testosterone

Androstenedione

Cholesterol

DHEA

Adrenal Cortex

Leydig Cell

Testosterone

Dehydroepiandrosterone (DHEA)

Androstenedione

Dihydrotestosterone (DHT)

5-α reductase

Testosterone

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Testosterone

Aromatase

Estradiol (17β-estradiol)
**Testosterone Effects**

**Males**

- **Leydig cells**
  - Testosterone → Effects
  - Testosterone → Dihydrotestosterone (DHT) → Estradiol (17β-estradiol) → Effects

**Fetus**

- Development of testes requires Y chromosome
  - SRY *gene* produces testis determining factor
  - All males (XY) born with testes
  - "Chromosomal sex" determined by XX/XY
  - Internal/external genitalia requires hormones

**Leydig cells**

- **Testosterone**
  - Estradiol (17β-estradiol)
  - Dihydrotestosterone (DHT)

**Males**

- Different effects on different growth stages
  - Fetus
  - Puberty
  - Adult

**Testosterone Effects**

**Fetus**

- **Development of testes requires Y chromosome**
  - SRY *gene* produces testis determining factor
  - All males (XY) born with testes
  - "Chromosomal sex" determined by XX/XY
  - Internal/external genitalia requires hormones

**Testosterone Effects**

**Fetus**

- **Testes**
  - Sertoli cells
  - Spermatogonia

**Testosterone**

- **Estradiol**
  - **(17β-estradiol)**
  - **Dihydrotestosterone (DHT)**

**5-α Reductase Deficiency**

- Autosomal recessive disorder of sexual development
- 46,XY male able to make testosterone, not DHT
5-α Reductase Deficiency

- Normal internal genitalia
  - Normal epididymis, vas deferens, seminal vesicles
  - Empty into a blind-ending vagina
- External genitalia predominately female
  - Absent external male genitalia
  - Range of female genitalia seen +/- hypospadias
  - Sometimes diagnosed at birth due to ambiguous genitalia

- Typical case
  - Male with ambiguous genitalia
  - Female child with masculinization at puberty
  - Blind vagina
  - Absence of uterus
  - Bilateral undescended testes
  - Normal testosterone levels

Testosterone Effects

Puberty

- Enlargement of the scrotum, and testes
- Increased penis size
- Enlargement of seminal vesicles/prostate
- Growth of pubic hair
- Hair on face/underarms
- Deepening of voice

- Growth spurt (via estrogens)
  - Increased linear growth
  - Closure of epiphyseal plates

Acne

- Associated with increased sebum
- Secretion of sebaceous glands
- Androgen receptors on sebaceous glands
- Androgens stimulate growth/secretions
- Acne common in puberty
- Also common in other forms androgen excess
  - Polycystic ovarian syndrome
  - Congenital adrenal hyperplasia

- Prostate growth
  - Finasteride \( \rightarrow \) DHT \( \rightarrow \) Treatment of BPH
  - Testosterone therapy \( \rightarrow \) BPH
  - May effect lipids
  - Exogenous testosterone \( \rightarrow \) HDL/\( \) LDL
  - Male pattern balding
Spironolactone

- **Potassium sparing diuretic**
- Blocks effects of aldosterone
- Used in hypertension, heart failure
- **Key side effect:** gynecomastia (~10%)
- Blocks androgen receptor
- ↓ androgen production from androstenedione
- Result:
  - ↑ estrogen effects
  - ↓ androgen effects

Anabolic Steroids

- **High dosages** of androgens used by body builders
- Exogenous testosterone
- Androgen precursors
- All lead to ↑ testosterone effects → ↑ muscle mass
- **Adverse effects**
  - ↑ HDL/↑ LDL
  - Erythrocytosis
  - Small testes (suppression of FSH/LH)
  - Anospermia
  - Gynecomastia

Testosterone Therapy

- Used in male hypogonadism
- Results in:
  - Increased muscle mass
  - Increased bone density
- **Potential adverse effects**
  - ↑ hematocrit
  - Acne
  - Balding
  - Worsening BPH

Male Hypogonadism

- Many congenital and acquired causes
- May occur with **aging**
  - ↓ serum testosterone
  - ↑ sex hormone-binding globulin (SHBG)
  - ↓ serum free testosterone
- May be associated with:
  - ↓ sexual function
  - ↓ bone mass
  - Anemia
- Limited data on hormone replacement for decreased testosterone due to aging

Spermatogenesis

- Suppressed by exogenous testosterone
- Testosterone suppresses LH secretion
- ↑ testosterone from Leydig cells
- Exogenous hormone weak activity in testes
- ↓ spermatogenesis

Androgenic Alopecia

- Most common type of hair loss in men
- Anterior scalp, mid scalp, temporal scalp, and vertex
- Caused by **androgens**
  - Occurs after puberty
  - Will not occur with androgen deficiency
- **DHT** is key androgen
  - Responds to finasteride treatment

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**Sertoli Cells**
- Form **blood-testis barrier**
- Tight junctions between adjacent Sertoli cells
- Isolates sperm
- Protection from autoimmune attack

**Spironolactone**
- Acne, hirsutism, alopecia in women
- Blunts testosterone effects
- Enhances estrogen effects
- Amenorrhea
  - Stimulates progesterone receptors

**Sertoli Cells**
- Support and nourish developing spermatozoa
- Regulate spermatogenesis

**Spironolactone**
- Eplerenone
  - Alternative to spironolactone
  - Does not cause gynecomastia
  - Can be used in heart failure

**Sertoli Cells**
- Stimulated by FSH
- Supported by Leydig cell testosterone (paracrine)
- Need FSH and LH for normal spermatogenesis

**Spironolactone**
- Acne, hirsutism, alopecia in women
- Blunts testosterone effects
- Enhances estrogen effects
- Amenorrhea
  - Stimulates progesterone receptors

**Spironolactone**
- Eplerenone
  - Alternative to spironolactone
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**Sertoli Cells**
- Secrete **inhibin B**: Inhibits FSH
**Disorders of Sex Development**

**Ambiguous Genitalia**
- Abnormal Puberty
- 46, XX 46, XY

**Mullerian Structures**
- YES
- Often
- CAH

**Gonadal Dysgenesis**
- NO
- Lack of androgens
- CAH
- CAIS
- ↓ DHT

---

**Male Development**

- **Y Chromosome**
  - SRY
  - Testes
  - Mesonephric Ducts

- **Testosterone**
  - DHT
  - External genitalia
  - Penis/Scrotum
  - Prostate

- **Internal Genitalia**
  - Seminal vesicles
  - Epididymis
  - Vas deferens

---

**Anti-mullerian Hormone**

- In utero (XX or XY): Two systems
  - Indifferent gonad (can develop into ovaries or testes)
  - Paramesonephric (Mullerian) duct: female structure
  - Mesonephric (Wolffian) duct: male structures
  - Y chromosome → testes → Sertoli cells
  - Secretion of anti-mullerian hormone
  - Mullerian inhibitory hormone/substance
  - Degeneration of mullerian system
  - Leaves gonad and mesonephric ducts

---

**CAIS**

- Complete Androgen Insensitivity Syndrome
  - Mutation of androgen receptor in males (XY)
  - No ovaries; testes form in utero (SRY gene)
  - No cellular response to androgens
  - No internal or external male genital development
  - Sertoli cells (testes) present → MIH
  - Degeneration of mullerian structures
  - Absent uterus, fallopian tubes

---

**CAIS**

- Complete Androgen Insensitivity Syndrome
  - At puberty:
    - Breasts develop (testosterone → estrogen)
    - No armpit/pubic hair (depends on androgens)
    - Amenorrhea (no uterus)
    - Abdominal testes

---

**Sertoli Cells**

- Secrete androgen-binding protein (ABP)
  - Raises/maintains local testosterone levels
  - Intra-testicular testosterone concentration 100x peripheral
- Produce anti-mullerian hormone
  - Results in degeneration of mullerian ducts

---

**Anti-mullerian Hormone**

- Secrete androgen-binding protein (ABP)
  - Raises/maintains local testosterone levels
  - Intra-testicular testosterone concentration 100x peripheral
- Produce anti-mullerian hormone
  - Results in degeneration of mullerian ducts

---

**Disorders of Sex Development**

- Ambiguous Genitalia
  - Abnormal Puberty
  - 46, XX
- Mullerian Structures
  - YES
  - Often
  - CAH
- YES
  - Gonadal Dysgenesis (No MIH)
  - Lack of androgens
  - CAH
  - CAIS
  - ↓ DHT
**Varicocele**
- Dilatation of pampiniform plexus of spermatic veins

**Bilateral Undescended Testes**
- Phenotypical male with bilateral non-palpable testes
- Dangerous cause: **congenital adrenal hyperplasia**
  - Female (XX) exposed to increased androgens
  - Ambiguous genitalia may appear male with absent testes
  - Risk of shock from low cortisol
  - Key tests: ACTH, Cortisol
- Testes may be absent
  - Agenesis or atrophy (intrauterine vascular compromise)
  - Serum testing often done
  - Absent testes: ↑LH/FSH, absence of MIH

**Cryptorchidism**
- “Hidden testes”
- Usually due to undescended testes
  - Abdominal
  - Inguinal canal
  - Can be unilateral/bilateral
- Treatment
  - Testes may descend on their own
  - Usually occurs by 6 months of age
  - **Orchiopexy**
    - Surgical placement of the testis in scrotum
  - Sperm counts usually become normal
  - Done after 6 months of age

**Temperature Effects**
- Spermatogenesis requires ↓ temperature
- Sertoli cells sensitive to temperature
  - ↓ spermatogenesis with higher temperature
  - ↓ inhibin production with higher temperature (FSH)
  - Leydig cells less sensitive
    - Testosterone production usually maintained higher temps

**Cryptorchidism Complications**
- Low sperm counts
  - ↑ temperature effects on Sertoli cells
  - **Low inhibin levels**
  - ↑ risk of germ cell tumors
  - Inguinal hernias
  - Testicular torsion
    - Testicle rotates → twists spermatic cord
    - Compression of veins → ↓ blood flow
    - Hemorrhagic infarction

**Cryptorchidism Temperature Effects**
- Spermatogenesis requires ↓ temperature
- Sertoli cells sensitive to temperature
  - ↓ spermatogenesis with higher temperature
  - ↓ inhibin production with higher temperature (↑FSH)
- Leydig cells less sensitive
  - Testosterone production usually maintained higher temps
Varicocele

- Caused by obstruction to outflow of venous blood
- More common on left
  - Left spermatic vein → left renal (long course)
  - Compressed between aorta and superior mesenteric artery
  - "Nutcracker effect"
  - Right vein drains directly to IVC
- Associated with renal cell carcinoma
  - Invades renal vein

Varicocele

- Scrotal pain and swelling
  - "Bag of worms"
- More swelling with:
  - Valsalva
  - Standing
- Diagnosed by ultrasound
- Can cause infertility
  - ↑ temperature
  - Poor blood flow

Varicocele

- Treatment
  - Surgery (varicocelectomy)
    - Isolate dilated/abnormal veins
    - Redirect blood flow to normal veins
  - Embolization
    - Interventional radiology procedure
    - Catheter inserted into dilated/abnormal veins
    - Coil or sclerosants used to clot off veins

Varicocele

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Female Reproductive Hormones

**Estrogens**

- **Potency:** Estradiol > Estriol > Estrone

**Theca Cells**
- Convert cholesterol into androstenedione
- Stimulated by LH (via cAMP 2nd messenger)

**Granulosa Cells**
- Convert androstenedione into estradiol
- Stimulation by FSH (via cAMP 2nd messenger)
- Also produce inhibin → suppresses FSH

**Ovarian Follicle**
- Egg surrounded by cells
- Two key cell types: theca and granulosa cells

**Hormone Synthesis**

- **Estradiol (17β-estradiol)**
- **Estriol**
- **Estrone**

**Potency:** Estradiol > Estriol > Estrone
Estrogen Effects
• Growth of follicle
  • Theca/Granulosa cells → estradiol → follicular growth
• In crease SHBG
  • Amplifies estrogen effects
• Lipids
  • Raises HDL
  • Lowers LDL

Estrogen Effects
Puberty
• Breast enlargement
• Pigmentation of areolas
  • Also seen in pregnancy
• Female body habitus
  • Narrow shoulders, broad hips
  • Female fat distribution in breasts and buttocks
  • Note: Pubic and axillary hair from androgens

Estrogen Effects
Pituitary
• ↓ FSH secretion (negative feedback)
• ↓ LH secretion (negative feedback)
• Exception: Can trigger LH surge (positive feedback)

Estrogen Effects
• Growth of follicle
  • Theca/Granulosa cells → estradiol → follicular growth
• Increase SHBG
  • Amplifies estrogen effects
• Lipids
  • Raises HDL
  • Lowers LDL

Progesterone
• Synthesized by corpus luteum
  • Also placenta, adrenal glands, testes
• Most bound to albumin
• Short half life → metabolized by liver
• Main target is uterus, cervix, vagina

Progesterone Effects
• Many effects oppose estrogen
  • Decreases expression estrogen receptors
  • Many effects favorable to pregnancy

Progesterone Effects
• Secretory phase of uterine cycle
• Thickens cervical mucus
  • Prevents sperm entry
• Prevents uterine contractions
  • ↓ uterine excitability
  • ↑ membrane potential of uterine smooth muscle
  • Uterine smooth muscle relaxation
• Raises body temperature (seen in pregnancy)
• Inhibits LH/FSH release
**Hormonal Changes**

- Estrogen levels high during reproductive years
- Higher in obese women
  - Androgens → estrone in adipose tissue
- High estrogens levels may lead to pathology:
  - Endometriosis
  - Uterine fibroids

![Hormonal Changes Diagram](image)

**Oral Contraceptives**

- Analogs of estrogens and progesterone
  - "Estrogens and progestins"
- Progestin only
  - Oral "mini pill"
  - Medroxyprogesterone injection (Depo-Provera)
- Combination pills
  - Contain estrogen and progesterone

**Progestin Only**

- Suppress ovulation via negative feedback on FSH/LH
- Thickens cervical mucus
- Obstructs sperm
- May protect against PID
- Thins endometrium
- Prevents implantation

**Progestin Only**

- Disadvantages
  - Same time every day (+/- 3 hours)
  - Irregular bleeding, spotting
- Advantages
  - No estrogen risks/side effects
Combination OCPs

- Combination of progestin and estrogen
- Estrogen stabilizes endometrium
  - Less breakthrough bleeding
- Better suppression of follicular growth
  - Progesterone suppresses LH
  - Estrogen suppresses FSH
- Estrogen increases effect of progesterone
  - More progesterone receptors

Combination OCP Risks

- Thrombosis
  - Estrogen increases clotting factors
  - Usually venous thrombosis: DVT/PE
  - Rarely arterial thrombosis: stroke/MI
- Cancer
  - Conflicting data
  - May ↓ risk of endometrial and ovarian cancer
  - May ↑ risk breast, cervical, liver cancer

Combination OCPs

- Contraindications
  - Smokers >35 years of age
  - Risk of CV events
  - History of DVT/PE

Medroxyprogesterone

- Depo-Provera
  - Injectable, progestin-only contraceptive
  - Intramuscular or subcutaneous
  - Once every 3 months

Combination OCP Risks

- Breakthrough bleeding
  - Most common side effect
  - More frequent if low estrogen component
  - Hypertension (usually mild)
Menstrual Cycle

Basic Principles

- Phases
  - Follicular (growth of follicles)
  - Ovulation
  - Luteal (preparation for pregnancy)

Ovaries

Basic Principles

- Contain follicles
  - Spherical collection of cells
  - Contains a single oocyte
  - Each menstrual cycle one egg matures/releases

Ovarian Follicle

- Egg surrounded by cells
- Two key cell types: theca and granulosa cells

During menstrual cycle, follicles mature
One “dominant” follicle will release egg

Menstrual Cycle

Basic Principles

- Phases
  - Follicular (growth of follicles)
  - Ovulation
  - Luteal (preparation for pregnancy)
Menstrual Cycle

**Follicular phase**
- ↑ GnRH pulse frequency
- ↑ FSH → ↑ estradiol production from ovaries
- Recruitment of follicles
- ↑ estradiol → ↓ FSH/LH (negative feedback)
- Selection of one dominant/ovulatory follicle
- 10-14 days (varies in length)

**Luteal phase**
- Eventually corpus luteum degrades
- ↓ progesterone → menstruation
- Occurs 14 days after ovulation
- If fertilization occurs:
  - Embryo makes human chorionic gonadotropin (hCG)
  - Maintains the corpus luteum and progesterone production
  - Progesterone maintains suppression of LH/FSH

**Corpus luteum** forms
- Temporary endocrine gland formed from follicle
- Produces large amounts of progesterone
- Also some estradiol
- Progesterone/estradiol → ↓ LH/FSH
- Negative feedback

**Mittelschmerz**
- Mid-cycle pain
- Due to:
  - Enlargement of follicle or follicular rupture with bleeding
- Usually mild, unilateral pain
- Usually resolves in hours to days
- Can mimic other disorders (appendicitis)

**Mid-cycle surge**
- Switch from negative feedback to positive feedback
- Estradiol triggers ↑ frequency GnRH pulses → LH surge
- Oocyte released from follicle ~36 hours after LH surge
- Basis for ovulation testing
  - Urine detection of LH

**Ovulation**
- Basis for ovulation testing
  - Urine detection of LH

**Follicular phase**
- ↑ GnRH pulse frequency
- ↑ FSH → ↑ estradiol production from ovaries
- Recruitment of follicles
- ↑ estradiol → ↓ FSH/LH (negative feedback)
- Selection of one dominant/ovulatory follicle
- 10-14 days (varies in length)
Menstrual and Uterine Cycles

Uterine Cycle

- Changes in endometrium
- Driven by estrogens and progesterone
- Parallels ovarian cycle
- Two phases:
  - Proliferative phase = follicular phase of ovary
  - Secretory phase = luteal phase of ovary

Menstruation

- Occurs after ovulation
- Progesterone inhibits proliferation of endometrium
- Numerous secretions released to prepare for embryo
- Changes in blood vessels
  - Vessels grow and coil
  - Form "spiral arteries" about 9th postovulatory day
  - Critical for implantation, support of fertilized egg

Uterine Cycle

- Stimulation by estrogens
- Endometrial thickness increases (>10x)
- Growth of glands, stroma, blood vessels

Amenorrhea

- Primary amenorrhea
  - Failure of menses at puberty
  - Usually anatomic or genetic abnormality
- Secondary amenorrhea
  - Cessation of normal menses after prior normal periods
Secondary Amenorrhea

- Low body weight
- "Functional hypothalamic amenorrhea"
- Stress plus low caloric intake → ↓ GnRH/LH/FSH
- Patients respond to pulsatile GnRH
- Can occur in anorexia

Secondary Amenorrhea

- Most common cause: pregnancy
- Screen with HCG measurement
- Thyroid disease (hypo/hyper)
- Prolactinoma
  - Inhibition of GnRH release → ↓ LH/FSH
- Cushing syndrome

Progestin Challenge

- Older test for causes of amenorrhea
- Many false positives
- Administration of progestin (oral or IM)
- Observation of menstrual bleeding within 7 days

Progestin Challenge

- Bleeding
  - Indicates estrogen is present
  - Suggests anovulation
  - Corpus luteum not forming (inadequate progesterone)
  - Classic cause: PCOS
- No bleeding
  - Suggests estrogen not present (ovarian dysfunction)
  - Or menstrual outflow problem
  - Can follow-up with estrogen-progestin challenge
- Common cause: Menopause

Mullerian Dysgenesis

- Cause of primary amenorrhea
- Failure of Mullerian duct development
- Absent upper vagina and/or uterus
- Ovaries normal
- Estrogen/progesterone levels normal
- Normal LH/FSH levels

Secondary Amenorrhea

- Low body weight
  - "Functional hypothalamic amenorrhea"
  - Stress plus low caloric intake → ↓ GnRH/LH/FSH
  - Patients respond to pulsatile GnRH
  - Can occur in anorexia
Menopause

- Permanent cessation of menstrual periods
- Cause by depletion of ovarian follicles
- Median age = 51 years
- Usually preceded by abnormal periods
- Loss of estrogens and progesterone from ovaries

Menopause

- Loss of estradiol production from ovaries
- Source of estrogen becomes adipose tissue
- Aromatase converts androstenedione to estrone
- Also loss of inhibin production from follicles
- Inhibin normally suppresses FSH release
- ↑ FSH is an early finding approaching menopause
- Eventually FSH and LH levels both elevated

Menopause

Symptoms

- Hot flashes
  - Subjective sensation of warmth
  - Usually lasts a few minutes and passes
  - Associated with drop in estrogen levels
  - Can be treated with hormone replacement
- Vaginal atrophy
  - Thin, dry, friable
  - Loss of estrogen stimulation

Menopause

Symptoms

- Osteoporosis
  - Bone loss from lack of estrogen
- Cardiovascular disease
  - Risk increases after menopause
  - May be due in part due to estrogen deficiency

HRT

Hormone Replacement Therapy

- Oral or transdermal estradiol
- Progestin added in women with intact uterus
- Prevents endometrial hyperplasia

HRT

Hormone Replacement Therapy

- Benefits:
  - Relieves hot flashes
  - Improves bone density
- Possible risks:
  - ↑ risk of DVT/Stroke/MI
  - ↑ risk of breast cancer
PCOS
Polycystic Ovarian Syndrome
- Common cause secondary amenorrhea
- Genetics plus diet/obesity \(\rightarrow\) ↑ LH:FSH ratio
- LH drives androstenedione from theca cells
- Some androgens \(\rightarrow\) estrone in adipose tissue
- Estrone \(\rightarrow\) ↓ FSH \(\rightarrow\) anovulation

Hyperinsulinemia
- PCOS associated with insulin resistance
- More than expected for degree of obesity
- Can lead to diabetes

PCOS
Clinical features
- Occurs in obese females
- Hirsutism (facial hair)
- Acne
- Amenorrhea
- Infertility
- Ultrasound: multiple follicular cysts

PCOS
Diagnosis
- Usually diagnosed clinically
- Can measure total testosterone
- LH and FSH may be within normal range
  - But LH:FSH ratio usually > 2:1 or 3:1

PCOS
Treatment
- Weight loss
- Oral contraceptives
  - Supress LH
  - Estrogen \(\rightarrow\) ↑ SHBG \(\rightarrow\) ↓ androgens
- Spironolactone
  - Blocks androgens
- Metformin/TZDs
  - Diabetes drugs that improves insulin resistance
  - Not routinely used unless patient develops diabetes
PCOS
Other Features
• Risk of diabetes
  • ~10% of women with PCOS develop DM by 40 years old
• Acanthosis Nigricans
  • Plaques of darkened skin
  • Associated with insulin resistance
  • Common in diabetes, PCOS, also gastric cancer
• Endometrial cancer
  • Unopposed estrogen (lack of progesterone)
  • ↑ risk of endometrial hyperplasia and carcinoma

Amenorrhea Workup
Rule out:
- Pregnancy
- Thyroid
- Cushing
- Prolactin
- Anorexia

<table>
<thead>
<tr>
<th>↓FSH</th>
<th>↑FSH</th>
<th>Normal FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>↑LH:FSH</td>
<td>Menopause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mullerian Dysgenesis</td>
</tr>
</tbody>
</table>
**Pituitary Gland**

*Master gland*

- Endocrine gland at base of brain
- Sits in small cavity of sphenoid bone: sella turcica

**Anterior Pituitary Gland**

Derived from Rathke's pouch

- Outgrowth of oral cavity
- Contains five cell types that make hormones

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotrophs</td>
<td>Adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Thyrotrophs</td>
<td>Thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Gomatosrophs</td>
<td>Luteinizing hormone (LH)</td>
</tr>
<tr>
<td>Somatotrophs</td>
<td>Growth hormone (GH)</td>
</tr>
<tr>
<td>Lactotrophs</td>
<td>Prolactin</td>
</tr>
</tbody>
</table>

**Posterior Pituitary Gland**

Neurohypophysis

- Secretes ADH (vasopressin) and oxytocin
- Derived from neural ectoderm in floor of forebrain
- Contains axons and nerve terminals
- Neurons originate in hypothalamus
- **Paraventricular and supraoptic nuclei**
  - Paraventricular: Oxytocin
  - Supraoptic: ADH

**Hypothalamic Portal System**

- Main blood supply to anterior pituitary gland
- Delivers releasing/inhibiting hormones

<table>
<thead>
<tr>
<th>Hypothalamus</th>
<th>Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>ACTH</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>TSH</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>LH/TSH</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>GH</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Prolactin</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>GH, TSH</td>
</tr>
</tbody>
</table>
Prolactin
- Protein hormone
- Regulates milk production in mothers

Prolactin
- Under inhibitory control from hypothalamus
  - Hypothalamus releases dopamine
  - Inhibits lactotrophs via binding to D2 receptors
  - Destruction of hypothalamus: ↑ prolactin
- Prolactin feedback on hypothalamus
  - Increases dopamine release → ↓ prolactin

Prolactin
- Many other substances affect prolactin release
  - VIP, Oxytocin, TRH, others
  - TRH (thyrotropin-releasing hormone)
    - Elevated in hypothyroidism
    - Hypothyroidism predisposes to hyperprolactinemia
    - Hypothyroidism in differential for:
      - Pituitary enlargement
      - Hyperprolactinemia

Prolactin
- Estrogen stimulates prolactin release
  - Stimulates gene transcription
  - Stimulates release from lactotrophs
  - Marked increase in lactotrophs during pregnancy
  - Pituitary can grow in size

Prolactin in Pregnancy
- Prolactin inhibits GnRH release
- Results in cessation of ovulation/menstruation

Prolactin in Pregnancy
- Prolactin stimulates growth of mammary glands
- Milk production in pregnancy does not occur
  - Estradiol and progesterone block prolactin effect on milk
- After childbirth → ↓ estradiol and progesterone
  - Milk production occurs
Dopamine Antagonists
- Antipsychotics: Haloperidol, Risperidone
- Antiemetics: Metoclopramide
- Blockade of D2: ↑ prolactin
- Side Effects:
  - Amenorrhea
  - Breast engorgement
  - Galactorrhea
  - Sexual dysfunction
  - Can also cause Parkinsonian symptoms

Prolactinoma
- Most common hormone secreting tumor
- Headache, vision loss
- Rarely seizures
- Women: amenorrhea, fractures (low bone density)
- Men: Loss of libido, impotence
- Diagnosis: serum prolactin; CNS imaging
- Treatment: Bromocriptine, cabergoline

Hyperprolactinemia
- Women
  - Amenorrhea (lack of GnRH/LH/FSH)
  - Galactorrhea (prolactin)
- Men
  - "hypogonadotropic hypogonadism"
  - Decreased libido
  - Impotence
  - Infertility
  - Gynecomastia
  - Usually no galactorrhea (not enough breast tissue)

Pituitary Adenomas
- Tumors of any cell type of anterior pituitary
- May result in increased secretion of hormones
- Most common secreting tumor: prolactinoma

<table>
<thead>
<tr>
<th>Cell Type</th>
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<td>Cushing's disease</td>
</tr>
<tr>
<td>Somatotrophs</td>
<td>Acromegaly/Gigantism</td>
</tr>
</tbody>
</table>

Dopamine Agonists
- Cabergoline, Bromocriptine
- Can be used to treat Parkinson’s disease
- Also used to treat prolactinomas
- Will inhibit prolactin release (via D2 receptors)

Pituitary Adenomas
- General Symptoms
  - Headaches
  - Classic cause of bitemporal hemianopsia
  - Compression of optic chiasm

Pituitary Adenomas
- Tumors of any cell type of anterior pituitary
- May result in increased secretion of hormones
- Most common secreting tumor: prolactinoma
Sheehan Syndrome

- Pituitary gland enlarged in pregnancy
- Vulnerable to infarction from hypovolemic shock
- Postpartum hemorrhage → hypopituitarism
- Can present as shock after delivery
- Also can see failure to lactate

Pituitary Apoplexy

- Sudden hemorrhage into the pituitary gland
- Often occurs into pre-existing adenoma
- Risk factors for bleeding may be present (warfarin)
- Sudden onset severe headache
- Diplopia (pressure on oculomotor nerves)
- Hypopituitarism (shock from loss of cortisol)

Empty Sella Syndrome

- Enlarged sella turcica partially filled with CSF
- Rarely can compress pituitary → hypopituitarism
- More common in women with obesity, hypertension

Craniopharyngioma

- Benign tumor
- Usually occurs in children 10-14 years old
- Symptoms from compression
  - Hypopituitarism
  - Headache, visual field defects
  - Behavioral change (frontal lobe dysfunction)
  - Derived from remnants of Rathke's pouch

Hypopituitarism

- Caused by damage to anterior pituitary
  - Mass: Nonfunctional adenoma, craniopharyngioma
  - Ischemia, brain injury, hemorrhage
  - ACTH deficiency
    - Low cortisol → shock
  - No loss of aldosterone → no salt wasting
  - Lack of hyperpigmentation (see in primary adrenal failure)
  - TSH deficiency → hypothyroidism
  - LH/FSH deficiency → hypogonadism

Radiation

- Some head and neck tumors treated with radiation
  - Brain tumors or nasopharyngeal carcinomas
- Some pituitary adenomas treated with radiation
- Can cause damage to hypothalamus or pituitary

Stevenfruitsmaak/Wikipedia

Surgical Excision/Wikipedia
**Growth Hormone**

**Somatotropin**
- Protein hormone
- Important for **linear (height)** growth in childhood
- Released in a pulsatile manner
- Between pulses levels may become undetectable

**Growth Hormone Receptor**
- Bind to a **membrane-bound** receptor
- Activates janus kinase 2 (JAK2) enzyme
- Cytoplasmic tyrosine kinase
- Phosphorylates tyrosine residues
- Within JAK2 itself and on GH receptor
- Forms binding sites for many signaling molecules
- Alters gene expression

**Hypopituitarism**
**Treatment**
- Hormone therapy
  - Corticosteroids
  - Thyroid hormone
  - Growth hormone
  - Estrogen/testosterone

**Growth Hormone**
- Liver contains many growth hormone receptors
- GH → Liver → IGF-1 secreted
- Insulin-like growth factor 1/Somatomedin
- Hormone that mediates many growth hormone effects
- Can be measured in serum as indicator of GH function
- IGF-1 also produced in peripheral tissues
- Paracrine effects on nearby sites

**Growth Hormone**
**Direct Effects**
- ↓ glucose uptake by cells
  - Anti-insulin
  - Will raise blood sugar ("Diabetogenic")
- Peripheral tissues become insulin resistant
- Hyperinsulinemia

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Growth Hormone Excess
- Most common cause is somatotroph adenoma
- High GH and IGF-1
- Low GHRH from hypothalamus (negative feedback)
- High somatostatin (negative feedback)
- May present with headache, vision loss
- Rare cause: GHRH secreting tumors
- Hypothalamic tumors, carcinoid tumors, small-cell lung CA
- GHRH level will be high

Growth Hormone Deficiency
- Most commonly from pituitary tumor
- Mass effect
- Consequence of surgery/radiation
- Treatment: Synthetic growth hormone
- Monitoring: Serum IGF-1 level

Growth Hormone Effects
- Bone/Muscle
  - Linear Growth
  - Lean muscle Mass
- Glucose
  - Opposes Insulin
  - Raises blood sugar
- Fat
  - Increased lipolysis

Growth Hormone Deficiency Effects
- Chondrocytes
  - Increased linear growth
- Muscle
  - Lean muscle mass
- Organs
  - Increased organ size

Growth Hormone Excess Effects
- Promotes lipolysis
  - Activates hormone sensitive lipase
  - Production of IGF-1 from liver

Growth Hormone Deficiency Effects
- Children:
  - Failure to grow
- Adults
  - ↑ fat
  - ↓ lean body mass
  - Low energy
Growth Hormone Excess

- Children:
  - Excessive growth: Gigantism
  - Linear growth: Very tall child
- Adults: Acromegaly

Acromegaly

- Insidious onset
  - Average duration symptoms → diagnosis = 12 years
- Enlarged jaw
  - Coarse facial features
    - Enlargement of nose, frontal bones

Acromegaly

- Enlarged hands and feet
  - Classic sign: Increasing glove/shoe size
  - Rings that no longer fit

Acromegaly

- Visceral organs enlargement
  - Thyroid, heart, liver, lungs, kidneys, prostate
- Synovial tissue/cartilage enlargement
  - Joint pain in knees, ankles, hips, spine
  - Common presenting complaint is joint pain
- Cardiovascular disease
  - Hypertension, left ventricular hypertrophy, cardiomyopathy
  - Mortality increased in acromegaly due to CV disease

Growth Hormone Excess

Diagnosis

- Serum IGF-1 concentration
  - IGF-1 level is constant (contrast with GH)
- Oral glucose tolerance testing
  - Glucose should suppress growth hormone levels
  - Normal subjects: GH falls within two hours
  - Post glucose levels high
- CNS imaging (MRI)
Somatostatin
- Inhibits release of many hormones
- Released by D cells throughout GI tract
- Also found in nerves throughout entire body
- Originally discovered in hypothalamus
- Inhibits growth hormone release
- Used therapeutically (Octreotide):
  - Acromegaly
  - Carcinoid syndrome
  - Glucagonoma/insulinoma
  - Upper GI bleeding (↓ splanchnic blood flow)

Oxytocin
- Produced in paraventricular nuclei of hypothalamus
- Causes milk release in response to suckling
  - Afferent fibers nipple → spinal cord
  - Triggers release oxytocin from posterior pituitary
  - Oxytocin triggers contraction of myoepithelial cells in breast

MSH
- Melanocyte Stimulating Hormone
  - Proopiomelanocortin: Precursor of ACTH
  - Also precursor of MSH (α/β/γ)
  - MSH: Stimulates melanocytes to produce melanin
  - Causes hyperpigmentation in Cushing’s disease

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Growth Hormone Excess
- Treatment
  - Octreotide
    - Analog of somatostatin
    - Suppresses release of growth hormone
    - Also surgery, radiation
    - Goal: Lower IGF-I to within reference range
    - Bony abnormalities do not regress
    - Joint symptoms often continue

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Oxytocin
- Also causes contraction of uterus
  - Oxytocin receptors upregulate in uterus near term
  - Pitocin (synthetic oxytocin)
    - Induction of labor
    - Postpartum uterine bleeding
Parathyroid Glands

Parathyroid Glands

Parathyroid Hormone

• Protein hormone
• Binds to cell surface receptors in bone and kidney
• Synthesized by chief cells of parathyroid gland

Parathyroid Hormone Effects

• Net Effects:
  • ↑ [Ca\(^{2+}\)] plasma
  • ↓ [P04\(^{3-}\)] plasma
  • ↑ [P04\(^{3-}\)] urine
  • Some due to direct action PTH
  • Some due to activation of vitamin D (indirect)

Parathyroid Hormone

• Secreted in response to:
  • ↓ [Ca\(^{2+}\)] (major stimulus; fastest response)
  • ↑ plasma [P04\(^{3-}\)]
  • ↓ 1,25-(0H)\(_2\) vitamin D
  • Calcium activates calcium-sensing receptors (CaSRs)
  • ↓ PTH

Parathyroid Hormone

• High magnesium
  • ↑ PTH (same effect as calcium)
  • Magnesium can activate CaSRs
• Low Mg
  • ↑ PTH release (same effect as calcium)
  • ↑ GI and renal magnesium along with calcium
Parathyroid Hormone

Magnesium

- Very low Mg → inhibits PTH release
- Some Mg required for normal CaSR function
- Abnormal function → suppression of PTH release
- Hypocalcemia often seen in severe hypomagnesemia

Parathyroid Hormone Effects

- Kidney:
  - ↑Ca\(^{2+}\) resorption (DCT)
  - ↓P04\(^{3-}\) resorption (PCT)
  - ↑1,25-(OH)\(^2\) vitamin D production
- GI:
  - ↑Ca\(^{2+}\) and P04\(^{3-}\) absorption (via vitamin D)
- Bone:
  - ↑Ca\(^{2+}\) and P04\(^{3-}\) resorption (direct and via vitamin D)

Qt Interval

Normal Qt

Prolonged Qt: ↓Mg, ↓Ca

Short Qt: ↑Ca

Parathyroid Hormone

Lumen (Urine) Interstitium/Blood

PTH

1,25-(OH)\(^2\) Vitamin D

Vitamin D and the Kidney

- Proximal tubule converts vitamin D to active form
- Can occur independent of kidney in sarcoidosis
- Leads to hypercalcemia
**Types of Bone**

- **Cortical bone**
  - Hard, outer layer of bone
  - ↑ in response to continuous PTH

- **Trabecular bone**
  - Sponge, inner layer of bone
  - ↑ in response to intermittent, low dose PTH

---

**Parathyroid Hormone**

- Multiple effects on bone
  - Stimulates bone resorption and formation
  - Dominant effect varies with dosage/timing of administration of PTH to bone

---

**Parathyroid Hormone**

- Continuous administration of PTH
  - Bone resorption → ↑ serum calcium
  - Important physiologically
  - Low dose once daily bolus administration
    - Increased bone mass (bone formation)
    - Teriparatide used to treat osteoporosis

---

**Parathyroid Hormone**

- Osteoblasts
  - Bone forming cells
  - Contain PTH receptors
  - Can ↑ bone mass in response to PTH

- Osteoclasts
  - Bone resorbing cells
  - No PTH receptors
  - Activated indirectly by osteoblasts

---

**Parathyroid Hormone**

- M-CSF
  - Macrophage colony stimulating factor
  - Secreted by osteoblasts

- RANK-L
  - Receptor activating nuclear factor κB ligand
  - Expressed on surface of osteoblasts
  - Both produced by osteoblasts → activate osteoclasts
Primary Hyperparathyroidism
• Inappropriate secretion of PTH
• Not due to low calcium
• Commonly caused by parathyroid adenoma

Hyperparathyroidism
• Primary (overactive glands)
• Secondary (hypocalcemia)
• Tertiary (seen in renal failure)

PTHrP
Parathyroid hormone-related protein
• Produced in many tissues
• Numerous normal effects
• Synthesized in large amounts by some tumors
  • Renal cell carcinoma
  • Squamous cell lung cancer
• Leads to hypercalcemia in malignancy

Primary Hyperparathyroidism
• Urinary calcium usually high or normal
• ↑ PTH → ↑ Ca urinary reabsorption → ↑ serum Ca
• ↑ serum Ca → ↑ urinary calcium

Primary Hyperparathyroidism
• Causes hypercalcemia
  • ↑ renal reabsorption of Ca
  • ↑ vitamin D activation
  • ↑ bone resorption (loss of cortical bone)
  • Phosphaturia

↑PTH  ↑Ca

Primary Hyperparathyroidism
• "Stones, bones, groans, and psychiatric overtones"
  • Largely historical
  • Modern era, most patients diagnosed early
  • Often asymptomatic; diagnosis by routine blood work
  • Recurrent kidney stones is common presentation
  • Other signs/symptoms more often seen malignancy

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  • ↑ bone resorption (loss of cortical bone)
  • Phosphaturia
Primary Hyperparathyroidism
Symptoms

- Stones (kidney)
  - High Ca in urine can cause stones
- Dehydration
  - Calcium blunts effects of ADH (nephrogenic DI)
  - Polyuria and polydipsia
  - Can lead to renal failure

- Groans (abdominal pain)
  - Constipation, anorexia, nausea
  - Increased stomach acid production (unclear mechanism)
  - Recurrent peptic ulcers
  - Psychiatric overtones
    - Anxiety, altered mental status

- Bones (bone pain)

Primary Hyperparathyroidism

- Adverse effects on bones of long-standing high PTH

- Groans (abdominal pain)
  - Constipation, anorexia, nausea
  - Increased stomach acid production (unclear mechanism)
  - Recurrent peptic ulcers
  - Psychiatric overtones
    - Anxiety, altered mental status

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  - High Ca in urine can cause stones
  - Dehydration
  - Calcium blunts effects of ADH (nephrogenic DI)
  - Polyuria and polydipsia
  - Can lead to renal failure

Osteitis Fibrosa Cystica

- Classic bone disease of hyperparathyroidism
- Clinical features: Bone pain and fractures

- Subperiosteal bone resorption
  - Commonly seen in bones of fingers
  - Irregular or indented edges to bones
- Brown tumors (osteoclastoma)
  - Collections of giant osteoclasts in bone
  - Mixed with stromal cells and matrix proteins
  - Appear as black spaces in bone on x ray

Osteitis Fibrosa Cystica

- Parathyroidectomy
  - Removal of gland with adenoma
  - Pre-op nuclear imaging often done to identify location
  - Risks of recurrent laryngeal nerve damage
    - May result in hoarseness
  - Post-op hypocalcemia
    - Remaining parathyroid glands may be suppressed
    - Numbness or tingling in fingertips, toes, hands
    - If severe: twitching or cramping of muscles

Primary Hyperparathyroidism

- Post-op hypocalcemia
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  - Numbness or tingling in fingertips, toes, hands
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2\textsuperscript{o} Hyperparathyroidism

- Occurs in renal failure patients
- Chronically low serum calcium $\rightarrow$ ↑PTH
- No symptoms of hypercalcemia
- Results in \textit{renal osteodystrophy}
  - Bone pain (predominant symptom)
  - Fractures (weak bones $2\textsuperscript{o}$ chronic high PTH levels)
  - If severe, untreated can lead to osteitis fibrosa cystica

↑PTH \hspace{1cm} ↓Ca

3\textsuperscript{o} Hyperparathyroidism

- Consequence of chronic renal failure
- Chronically low calcium $\rightarrow$ chronically ↑PTH
- Parathyroid becomes autonomous
- VERY high PTH levels
- Calcium may become elevated
- Often requires parathyroidectomy

↑PTH \hspace{1cm} ↓Ca

Calcium-Phosphate in Renal Failure

Sick Kidneys

↑Phosphate

1,25-OH\textsubscript{2} Vitamin D

↓Ca from gut

↓Ca from plasma

Hypocalcemia

↑PTH

FHH

Familial Hypocalciuric Hypercalcemia

- Rare, autosomal dominant disorder
- \textbf{Abnormal calcium sensing}
  - Abnormal calcium sensing receptors (CaSRs)
  - G-protein membrane receptors
  - Found in parathyroid and also kidneys
- Higher than normal set point for calcium
  - Normal PTH $\rightarrow$ ↑calcium
- More renal resorption of calcium
  - Low urinary calcium

↑PTH \hspace{1cm} ↓Ca

FHH

Familial Hypocalciuric Hypercalcemia

- Findings:
  - Usually normal PTH
  - Mildly elevated serum calcium
  - \textbf{Low urinary calcium} (key finding!)
  - May looks like 1\textsuperscript{o} hyperparathyroidism
  - Real world distinction from 1\textsuperscript{o} disease difficult
  - Genetic testing available
  - Usually does not require treatment

Hypoparathyroidism

- Inappropriately low PTH secretion
- Not due to hypercalcemia
- Causes \textbf{hypocalcemia}

↑PTH \hspace{1cm} ↓Ca
Pseudohypoparathyroidism
• Group of disorders
• Kidney and bone unresponsiveness to PTH
• Abnormal PTH receptor function
• Many cases due to impaired G protein signaling
• Usually presents in childhood
• Hypocalcemia, hyperphosphatemia
• Elevated PTH (appropriate)

↑PTH    ↓Ca

Thymic Aplasia
DiGeorge Syndrome
• Immunodeficiency syndrome
• Failure of 3rd/4th pharyngeal pouch to form
• Classic triad:
  • Loss of thymus (Loss of T-cells, recurrent infections)
  • Loss of parathyroid glands (hypocalcemia, tetany)
  • Congenital heart defects
• Presents in infancy/childhood with:
  • Hypocalcemia (hypoparathyroidism)
  • Recurrent infections
  • Congenital heart defects

APS-I
Autoimmune Polyendocrine Syndrome Type 1
• Rare autosomal recessive disorder
• Mutations of autoimmune regulator (AIRE) gene
• AIRE also associated with chronic mucocutaneous candidiasis
• Triad:
  • Mucocutaneous candidiasis
  • Autoimmune hypoparathyroidism
  • Addison’s disease

Hypoparathyroidism
Treatment
• Calcium and calcitriol (vitamin D3)
• Recombinant human PTH available

Hypocalcemia
Signs/Symptoms
• Neuromuscular irritability
  • Nerves: tingling of fingers, toes, around mouth
  • Muscles: intermittent spasms (tetany)
• Tetany
  • Trousseau’s sign: Hand spasm with BP cuff inflation
  • Chvostek’s sign: Facial contraction with tapping on nerve
• Seizures

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• Seizures

Hypoparathyroidism
Causes
• Surgical excision
  • Often accidental after thyroid or neck surgery
• Key findings: post-op tingling, spasms
• Systemic diseases
  • Hemochromatosis (iron)
  • Wilson’s (copper)
  • Metastatic cancer
Calcium and PTH

- 1st look at calcium: Low/High
- Next, look at PTH: Low/High
- Same direction = parathyroid problem
  - Both ↑: Hyperparathyroidism
  - Both ↓: Hypoparathyroidism
- Opposite direction
  - Normal response to calcium problem
  - Renal failure (low serum calcium – 2nd hyperparathyroidism)
  - Renal losses (pseudohypoparathyroidism)

AHO
Albright’s Hereditary Osteodystrophy
- Form of pseudohypoparathyroidism
- Autosomal dominant
- Hypocalcemia, hyperphosphatemia, ↑ PTH
- Collection of clinical features
  - Short stature
  - Shortened fourth and fifth metacarpals
  - Rounded facies
MEN Syndromes

MEN 1

- 3 P’s
  - Pituitary adenoma
  - Parathyroid adenoma
  - Pancreatic tumors

- Autosomal dominant
- Germline mutation of MEN1 gene (11q13)
- Codes for the protein menin
- Tumor suppressor
- Classic example of 2 hit hypothesis
- Patients born with 1 abnormal MEN 1 gene
- Second “hit” occurs in endocrine glands

MEN 1

- Pituitary adenoma
- Occurs in up to 70% of patients
- Most commonly a prolactinoma
- 2nd most common: GH secreting adenoma
- Pituitary adenomas not seen in other MEN syndromes
- Pituitary disease = MEN 1

MEN Syndromes

Multiple Endocrine Neoplasia

- Group of rare genetic disorders
- All autosomal dominant
- Germline mutations in genes
- Lead to tumors in multiple endocrine glands
- MEN 1, 2A, 2B

MEN Syndromes

Jason Ryan, MD, MPH

MEN Syndromes

Multiple Endocrine Neoplasia

- Group of rare genetic disorders
- All autosomal dominant
- Germline mutations in genes
- Lead to tumors in multiple endocrine glands
- MEN 1, 2A, 2B
MEN 2A and 2B

- Medullary tumors
  - Medullary thyroid carcinoma
  - Pheochromocytoma (adrenal medulla)

MEN 2A and 2B

- MEN 2A
  - Medullary plus parathyroid
  - No physical findings
- MEN 2B
  - Medullary plus M's
  - Two key "phenotype" findings
  - Mucosal neuromas
  - Marfanoid appearance
  - Usually no parathyroid involvement

Medullary Carcinoma

- Cancer of parafollicular cells (C cells)
- Produces calcitonin
  - Lowers serum calcium
  - Normally minimal effect on calcium levels
  - With malignancy → hypocalcemia

MEN 2A and 2B

- MTC occurs earlier than sporadic cases
  - Sporadic: 60s
  - MEN: 30s
  - ~100% risk of MTC
  - Pheochromocytoma usually occurs after MTC

MEN 2B

- Same as 2A except:
  - Usually no parathyroid involvement
  - Two key physical findings
    - #1: Mucosal neuromas
      - Lips, tongue
    - #2: Marfanoid body habitus
MEN Syndromes

- Pituitary adenoma = MEN 1
- MTC or pheochromocytoma = MEN 2
- Parathyroid = MEN 1 or MEN 2A

MEN 2B Neuromas

- Benign growth of nerve tissue
- Often lips and tongue
- Sometimes intestinal neuromas

MEN 2B: Marfanoid

- Tall
- Long wing span
- High arched palate
- Skeletal deformations of spine:
  - Kyphoscoliosis: Curve to left/right
  - Lordosis: Curve forward
- No lens or aortic involvement (like Marfan's)

MEN 2A and 2B

- Autosomal dominant disorders
- Germline mutations in RET (chromosome 10)
- Proto-oncogene
- Codes for a receptor tyrosine kinase
- Important for cell growth/differentiation
- Gain of function mutations in MEN 2
  - Contrast with Hirschsprung disease of colon
  - Associated with loss of function mutations in RET

Thyroidectomy

- Often done prophylactically in MEN2 syndromes
- Usually at a young age (<5 years old)

MEN 2B:

- Marfanoid
  - Tall
  - Long wing span
  - High arched palate
  - Skeletal deformations of spine:
  - Kyphoscoliosis: Curve to left/right
  - Lordosis: Curve forward
  - No lens or aortic involvement (like Marfan's)

MEN 2B Neuromas

- Benign growth of nerve tissue
- Often lips and tongue
- Sometimes intestinal neuromas
Intracellular Hormones
- Receptor in cytoplasm/nucleus
  - Progesterone
  - Estrogen
  - Testosterone
  - Cortisol
  - Aldosterone
  - Thyroid hormone

Steroid Hormones
- Estradiol (17β-estradiol)
- Testosterone
- Progesterone
- Aldosterone
- Cortisol
- Cholesterol

Thyroid Hormones
- Two hormones: T3 and T4
- Synthesized from tyrosine and iodine
- Triiodothyronine (T3)
- Thyroxine (T4)

Hormone Effects
- Hormone → Cell → Effects

Intracellular Hormones
- All circulate bound to a protein
  - Estrogen/testosterone: sex binding globulin (SBG)
  - Thyroid hormone: thyroid binding globulin (TBG)
  - Cortisol: corticosteroid-binding globulin (CBG)
  - Aldosterone
  - Progesterone

Signaling Pathways
Jason Ryan, MD, MPH
**JAK2 Mutation**

- Associated with myeloproliferative disorders
- Gene for cytoplasmic tyrosine kinase
- Mutation → ↑ tyrosine phosphorylation
- Progenitor cells: hypersensitivity to cytokines
- More growth; longer survival

**Receptor Tyrosine Kinase**

- Many cytokines
  - IFN-γ, IL-2, IL-6
  - G-CSF (granulocyte-colony stimulating factor)
  - Thrombopoietin
  - Others
    - Prolactin
    - Growth hormone
Cyclic AMP

- Hormone
- adenyl cyclase
- Adenosine Triphosphate
- Cyclic Adenosine Monophosphate

G-Protein Linked Receptors

- Bind guanosine nucleotides (GDP, GTP)
- Transmit signals

Pituitary Hormones

- All have a cAMP second messenger system
- α-subunit
- FSH β
- LH β
- TSH β
- HCG β
- ATP
- cAMP
- Effects

MSH

- Melanocyte Stimulating Hormone
- Causes hyperpigmentation in Cushing’s disease
- Proopiomelanocortin: Precursor of ACTH
- Also precursor of MSH (α/β/γ)
- MSH: Stimulates melanocytes to produce melanin

Cyclic GMP

- Hormone
- Guanylate Cyclase
- Guanosine Triphosphate
- Cyclic Guanosine Monophosphate
G-Protein Linked Receptors

- Hypothalamus
  - GnRH, TRH
- Posterior Pituitary
  - Oxytocin
  - ADH (V1 receptor - vasoconstriction)
- Others
  - Histamine (H1-receptor – skin/lungs)
  - Angiotensin II
  - Gastrin

Cyclic GMP

- BNP/ANP
  - Release by cardiac myocytes
  - Antagonize RAAS system
  - Both bind natriuretic peptide receptors (NPR)
  - Vasodilation/diuresis
- Nitric oxide
  - Endothelium-derived relaxing factor (EDRF)
  - Synthesized by endothelial cells
  - Activates cGMP → smooth muscle relaxation/vasodilation
- All are vasodilators

Inositol Triphosphate (IP3)

- BNP/ANP
  - Release by cardiac myocytes
  - Antagonize RAAS system
  - Both bind natriuretic peptide receptors (NPR)
  - Vasodilation/diuresis
- Lipid
  - Hormone?
- YES
- NO
- Vasodilator?
  - (BNP/ANP/EDRF)
- NO
- Insulin/Growth factor?
- NO
- Cytokine/Bone marrow?
- NO
- Prolactin/Growth hormone?
  - Intracellular
  - YES
  - cGMP
  - Tyrosine Kinase
  - JAK/STAT
  - cAMP/IP3

Hypothalamus

<table>
<thead>
<tr>
<th>Hypothalamus</th>
<th>2nd Messenger</th>
</tr>
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<tbody>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>cAMP</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>IP3</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>IP3</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>cAMP</td>
</tr>
</tbody>
</table>

Inositol Triphosphate

- Hypothalamus
  - GnRH, TRH
- Posterior Pituitary
  - Oxytocin
  - ADH (V1 receptor - vasoconstriction)
- Others
  - Histamine (H1-receptor – skin/lungs)
  - Angiotensin II
  - Gastrin
### Anterior Pituitary

<table>
<thead>
<tr>
<th>Hormone</th>
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<tbody>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>cAMP</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>cAMP</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
<td>cAMP</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>cAMP</td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td>JAK/STAT</td>
</tr>
<tr>
<td>Prolactin</td>
<td>JAK/STAT</td>
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</table>

### Others

- IP3
- ADH (V1 receptor)
- Histamine (H1 receptor)
- Gastrin
- Angiotensin II
- cAMP
- Histamine (H2 receptor)
- ADH (V2 receptor)